TOWARD COMPREHENSIVE UNDERSTANDING OF THE SUICIDAL PHENOMENON

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OPINION
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Adding Suicide Prevention to the Triple Advantages of Injectable Long-Acting Second-Generation Antipsychotics

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Keywords: suicide, treatmeat outcome, relapse, adherence, prevention

INTRODUCTION

With the advent of new treatment perspectives for schizophrenic patients, long-acting injectable antipsychotics promise to provide relapse prevention, neuroprotection, and lower mortality rates (1). In preliminary studies, scholars have also indicated that such treatments could play a central role in suicide prevention in patients (2, 3) for whom suicide is the most likely cause of premature death, in addition to repercussions for caregivers and clinicians. Both Kraepelin (4) and Bleuler (5) highlighted the issue of suicide risk among patients suffering from schizophrenia. Modern studies provided an intricate list of risk factors for suicide, pointing to numerous issues in the management and treatment of schizophrenic patients. Individuals at higher risk are generally unmarried young white males who achieved proper functioning before the onset of the disorder (6). Such patients may easily be overwhelmed by hopelessness and depression, as well as becoming demoralized and being aware that their previous lifestyle cannot be maintained. Such patients feel socially isolated, fear further mental deterioration, have higher rates of substance abuse, and may lose faith in the treatments. Suicide attempts and hospitalizations are frequent, and each time they may realize that both medical and family support is limited; moreover, *ad hoc* interventions are not available or are difficult to implement. There are also further risk factors for suicide in schizophrenia, such as post-psychotic depression, agitation or motor restlessness, poor adherence to treatment, and command hallucinations (although not well ascertained in terms of statistical significance). However, risk factors often yield too many false positives, pointing to the need for suicide assessments based on factors such as an understanding of mental pain and demoralization, as well as therapeutic relationships, foreseeable life events that may impact the patient, social support, and the available resources. Furthermore, suicide risk is indirectly related to relapse, illness progression, the number of hospitalizations, and plans for rehabilitation after discharge (7).

Each admission to a psychiatric ward may represent a further loss of hope and faith in the treatments. The risk of suicide seems to peak not only shortly after discharge, as reported routinely in the literature, but also shortly after admission (7). This fact points to the implementation of human–environmental factors for providing ward safety and close supervision in both inpatient and community settings, especially in the cases of reduced adherence to treatment.

Among the various risk factors, preventative actions should be directed over those factors that are modifiable and can be targeted by proper treatment actions (8). Furthermore, suicide risk seems to be higher when patients develop demoralization syndrome, in which repeated exacerbations of psychotic symptoms, functional deterioration compared with premorbid abilities, and a non-

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delusional awareness of the effects of an illness can lead to feelings of hopelessness, depression, and, ultimately, suicide.

Suicidal behavior is also a major issue among patients with first-episode psychosis (9, 10). It is noteworthy that integrated compared with typical treatment proved to be effective in reducing both suicide and other causes of death; the Opus Study (9) demonstrated the effectiveness of this strategy. Such an intervention involved a) assertive community treatment (ACT); b) antipsychotic medication; c) psychoeducational family treatment; and d) social skills training. It resulted in lower mortality for any cause and lower suicide rates.

Mortality in Schizophrenia and Pharmacological Treatment

A recent study by Bitter et al. (11) highlighted the reduction in life expectancy among patients with schizophrenia. Of note is the fact that, compared with the controls, 20-year-old males with schizophrenia had their life expectancy reduced by 11.5 years and females by 13.7 years; the analogous numbers for 45-year-old schizophrenics were 8.1 and 9.6 years, respectively.

Taipale et al. (12) explored mortality in a large sample of approximately 30,000 patients and found that second-generation long-acting antipsychotic therapies [SG LATs; ranking: paliperidone palmitate > oral aripiprazole > long-acting injection (LAI) risperidone > LAI haloperidol > LAI perphenazine > oral perphenazine > LAI olanzapine > LAI zuclopenthixol] were associated with the lowest cumulative mortality rate. In 7.5 years, a follow-up SG LAT observation revealed the lowest cumulative mortality rate as compared with first-generation (FG) and SG oral and with no antipsychotic use. The use of LATs reduces the risk of death by 33% when compared to the corresponding oral equivalent. Such results are in line with further investigations by the same group of researchers (13), who reported their observations over 8 years. They observed that the risk of treatment failure or relapse after discontinuing antipsychotics does not decrease over time and that patients maintaining long-term antipsychotic treatment had increased survival rates.

Pharmacological Treatment and Outcome

Most of the challenges in managing schizophrenia are connected to relapses (a variable correlated with increased time to remission, increased residual symptom severity, increased risk of treatment resistance, increased cerebral toxicity, cognitive decline and functional impairment, increased risk of mortality, and increased duration of time to remission).

In this regard, suicide risk has been associated with reduced adherence to treatment and relapse rates (14). Seminal papers (15, 16) indicated that extended periods of relapse in schizophrenia might harm brain integrity. Evidence supports the notion that the risk increases immediately after stopping antipsychotics and remains high over time; on the other hand, maintaining antipsychotic treatment is associated with a reduced risk of relapse, fewer hospitalizations, and a better quality of life compared with a placebo or no treatment.

Heres et al. (17) pointed out the risks of using antipsychotic medications inappropriately as related to an increased risk of symptom worsening or relapse. Zipursky et al. (18), investigating the 1-year mean risk of psychotic symptoms in patients who have remitted after their first episode, found that recurrence after medication discontinuation is 77% compared to 3% under maintenance treatment. Each time, the exacerbation of symptoms is associated with mental pain and hopelessness. The concept of mental pain is of great importance as suicide may be considered an escape from intolerable suffering, emphasizing that suicide is not a movement toward death but rather an escape from pain and unendurable or unacceptable anguish. Experiencing negative emotions alongside an internal dialogue causes a painful flow of consciousness and leads the individual to the ultimate conclusion: death. This may be related to the fact that, if tormented individuals could somehow stop their consciousness and remain alive, they would opt for that solution. We may, therefore, hypothesize that proper pharmacological treatment targets those conditions which otherwise cause the individual to suffer, feel hopeless, and go on to die by suicide. It is, therefore, not necessarily the emergence of specific symptoms in each relapse, but the impact of the vivid reflection of the course of illness that potentiates suicide risk.

Of interest are the results reported by Hui et al. (19). These authors found that over 10 years, poor clinical outcomes occurred in 39% of patients who had interrupted their treatments versus 21% of patients in the maintenance treatment group. Incidentally, suicide was the only serious adverse event that occurred in the follow-up phase. This study also reveals that first-episode psychosis with a full initial response to treatment and medication continuation for at least the first 3 years after starting treatment decreases the risk of relapse and poor long-term clinical outcomes.

The number of hospitalizations is a central risk factor for suicide as each admission is indicative of poor outcomes, a painful awareness of ineffective treatment, and a fear of further mental disintegration. Kishimoto et al. (20) demonstrated that treatment with LAIs is associated with a reduced risk of hospitalization. Considering that such a reduction may increase patients' faith in treatment, as well as their faith in the future, this treatment may protect patients against suicide risk. In a substantial sample comprising almost 30,000 patients, Tiihonen et al. (21) found that treatments with some of the LAIs available (ranking: LAI paliperidone > LAI zuclopenthixol > oral clozapine > LAI perphenazine > LAI olanzapine > LAI risperidone) led to a reduction in hospitalizations. Furthermore, clozapine and LAIs were found to be the best treatment for relapse prevention.

In a pilot study, recently diagnosed patients with schizophrenia showed more significant improvements versus patients diagnosed for more than 5 years in an adjusted mean Global Assessment of Functioning (GAF) score, Positive and Negative Syndrome Scale (PANSS) factor score for negative and depressive symptoms, and the severity and intensity of their suicidal ideation (patients were treated with LAI-SGA during a follow-up period of 12 months). Our preliminary findings support the hypothesis that long-acting injection second-

generation antipsychotics (LAI-SGA) may influence the course of the illness if administered in the early phase of the illness (3).

DISCUSSION

Recently, Stahl (22) challenged out the traditional association between LAI formulations of antipsychotics and patients with schizophrenia with the most severe symptoms, in addition to those with the poorest adherence to treatment, numerous hospitalizations, and chronicity of the disorder. On the other hand, LAI antipsychotics may represent a strategic treatment in early-episode patients, resulting in the administration of treatments when schizophrenia is most treatable. In turn, such an approach may reduce recurrences and rehospitalizations. Since the first hospitalization is usually a crucial turning point for influencing the outcome, proper innovative treatment with LAI antipsychotics may make the difference in the moderation of a number of key risk factors for suicide in schizophrenia.

Aside from proper pharmacological properties, LAIs also possess several other advantages over oral antipsychotics, including those that may provide suicide prevention; they are administered by a mental health professional, and so, therefore, have a secondary gain which is shared by lithium and clozapine. In fact, in such treatments (both with consolidating evidence of their anti-suicidal action), patients need to regularly check their lithium blood levels; the same applies to clozapine, for which patients need to have regular blood count check to avoid agranulocytosis. Such small actions have the potential to strengthen therapeutic relationships and, in turn, diminish the suicide risk, as well as increase therapeutic contact and verify patients' adherence to treatment.

In summary, apart from being associated with the lowest cumulative mortality rate, SG LATs have the potential to influence various risk factors for suicide among patients with schizophrenia. The improvement of patients' functioning is of great importance as patients may consider suicide, especially during phases with the absence of positive and negative symptoms. The experience of painful insights, social isolation, and a fear of further mental deterioration associated with any condition contributing to patients' mental pain seem to be related to the risk of suicide. Appropriate treatment, as in the case of LAIs, which ensures the same concentration over time, may mitigate aggression and impulsivity, as well as substance abuse.

It is essential to take advantage of the benefits LAIs offer by combining drug treatment with psychosocial–psychotherapeutic interventions for a better outcome. Such patients can benefit from programs involving a psychotherapist as a critical figure in order to overcome painful periods, as well as be able to better cope with their conflicts. Clinicians should acknowledge the patient's despair, discuss their losses and daily difficulties, and help them to establish new and accessible goals.

Future studies should comprehensively assess how much injectable long-acting antipsychotics can affect suicide rates among patients with schizophrenia. Nowadays, it seems clinically reasonable to conclude that such treatments are promising in their management of symptoms more associated with suicide risk.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Corrigendum: Adding Suicide Prevention to the Triple Advantages of Injectable Long-Acting Second-Generation Antipsychotics

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The author apologizes for this error and states that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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ORIGINAL RESEARCH
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Gender Differences in the Relationship Between Sleep Problems and Suicide Attempt in Adolescents

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There are few studies examining which types of sleep problems are independently associated with suicide attempt (SA) and gender difference in adolescents. The aim of the present study was to examine whether specific sleep problems were uniquely associated with suicide attempt in adolescents and explore gender differences in the association. A school-based health survey was conducted in four provinces within China from November 2014 to January 2015. A total of 15,132 students aged 10–21 years completed standard questionnaires assessing past 12 month suicide attempt in addition to measures of sleep quality, quantity and sleep beliefs. 5.4% of participants reported a suicide attempt within the last 12 months. After adjustment for sociodemographic variables and psychological symptoms, almost all sleep problems remained significantly associated with a greater endorsement of suicide attempt. Further adjustment for co-occurring sleep problems revealed that weekday sleep duration (<6, 8–10, and ≥10 h), insomnia (often), and nightmares (sometimes and often) remained independently associated with suicide attempt in boys ($p < 0.05$). However in girls, weekday sleep duration (<6 and ≥10 h), weekend sleep duration (<6 h), midday nap (0 or 1–2 d/week), insomnia (sometimes and often), nightmare (often) and sleep beliefs (high) were independently associated with suicide attempt ($p < 0.05$). Multiple sleep problems are associated with suicide attempt in adolescents, however the relationship varies by gender.

Keywords: sleep problem, suicide attempt, adolescents, gender, sleep duration

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INTRODUCTION

As the second leading cause of death in young people worldwide (1), adolescent suicide continues to exact a substantial economic, social and psychological burden for individuals, families, and communities globally. Whilst progress has been made in our understanding of the phenomenology and risk factors associated with adolescent suicidality, less is known about the role of sleep in suicidal behavior. This is despite sleep problems being linked to a myriad of other psychosocial and general health complications in adolescent populations (2).

Prevalence studies suggest that sleep problems are relatively common among adolescents (3). To date, several measures of sleep including sleep duration, sleep quality and sleep disturbances have been examined in relation to youth suicidality (4, 5). A study in Scottish secondary schools found that both insomnia symptoms and nightmares were associated with an increased likelihood of reporting suicidal ideation (6). Nevertheless, there remains enduring inconsistencies surrounding the relationship between other aspects of sleep (e.g., sleep duration) and youth suicidality (7). For example, using a student sample, Guo et al. concluded that there was a U-shaped association between sleep duration, suicidal ideation, and suicide attempt (SA). Students who reported a total sleep time of 5–7 h/day were less likely to ideate (adjusted odds ratio, AOR = 1.59) or attempt (AOR = 1.53). Conversely, students who reported sleeping <5 h/day demonstrated an increased risk of suicidal ideation (AOR = 2.28), and attempt (AOR = 3.20) but likewise students who reported sleeping >9 h/day (AOR = 2.67) also exhibited an increased likelihood of suicide attempt (8).

Moreover, trends within sleep and suicide research tend to focus on singular sleep problems in isolation (3). This has resulted in few studies examining which types of sleep problems are independently associated with SA after adjusting for the influence of other inter-correlated sleep parameters. One existing study which has differentiated the impact of multiple sleep problems, found suicide attempt (SA) to be more strongly related to the presence of nightmares than other sleep problems (difficulties initiating sleep, maintaining sleep, and early morning awakening) (9). Notwithstanding the commonalities between sleep duration and insomnia, they represent distinct sleep parameters, with divergent gender patterns and differential effects on outcomes such as school performance (10). It is therefore important to assess a wide range of sleep problems simultaneously in order to ascertain the true nature of the relationships.

Research examining gender differences in the relationships has also been mixed. Whilst some studies have reported that a stronger relationship between short sleep durations and suicide attempt in girls (11), others have concluded that short sleep durations are associated with a heightened likelihood suicidal ideation in males only (12). Yet further studies have failed to document any discernible gender differences in the relationship between nightmares and suicide risk (13). In light of apparent disparities and evidenced gender differences in sleep requirements (14), the impact of sleep problems (15) and the presentation of SA (16), this study sought to firstly investigate whether specific sleep problems were uniquely associated with SA, and secondly, to explore gender differences across these associations.

METHODS

Study Sample and Procedures

The sample was derived from an anonymous health survey conducted from November 2014 to January 2015 involving adolescents from eight-middle schools located in 4 provinces within China. China is a vast territory with diverse geographic and economic development. In order to derive a sample broadly reflective of this diversity, eight schools (four rural and four urban) from four cities: southern Yangjiang (Guangdong province), central Xinxiang (Henan province), northern Shenyang (Liaoning province), and the western Chongqing area were selected. Collectively, these cities represent the economically developed region and the developing interior regions of the country.

In each region, eight general junior and senior schools (four from rural areas) were randomly chosen to recruit participants. As eight schools were combined junior and senior schools, only 24 schools in total were selected for inclusion into the survey. A sample of 15,713 adolescents from grades 7–12, aged 10–21 years were recruited. Of the 15,713 school adolescents, 581 (3.7%) were excluded from the study because of (1) absence from school on the day of the survey or unwillingness to respond to the questionnaire, (2) missing data through fictitious or inconsistent responses. A final sample of 15,132 (96.3%) was retained for analysis. The design and data collection procedures were approved by the Ethics Committee of Anhui Medical University (2012534). Written, informed consent was obtained from the parents of all participants in the study. Assent was obtained from all participants.

Measurements

Sociodemographic Profile and Psychological Symptoms

The model was adjusted for a range of demographic and psychosocial factors known to be associated with suicide including: age, gender, urban/rural residency, parents' education level (less than junior middle school, junior middle school, senior middle school, college or more), self-perceived economic status of the family (poor, moderate, or good). Psychological symptoms in the past 3 months were evaluated using the psychological domain of the "Multidimensional Sub-health Questionnaire of Adolescents" (17), which consists of 39 questions in 3 dimensions, as follows: emotional symptoms, e.g., "Do you always feel distressed?," conduct symptoms, e.g., "Do you always have the impulse to damage something?," and social adaptation symptoms, e.g., "Do you always hate learning at school?." The internal consistency of the psychological domain was satisfactory (Cronbach's $\alpha = 0.958$ in present study). Psychological symptoms were dichotomized by national norm of Chinese adolescents for analysis (17).

Sleep Problems

Sleep duration

Participants were asked about their *weekday* and *weekend* sleep duration via "During the past month, on an average school day, how many hours of actual sleep do you get at night?," "Dring the past month, on an average weekend, how many hours of actual sleep do you get at night?" In line with other research, we converted the sleep duration into 4 groups (<6, 6–8, 8–10, and ≥10 h) (18). In the analysis, the most common duration was selected as reference, thus 6–8 h was selected as the reference category for weekday sleep duration, 8–10 h was selected as the reference category for weekend sleep duration. As it is common

for Chinese workplaces and schools to take a *midday nap*, the frequency of naps (0–7) per week was also surveyed. To facilitate interpretation, this was divided into three levels (None: 0, Sometimes: 1–2, Often: ≥3).

Sleep disturbances

Participants were asked about their experience of sleep disturbances (i.e., symptoms of insomnia, nightmare, non-restorative sleep and daytime fatigue) during the past month (19). Those who endorsed at least 1 of the 3 types of *insomnia symptoms* (difficulty initiating sleep, difficulty maintaining sleep, early awakening and difficulty resuming sleep) with a frequency of ≥3 events/week were classified as having insomnia symptoms "Often." Individuals who endorsed a minimum of 1 type with a frequency of 1–2 events/week were categorized as having insomnia symptoms 'Sometimes'. Those with no symptoms were defined as 'None' (7). *Nightmare* occurrences was similarly denoted as "Often" (≥3/week), "Sometimes" (1–2/week), and "None." *Non-restorative sleep* was indexed by one item "Did you feel refreshed after sleeping over the last month?" and *daytime fatigue* was also indexed by one item "Did you feel fatigue and easily nod off during the daytime over the last month?" Responses ranged from "Often," "Sometimes," and "Never."

Sleep beliefs

Sleep beliefs was measured using the "Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS-16) (20). The scale is a 16-item version, used to identify specific sleep-related beliefs and attitudes about sleep that may be irrational or may lead to over-concern about sleep. Each item ranges from 1 (strongly disagree) to 5 (strongly agree). There are four factors within the DBAS-16: perceived consequences of insomnia, worry/helplessness about insomnia, sleep expectations, and medication. A higher total score indicates more dysfunctional beliefs and attitudes about sleep. In the present study, the DBAS-16 evidenced good internal consistency (Cronbach alpha) of 0.894. To facilitate interpretation, the scores were divided into three levels (high: P_{75}-P_{100}, moderate: P_{25}-P_{75}, and low: P_0-P_{25}) for analyses.

Suicide Attempt

One question was used to assess respondent's recent history of suicide attempt, specifically, "Have you ever tried to kill yourself in the past 12 months?" (Yes/No) (21).

Statistical Analysis

Descriptive analysis was used to outline the sociodemographic characteristics of the data (i.e., prevalence of sleep problems and suicide attempt for the total sample and for boys and girls separately). Gender differences were assessed using chi-squared test for categorical variables and one-way analysis of variance for continuous outcomes. Binomial logistic regression models were used to examine the associations between sleep problems and suicide attempt, followed by multivariate logistic regressions. In the multivariate regressions, adjustment was made for age, gender, regional areas, schools, urban/rurality, parents' education level, economic status of family and psychological symptoms. In the final model, independent sleep variables

TABLE 1 | Characteristics of participants by gender, *n* (%): 24 schools study, China.

Variables	Total	Boy	Girl	*p*-value
Age (mean, SD)	15.2 (1.8)	15.2 (1.8)	15.2 (1.7)	0.071
Regional areas				
Yangjiang	3,648 (24.1)	1,866 (25.5)	1,782 (22.8)	0.001
Shenyang	3,252 (21.5)	1,558 (21.3)	1,694 (21.7)	
Xinxiang	4,092 (27.0)	1,909 (26.1)	2,183 (27.9)	
Chongqing	4,140 (27.4)	1,981 (27.1)	2,159 (27.6)	
Urban/Rurality				
Urban	7,405 (48.9)	3,675 (50.2)	3,730 (47.7)	0.002
Rural	7,727 (51.1)	3,936 (49.8)	4,088 (52.3)	
Father's education level				
College or more	2,096 (13.9)	1,138 (15.6)	958 (12.3)	<0.001
Senior middle school	4,380 (28.9)	2,067 (28.3)	2,313 (29.6)	
Junior middle school	6,411 (42.4)	3,030 (41.4)	3,381 (43.2)	
Less than junior middle school	2,245 (14.8)	1,079 (14.8)	1,166 (14.9)	
Mother's education level				
College or more	1,698 (11.2)	915 (12.5)	783 (10.0)	<0.001
Senior middle school	4,146 (27.4)	2,027 (27.7)	2,119 (27.1)	
Junior middle school	6,501 (43.0)	3,034 (41.5)	3,467 (44.3)	
Less than junior middle school	2,787 (18.4)	1,338 (18.3)	1,449 (18.5)	
Economic status of family				
Good	1,877 (12.4)	992 (13.6)	885 (11.3)	<0.001
Moderate	1,1125 (73.5)	5,102 (69.8)	6,023 (77.0)	
Poor	2,130 (14.1)	1,220 (16.7)	910 (11.6)	
Psychological symptoms				
Yes	4,222 (27.9)	2,071 (28.3)	2,151 (27.5)	0.272
No	10,910 (72.1)	5,243 (71.7)	5,667 (72.5)	
Weekday sleep duration (/night)				
<6 h	1,482 (9.8)	725 (9.9)	757 (9.7)	<0.001
6–8 h	8,917 (58.9)	3,955 (54.1)	4,962 (63.5)	
8–10 h	4,236 (28.0)	2,319 (31.7)	1,917 (24.5)	
≥10 h	497 (3.3)	315 (4.3)	182 (2.3)	
Weekend sleep duration(/night)				
<6 h	604 (4.0)	402 (5.5)	202 (2.6)	<0.001
6–8 h	2,117 (14.0)	1,130 (15.4)	987 (12.6)	
8–10 h	6,662 (44.0)	3,065 (41.9)	3,597 (46.0)	
≥10 h	5,749 (38.0)	2,717 (37.1)	3,032 (38.8)	
Midday nap (day/week)				
None	4,256 (28.1)	2,281 (31.2)	1,975 (25.3)	<0.001
Sometime	2,171 (14.3)	1,006 (13.8)	1,165 (14.9)	
Often	8,705 (57.7)	4,027 (55.1)	4,678 (59.8)	
Insomnia				
None	6,792 (44.9)	3,486 (47.7)	3,306 (42.3)	<0.001
Sometime	5,826 (38.5)	2,586 (35.4)	3,240 (41.4)	
Often	2,514 (16.6)	1,242 (17.0)	1,272 (16.3)	
Nightmare				
None	11,293 (74.6)	5,692 (77.8)	5,601 (71.6)	<0.001
Sometime	3,223 (21.3)	1,320 (18.0)	1,903 (24.3)	

(Continued)

TABLE 1 | Continued

Variables	Total	Boy	Girl	*p*-value
Often	616 (4.1)	302 (4.1)	314 (4.0)	
Non-restorative sleep				
None	7,810 (51.6)	4,070 (55.6)	3,740 (47.8)	<0.001
Sometime	5,008 (33.1)	2,173 (29.7)	2,835 (36.3)	
Often	2,314 (15.3)	1,071 (14.6)	1,243 (15.9)	
Daytime fatigue				
None	1,315 (8.7)	805 (11.0)	510 (6.5)	<0.001
Sometime	9,244 (61.1)	4,405 (60.2)	4,839 (61.9)	
Often	4,573 (30.2)	2,104 (28.8)	2,469 (31.6)	
Sleep beliefs				
High	3,897 (25.8)	2,039 (27.9)	1,858 (23.8)	<0.001
Moderate	7,395 (48.9)	3,372 (46.1)	4,023 (51.5)	
Low	3,840 (25.4)	1,903 (26.0)	1,937 (24.8)	
Suicide attempt (SA)				
Yes	817 (5.4)	371 (5.1)	446 (5.7)	0.085
No	14,315 (94.6)	6,943 (94.9)	7,372 (94.3)	

associated with suicide attempt were examined after adjusting for sociodemographic, psychosocial factors and all other sleep variables. All analyses were conducted with SPSS software, version 16.0 (SPSS Inc., Chicago, IL). A p-value of <0.05 was considered statistically significant.

RESULTS

Characteristics of Participants

In 15,132 participants, the mean age was 15.2 years (SD = 1.8), and 51.7% (n = 7,823) of the sample were girls. In terms of sleep duration, 9.8% of the sample slept <6 h at night during weekdays, while 3.3% slept more than 10 h. Four percentage reported sleeping <6 h at night during weekends, and 38.0% reported sleeping more than 10 h.

A total of 8,705 (57.7%) reported taking a midday nap 3 days or more a week. The reported rates of infrequent (i.e., sometimes) "insomnia," "nightmare," "non-restorative sleep," and "daytime fatigue" were 16.6, 4.1, 15.3, and 30.2%, respectively. A total of 5.4% reported attempted suicide in the last 12 months. Gender disaggregated descriptive statistics and sociodemographic factors are shown in **Table 1**.

Sleep Problems and SA

As shown in **Table 2**, the unadjusted model showed that various sleep problems were significantly associated with an increased risk of suicide attempt. After adjustment for gender, age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms, almost all of the sleep variables remained significantly associated with an increased likelihood of SA, although the associations were attenuated.

After entering sociodemographic factors and sleep variables into the final model, weekday sleep duration (<6 h, OR = 2.17, 95%CI = 1.76–2.67; 8–10 h, OR = 1.27, 95%CI = 1.03–1.56; ≥10 h, OR = 3.00, 95%CI = 2.13–4.24), weekend sleep duration (<6 h, OR = 1.56, 95%CI = 1.15–2.13; 6–8 h, OR = 1.26, 95%CI = 1.01–1.58), midday nap (none, OR = 1.43, 95%CI = 1.18–1.72; sometime, OR = 1.27, 95%CI = 1.01–1.59), insomnia (sometime, OR = 1.36, 95%CI = 1.12–1.66; often, OR = 1.52, 95%CI = 1.22–1.90), nightmare (sometime, OR = 1.39, 95%CI = 1.16–1.67; often, OR = 2.41, 95%CI = 1.86–3.12) and sleep beliefs (high, OR = 1.26, 95%CI = 1.00–1.58) were independently associated with past 12 month suicide attempt.

Sleep Problems and SA by Gender

Table 3 shows the relationships between sleep problems and SA in male adolescents. The final adjusted model revealed that weekday sleep duration (<6 h, OR = 2.75, 95%CI 2.02–3.75; 8–10 h, OR = 1.52, 95%CI = 1.12–2.06; ≥10 h, OR = 3.82, 95%CI = 2.44–5.98), insomnia (often, OR = 1.60, 95%CI = 1.15–2.22) and nightmare (sometime, OR = 1.73, 95%CI = 1.31–2.28; often, OR = 2.63, 95%CI = 1.79–3.85) were independently associated with SA.

Table 4 shows the relationships between sleep problems and SA in female adolescents. Results indicated that weekday sleep duration (<6 h, OR = 1.83, 95%CI = 1.37–2.43; ≥10 h, OR = 2.30, 95%CI = 1.29–4.09), weekend sleep duration (<6 h, OR = 1.76, 95%CI = 1.09–2.85), midday nap (none, OR = 1.72, 95%CI = 1.32–2.24; sometime, OR = 1.39, 95%CI = 1.03–1.89), insomnia (sometime, OR = 1.36, 95%CI 1.05–1.77; often, OR = 1.45, 95%CI = 1.07–1.97), nightmare (often, OR = 2.23, 95%CI 1.57–3.18), and sleep beliefs (high, OR = 1.61, 95%CI = 1.15–2.25) were independently associated with SA.

DISCUSSION

The present study used data from a large-school survey conducted in China to investigate whether specific sleep problems were uniquely associated with SA and whether the relationship varied by gender. Our analysis suggests that various sleep problems are associated with suicide attempt in adolescents with extended weekday sleep durations and frequent nightmares shown to be among the strongest risk factors. Furthermore, results showed some discernible gender differences. Whilst sleep duration, insomnia, and nightmares were associated with suicide risk across genders, weekend sleep duration, midday nap, and sleep beliefs only reached significance within female adolescents. Moreover, although there was a broadly similar pattern observed for weekday sleep duration, insomnia and nightmare; there were slight variations in the strength and the presentation of the effects. For instance, both low and high weekday sleep durations were more strongly associated with SA in male adolescents. Moreover, even infrequent occurrences of nightmares (i.e., sometimes) were found to be associated with an elevated risk of suicide attempt amongst male adolescents, while only more frequent nightmare occurrences (i.e., often) reached significance within females. In contrast, infrequent episodes of insomnia were significant risk factors for suicide attempt among females but not males.

TABLE 2 | Number, % and OR of SA by sleep problems: 24 schools study, China.

Sleep problems	*n* (%)	Unadjusted analysis		Adjusted analysis[a]		Adjusted analysis[b]	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95% CI)	*P*-value
Weekday sleep duration							
<6 h	208 (14.0)	3.68 (3.08–4.40)	<0.001	2.82 (2.33–3.41)	<0.001	**2.17 (1.76–2.67)**	**<0.001**
6–8 h	379 (4.3)	1.0		1.0		1.0	
8–10 h	178 (4.2)	0.99 (0.82–1.19)	0.898	1.17 (0.96–1.42)	0.132	**1.27 (1.03–1.56)**	**0.025**
≥10 h	52 (10.5)	2.63 (1.94–3.57)	<0.001	2.98 (2.14–4.14)	<0.001	**3.00 (2.13–4.24)**	**<0.001**
Weekend sleep duration							
<6 h	85 (14.1)	3.67 (2.83–4.74)	<0.001	2.52 (1.91–3.36)	<0.001	**1.56 (1.15–2.13)**	**0.005**
6–8 h	137 (6.5)	1.55 (1.26–1.91)	<0.001	1.40 (1.13–1.74)	0.002	**1.26 (1.01–1.58)**	**0.044**
8–10 h	285 (4.3)	1.0		1.0		1.0	
≥10 h	310 (5.4)	1.28 (1.08–1.50)	0.004	1.18 (0.99–1.39)	0.066	0.99 (0.82–1.18)	0.876
Midday nap (day/week)							
None	280 (6.6)	1.42 (1.21–1.66)	<0.001	1.55 (1.29–1.87)	<0.001	**1.43 (1.18–1.72)**	**<0.001**
Sometime	125 (5.8)	1.23 (1.00–1.51)	0.049	1.34 (1.08–1.67)	0.009	**1.27 (1.01–1.59)**	**0.038**
Often	412 (4.7)	1.0		1.0		1.0	
Insomnia							
None	219 (3.2)	1.0		1.0		1.0	
Sometime	321 (5.5)	1.75 (1.47–2.09)	<0.001	1.49 (1.24–1.79)	<0.001	**1.36 (1.12–1.66)**	**0.002**
Often	277 (11.0)	3.72 (3.09–4.47)	<0.001	2.21 (1.82–2.69)	<0.001	**1.52 (1.22–1.90)**	**<0.001**
Nightmare							
None	436 (3.9)	1.0		1.0		1.0	
Sometime	242 (7.5)	2.02 (1.72–2.38)	<0.001	1.59 (1.35–1.89)	<0.001	**1.39 (1.16–1.67)**	**<0.001**
Often	139 (22.6)	7.26 (5.87–8.97)	<0.001	3.75 (2.99–4.71)	<0.001	**2.41 (1.86–3.12)**	**<0.001**
Non–restorative sleep							
None	262 (3.4)	1.0		1.0		1.0	
Sometime	280 (5.6)	1.71 (1.44–2.03)	<0.001	1.34 (1.12–1.60)	0.002	1.14 (0.94–1.39)	0.182
Often	275 (11.9)	3.89 (3.26–4.63)	<0.001	1.98 (1.64–2.40)	<0.001	1.19 (0.95–1.49)	0.140
Daytime fatigue							
None	74 (4.0)	1.0		1.0		1.0	
Sometime	358 (3.9)	0.97 (0.75–0.1.25)	0.800	0.93 (0.72–1.22)	0.610	0.92 (0.69–1.22)	0.535
Often	385 (9.6)	2.08 (1.58–2.73)	<0.001	1.52 (1.16–2.00)	0.003	1.17 (0.87–1.58)	0.308
Sleep beliefs							
High	350 (9.0)	2.69 (2.19–3.29)	<0.001	1.55 (1.25–1.93)	<0.001	**1.26 (1.00–1.58)**	**0.049**
Moderate	331 (4.5)	1.28 (1.04–1.56)	0.019	1.01 (0.82–1.25)	0.898	1.03 (0.83–1.29)	0.763
Low	136 (3.5)	1.0		1.0		1.0	

SA, suicidal attempt.

[a]*Adjusted for gender, age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms.*

[b]*Adjusted for gender, age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms, all sleep variables. P < 0.05 were in bold.*

Sleep Duration

We observed a similar U-shaped association between weekday sleep duration and suicide attempts that has been demonstrated in previous studies within adolescent populations (7, 8, 22, 23). In general, existing studies have indicated that short sleep durations increase the risk of suicidal behaviors, although there is currently no consensus on the definition of "short sleep" across published literature (24, 25). However, our finding that extended weekday sleep durations are associated with a higher suicide risk diverge from Gangwisch et al.'s conclusion that long sleep durations had no significant relationship with suicidal behaviors (26, 27). Further exploration of the relationship between long sleep durations and SA are warranted.

The relationship between weekday sleep duration and suicide attempt was found to be marginally stronger for boys compared to girls, but no significant difference was found. This conflicts with earlier research which has shown distinguishable gender associations. For instance, Meijer et al. reported that short sleep durations were more strongly associated with suicidal behaviors in boys than in girls (23, 28). In contrast, a web-based survey in Korean adolescents found that short sleep durations had a stronger relationship with SA in girls than in boys (11). Nevertheless, the current study extends existing knowledge

TABLE 3 | Number, % and OR of SA by sleep problems in boys: 24 schools study, China.

Sleep problems	*n* (%)	Unadjusted analysis		Adjusted analysis[a]		Adjusted analysis[b]	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95% CI)	*P*-value
Weekday sleep duration							
<6 h	107 (14.8)	4.62 (3.54–6.01)	<0.001	3.50 (2.65–4.63)	<0.001	**2.75 (2.02–3.75)**	**<0.001**
6–8 h	143 (3.6)	1.0		1.0		1.0	
8–10 h	86 (3.7)	1.03 (0.78–1.35)	0.850	1.39 (1.03–1.86)	0.031	**1.52 (1.12–2.06)**	**0.008**
≥10 h	35 (11.1)	3.33 (2.26–4.92)	<0.001	3.59 (2.36–5.46)	<0.001	**3.82 (2.44–5.98)**	**<0.001**
Weekend sleep duration							
<6 h	54 (13.4)	4.09 (2.90–5.77)	<0.001	2.52 (1.74–3.65)	<0.001	1.40 (0.92–2.12)	0.117
6–8 h	73 (6.5)	1.82 (1.35–2.47)	<0.001	1.58 (1.16–2.17)	0.004	1.38 (0.99–1.90)	0.055
8–10 h	112 (3.7)	1.0		1.0		1.0	
≥10 h	132 (4.9)	1.35 (1.04–1.74)	0.023	1.26 (0.96–1.65)	0.092	0.99 (0.75–1.32)	0.970
Midday nap (day/week)							
None	118 (5.2)	1.04 (0.82–1.31)	0.751	1.24 (0.95–1.62)	0.123	1.15 (0.87–1.51)	0.332
Sometime	52 (5.2)	1.04 (0.76–1.42)	0.818	1.18 (0.85–1.64)	0.334	1.12 (0.80–1.58)	0.511
Often	201 (5.0)	1.0		1.0		1.0	
Insomnia							
None	106 (3.0)	1.0		1.0		1.0	
Sometime	130 (5.0)	1.69 (1.30–2.19)	<0.001	1.45 (1.11–1.91)	0.007	1.35 (1.00–1.83)	0.053
Often	135 (10.9)	3.89 (2.99–5.06)	<0.001	2.33 (1.76–3.08)	<0.001	**1.60 (1.15–2.22)**	**0.005**
Nightmare							
None	196 (3.4)	1.0		1.0		1.0	
Sometime	108 (8.2)	2.50 (1.96–3.19)	<0.001	1.92 (1.49–2.47)	<0.001	**1.73 (1.31–2.28)**	**<0.001**
Often	67 (22.2)	8.00 (4.96–8.91)	<0.001	4.22 (3.03–5.88)	<0.001	**2.63 (1.79–3.85)**	**<0.001**
Non-restorative sleep							
None	135 (3.3)	1.0		1.0		1.0	
Sometime	113 (5.2)	1.60 (1.24–2.06)	<0.001	1.22 (0.94–1.60)	0.141	1.01 (0.75–1.37)	0.925
Often	123 (11.5)	3.78 (2.93–4.88)	<0.001	1.88 (1.42–2.48)	<0.001	1.04 (0.74–1.46)	0.816
Daytime fatigue							
None	43 (3.9)	1.0		1.0		1.0	
Sometime	155 (3.5)	0.91 (0.64–1.28)	0.585	0.89 (0.62–1.27)	0.527	0.97 (0.66–1.42)	0.863
Often	173 (9.5)	2.58 (1.83–3.64)	<0.001	1.48 (1.03–2.14)	0.035	1.18 (0.79–1.79)	0.419
Sleep beliefs							
High	170 (8.3)	2.19 (1.66–2.89)	<0.001	1.23 (0.91–1.66)	0.177	1.03 (0.75–1.41)	0.855
Moderate	125 (3.7)	0.93 (0.69–1.24)	0.602	0.76 (0.56–1.03)	0.074	0.80 (0.58–1.10)	0.172
Low	76 (4.0)	1.0		1.0		1.0	

SA, suicidal attempt.

[a]*Adjusted for age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms.*

[b]*Adjusted for age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms, all sleep variables. P < 0.05 were in bold.*

by demonstrating that low weekend sleep duration and fewer midday naps also increases the risk of suicide attempt, but only in girls. By implication, the relationship between gender, sleep duration and suicide attempt require further examination.

Sleep Distsurbances

The majority of previous studies which have investigated the role of sleep disturbance in suicidal behaviors have centered on insomnia and nightmares specifically (29–31). Uniquely, we chose to utilize a more comprehensive measure of sleep disturbance encompassing non-restorative sleep and daytime fatigue in addition to traditional assessment measures. The results suggest that insomnia and nightmares are stronger risk factors of suicide attempt than some of the other types of sleep disturbance. These findings support Wong et al.'s results that after controlling for nightmares, overtiredness and other variables, those who had trouble sleeping in early adolescence were more likely than those without trouble sleeping to think about killing oneself in late adolescence (32). Our findings also corroborate prospective research which indicates that persistent nightmares are a dominant risk factor for repeated suicide attempts over and above persistent difficulties maintaining sleep and early morning awakening (33). Future studies should continue to simultaneously model multiple sleep variables on

TABLE 4 | Number, % and of SA by sleep problems in girls: 24 schools study, China.

Sleep problems	*n* (%)	Unadjusted analysis		Adjusted analysis[a]		Adjusted analysis[b]	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95% CI)	*P*-value
Weekday sleep duration							
<6 h	101 (13.3)	3.08 (2.41–3.95)	<0.001	2.39 (1.84–3.10)	<0.001	**1.83 (1.37–2.43)**	**<0.001**
6–8 h	236 (4.8)	1.0		1.0		1.0	
8–10 h	92 (4.8)	1.01 (0.78–1.29)	0.940	1.03 (0.78–1.35)	0.842	1.11 (0.83–1.46)	0.486
≥10 h	17 (9.3)	2.06 (1.23–3.46)	0.006	2.45 (1.42–4.24)	0.003	**2.30 (1.29–4.09)**	**0.005**
Weekend sleep duration							
<6 h	31 (15.3)	3.59 (2.38–5.42)	<0.001	2.66 (1.71–4.12)	<0.001	**1.76 (1.09–2.85)**	**0.022**
6–8 h	64 (6.5)	1.37 (1.02–1.85)	0.036	1.28 (0.94–1.74)	0.118	1.17 (0.86–1.61)	0.322
8–10 h	173 (4.8)	1.0		1.0		1.0	
≥10 h	178 (5.9)	1.23 (1.00–1.53)	0.055	1.13 (0.90–1.41)	0.301	0.97 (0.77–1.23)	0.818
Midday nap (day/week)							
None	162 (8.2)	1.89 (1.53–2.34)	<0.001	1.86 (1.44–2.40)	<0.001	**1.72 (1.32–2.24)**	**<0.001**
Sometime	72 (6.3)	1.42 (1.08–1.86)	0.013	1.46 (1.08–1.96)	0.013	**1.39 (1.03–1.89)**	**0.032**
Often	211 (4.5)	1.0		1.0		1.0	
Insomnia							
None	113 (3.4)	1.0		1.0		1.0	
Sometime	191 (5.9)	1.77 (1.40–2.25)	<0.001	1.53 (1.20–1.96)	0.001	**1.36 (1.05–1.77)**	**0.022**
Often	142 (11.2)	3.55 (2.75–4.59)	<0.001	2.14 (1.63–2.82)	<0.001	**1.45 (1.07–1.97)**	**0.016**
Nightmare							
None	240 (4.3)	1.0		1.0		1.0	
Sometime	134 (7.0)	1.69 (1.36–2.10)	<0.001	1.40 (1.12–1.76)	0.003	1.20 (0.95–1.53)	0.129
Often	72 (22.9)	6.65 (4.96–8.91)	<0.001	3.43 (2.50–4.70)	<0.001	**2.23 (1.57–3.18)**	**<0.001**
Non-restorative sleep							
None	127 (3.4)	1.0		1.0		1.0	
Sometime	167 (5.9)	1.78 (1.41–2.26)	<0.001	1.48 (1.16–1.89)	0.002	1.28 (0.98–1.68)	0.071
Often	152 (12.2)	3.96 (3.10–5.07)	<0.001	2.12 (1.63–2.78)	<0.001	1.34 (0.99–1.83)	0.062
Daytime fatigue							
None	31 (4.1)	1.0		1.0		1.0	
Sometime	203 (4.1)	1.00 (0.68–1.48)	0.987	0.99 (0.67–1.48)	0.970	0.86 (0.56–1.31)	0.478
Often	212 (9.8)	2.52 (1.71–3.71)	0.001	1.61 (1.07–2.44)	0.024	1.13 (0.72–1.78)	0.582
Sleep beliefs							
High	180 (9.7)	3.36 (2.49–4.53)	<0.001	2.04 (1.48–2.81)	<0.001	**1.61 (1.15–2.25)**	**0.006**
Moderate	206 (5.1)	1.69 (1.26–2.26)	<0.001	1.36 (1.01–1.85)	0.046	1.36 (0.99–1.86)	0.053
Low	60 (3.1)	1.0		1.0		1.0	

SA, suicidal attempt.

[a]*Adjusted for age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms.*

[b]*Adjusted for age, regional areas, urban/rurality, parent's education level, economic status of family, psychological symptoms, all sleep variables. P < 0.05 were in bold.*

suicide attempt in order to fully comprehend the distinctive role of specific forms of sleep disturbance.

The independent effects of insomnia and nightmare on SA were confirmed across genders in the current study. However, research examining gender differences in the relationship between sleep problems and suicidality and related risk factors (e.g., depression) has been mixed in previous studies (13, 15). Marinova et al. observed no significant gender differences in a sample of depressed patients when examining the link between nightmares and suicide attempt (13). One study in Norwegian adolescents found a significant relationship between insomnia and depression for both genders, but found the results to be stronger among boys (15). Further studies may look to clarify the comparative influence of sleep disturbances on SA in boys, distinct from girls.

Sleep Beliefs

Unlike the research interest surrounding sleep duration and sleep disturbances in adolescent suicidality, little attention has been directed toward the role of sleep beliefs in adolescent suicide attempt. Of the few existing studies which have addressed this area, a link between more dysfunctional sleep beliefs and risk of suicidality has been observed (34–36). One qualitative interview study indicated that those with dysfunctional beliefs about sleep were more likely to report dissatisfaction with their sleep as well as increased negative thinking, attention difficulties and

inactivity, which in turn led to suicidal thoughts and behaviors (36). A significant relationship between sleep beliefs and suicidal ideation was found in an adolescent patients sample (34). McCall et al. also showed that dysfunctional beliefs and attitudes about sleep mediated the relationship between symptoms of insomnia and suicidal ideation (35). The current study therefore builds upon the literature by showing that dysfunctional sleep beliefs are associated with an increased risk of suicide attempt but only in girls. Due to the scarcity of research in this area, replication studies are needed before definitive conclusions can be drawn.

Strength and Limitation

The main strengths of this study include (i) a large representative sample from both junior and senior middle schools, and from urban and rural areas across four distinct regions in China (ii) a high response rate (96.3%), (iii) a comprehensive assessment of a variety of sleep problems, including sleep duration, sleep disturbance and sleep beliefs. Furthermore, we strengthen the limited literature by examining gender differences in the links between sleep problems and adolescent suicide attempt which has thus far been a particularly neglected area of research.

That said, the study has some potential limitations worth discussing. First, the study was cross-sectional therefore it is difficult to establish a causal relationship between sleep problems and suicide attempt. It is equally probable that the observed relationship reflects the impact of poor mental health on sleeping difficulties. Nonetheless, our conclusions linking sleep problems to suicide attempt were similar to those documented in previous prospective studies (36, 37). Second, our study only included self-report questionnaire measures, which may have contributed to mono-informant biases. Although it was impractical to assess sleep via experimental methods in large-scale population-based studies, self-reported sleep behavior has been shown to have good concordance with objectively-measured sleep (38, 39). Accordingly, future studies may seek to incorporate objective measures of sleep functioning (e.g., actigraphy) and SA. Third, previous studies have shown that physical illnesses, chronic conditions and circadian chronotype are also important predictors of adolescent sleep outcomes with the exception of sleep duration and quality (40, 41). Due to the lack of available data, we were unable to adjust for these factors in the current study which may have the effect of obscuring the accurate nature of the relationship between sleep and suicidality, thus, subsequent research should look to include a measure of youth circadian chronotype and physical ailments. Furthermore, despite the large sample, the failure to include a weighting system which takes account of the multi-stage sampling design and adjusts for sample selection within geographical region and school as well as non-response and differential socio-demographic distributions, the possibility of selection must be acknowledged as a weakness, thus caution should be exercised in extrapolating the findings to the wider population of adolescents in China. The extent to which these findings can be generalized to adolescents in other countries or cultures is also unclear as all participants in this study were located in mainland China. Finally, the results of the current study represent a preliminary investigation into the relationship between sleep problems and SA. Whilst initial work has been conducted to better understand the theoretical mechanisms underpinning insomnia and suicide associations (42), this work needs to be expanded to help account for the link between suicidal behaviors and other sleep parameters.

IMPLICATION

An increased focus on the role of sleep problems is needed at multiple levels in order to optimize mental health outcomes. Sleep and potentially even mental health problems could be enhanced through improvements in adolescents' physical and psychosocial conditions, controlling visual screen exposure, improving sleep hygiene and daytime behaviors, and altering parents' sleep habits (43, 44). In addition, alleviating the burden of homework and tailoring school timetables could reduce circadian misalignment, along with multiple positive mental health and cognitive benefits (45, 46). As sleep is a modifiable suicide risk factor, it is important to fully explore sleep patterns in screening and assessment processes (31). Healthy sleep has been recommended as an important protective factor in the prevention of suicide attempt in adolescents (47). There is evidence that cognitive behavioral therapy for insomnia could be used to target suicide risk prevention and intervention (31). Moreover, dysfunctional beliefs and high concern about sleep offer potential targets for psychotherapy of mental health and suicidal behavior (34, 48). In any event, further studies are required to determine whether sleep screening/interventions, incorporating global sleep problems or more specific sleep domains, are effective in suicide treatment or prevention.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The design and data collection procedures were approved by the Ethics Committee of Anhui Medical University (2012534). Written, informed consent was obtained from the parents of all participants in the study.

AUTHOR CONTRIBUTIONS

YW obtained funding, reviewed the topic related literature, and drafted the first version of the manuscript. HX, SW, SZ, YS, and FT performed the study design, coordination and data collection. YW and RC worked on data analysis. YW, DB, DM, and RC were involved in the interpretation of the data and revision of the manuscript. FT performed the study design and carried out study supervision and revision of the manuscript. All authors checked and interpreted the results and approved the final version. RC and FT are the guarantors for the study.

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Coping Strategies and Suicidality: A Cross-Sectional Study From China

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Background and Objective: Suicide is a leading cause of death in young people. Suicidal thoughts and behaviors can be triggered by life and study stresses; therefore, it is important to understand the role of coping strategies. The current study analyzed the link between different coping strategies and suicidality in university students in China.

Methods: A cross-sectional study of 2,074 undergraduate students from China used a stratified-clustered-random sampling method (response rate 94.4%). The Suicidal Behaviors Questionnaire–Revised Scale was used to identify suicidal risks, while the Brief COPE scale was used to measure different coping strategies. Univariate and multivariate logistic regression analyses were utilized to examine coping strategies and suicidality.

Results: A negative association of some coping skills (active coping and positive reframing) with suicidality and a positive association of some other coping skills (self-distraction, substance abuse, behavioral disengagement, venting, and self-blame) with suicidality were observed after adjusting for sociodemographic and mental health variables.

Conclusions: Training and supporting young people to identify and apply adaptive coping strategies to deal with life stress could help to reduce suicidal ideation and behavior.

Keywords: China, coping skills, suicidal behavior, mental health, students

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INTRODUCTION

Suicidal behavior in young people is a public health and social issue globally (1–3). Suicide is a leading cause of death in young people (4); furthermore, nonfatal suicidal behavior is more prevalent in younger age groups (5, 6). Similarly to other countries, China is reporting a high prevalence of suicidal behavior among young people, including college students (7–9). Transitioning from adolescence to young adults, university students are considered as the future elite; however, academic and career expectations from themselves and their parents, competitive environments, achieving less than hoped, and failing a grade may lead to interpersonal conflicts and a sense of isolation, and further to stress, low personal control, autistic traits, internet addiction, depression, anxiety, and suicidal thoughts and attempts (10–15).

There is currently limited knowledge about protective factors for suicidal behavior and ideation. Existing research has examined various coping strategies impacting suicidal behaviors (16) and has

analyzed gender-specific coping strategies associated with suicidal ideation in university students (17). Nevertheless, there has been relatively limited research that has focused on protective and risk effects of specific coping styles (18–20).

The available literature is inconsistent in conceptualizing and categorizing different coping styles (21, 22). This might be partly attributable to a number of different scales used to investigate coping strategies in various social and cultural contexts, such as the COPE (23), the Brief COPE (24), and the Coping Styles Questionnaire (CSQ) (25). Nevertheless, one common view is that individuals would apply adaptive and/or maladaptive (dysfunctional) coping skills when they face stress and threats (23, 26, 27). A recent study using Brief COPE from China showed that having a meaning of life is a protective factor, while self-distraction and self-blame are risk factors for suicidality in collage students (28). In another cross-sectional study, Zhang et al. (9) used CSQ to evaluate suicidality of university students in China. They found that passive coping (especially fantasizing) was positively associated with suicidal ideation. The results of Horwitz et al. (29), based on a cross-sectional study using Brief COPE, showed that behavioral disengagement and self-blame increased suicidal vulnerability. Furthermore, in a prospective study in college students using COPE, Chou et al. (30) reported that ineffective coping skills together with persistence stress and negative emotions could generate higher risk of suicidality.

Research has also shown mixed results regarding the relationship between avoidant coping and suicidality. Some studies indicate that avoidance coping strategies heighten the risk of suicidality as individuals tend to resign themselves to the problem, and do not undertake further efforts to reduce stressors (31–33). Others suggest that avoidance coping with a good purpose (such as decreasing the negative feelings of life stressors and temporary shifting focus from the stressors to other important things in life) could prevent suicidal behavior in adolescents and young people (20, 34). Nevertheless, none of the studies above used Brief COPE in measuring avoidant coping. It is important to better understand the relationship between different coping strategies (particularly avoidance strategies) and suicidality in young people. Therefore, this paper aims to analyze the association between specific coping strategies and suicidality (suicidal ideation and behavior) in a sample of university students in China.

METHODS

Participants and Recruitment

In November 2016, undergraduate university students from two universities in Jinan (the capital city of Shandong province), China, voluntary participated in a cross-sectional survey. In total 2,074 students responded, with a response rate of 94.4%. A stratified–clustered–random sampling method was applied to select from three or four classes of students for each grade. The study received ethics approval from the institutional review board of the Ethics Committee at the School of Public Health, Shandong University (No. 20161103). Each participant signed an informed consent form before undertaking the questionnaire. The survey contained a brief battery of self-report psychosocial instruments, as described below.

Abbreviations: WHO, World Health Organization; SBQ-R, The Suicidal Behaviors Questionnaire–Revised Scale; DASS-21, Depression, Anxiety & Stress Scale; OR, odds ratio; CI, confidence intervals.

Scales

The Suicidal Behaviors Questionnaire Revised Scale (SBQR) (35), adapted from Osman et al. (36), contains four items that assess suicidal thoughts and behaviors from different perspectives: lifetime suicidal ideation and attempt(s), frequency of suicidal ideation over the past year, risk of suicide attempt, and likelihood of suicidal behavior in the future. The Chinese version of the SBQ-R was validated (35) and adapted for this study. The total score of the scale was calculated, and a cut-off value of 7 was applied as recommended by Osman et al. (36).

Depression, Anxiety & Stress Scale (DASS-21) (37) is a 21-item scale that measures three dimensions of mental health: depression (Cronbach's alpha = 0.84), anxiety (Cronbach's alpha = 0.79), and stress (Cronbach's alpha = 0.82). Responses for all items range from "0—Did not apply to me at all" to "3—Applied to me very much or most of the time."

The Brief COPE Scale consists of 28 items to measure 14 different coping strategies (24). In this study, the Chinese version of the scale (38) was adapted. The scale presents good internal reliability, with Cronbach's alpha = 0.83. The 14 dimensions of coping strategies are comprised of self-distraction, active coping, denial, substance abuse, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. Each dimension contains two items, with sum score as the total dimension score.

The questionnaire also included sociodemographic categories, such as gender, ethnicity, residency, being an only child (with no siblings), general physical health and mental health, academic performance, family economic status, parent education level, parental bonding, and religious affiliation.

Statistical Analysis

Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to explore differences between the suicidal and non-suicidal groups by the categorical sociodemographic variables. Independent sample *t*-tests were used to identify differences between the two groups by coping strategies, and effect size (Cohen's d) was calculated for each coping skill. The Cohen's d cut-off values were considered as small ($\geq$0.2), medium ($\geq$0.5), and large ($\geq$0.8) (39). Further, each coping skill was entered as a predictor into a logistic regression with suicidality (suicidal vs. non-suicidal) as the dependent variable. The calculations were adjusted for confounding effect of other factors: (1) a coping skill + sociodemographic variables; (2) a coping skill + sociodemographic variables + Depression + Anxiety + Stress. A probability level of 0.05 was applied for all statistical tests. SPSS version 22.0 was used for data analysis (IBM SPSS, Inc. in Chicago, Illinois, USA).

TABLE 1 | Sociodemographic background of non-suicidal group and suicidal group in the study.

	Suicidal (n = 428)		Non-suicidal (n = 1,646)		OR	95% CI	
	N	%	N	%		Lower	Upper
Gender							
Female	290	67.8	1,078	65.5	1.22	0.96	1.55
Male	138	32.2	568	34.5	1		
Residency							
Urban	225	52.6	790	48.0	**1.39**	**1.08**	**1.80**
Rural	203	47.4	856	52.0	1		
Only child							
Yes	213	49.8	799	48.5	1.01	0.78	1.31
No	215	50.2	847	51.5	1		
Academic performance							
Poor	90	21.0	172	10.4	**2.17**	**1.62**	**2.91**
Neutral	291	68.0	1185	72.0	1		
Good	47	11.0	289	17.6	0.74	0.52	1.05
Family economic status							
Very poor	9	2.1	47	2.9	0.68	0.32	1.44
Poor	76	17.8	213	12.9	**1.40**	**1.03**	**1.90**
Neutral	301	70.3	1118	67.9	1		
Good	38	8.9	239	14.5	**0.61**	**0.41**	**0.89**
Very good	4	0.9	29	1.8	0.62	0.21	1.83
Religious affiliation							
Yes	26	6.1	106	6.4	0.84	0.53	1.32
No	402	93.9	1540	93.6	1		

Results in bold indicate to a significance level of 0.05.

TABLE 2 | Suicidal and non-suicidal group by copying styles (as per the Brief COPE Scale).

Coping style	Suicidal (n = 428)	Non-suicidal (n = 1,646)			Effect size
	M (SD)	M (SD)	t (df)	p -value	(Cohen's d)
Self-distraction	5.92 (1.42)	5.74 (1.44)	−2.22 (2072)	**0.026**	0.126
Active coping	6.13 (1.40)	6.67 (1.33)	7.44 (2072)	**<0.001**	0.395
Denial	4.01 (1.49)	3.59 (1.33)	−5.71 (2072)	**<0.001**	0.297
Substance use	3.22 (1.68)	2.68 (1.27)	−6.23 (560.7)[a]	**<0.001**	0.363
Use of emotional support	5.61 (1.58)	5.57 (1.51)	−0.44 (2072)	0.659	0.026
Use of instrumental support	5.76 (1.54)	5.97 (1.46)	2.54 (638.7)[a]	**0.011**	0.140
Behavioral disengagement	4.11 (1.43)	3.52 (1.35)	−7.95 (2072)	**<0.001**	0.424
Venting	5.47 (1.42)	5.26 (1.51)	−2.50 (2072)	**0.012**	0.143
Positive reframing	5.76 (1.47)	6.21 (1.44)	5.69 (2072)	**<0.001**	0.309
Planning	6.04 (1.30)	6.40 (1.33)	5.05 (678.7)[a]	**<0.001**	0.274
Humor	4.44 (1.57)	4.07 (1.48)	−4.40 (637.7)[a]	**<0.001**	0.243
Acceptance	6.06 (1.33)	6.27 (1.32)	3.00 (2072)	**0.003**	0.158
Religion	3.78 (1.48)	3.52 (1.41)	−3.43 (2072)	**0.001**	0.180
Self-blame	5.45 (1.39)	4.94 (1.42)	−6.64 (2072)	**<0.001**	0.363

[a] *Equal variances not assumed.*
Results in bold indicate to a significance level of 0.05.

RESULTS

Among the 2,074 students, 20.6% (n = 428) were identified to have an SBQ-R total score of 7 or above and were included in the suicidal group, and the remaining 79.4% (n = 1,646) were assigned to the non-suicidal group. **Table 1** presents the sociodemographic backgrounds of participants in the suicidal and non-suicidal groups. Gender, being an only child, and religious affiliation did not differ significantly between the suicidal and non-suicidal groups. However, there were significant differences on residency, academic performance, and family economic status between the suicidal and non-suicidal groups. Students from urban areas, with poor academic performance, and from families with poorer socioeconomic background were more likely to be suicidal (see **Table 1**).

As shown in **Table 2**, there were significant differences between the suicidal and non-suicidal groups for all coping strategies except "Use of emotional support." The effect size of the coping strategies were between a small and medium level. **Table 3** presents ORs and 95% CIs after adjusting for the sociodemographic variables (gender, residency, being an only child, academic performance, family economic status, and religious affiliation). Self-distraction [Adj' OR = 1.09, 95%CI (1.01–1.18)], denial [Adj' OR = 1.23, 95% CI (1.14–1.33)], substance abuse [Adj' OR = 1.33, 95% CI (1.23–1.43)], behavioral disengagement [Adj' OR = 1.32, 95% CI (1.22–1.43)], venting [Adj' OR = 1.10, 95% CI (1.02–1.18)], humor [Adj' OR = 1.17, 95% CI (1.09–1.26)], religion [Adj' OR = 1.15, 95% CI (1.07–1.24)], and self-blame [Adj' OR = 1.28, 95% CI (1.18–1.38)] were significantly more likely to be used by students in the suicidal group. Active coping [Adj' OR = 0.77, 95% CI (0.71–0.83)], use of instrumental support [Adj' OR = 0.90, 95% CI (0.84–0.97)], positive reframing [Adj' OR = 0.82, 95% CI (0.76–0.89)], planning [Adj' OR = 0.84, 95% CI (0.77–0.91)], and acceptance [Adj' OR = 0.90, 95% CI (0.83–0.97)] were significantly less likely to be used by the suicidal group.

Further adjustment for the sociodemographic variables and three dimensions of the DASS-21 (depression, stress, anxiety) showed that self-distraction [Adj' OR = 1.11, 95% CI (1.02–1.20)], substance abuse [Adj' OR = 1.17, 95% CI (1.08–1.27)], behavioral disengagement [Adj' OR = 1.13, 95% CI (1.04–1.24)], venting [Adj' OR = 1.08, 95% CI (1.00–1.17)], and self-blame [Adj' OR = 1.16, 95% CI (1.07–1.26)] remained significantly associated in a positive direction with suicidality. Active coping [Adj' OR = 0.86, 95% CI (0.79–0.94)] and positive reframing [Adj' OR = 0.90, 95% CI (0.83–0.98)] remained negatively associated with suicidality (**Table 3**).

DISCUSSION

The present study aimed to better understand the association between specific coping strategies and suicidality using the Brief COPE scale and measures of suicidality in a sample of Chinese university students. A significant association was found. More specifically, after controlling for sociodemographic

TABLE 3 | Multivariate logistic regression analyses of the association between copying skills and suicidality (suicidal vs. non-suicidal) adjusted for sociodemographic factors and mental health.

Coping style	Adj' OR[a]	95%CI		Adj' OR[b]	95%CI	
		Lower	Upper		Lower	Upper
Self-distraction	**1.09**	**1.01**	**1.18**	**1.11**	**1.02**	**1.20**
Active coping	**0.77**	**0.71**	**0.83**	**0.86**	**0.79**	**0.94**
Denial	**1.23**	**1.14**	**1.33**	1.08	1.00	1.18
Substance use	**1.33**	**1.23**	**1.43**	**1.17**	**1.08**	**1.27**
Use of emotional support	1.02	0.95	1.09	0.99	0.92	1.07
Use of instrumental support	**0.90**	**0.84**	**0.97**	0.94	0.87	1.02
Behavioral disengagement	**1.32**	**1.22**	**1.43**	**1.13**	**1.04**	**1.24**
Venting	**1.10**	**1.02**	**1.18**	**1.08**	**1.00**	**1.17**
Positive reframing	**0.82**	**0.76**	**0.89**	**0.90**	**0.83**	**0.98**
Planning	**0.84**	**0.77**	**0.91**	0.92	0.84	1.00
Humor	**1.17**	**1.09**	**1.26**	1.06	0.98	1.15
Acceptance	**0.90**	**0.83**	**0.97**	0.97	0.89	1.06
Religion	**1.15**	**1.07**	**1.24**	1.02	0.94	1.11
Self-blame	**1.28**	**1.18**	**1.38**	**1.16**	**1.07**	**1.26**

[a]*Adjusted for sociodemographic variables.*
[b]*Adjusted for sociodemographic variables, and depression, anxiety, stress (DASS-21). Results in bold indicate to a significance level of 0.05.*

circumstances, stress, depression, and anxiety, the strategies of active coping and positive reframing were less likely to be used by the suicidal group compared to the non-suicidal group. Self-distraction, substance abuse, behavioral disengagement, venting, and self-blame were more likely to be used by the suicidal group.

Active coping has been found to buffer suicidality (9, 40), and a similar effect has also been shown for positive reframing (19, 41). These are both adaptive coping skills, with active coping referring to actively removing or reducing the stressors, and positive reframing to cognitively constructing a stressful transaction in a positive way (23). The findings of this study suggest that the application of these two coping skills could be beneficial to students in reducing their suicidality. Furthermore, the use of instrumental support, planning, and acceptance were also negatively associated with suicidality after controlling for sociodemographic circumstances, indicating that these coping strategies may also be helpful in reducing suicidality in young people (42).

Several coping strategies related to avoidance, such as behavioral disengagement, self-distraction, venting, and humor, were more likely to be used by suicidal students in the current study; however, previous research has not clearly specified the adaptive or maladaptive effect of these strategies in dealing with stress (23, 43) or suicidality (20). Behavioral disengagement was positively associated with suicidality in our study, echoing results from some earlier studies in late adolescence (29) and in university students (44). Nevertheless, some scholars argue that behavioral disengagement could help reduce the risk of suicidality by temporarily shifting focus away from the stressors, to release negative emotions, and finally to turn back to problem-solving (20, 34).

The results showed that self-blame and use of alcohol and drugs to cope with problems and escape from stress ("substance use" by the Brief COPE scale) were significantly more likely to be used by suicidal students and also showed the highest adjusted OR after controlling for the confounding effects of sociodemographic circumstances, stress, depression, and anxiety. Several studies have demonstrated an association between alcohol and substance use in suicidality (45, 46). Drink to cope could associate with poor problem-solving skills, avoidance coping, and negative urgency in young people who have suicidal risk (47). In addition, a rapid increase in alcohol use in China and alcohol consumption becoming more normalized in recent decades call for further public health actions (48).

Although having a religious affiliation was not significantly different in suicidal and non-suicidal groups, contrary to our expectations, we found "religion" as a coping strategy to be significantly more frequent in the suicidal group. Nevertheless, after controlling for sociodemographic factors, stress, anxiety, and depression, this association became non-significant. It is also important to note that in the Brief COPE scale, the items under "religion" also include spirituality. Cook (49) indicates that there have been mixed results on this topic and argues that those who are spiritual but not religious may not experience buffering or protection against depression or suicidal behavior. Furthermore, remarkable differences in the relationship between religion and suicidality between countries have been reported (50).

It is important to note some of the limitations of this study. Despite a large sample size, a relatively small number of students were identified as having experienced suicidal ideation and attempted suicide. Therefore, we were unable to separately analyze the differences between those who experienced suicidal ideation and those who (also) attempted suicide. The Brief COPE scale helped articulate the coping strategies that the students preferred/applied; however, it is not necessarily comparable with other studies that used different coping scales. Furthermore, the cross-sectional nature of the study limits the analyses to the association between coping styles and suicidality, and does not allow us to determine causality, and we cannot present the effectiveness of each coping strategy (51). It is also important to note that we merged suicidality as measured by SBQ-R, and therefore it may not be applicable specifically to the risk of suicide attempts or suicides. Lastly, the research participants were university students, and therefore the results are not generalizable to all young people in China.

Nevertheless, these results may present some important implications. Using active coping skills to solve problems and developing a positive self-appraisal (52) have been shown to be important for young people facing stressful events and may help to reduce their suicide risks. It is also important to encourage help-seeking from families, peers, and other professionals while having suicidal thoughts (6). In addition, we could help young people to identify the negative impacts of maladaptive coping strategies (such as using drugs or alcohol to manage stress) and replace them with more adaptive coping strategies to reduce the risks of suicide. Programs and services, such as cognitive behavioral therapy (2), mindfulness training to manage stress (53), and routine counseling screening to identify the

individuals who rely heavily on avoidance coping (33), could be put in place for young people suicide prevention. The student-friendly university mental health services could also be helpful in connecting students with broader public health resources, and in educating them to cope effectively with academic and life stress (54).

CONCLUSION

This study provides new insights on the relationship between coping strategies and suicidality in young people. After controlling for the possible confounding effects of sociodemographic circumstances, stress, depression, and anxiety, active coping and positive reframing were negatively associated with suicidality, whereas self-distraction, substance abuse, behavioral disengagement, venting, and self-blame were positively associated with suicidality. There is a need to support young people to develop adaptive and effective coping strategies in order to reduce suicide ideation and attempts.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Ethics Committee at the School of Public Health, Shandong University (No. 20161103). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BL, CJ, and KK designed the study. CJ, LY, and BL organized data collection. JL and KK analyzed and interpreted the data. JL and KK were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Suicide Attempt and Suicidal Drug Overdose in Chronic Obstructive Pulmonary Disease Patients With or Without Depression

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Background: To determine differences in the incidence and risks of suicide attempt (SA) and suicidal drug overdose (SDO) between chronic obstructive pulmonary disease (COPD) patients with and without comorbid depression by using data from Taiwan's National Health Insurance Research Database.

Methods: We analyzed the data of patients aged ≥20 years who had received a COPD diagnosis between 2000 and 2012. These COPD patients were divided into those with and without depression, and they were compared against a cohort from the general population. We calculated adjusted hazard ratios and the corresponding 95% confidence intervals for SA and SDO in the three cohorts after adjustment for age, sex, and comorbidities.

Results: Until the end of 2012, 5.81% of patients with COPD developed depression. The incidence of SA and SDO in COPD patients with and without depression was 29.7 and 4.69 per 10,000 person-years and 71.2 and 20.9 per 10,000 person-years, respectively. COPD patients with depression had 13.6- and 10.0-fold higher risks of SA and SDO, respectively, than did controls. Particularly, an increased risk of SA caused by the enhancement effects of depression on COPD was noted in patients aged less than 50 years.

Conclusion: SA and SDO risks are extremely high in Taiwanese COPD patients with depression. Our findings suggest that clinicians should be aware that for COPD patients with comorbid depression, prescribing a large amount of medications may be associated with SA risk through SDO.

Keywords: chronic obstructive pulmonary disease, depression, National Health Insurance, suicide, suicidal drug overdose

INTRODUCTION

Globally, more than 800,000 people commit suicide every year, and the prevalence of completed suicide has progressively increased over the past decades (1). The annual prevalence of suicidal ideation and suicide attempt (SA) has been estimated to be 2.3% and 0.4% in Austria and 3.7% and 0.5% in the United States, respectively (2, 3). In European countries, the estimated rate of suicidal lethality is much higher in men than in women (13.9% vs. 4.1%) (4). The main possible reason for this sex difference is the different methods of SA adopted by men and women; violent methods are more common among men, and self-intoxication or suicidal drug overdose (SDO) is the most frequently chosen method among women (5). Therefore, we believe that adequately identifying individuals at a high risk of SA and interrupting their SA are urgently required for preventing suicide (6).

Depression is a well-established predictor of suicidal behaviors (7, 8). Researchers have investigated interactions between suicidality and medical conditions for years; however, only few researchers have conducted population-based studies on this topic (9, 10). In a recent large population-based cross-national study, Scott et al. reported several physical conditions that are potential independent risk factors for suicidality (10). Whether the probability of suicide is high in patients with chronic medical conditions or whether it is noted only in patients with specific disorders remains controversial (11). Sanna et al. reported an association between suicidality and several medical disorders; however, no association was noted between suicidality and pulmonary disease (12).

The Taiwanese government established the National Health Insurance (NHI) program in 1995, which covers approximately 99% of the residents of Taiwan for the past 2 decades (13). Both chronic obstructive pulmonary disease (COPD) and depression are common chronic disorders in the National Health Insurance Research Database (NHIRD). Furthermore, pneumonia and COPD were the third and seventh causes of death in 2018 in Taiwan. As COPD is one of the major chronic physical disorders among elderly people, we believe that SA and SDO risks should be different between the general population and COPD patients with and without comorbid depression. Investigating these differences might be beneficial for the medical care systems in both Taiwan and other East Asian countries due to similarities in their ethnicity and cultural heritage (14).

METHODS

Data Source

The NHIRD of Taiwan is maintained by the National Health Research Institutes of Taiwan. It contains comprehensive NHI records of almost 99% of the population of Taiwan (13). The database includes the de-identified medical records of inpatients and outpatients and their prescription drug and other medical service records. Only patients with hospitalization records were included in this study. Diagnoses were defined based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH104-REC2-115-CR4).

Study Population

To assess the differences in SA and SDO risks between COPD patients with and without depression, 4 cohorts were defined in this study: the total COPD cohort comprising patients aged ≥20 years diagnosed with COPD (ICD-9-CM codes 491, 492, 494, and 496), the COPD with depression cohort comprising COPD patients with depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, and 311), the COPD without depression cohort comprising COPD patients without depression, and the comparison cohort comprising individuals without COPD and depression during 2000–2012. The index date was the date of COPD diagnosis. Controls (individuals without COPD and depression) were frequency matched based on sex, age, and index year at a ratio of 1:2. The primary outcome was the occurrence of SA (ICD-9-CM codes E950–E959) and SDO in NHIRD records. SDO was defined based on an emergency department visit, a clinic visit, or hospitalization with the ICD-9-CM codes 960-979 but without E codes. The study excluded patients aged <20 years and patients with SA or SDO before the index date. The same exclusion criteria were applied for the comparison cohort.

Comorbidities comprised several mental-health-associated diseases such as schizophrenia (ICD-9-CM code 295), alcohol-related illness (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0, 571.1, 571.3, 790.3, and V11.3), anxiety (ICD-9-CM code 300.00), mental disorders (ICD-9-CM codes 290-319), and insomnia (ICD-9-CM codes 307.4 and 780.5), and these comorbidities with at least one hospitalization record before the index date were included in the analysis. The end date of the follow-up period was the date of SA or SDO occurrence, patient death, patient withdrawal from the NHI program, or December 31, 2012, whichever occurred first.

Statistical Analyses

Categorical and continuous variables in this study are presented by number (%) and mean ± standard deviation, respectively. The chi-square test for categorical variables and analysis of variance for continuous variables were performed to examine the differences in these variables among the cohorts. Incidence rates of SA and SDO were calculated by dividing SA and SDO events by person-years (every 10,000 person-years). Cumulative incidence curves of SA and SDO in the cohorts were plotted using the Kaplan–Meier method, and log-rank tests were applied to test the differences in the curves. Hazard ratios (HRs), adjusted HRs (aHRs), and 95% confidence intervals (95% CIs) of SA and SDO were calculated using Cox proportional hazard models to evaluate the risks of SA and

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NTD, New Taiwan Dollar; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; SA, suicide attempt; SDO, suicidal drug overdose.

SDO among the cohorts. The level of significance was set at.05. All data were analyzed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Four cohorts were defined in this study: total COPD (n = 361,703), COPD without depression (n = 340,694), COPD with depression (n = 21,009), and comparison (n = 721,550; without COPD and depression) cohorts. Because sex, age, and index year were frequency matched, no significant differences were found in sex (P =.39) and age (P =.78) among the cohorts. Significant differences were observed in monthly income, urbanization level, occupation category, and comorbidities among these cohorts (P < .001; **Table 1**).

Figure 1 displays the cumulative incidence of SA and SDO. The figure indicates significant differences in the cumulative incidence rates of SA and SDO among the COPD with and without depression cohorts and the comparison cohort. **Table 2** presents the incidence rates of and HRs of SA across different demographic characteristics. Compared with the reference group for each variable, a significantly high SA risk was observed after adjustment for demographic characteristics and comorbidities in COPD patients (aHR, 3.06; 95% CI, 2.72–3.45), COPD patients without depression (aHR, 2.49; 95% CI, 2.19–2.82), and COPD patients with depression (aHR, 13.6; 95% CI, 11.3-16.4) as well as in patients aged <50 years (aHR, 1.37; 95% CI, 1.11–1.69), with monthly incomes of New Taiwan Dollar (NTD) < 15,000 (aHR, 1.50; 95% CI, 1.19–1.87) and NTD15,000–19,999 (aHR, 1.48, 95% CI, 1.19–1.83), living in a residential area with a low urbanization level (level 2: aHR, 1.36; 95% CI, 1.14–1.62; level 3: aHR, 1.32; 95% CI, 1.08–1.61; and level 4: aHR, 1.33; 95% CI, 1.11–1.59), who worked as laborers (aHR, 1.37; 95% CI, 1.16–1.62), with alcohol-related illness (aHR, 2.14; 95% CI, 1.64–2.79), and with anxiety (aHR, 1.38; 95% CI, 1.02–1.87) (**Table 2**).

Table 3 presents that compared with COPD patients without depression, a significantly high SA risk was observed in COPD patients with depression (aHR, 3.09; 95% CI, 2.78–3.44) as well as in patients aged <50 years (aHR, 9.14; 95% CI, 6.02–13.9), 50–64 years (aHR, 6.94; 95% CI, 4.65–10.4), and >65 years (aHR, 4.61; 95% CI, 3.63–5.85); female (aHR, 6.93; 95% CI, 5.16–9.29) or male patients (aHR, 5.13; 95% CI, 4.06–6.48); patients with monthly incomes of NTD <15,000 (aHR, 4.60; 95% CI, 3.38–6.27), 15,000–19,999 (aHR, 5.99; 95% CI, 4.67–7.68), and >20,000 (aHR, 7.50; 95% CI, 4.52–12.5); patients living in areas with urbanization level 1 (aHR, 7.46; 95% CI, 4.83–11.5), level 2 (aHR, 7.74; 95% CI, 5.64–10.6), level 3 (aHR, 5.01; 95% CI, 3.16–7.95), and level 4 (aHR, 3.91; 95% CI, 2.84–5.38); patients employed as office workers (aHR, 6.86; 95% CI, 4.90–9.59),

TABLE 1 | Distribution of demographic characteristics and comorbidities among COPD cohorts and the comparison cohort.

	Total COPD (N=361,703)		COPD without depression (N=340,694)		COPD with depression (N=21,009)		Comparison cohort (N=721,550)		p-value[a]
	n	%	n	%	n	%	n	%	
Sex									0.39
Women	232,082	32.2	108,264	31.8	7,779	37.0	116,043	32.1	
Men	489,468	67.8	232,430	68.2	13,230	63.0	245,660	67.9	
Age stratified									0.78
≤49	54,800	7.59	25,334	7.44	2,066	9.83	27,400	7.58	
50–64	118,596	16.4	55,627	16.3	3,671	17.5	59,298	16.4	
≥65	548,154	76.0	259,733	76.2	15,272	72.7	275,005	76.0	
Age, mean ± SD[§]	72.3 ± 13.6		72.4 ± 13.6		70.9 ± 13.9		71.3 ± 13.6		<0.001
Monthly income[†]									<0.001
<15,000	266,408	36.9	128,651	37.8	9,781	46.6	138,432	38.3	
15,000–19,999	310,350	43.0	166,514	48.9	8,738	41.6	175,252	48.5	
≥20,000	144,792	20.1	45,529	13.4	2,490	11.9	48,019	13.3	
Urbanization level[‡]									<0.001
1 (highest)	192,102	26.6	67,221	19.7	4,334	20.6	71,555	19.8	
2	197,342	27.4	90,418	26.5	6,160	29.3	96,578	26.7	
3	117,049	16.2	57,617	16.9	3,198	15.2	60,815	16.8	
4 (lowest)	215,057	29.8	125,438	36.8	7,317	34.8	132,755	36.7	
Occupation category[&]									<0.001
Office worker	303,590	42.1	112,169	32.9	6,349	30.2	118,518	32.8	
Laborer	294,313	40.8	162,148	47.6	8,416	40.1	170,564	47.2	
Other	123,647	17.1	66,377	19.5	6,244	29.7	72,621	20.1	
Comorbidity									
Schizophrenic	1,835	0.25	2,696	0.79	47	2.26	3,170	0.88	<0.001
Alcohol-related illness	3,416	0.47	8,400	2.47	1,582	7.53	9,982	2.76	<0.001
Anxiety	2,918	0.40	5,740	1.68	2,283	10.9	8,023	2.22	<0.001
Mental disorders	16,367	2.27	33,533	9.84	–	–	33,533	9.27	<0.001
Insomnia	7,350	1.02	15,367	4.51	4,010	19.1	19,377	5.36	<0.001

[a]COPD, chronic obstructive pulmonary disease; Chi-square test; [§]ANOVA, analysis of variance; SD, standard deviation. [†]New Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD. [‡]The urbanization level was divided into 4 levels based on the population density of the residential area, where level 1 was the most urbanized and level 4 was the least urbanized. [&]Other occupation categories included those who were primarily retired, unemployed, and low-income people.

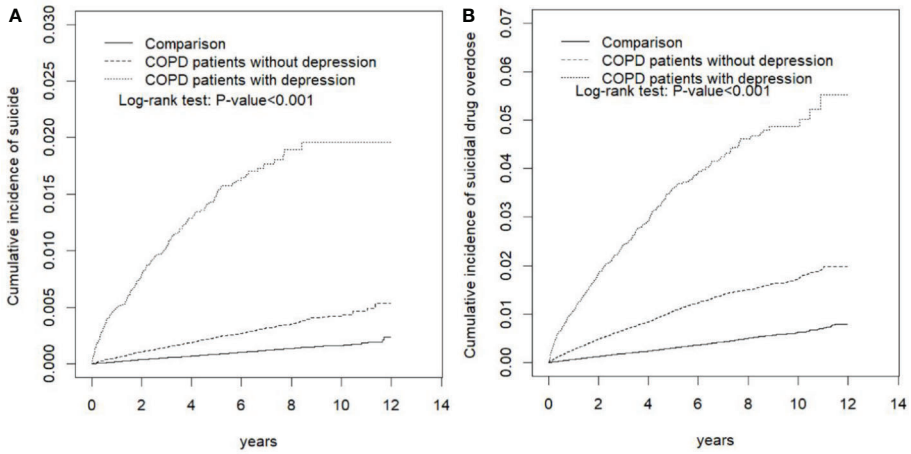

FIGURE 1 | Comparison of the Cumulative Incidence of **(A)** Suicide Attempt and **(B)** Suicidal Drug Overdose Among COPD Patients With Depression, COPD Patients Without Depression, and the Normal Population. COPD, chronic obstructive pulmonary disease.

laborers (aHR, 5.43; 95% CI, 4.19–7.03), and other types of workers (aHR, 4.63; 95% CI, 3.14–6.82); patients without any comorbidity (aHR, 6.49; 95% CI, 5.29–7.96); and patients with any one of the comorbidities (aHR, 4.11; 95% CI, 3.06–5.52) (**Table 3**).

The event numbers, incidence rates, and HRs of SDO of COPD patients with and without depression are shown in **Table 4**. Patients with COPD (aHR: 3.59; 95% CI, 3.37–3.81), COPD patients without depression (aHR, 3.24; 95% CI, 3.04–3.45), and COPD patients with depression (aHR, 10.0; 95% CI, 8.99–11.2) had a significantly higher SDO risk than controls. Specifically, COPD patients with depression had a higher incidence (71.2 per 10,000 person-years) and risk of SDO than COPD patients without depression (aHR, 3.09; 95% CI, 2.77–3.40) (**Table 4**).

Moreover, to evaluate whether patients with COPD and depression might have higher SA and SDO risks than patients with depression without COPD, we further compared COPD patients with depression (n = 19,725) with non-COPD patients with depression who were frequency matched based on sex, age, and index year (**Supplementary Tables**). COPD patients with depression had a moderately high risk of SA (aHR, 3.59; 95% CI, 2.85–4.52) and SDO (aHR, 4.97; 95% CI, 4.20–5.88) than non-COPD patients with depression.

To assess the incidence and risk of different SDO types, patients with SDO were classified based on the different methods of suicide (**Table 5**), such as poisoning through drugs or medical substances, benzodiazepine-based tranquilizers, and other methods. Compared with controls, patients with COPD (aHR, 2.82; 95% CI, 2.44–3.26), COPD patients without depression (aHR, 2.37; 95% CI, 2.04–2.77), and COPD patients with depression (aHR, 10.9; 95% CI, 8.57–13.8) had a significantly high risk of poisoning through drugs or medicinal substances. Specifically, COPD patients with depression had a higher incidence (16.5 per 10,000 person-years) and risk of poisoning through drugs or medical substances (aHR, 4.59; 95% CI, 3.62–5.83) than those without depression.

Compared with controls, patients with COPD (aHR, 3.34; 95% CI, 2.73–4.08), COPD patients without depression (aHR, 2.76; 95% CI, 2.24–3.41), and COPD patients with depression (aHR, 13.9; 95% CI, 10.2–19.0) had a significantly high risk of poisoning through benzodiazepine-based tranquilizers. Specifically, COPD patients with depression had a higher incidence (10.5 per 10,000 person-years) and risk of poisoning through benzodiazepine-based tranquilizers (aHR, 4.97; 95% CI, 3.66–6.73) than those without depression.

Compared with controls, a significantly high risk of poisoning through other methods was observed in patients with COPD (aHR, 3.85; 95% CI, 3.58–4.14), COPD patients without depression (aHR, 3.56; 95% CI, 3.31-3.83), and COPD patients with depression (aHR, 9.35; 95% CI, 8.16–10.7). Specifically, a significantly higher risk of poisoning through other methods was observed in COPD patients with depression (aHR, 2.59; 95% CI, 2.27–2.95) than in those without depression (**Table 5**).

DISCUSSION

Despite the urgency and necessity of reducing suicidality worldwide, several developed countries have not invested sufficient resources in SA research and prevention (5). An obvious imbalance exists between the magnitude of the suicide problem and the knowledge required to address it. The present study involved a 13-year follow-up of patients aged ≥20 years, and the results revealed that 5.81% of patients with COPD developed depression. One of our previous studies with a similar design showed that the incidence of SA and SDO in patients with depression was 3.76 and 6.97, respectively, per 10,000 person-years (15). The current study revealed that the incidence of SA and SDO in COPD patients with depression was 29.7 and 71.2 per

TABLE 2 | Incidence and risk factors for suicide attempt across different factors.

Variable	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[$] (95% CI)
COPD					
None	508	300,7849	1.69	1.00	1.00
All	712	1,156,091	6.16	3.58(3.20, 4.02)***	3.06(2.72, 3.45)***
COPD without depression	511	1,088,444	4.69	2.73(2.41, 3.09)***	2.49(2.19, 2.82)***
COPD with depression	201	67,467	29.7	17.3(14.7, 20.4)***	13.6(11.3, 16.4)***
Age group, years					
≤49	153	399,532	3.83	1.52(1.23, 1.87)***	1.37(1.11, 1.69)**
50-64	202	792,705	2.55	1.00	1.00
≥65	865	2,971,704	2.91	1.11(0.96, 1.30)	1.14(0.97, 1.34)
Sex					
Women	372	1,384,182	2.69	1.00	1.00
Men	848	2,779,758	3.05	1.13(1.00, 1.28)	
Monthly income[†]					
<15,000	433	1,535,721	2.82	1.69(1.39, 2.06)***	1.50(1.19, 1.87)***
15,000–19,999	660	1,862,091	3.54	2.13(1.76, 2.58)***	1.48(1.19, 1.83)***
≥20,000	127	766,128	1.66	1.00	1.00
Urbanization level[‡]					
1 (highest)	198	1,023,850	1.93	1.00	1.00
2	350	1,139,992	3.07	1.59(1.33, 1.89)***	1.36(1.14, 1.62)***
3	205	680,968	3.01	1.56(1.28, 1.89)***	1.32(1.08, 1.61)***
4 (lowest)	467	1,319,131	3.54	1.83(1.55, 2.16)***	1.33(1.11, 1.59)***
Occupation category[&]					
Office worker	346	1,649,829	2.10	1.00	1.00
Laborer	644	1,772,567	3.63	1.73(1.52, 1.97)***	1.37(1.16, 1.62)***
Other	230	741,545	3.10	1.47(1.25, 1.74)***	1.07(0.88, 1.29)
Comorbidity					
Schizophrenia					
No	1205	4,147,187	2.91	1.00	1.00
Yes	15	16,754	8.95	3.03(1.82, 5.04)***	1.29(0.77, 2.16)
Alcohol-related illness					
No	1151	4,120,394	2.79	1.00	1.00
Yes	69	43,547	15.8	5.57(4.37, 7.10)***	2.14(1.64, 2.79)***
Anxiety					
No	1171	4,127,221	2.84	1.00	1.00
Yes	49	36,720	13.3	4.62(3.47, 6.15)***	1.38(1.02, 1.87)*
Mental disorders					
No	1158	4,045,473	2.86	1.00	1.00
Yes	62	118,468	5.23	1.73(1.34, 2.24)***	1.21(0.93, 1.59)
Insomnia					
No	1135	4,082,986	2.78	1.00	1.00
Yes	85	80,955	10.5	3.67(2.95, 4.58)***	1.24(0.97, 1.57)

*CI, confidence interval; HR, hazard ratio; PY, person-years. [#]Incidence rate per 10,000 person-years. [$]Multivariable analysis included age, monthly income, urbanization level, occupation category, and comorbidities of schizophrenia, alcohol-related illness, anxiety, mental disorders, and insomnia. [†]New Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD. [‡]The urbanization level was divided into 4 levels based on the population density of the residential area, where level 1 was the most urbanized and level 4 was the least urbanized. [&]Other occupation categories included those who were primarily retired, unemployed, and low-income people. *P < .05, **P < .01, ***P < .001.*

10,000 person-years, respectively. COPD patients with depression had a 13.6- and 3.09-fold higher SA risk than did controls and COPD patients without depression, respectively. Furthermore, COPD patients with depression had a 10.0- and 3.09-fold higher SDO risk than did controls and COPD patients without depression, respectively. Contrary to the belief that COPD moderately increases SA and SDO risks in patients with depression, this large-scale study revealed enhancement of SA and SDO risks in COPD patients with coexisting depression. Furthermore, regardless of the confounding effects of socioeconomic factors such as monthly income, urbanization level, and occupation category, age less than 50 years is a specifically high risk factor for SA in COPD patients that interact with depression. Moreover, no differences were observed in SA risk between male and female patients in this study when considering the overwhelming enhancement effects of depression on COPD.

We usually evaluate suicidality using self-reported passive and active death-related thoughts collected through a questionnaire with a binary (yes/no) response. Using this method, suicidal ideation can be investigated; however, valid methods for assessing suicidal behavior, SA, and suicidal death risk are unavailable. Moreover, in the United Kingdom, 1 of 5 adults considers suicide; however, only one in 15 attempts suicide (6). Another study reported that only a small proportion of individuals who exhibit suicidal ideation actually attempt suicide (16). Our study showed proportionally extreme increases in SA and SDO risks resulting from the effects of comorbid depression on COPD. Compared with the annual SA prevalence of 0.4%–0.5% in

TABLE 3 | Comparison of incidence and hazard ratio of suicide attempt stratified based on age, sex, and comorbidities between copd patients with and without depression.

	COPD without depression (N=340,694)	COPD with depression (N=21,009)
	Adjusted HR[$] (95% CI)	Adjusted HR[$] (95% CI)
All	1.00	3.09(2.78, 3.44)***
Age, year		
≤49	1.00	9.14(6.02, 13.9)***
50-64	1.00	6.94(4.65, 10.4)***
65+	1.00	4.61(3.63, 5.85)***
P for interaction		< 0.001
Sex		
Female	1.00	6.93(5.16, 9.29)***
Male	1.00	5.13(4.06, 6.48)***
P for interaction		0.04
Monthly income[†]		
<15,000	1.00	4.60(3.38, 6.27)***
15,000–19,999	1.00	5.99(4.67, 7.68)***
≥20,000	1.00	7.50(4.52, 12.5)***
P for interaction		0.02
Urbanization level[‡]		
1 (highest)	1.00	7.46(4.83, 11.5)***
2	1.00	7.74(5.64, 10.6)***
3	1.00	5.01(3.16, 7.95)***
4 (lowest)	1.00	3.91(2.84, 5.38)***
P for interaction		0.002
Occupation category[&]		
Office worker	1.00	6.86(4.9, 9.59)***
Laborer	1.00	5.43(4.19, 7.03)***
Other	1.00	4.63(3.14, 6.82)***
P for interaction		0.03
Comorbidity[§]		
None	1.00	6.49(5.29, 7.96)***
With any one	1.00	4.11(3.06, 5.52)***
P for interaction		0.06

*CI, confidence interval; HR, hazard ratio. [$]Multivariable analysis included age, monthly income, urbanization level, and comorbidities of schizophrenia, alcohol-related illness, anxiety, mental disorders, insomnia, diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, stroke, and cirrhosis. [†]New Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD. [‡]The urbanization level was divided into 4 levels based on the population density of the residential area, where level 1 was the most urbanized and level 4 was the least urbanized. [&]Other occupation categories included those who were primarily retired, unemployed, and low-income people. [§]Individuals with schizophrenia, depression, alcohol-related illness, anxiety, mental disorders, and insomnia were classified into the comorbidity group. ***P < .001.*

Western countries (2, 3), the prevalence in our patients with COPD and depression was lower than expected. However, as a nonviolent method of SA, SDO is frequently noted in Taiwanese patients with COPD and depression. Although more than 95% of the people who attempt SDO could eventually survive in Europe (17), SDO causes considerable burden in Asian countries; hence, SA through SDO should be effectively prevented (18, 19). Our results implied that COPD patients could be dangerously abuse prescribed medicines and tranquilizers for attempting suicide through overdose, especially when these patients have comorbid depression. This study reiterates that medicines and tranquilizers used for self-poisoning are highly accessible in Taiwan, because of the restricted access to firearms in Taiwan, similar to most Asian countries. Therefore, careful and long-term accurate assessment should be performed before prescribing multiple medicines or tranquilizers to COPD patients with depression. Moreover, rather than focusing on their suicidal ideation only, awareness of the relationships of different physical disorders with depression would help identify patients at a high SA risk, thereby preventing suicidal death.

However, depression mediates the relationship between value strain, deprivation strain, aspiration strain, coping strain, and suicidality (8). Psychological strain may cause suicidal behaviors or impulsive suicide in patients with a lack of social support/coping capacities (20), poor functional status (21, 22), and disorders of subjective perception including anxiety, panic, or other mental disorders (23, 24). Those might partially explain the enhancement of depression on suicidal behaviors in COPD patients. Nonetheless, the actual interactions between COPD and depression on suicidality warrant additional investigational studies. Given the neuro-psychological pathology of COPD, considerable biological evidence has demonstrated that chronic inflammation, such as that in COPD, may increase the pathologies over the blood–brain barrier, glutamate regulation, microglia activation, and autoimmune response (25, 26). These can affect patients' physical endurance, sleep, chronic cognition, and associated psychosocial sequelae, thereby contributing to patients' suicidality. Furthermore, oxidative stress in COPD could decrease serotonin synthesis owing to the effects of hypoxemia on tryptophan hydroxylase, and oxidative stress

TABLE 4 | Overall incidence of suicidal drug overdose (per 10,000 person-years) and estimated hazard ratio according to copd patients with or without depression through the cox method.

	Comparison cohort	Total COPD	COPD without depression	COPD with depression
Variable	(N=109,040)	(N=54,520)	(N=48,879)	(N=5,641)
Person-years				
Event, n	1835	2741	2265	476
Rate[#]	6.11	23.8	20.9	71.2
Crude HR (95% CI)	1(Reference)	3.83(3.61, 4.07)***	3.36(3.16, 3.58)***	11.5(10.4, 12.7)***
Adjusted HR[$] (95% CI)	1(Reference)	3.59(3.37, 3.81)***	3.24(3.04, 3.45)***	10.0(8.99, 11.2)***
Crude HR (95% CI)			1(Reference)	3.42(3.10, 3.78)***
Adjusted HR[$] (95% CI)			1(Reference)	3.09(2.77, 3.4)***

*[#]Incidence rate per 10,000 person-years. [$]Multivariable analysis included age, monthly income, urbanization level, and comorbidities of schizophrenia, alcohol-related illness, anxiety, mental disorders, insomnia, diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, stroke, and cirrhosis. ***P < .001.*

TABLE 5 | Overall incidence with different methods of suicidal drug overdose (per 10 000 person-years) and estimated hazard ratio according to copd patients with or without depression through the cox method.

	Comparison cohort	Total COPD	COPD without depression	COPD with depression
Variable	(N=721,550)	(N=361,703)	(N=340,694)	(N=21,009)
Poisoning by drugs or medical substances				
Event, n	366	445	335	110
Rate[#]	1.22	3.87	3.09	16.5
Crude HR (95% CI)	1(Reference)	3.15(2.74, 3.62)***	2.52(2.17, 2.92)***	13.4(10.8, 16.6)***
Adjusted HR[$] (95% CI)	1(Reference)	2.82(2.44, 3.26)***	2.37(2.04, 2.77)***	10.9(8.57, 13.8)***
Crude HR (95% CI)			1(Reference)	5.34(4.31, 6.63)***
Adjusted HR[$] (95% CI)			1(Reference)	4.59(3.62, 5.83)***
Poisoning by benzodiazepine-based tranquilizers				
Event, n	172	0.57	192	70
Rate[#]	2.62	2.28	1.77	10.5
Crude HR (95% CI)	1(Reference)	3.91(3.22, 4.74)***	3.04(2.47, 3.74)***	18.0(13.7, 23.8)***
Adjusted HR[$] (95% CI)	1(Reference)	3.34(2.73, 4.08)***	2.76(2.24, 3.41)***	13.9(10.2, 19.0)***
Crude HR (95% CI)			1(Reference)	5.95(4.52, 7.82)***
Adjusted HR[$] (95% CI)			1(Reference)	4.97(3.66, 6.73)***
Others				
Event, n	1297	2034	1738	296
Rate[#]	4.32	17.7	16.0	44.3
Crude HR (95% CI)	1(Reference)	4.01(3.74, 4.31)***	3.64(3.39, 3.91)***	10.1(8.89, 11.4)***
Adjusted HR[$] (95% CI)	1(Reference)	3.85(3.58, 4.14)***	3.56(3.31, 3.83)***	9.35(8.16, 10.7)***
Crude HR (95% CI)			1(Reference)	2.78(2.45, 3.14)***
Adjusted HR[$] (95% CI)			1(Reference)	2.59(2.27, 2.95)***

*[#]Incidence rate per 10 000 person-years. [$]Multivariable analysis included age, monthly income, urbanization level, and comorbidities of schizophrenia, alcohol-related illness, anxiety, mental disorders, insomnia, diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, stroke, and cirrhosis. ***P < .001.*

could cause depression and suicidality (27). These findings revealed a notably bidirectional relationship between depression and COPD that increases suicidality in affected patients.

Our findings proved that depression is an extreme factor enhancing suicidal behaviors in patients with COPD. However, this study has some limitations. First, this was a retrospective study that used NHIRD claims data with hospitalization records related to COPD and depression during the study period. Although the accuracy of inpatient data is assured because of severe penalty associated with providing incorrect data, identifying SA, SDO, COPD, and depression based on the ICD-9-CM coding system is still associated with a possibility of underdiagnosis and underestimation. Minor SA and SDO in patients with COPD might not require medical services, resulting in the underestimation of SA and SDO risks. Second, we could not directly contact patients to determine the severity of COPD and depression, their actual taken medications, or treatments for their disorders because patients' identities were anonymized in the NHIRD. These details may confound their suicidality. Finally, even though our study design controlled for numerous confounders to the best of our knowledge, some unmeasured or unknown confounders may remain. Further large-scale studies are necessary to gain a comprehensive understanding of suicidality in patients with COPD with and without depression; such studies would help establish an effective prevention system in Taiwan and worldwide.

CONCLUSIONS

COPD and depression increase the risk of suicidality individually and synergistically. COPD patients with depression have increased SA and SDO risks. Specifically, COPD patients with depression aged less than 50 years have high SA risk. Our findings provide crucial information for suicide prevention for clinicians and the governments of Taiwan and other Asian countries. In COPD patients with depression, long-term medicines or tranquilizers should be prescribed and dispensed with caution.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH104-REC2-115-CR4). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Study conception/design: TH, C-HK. Provision of study material and patients: C-HK. Collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript: all authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00270/full#supplementary-material

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The Presence and the Search Constructs of Meaning in Life in Suicidal Patients Attending a Psychiatric Emergency Department

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Meaning in Life (MiL) is considered protective against suicidal behavior (SB). However, few studies specifically addressed the role of the constructs, "presence of MiL" and "search for MiL," and their dynamic interplay. In this cross-sectional study of patients with SB (N = 199) visiting a psychiatric Emergency Department for either suicidal ideation (SI) or suicide attempt (SA), we pursued the following objectives: 1) to explore the relationship between the two constructs; 2) to verify the protective value of presence of MiL on SB; and 3) to assess the influence of search for MiL on the relationship between presence of MiL and SI. The two constructs were found to be independent of one another. Higher presence of MiL was globally associated with lower SB levels, particularly SI. Search for MiL was not related to SB and did not moderate the relationship between presence of MiL and SI. In conclusion, formal support for the role of presence of MiL against SB in a psychiatric sample was demonstrated. These findings, with a view toward refinement of SB risk assessment and new psychotherapeutic approaches, may lead to an enrichment of the dialogue with suicidal patients to help alleviate their unbearable suffering. Our conclusions must be replicated in psychiatric clinical populations in settings other than a psychiatric ED and by using a longitudinal prospective and case-control study design.

Keywords: suicide, suicidal behavior, suicidal ideation, suicide attempt, Meaning in Life, protective factors

INTRODUCTION

The presence of Meaning in Life (MiL) has long been associated with protection against suicide, as initially observed in prisoners of Nazi concentration camps (1, 2). More recently, MiL has been conceptualized as a psychological dimension (3–6), and a differentiation between "presence of" and "search for" MiL constructs has been proposed (7, 8). The former construct has been associated with benefits in various functioning aspects, including adaptive resources, overall psychological well-

being, and positive affects (9). The impact of the latter construct has been more debated: some have considered it to be a primary human endeavor aimed at the challenges of life experiences to avoid pathological responses to negative situations (2, 10, 11), whereas others have associated its emergence with MiL dysfunction (12, 13). It has been proposed that the search for MiL is influenced by adaptive or non-adaptive aspects depending on the motivation, personality, and cognitive style of the individual (5, 14).

To our knowledge, only four studies have investigated the roles of both constructs of MiL in the development of suicidal behavior (SB) [(15–18); for a review, see (19)]. These studies were performed in undergraduate students (16), military personnel and veterans (15, 16, 18), and HIV-positive patients (17). All of these studies have reported that the presence of MiL has a protective function on SB, directly or through mediation-moderation models. Data describing search for MiL were less consistent but generally not associated with protection against SB (15–19). Although only a limited number of studies have reported on MiL in relation to SB, more research is available on MiL in those who live with chronic pain. For example, in a typological study among patients with chronic pain, five MiL profiles emerged that resulted from five different combinations of the two MiL constructs (20, 21). Both constructs and the related MiL profile were found to be fairly stable over time, leading to the hypothesis that they can reflect a trait aspect rather than a state aspect of the individual functioning (20, 21). However, the included patients were selected individual members of a pain management organization who had reported a relatively longer duration of chronic pain. It was suggested that this group had possibly completed the psychological acceptation and integration process of their pathological condition and were spared from experiencing it as a destabilizing event at the time of the study. Although the MiL profiles were not studied here in relation to SB, the authors proposed replicating such analyses in a sample of newly diagnosed chronic pain patients to possibly observe more changes in maintaining, losing, or restoring their MiL (20, 21) In patients suffering from chronic pain, a protective role of the presence of MiL against suicidal ideation was postulated (22). These data suggest that clinical interventions that take into account both of the constructs could enrich the encounter and the dialogue with the suicidal patient, to refine the SB risk assessment, and to offer new approaches for psychotherapeutic interventions (23–26).

The limited amount of research conducted in this area suggests that further investigation is necessary to draw definitive conclusions on the clinical applicability of MiL in SB management. With this study, we aimed to investigate the impact of both MiL constructs in a clinical population composed of patients visiting the psychiatric Emergency Department (ED) of a general hospital for SB, namely suicidal ideation (SI) or suicide attempt (SA). To this end, we pursued the following objectives: 1) to explore the relationship between the two constructs; 2) to verify the protective value of presence of MiL on SB; and 3) to assess the influence of search for MiL on the relationship between presence of MiL and SI. Based on the aforementioned published studies, we hypothesized the following: 1) that the two constructs are independent of one another; 2) that the presence of MiL, but not search for MiL, has a protective impact on both SI and SA; and 3) search for MiL will have no impact on the relationship between presence of MiL and SI.

METHODS

Procedure

Every person referred to the adult division of the psychiatric EDs of the Geneva University Hospitals, Switzerland, from October 1, 2014, to February 1, 2016, for SB and not requiring admission to an inpatient somatic unit was offered the opportunity to participate in this study. Inclusion criteria were the occurrence of SI or SA, being aged 16 years (the minimal age to be admitted in adult healthcare departments in Geneva) or more, giving written consent, and completing the study procedure within 7 days following inclusion. We used the nomenclature proposed by Posner (27), which defines SI as "passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior" and SA as "a potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury" (p. 1037). Participants answered inquiries regarding their sociodemographic situations as well as a series of questionnaires, some administered by the psychiatrist in charge of the study inclusion and some self-reported. Other aspects of this global project on suicide, not relevant to the present study, have resulted in five publications (28–32). This study was approved by the local Research Ethics Committee under the registration number 14-168.

Participants

129 of the 368 individuals offered to participate in this study declined for several reasons (e.g., lack of concentration, or interest, or insufficient fluency in the French language), and 40 were excluded by the psychiatrist in charge because of poor quality of data (e.g., repeated patterns in answers or questionnaires left blank) or procedural shortcomings (e.g., lack of a signed consent form). The final study group comprised of 199 participants, aged 33.3 ± 14.5 years (range, 16–82 years). The majority had a psychiatric diagnosis according to the Mini-International Neuropsychiatric Interview (33). The most prevalent diagnoses were episodes of major depression (69.8%), alcohol dependence (17.1%), and non-alcohol substance dependence (10.1%). Additional sociodemographic characteristics are summarized in **Table 1**.

Instruments

SI was evaluated using the Scale for Suicide Ideation (SSI) (34), a self-administered questionnaire of 19 items rated on a three-

TABLE 1 | Psychosocial characteristics (*N* = 199).

		n	Percentage
Sex	Female	120	60.3
	Male	79	39.7
Age group	<20 years	42	21.1
	20 to <30 years	52	26.1
	30 to <40 years	39	19.6
	40 to <50 years	32	16.1
	50 to 60 years	26	13.1
	>60 years	8	4.0
Citizenship	Swiss	115	57.8
	Non-Swiss	84	42.2
Marital status	In a relationship	68	34.2
	Single	131	65.8
Children	Yes	78	39.2
	No	121	60.8
Professional status	Employed/Student	115	57.8
	No activity	84	42.2
Perceived wealth status	High (categories 1–3)	36	18.1
	Low (categories 4–6)	163	81.9
Inclusion criterion	Suicidal ideation	131	65.8
	Suicide attempt	68	34.2
Psychiatric diagnosis	Yes	177	88.9
	No	22	11.1

Perceived wealth status was assessed by asking participants to rank themselves in one among six categories, from 1 (rich) to 6 (poor) on the basis of a short-written description.

point Likert scale (total score range, 0–38) with statements that varied from one item to another. The SSI has been validated in French (35, 36). Internal consistency was good within this data set (α = 0.844, 95% CI [0.811, 0.874]).

The Meaning in Life Questionnaire (MLQ) (8) is a self-reported 10-item inventory measuring the presence of MiL (5 items) and search for MiL (5 items) constructs. Each item was rated on a 7-point Likert scale from "absolutely true" to "absolutely untrue," leading to a score range of 5 to 35 for each subscale. The MLQ has been translated into French and is available on the author's website (http://www.michaelfsteger.com). However, to our knowledge, no formal validation study of the French version has been conducted. In our sample, internal consistency was good for the presence of MiL construct subscale (α = 0.802, 95% CI [0.755, 0.842]) and for search for MiL construct subscale (α = 0.877, 95% CI [0.848, 0.902]).

Statistical Analyses

To address the first objective of this study, bivariate Pearson's and point-biserial correlation analyses were conducted to explore the relationships between the variables of interest and sociodemographic parameters. To address the second objective, a 2-step hierarchical multiple linear regression model and a two-step logistic regression model were used. Finally, the third objective was pursued using a multiple linear regression model including the creation of an interaction variable.

All statistical analyses were conducted using Statistica version 13.0 (StatsSoft Inc., Tulsa, OK, USA), and a threshold of $p \leq 0.05$ was considered to be statistically significant.

RESULTS

Relationships Between the Variables of Interest

Bivariate Pearson's correlations were computed for the presence of MiL and search for MiL construct subscales of the MLQ for the entire sample and separately for those with SAs and SI, as grouping variables. The subscales were not significantly correlated in the whole sample (M_{Presence} = 18.357 ± 7.065, M_{Search} = 24.955 ± 7.161, r = −0.015, p = 0.831), nor for those with SAs (M_{Presence} = 20.353 ± 7.011, M_{Search} = 24.456 ± 7.170, r = −0.181, p = 0.139), nor with SI (M_{Presence} = 17.321 ± 6.893, M_{Search} = 25.214 ± 7.170, r = 0.087, p =.321). Additionally, a point-biserial correlation showed that participants recruited for a SA had higher presence of MiL construct scores compared to those with SI only (SI = 0, SA = 1, r_{pb} =.204, $p < 0.05$). No significant correlation was found between search construct subscale and SI/SA. Finally, unlike the search for MiL construct, the presence of MiL construct was negatively correlated with the SSI score (r = −0.485, $p < 0.05$).

We then measured the associations between the two constructs and several sociodemographic variables (i.e., age, children, marital status, professional situation, and perceived wealth). A bivariate Pearson's correlation showed that the presence of MiL construct was positively correlated with age (r = 0.225, $p < 0.05$), while point-biserial correlations underscored a positive relationship between the presence of MiL construct and having at least one child (when no children = 0 and at least one child =1, r_{pb} = 0.334, $p < 0.05$). Also, a positive relationship was found between the presence of MiL construct and being in a couple relationship (when single = 0 and in a relationship = 1, r_{pb} = 0.236, $p < 0.05$). No sociodemographic variable was significantly associated with the search for MiL construct.

Next, we explored the relationships between the two constructs and the psychiatric diagnoses defined by the Mini-International Neuropsychiatric Interview in conducting point-biserial correlations (0 = no diagnosis, 1 = diagnosis). There was a negative association between the presence of MiL construct and having a psychiatric diagnosis (r_{pb} = −0.157, $p < 0.05$). Similarly, a negative association was found between the presence of MiL construct and a diagnosis of past major depressive disorder (r_{pb} = −0.155, $p < 0.05$). Finally, while participants with current social phobias scored significantly higher on the search construct scale (r_{pb} = 0.149, $p < 0.05$), this result should be interpreted with caution since only 5 participants (2.5%) had this diagnosis.

Presence of MiL Construct as a Predictor of SB

A two-step multiple linear regression equation was built using the SSI score as the dependent variable. In the first step, we used the sociodemographic parameters that showed positive correlations with the presence of MiL construct, namely age, having children, and relationship status. As summarized in **Table 2**, this initial model significantly predicted the SSI score

TABLE 2 | Two-step hierarchical multiple regression equation with sociodemographic variables and presence of Meaning in Life (MiL) construct predicting suicidal ideation (N = 199).

Predictors entered as a set	F	df	R^2	Adjusted R^2	b	t	p
1	4.129	3, 195	0.060	0.045			**0.007**
Age					−0.000	−0.008	0.994
Children					−2.496	−1.799	0.074
Marital status					−2.506	−1.971	**0.050**
2	15.711	4, 194	0.245	0.229			**<0.001**
Age					0.021	0.520	0.604
Children					−0.715	−0.562	0.575
Marital status					−1.436	−1.245	0.215
MLQ presence of MiL construct					−0.530	−6.892	**<0.001**

In bold, p values significant at the ≤ 0.05 threshold. Coding for dummy variables are as follows. Children: 0 (no children) or 1 (at least one child); marital situation: 0 (single) or 1 (in a relationship).

(F [3, 195] = 4.129, p = 0.007) and accounted for 4.5% of the global variance in SI as measured by the adjusted R^2. The only sociodemographic variable predicting the SSI score was marital status (b = −2.506, p = 0.050), suggesting that being in a relationship reduces the likelihood of developing SI. In the second step, we added the presence of MiL construct as a predictor of the dependent variable. As shown in **Table 2**, this model predicted the SSI score (F [4, 194] = 15.711, $p < 0.001$) and accounted for 22.9% of the total variance. The presence of MiL construct was the only single variable that had a significant effect on SI (b = −0.530, $p < 0.001$).

We then built a logistic regression model using a criterion variable that dichotomized participants incorporated in the study for SI only (coded 0) from those included in the study for an SA (coded 1). As before, we first used the sociodemographic variables that showed positive correlations with the presence of MiL construct and in this case found that the model accounted for a small proportion of the variance in the study inclusion criterion (deviance = 252.839, df = 195, Cox-Snell R^2 = 0.014, Nagelkerke R^2 = 0.019), and the odds ratio (OR) of each sociodemographic variable did not predict the dependent variable at our significance threshold. Thereafter, we added the presence of MiL construct as predictor in a second model, and it accounted for a larger proportion of the variance in the dependent variable (deviance = 246.009, df = 194, Cox-Snell R^2 = 0.047, Nagelkerke R^2 = 0.065). In addition, the presence of MiL construct predicted the probability to be included in the study with an SA rather than with SI only (OR = 1.062, 95% CI [1.014, 1.112], p = 0.010).

Search for MIL Construct as a Moderator of Between Presence of MiL Construct and SI

To assess the moderating effect of the search for MiL construct on the relationship between the presence of MiL construct and SI as measured by the SSI score, a multiple linear regression analysis was designed with the SSI score as the criterion variable and the two constructs as predictors. In addition, we used an interaction variable between the two constructs. Because of multicollinearity effects, results for the two constructs were centered around their means, and the interaction variable was created from these mean-centered variables.

As shown in **Table 3**, this model significantly predicted the SSI score, (F [3, 195] = 21.094, $p < 0.001$), and explained 23.3% of its total variance (adjusted R^2). Although the presence of the MiL construct had a protective effect on SI (b = −0.538, $p < 0.001$), neither search construct nor the interaction variable between presence of MiL construct and search construct had a significant effect on the dependent variable.

DISCUSSION

This study investigated the role of the two MiL constructs in a clinical population of patients attending a psychiatric ED for SB, namely SI and SA.

Regarding our first hypothesis, our data confirmed that the two MiL constructs were independent of one another, in line with previous research (8, 14). Although not significant, the relationship between the two constructs in our study was negative, which corresponds to other studies that have consistently shown this trend, sometimes significant when the effect size was small (14, 37). The independence of the two constructs can create only an apparent conceptual paradox, which has been thoroughly discussed (8). Previous work has shown that because they are independent, these constructs can be assessed separately. In particular, this independence can override the debate over whether a beneficial versus dysfunctional role for the search for MiL construct and its dynamic interplay with the presence of MiL construct *via* a greater theoretical flexibility. For instance, it can allow the identification and distinction of individuals who feel great meaningfulness yet are still engaged

TABLE 3 | Multiple regression equation with presence and search constructs of Meaning in Life (MiL) predicting suicidal ideation (N = 199).

Predictors entered as a set	F	df	R^2	Adjusted R^2	b	t	p
1	21.094	3, 195	0.245	0.233			**<0.001**
Presence of MiL construct					−0.538	−7.386	**<0.001**
Search for MiL construct					0.030	0.415	0.678
Presence of MiL construct x search construct					0.011	1.457	0.147

In bold, p values significant at the ≤ 0.05 threshold.

in seeking life's meaning and contrast them with those who feel the same meaningfulness but are not engaged in further search for meaning (8).

We also investigated possible relationships between the constructs and other variables of interest, such as sociodemographic variables. To our knowledge, this kind of data has not yet been reported. The characteristics of our sample suggested that it was representative of individuals visiting ED for a non-lethal suicidal event with a predominance the female sex (38–42), a mean adult age less than 50 years (38, 41, 43, 44), and the presence of a psychiatric disorder in most participants (39, 44, 45). Although the search for MiL construct was not associated with any sociodemographic variable, the presence of MiL construct correlated positively with factors known to protect against SB, such as middle adult age, having at least one child, and being in a couple relationship (46, 47). Similarly, we found a negative correlation between the presence of MiL construct and having a psychiatric diagnosis, and this correlation notably applied to a diagnosis of a past major depressive disorder. A psychiatric diagnosis is among the most significant risk factors for suicide (46, 47). Thus, the presence of MiL construct could be considered a protective factor against the development of psychiatric disorders in general, and suicide in particular. Taken together, these findings suggest that the presence of MiL construct is not an innate attribute and does not boil down to a personality trait. Rather, it is likely a dynamic construct requiring time for maturation, as implied by its positive association with age. The presence of MiL construct also appears to be dependent on significant life events such as childbirth or marriage. Because of the cross-sectional design of this study, we were unable to confirm these assumptions.

The typological approach utilized in the aforementioned chronic pain studies relates to the discussion of our first hypothesis (i.e., the two constructs are independent of one another) by providing a research path that reinforces the proven independence of the two MiL constructs. It follows that a more nuanced and dynamic description of the individual's personal attitude toward MiL can be generated through investigation of the constructs in the following combinations: 1) high presence of MiL-high search for MiL (i.e., patients experiencing MiL and searching for MiL); 2) high presence of MiL-low search for MiL (i.e., patients experiencing MiL but not searching for MiL); 3) moderate presence of MiL-moderate search for MiL (i.e., patients moderately experiencing MiL and searching for MiL); 4) low presence of MiL-low search for MiL (i.e., patients not experiencing MiL and not engaged in any search for MiL); and 5) low presence of MiL-high search for MiL (i.e., patients not experiencing MiL but engaged in search for MiL) (20, 21). These distinctions, which can also be used in relation to chronic pain or SB, are in line with the possibility of overriding the debate over a beneficial versus dysfunctional role for the search for MiL construct by utilizing a more flexible theoretical perspective (14).

With regard to our second hypothesis, that is that the presence of MiL construct has a protective impact on both SI and SA, we found that higher presence of MiL was associated with lower SI. No significant correlation was found between the search for MiL construct and SI/SA. Previous studies that have addressed this issue (15–18) reported similar results in that the presence of MiL construct was negatively associated with SB, particularly with SI. This also included a protective function of the presence of MiL construct on SA (16), but this could not be confirmed in our study since the absence of a non-suicidal control group negated a definitive conclusion. Similarly, we did not find a significant relationship between the search for MiL construct and SB, contrary to research that noted a protective effect on SI (16) and, in contrast, positive relationships with SI and SA (15). With reference to the described MiL profiles in patients with chronic pain, it was found that they were associated with a unique adjustment outcome that was more favorable for those that scored high in presence of MiL (20, 21). As previously specified, however, their impact on SB was not examined.

Somewhat counterintuitively, the presence of MiL construct predicted the probability of being included in the study with an SA rather than with SI only. To our knowledge, this is the first study to report this finding. In our sample population, participants with an SA had lower SI than those included with SI only, possibly implying that the psychological process that unfolds after an SA can have mitigating effects on SI (30). Because the correlation between the presence of MiL construct and SI, as measured using the SSI, was strongly negative ($r = -0.485$), we can hypothesize that this MiL construct was influenced by the latter psychological process on SI and, consequently, possibly more so before rather than after an SA. Unfortunately, the data providing information on the attitudes and reactions of individuals following an SA are limited, but one study found that a process of awareness of life responsibilities occurred at an initial stage (48). Similarly, it was pointed out that patients undergo a change in self-perception toward redefinition of self-image, life goals, and coping strategies and that this process should be undertaken in consideration of significant others (49). In addition, patients having made an SA used paired testimony to develop a personal sense of hope (50). Though the temporal nature of our study makes it unlikely that participants benefited from the testimonies of others at the time of questionnaire completion, one can speculate whether a search for hope was already instilled at an unconscious level following their SA. Overall, these findings suggest that an SA is followed by increased consideration of existential factors in life and, thus, can provide an initial explanation for the improvement in the presence of MiL construct observed in our sample group. Future studies using a longitudinal design should attempt to further investigate this issue.

As for our explored third point, i.e., to assess the influence of the search for MiL construct on the relationship between the presence of MiL construct and SI, we did not find that the search for MiL construct moderated the relationship as hypothesized. This novel finding reinforced, along with our first hypothesis, that the two constructs are independent of one another.

In summary, this study provided formal support for the role of the presence of MiL construct against SB in a general psychiatric study group. In contrast, the search for MiL construct was not related to SB and did not moderate the

relationship between the presence of MiL construct and SI, suggesting, along with other findings, that the two constructs are independent of one another. This is the first study to examine the direct impacts of both constructs on SB in a clinical psychiatric population. To confirm these findings, our conclusions must be replicated in psychiatric clinical populations in settings other than a psychiatric ED and by using a longitudinal prospective and case-control study design.

This study had several limitations to consider. First, the use of regression analyses on cross-sectional data limited the interpretation of causality. Thus, this aspect should be interpreted with caution and replicated in longitudinal research. Second, we lacked a control group which limited the validity of our conclusions. Third, the MLQ questionnaire has not been formally validated in French. Fourth, the sample of patients we tested attended the psychiatric ED for SI and SA, and our results should be confirmed in suicidal patients belonging to more specialized psychiatric settings in order to be more generalizable. Finally, we did not test the impact of the two constructs using a typological methodology: the identification of different MiL profiles deriving from combinations of the two constructs can represent an opportunity to further refine individual diagnostic profiles with the goal of improving clinical outcomes by providing a more personalized approach.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The protocol was approved by the Research Ethics Committee of Geneva under the registration number 14-168. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ACo drafted the primary manuscript, contributed to the conceptualization of the study, and participated to data collection and data interpretation. MB contributed to the conceptualization of the study, participated to data collection and data interpretation, and made statistical analysis. HR-L contributed to the conceptualization of the study and participated to study data collection. KW contributed to the conceptualization of the study and participated to data collection and data interpretation. MP and ACa contributed to the conceptualization of the study, corrected the manuscript, supervised all the steps of the work, and provided the intellectual impetus. All authors approved the final manuscript.

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OPINION
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Intranasal Esketamine and Current Suicidal Ideation With Intent in Major Depression Disorder: Beat the Clock, Save a Life, Start a Strategy

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Keywords: suicidal ideation with intent, depression, esketamine, mental pain, hopelessness

INTRODUCTION

While many governments worldwide now consider major depression to be a main cause of disability and provide dedicated programs for treatment improvement, as is done for suicide, the situation seems to be more complicated in terms of assessment and treatment options. Considering depression as a quintessential element of suicide is insufficient due to suicide's multifactorial nature and clinicians are now requested to provide a critical appraisal of suicide risk, associated or not with major depression (1). Suicide risk does not always receive in-depth analysis when assessing psychiatric patients. Having a diagnosis at hand seems so necessary for paving the way to the next treatment option, suggesting that suicidal or not may ultimately become not so relevant for the therapeutics. On the other hand, being suicidal for some clinicians may be a marker of major depression, and the urgent need to treat such a condition provides the opportunity to explore why suicide risk emerges in a given individual.

The recent innovation in the management of major depression, either resistant to treatment or with suicidal ideation, provides promising opportunities for improving patients' needs. While antidepressants generally require weeks or even months to work, new options are now available for rapid improvements in depression with suicidal intent (the intent to carry out the suicidal act).

Esketamine is an NMDA receptor antagonist that modulates glutamatergic transmission (2). Recently this drug, available as an intranasal formulation, has been proposed for treatment-resistant depression and for the rapid reduction of symptoms of major depressive disorder in patients with suicidal ideation with intent. According to studies by Daly et al. (3), rapid onset of antidepressant effects was reported after single-dose intranasal esketamine administration to patients with treatment-resistant depression.

Clinicians up to now may have administered antidepressants to suicidal individuals and endorsed such treatment for taking care of individuals in need. From the time of taking antidepressants to the appearance of actual effects, the patients may be experiencing side effects but with no real beneficial effect on the symptoms. Furthermore, the rapid resolution of those components most associated with suicide, such as dysphoria, agitation, irritability, and anxiety, might be totally unaltered by the treatment. Patients may detect when mental pain is overwhelming and report changes in behavior. During the course of a suicidal crisis, the reduction of such suffering is therefore crucial for saving a life.

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The new opportunities brought about by recent pharmacological innovations for treating patients with major depressive disorder who have suicidal ideation with intent open up exciting clinical scenarios and a shift in paradigm for the management of such a complex phenomenon. First and foremost, clinicians are now requested to assess suicide risk at all times, a message also delivered by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (4), which dedicates a section to suicidal behavior and attention to patient suffering, regardless of the given diagnosis. In my dedicated clinical practice with suicidal individuals, I realized that suicide risk often referred to a specific time frame, which is suggestive of the fact that such risk may be also be reduced if proper intervention is delivered. Of course, in a highly suicidal individual, any intervention may be challenging for saving a life. However, rapid reduction of the pressure resulting from the rumination and inner dialogue which are motivating the wish to die often results in the opportunity to work effectively with these people and change their future.

FOCUS ON RECENT STUDIES

A small (n = 68) study by Canuso et al. (5) demonstrated a significantly greater improvement in the Montgomery–Åsberg Depression Rating Scale (MADRS) score for the intranasal esketamine group compared to the placebo group at 4 h and ∼24 h, but not at day 25 (patients were treated with either esketamine or placebo in addition to comprehensive standard-of-care treatment). Significantly greater improvement was also observed in the esketamine group on the MADRS "suicidal thoughts" score at 4 h (but not at 24 h or day 25). Patients included in this trial were also assessed with the Suicide Ideation and Behavior Assessment Tool (SIBAT), a newly introduced instrument developed for such a trial. Results from this trial show that overall, in both groups as time passed, the risk of suicide decreased, with most of the subjects progressively being evaluated on the MADRS "suicidal thoughts" item as "enjoying life or take it as it comes" or "weary of life, reporting fleeting suicidal thoughts." In other words, patients with suicide risk, in most cases, had been moved to a comfort zone with only mild suicidal wishes. These are very promising results for a selected population that, regardless of the type of treatment, received a valuable standard of care for the reduction of suicide risk. Of note is the fact that those receiving placebo plus standard of care also showed a consistent improvement in suicidal ideation during the study period. This was probably due to the fact that patients in the placebo group received the same assistance as patients in the esketamine group. This assistance consisted of medical supervision, assessment of various clinical and physical parameters, and presumably empathic understanding of these patients. Such a trial was also unique as it enrolled patients at imminent risk of suicide, surpassing the exclusion criteria for any other trial except for a few exceptions. It is therefore predictable that the research team and clinicians would have been particularly supportive toward these patients, contributing to the reduction of suicidal ideation by empathic understanding.

Furthermore, two recent large-scale investigations (N=224 and N=227) (6, 7) found that 24 h after the first dose of study medication, esketamine plus comprehensive standard of care (SOC) demonstrated a clinically meaningful and statistically significant reduction of depressive symptoms. Both treatment groups (placebo + SOC and esketamine + SOC) experienced an improvement in the severity of suicidality from baseline to 24 h after the first dose. However, the difference between treatment groups was not statistically significant, possibly due to the interventions towards suicide risk carried out since the beginning of inpatient psychiatric hospitalization. Unlike lithium and clozapine, whose anti-suicidal properties were recognized through observations in clinical practice, esketamine has promised to be a breakthrough since its introduction. Furthermore, lithium, despite considerable evidence, never managed to have official recognition for suicide prevention in mood disorders, whereas clozapine was recognized as being an anti-suicidal treatment for patients suffering from schizophrenia after years of observation and a major dedicated trial (8).

PAYING ATTENTION TO THE SUICIDAL MIND

The excitement over a new treatment for depressed patients with suicidal intentions should be re-evaluated after real-world experience. Clinicians should not only assess suicide appropriately but also pay attention to the drama occurring in the patient's mind by using an empathic approach. Treatment of suicide risk without proper acknowledgment of patient suffering would be counterproductive for many reasons. Suicide ideation or suicide, in general, should not be viewed at the same level as symptoms of depression; instead, it is a complex dimension sharing roots with being depressed. The fact that many depressed patients never think about suicide and have future expectations, even with severe depressive symptoms, should remind clinicians that in those with suicidal ideation, there is an inner private dialogue taking place. Such introspection refers to negative emotions, hopelessness, feelings of despair, or terrible hurt that make life a painful experience. This pain is not generally referred to as being sad or depressed; rather, it emerges from adverse circumstances in one's life: something missing or gripping the mind that causes both psychic and somatic anguish. When such pain is deemed to be intolerable, suicide is considered as an option in order to escape from such a state. It would, therefore, be reductive to dismiss any suicidal individual without a proper understanding of their suffering.

As a psychiatrist and committed suicidologist, I found a straightforward but extraordinary model useful to understand why an individual wishes to die by suicide. Edwin Shneidman (9) first posited that the individual suicidal experiences unbearable psychological pain (*psychache*) or suffering and that suicide might be, at least in part, an attempt to escape from this suffering. Shneidman (9) considered psychache to be the main ingredient of suicide. According to this model, suicide is an

escape from intolerable suffering. Suicide is not a movement toward death but rather an escape from intolerable emotion and unendurable or unacceptable anguish. Experiencing negative emotions, with an internal dialogue making the flow of consciousness painful and leading the individual to the ultimate conclusion, may be related to the fact that if tormented individuals could somehow stop consciousness and still live, they would opt for that solution (10). For Shneidman (11), suicide is the result of an explosive mixture consisting of four basic ingredients: heightened inimicality (acting against the individual's best interest); exacerbation of perturbation (how disturbed the individual is); increased constriction of intellectual focus; tunneling or narrowing of the mind's content (dichotomous thinking); and the idea of cessation (the insight that it is possible to stop consciousness and put an end to suffering).

Understanding the suicidal mind requires knowledge of the perturbed state of the individual in crisis, as this provides the motivation for the individual to contemplate suicide. Therefore, asking where the suffering comes from and how it has changed to become more acute is a method of intervention that, although simple and intuitive, is often forgotten by those who are responsible for managing the person in crisis. In the internal debate, essentially involving ambivalence, being able to tune into the suffering of the person makes it possible to stem such ruminations and bring the discussion back to a position of vitality and hope.

Perturbation supplies the motivation for suicide, and lethality is the fatal trigger. Everyone who dies by suicide feels driven to it and feels that suicide is the only option left (10). The concept of "constriction" is defined as tunnel vision or, rather, finding oneself with a reduced number of options to cope with the suffering. Suicidal individuals experience dichotomous thinking, wishing either for some specific (almost magical) total solution to their perturbation or for cessation by suicide. It seems that although there may be effective support from family and friends, the individual is unable to benefit from them.

Proper management of suicide risk should, therefore, consider a shared discussion in which both patient and doctor can explore the origin of suicidal wishes. The vast majority of suicidal patients think about death but also wish to live at the same time. In other words, these individuals want to live as long as there is a reduction in their mental pain. We can achieve the amelioration of such conditions by targeting those symptoms causing more pain and by understanding the patients through active listening, anodyne psychotherapy, and empathic understanding of each patient in their uniqueness as a human being.

CONCLUSIONS

Rapid reduction of suicidal ideation, especially if it is associated with intent, is crucial for saving lives. So far, there have been few pharmacological interventions dedicated to testing drugs relevant to this major clinical challenge. Clinical environments will encounter unprecedented opportunities to assess and manage suicide risk. However, it would be really disappointing if the understanding of why one individual wants to die by suicide is going to be missed. A vast literature is devoted to the subjective experience of patients while they are suicidal, as well as their perception of doctors and nurses during the crises. It would appear that the traditional directive model, with a collection of data, symptoms, etc., is deleterious by creating distance, thus discouraging the crucial alliance between patient and doctor. Patients may perceive such distance as confirmation of being isolated and helpless. Clinicians may also run the risk of a worse manifestation of suicide risk over time if a proper strategy is not adopted. A collaborative approach has been proposed for fostering the alliance between clinician and patient and for in-depth analysis of the components of suicidal wishes (12, 13). Fostering collaboration between patients and clinicians and collecting information through multimodal suicide risk assessment, as well as uncovering suicide risk in the absence of self-disclosure of suicide risk, is, of course, a major goal nowadays (14–16).

There are, of course, many models aimed at describing suicide, as recently reported (17). However, clinicians are encouraged to bridge the gap between theory and practice.

The fact that suicide rates remain mostly unchanged or are on the increase in some parts of the world (18) points to reflections on the paradigms that are more widely embraced in clinical practice. In proposing the phenomenological perspective for understanding suicidal individuals, clinicians can reach the inner and private parts that often allow unlocking of the suicidal mind.

It is worth considering that both ketamine and esketamine may potentially be associated with the risk of addiction. Such possibility should be counterbalanced by the fact that intranasal esketamine is given under strict medical supervision and patients can only receive such a drug in authorized clinics. Besides, it would be misleading to couple the drug discussed in this report with substances of abuse; although of similar origin, the regulatory processes that deliver them to patients are very different. Zhu et al. (19) found that repeated ketamine administration at weekly intervals was found to be safe and effective for maintaining the treatment response as a rapid-acting antidepressant.

There is still also a lack of education and proper information on preventing suicide and how to deal with suicidal individuals. Stigmatization, no doubt, plays a major role in obstructing the adoption of ideas for suicide prevention. The introduction of a new treatment specifically involving the assessment and management of suicide risk is a breakthrough innovation that paves the way a new era of the reduction of depressive symptoms in adults with major depressive disorder who have current suicidal ideation with intent. Clinicians will receive updates and continuous medical education, addressing the difficulties with suicidal individuals. Let us hope that such difficulties become opportunities for unlocking the suicidal mind, getting to know the drama occurring in the minds of these people, and, ultimately, facilitating their wish to live.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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"Out, out, brief candle! Life's but a walking shadow": *5-HTTLPR* Is Associated With Current Suicidal Ideation but Not With Previous Suicide Attempts and Interacts With Recent Relationship Problems

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Background: Suicide is an unresolved psychiatric and public health emergency, claiming 800,000 lives each year, however, its neurobiological etiology is still not understood. In spite of original reports concerning the involvement of *5-HTTLPR* in interaction with recent stress in the appearance of suicidal ideation and attempts, replication studies have yielded contradictory results. In our study, we analyzed the association between *5-HTTLPR* and lifetime suicide attempts, current suicidal ideation, hopelessness and thoughts of death as main effects, and in interaction with childhood adversities, recent stress, and different types of recent life events in a general population sample.

Methods: Two thousand and three hundred fifty-eight unrelated European volunteers were genotyped for *5-HTTLPR*, provided phenotypic data on previous suicide attempts, and current suicidal ideation, hopelessness and thoughts about death, and information on childhood adversities and recent life events. Logistic and linear regression models were run with age, gender, and population as covariates to test for the effect of *5-HTTLPR* as a main effect and in interaction with childhood adversities and recent life events on previous suicide attempts and current suicidal ideation. Benjamini-Hochberg FDR Q values were calculated to correct for multiple testing.

Results: *5-HTTLPR* had no significant effect on lifetime suicide attempts either as a main effect on in interaction with childhood adversities. *5-HTTLPR* had a significant main effect

on current suicidal ideation in the dominant model (Q=0.0344). *5-HTTLPR* did not interact with childhood adversities or total number of recent life events on any phenotypes related to current suicidal risk, however, a significant interaction effect between *5-HTTLPR* and current relationship problems emerged in the case of current suicidal ideation in the dominant model (Q=0.0218) and in the case of thoughts about death and dying in the dominant (Q=0.0094) and additive models (Q=0.0281).

Conclusion: While *5-HTTLPR* did not influence previous suicide attempts or interacted with childhood adversities, it did influence current suicidal ideation with, in addition, an interaction with recent relationship problems supporting the involvement of *5-HTTLPR* in suicide. Our findings that *5-HTTLPR* impacts only certain types of suicide risk-related behaviors and that it interacts with only distinct types of recent stressors provides a possible explanation for previous conflicting findings.

Keywords: suicide attempts, suicidal ideation, childhood adversities, recent life events, *5-HTTLPR*

INTRODUCTION

Suicide remains an unresolved psychiatric and public health emergency, claiming 800,000 lives each year, contributing to one death happening every 40 seconds (1), and it is the second leading cause of death in adolescents and young adults in the 15–29 age group (1). In spite of declining trends worldwide, in young people in the United States suicide shows an alarmingly increasing rate (2) which, in spite of decades of research aimed at uncovering its biopsychosocial aspects and determinants highlights that we are still far from understanding, and even further from effectively predicting and preventing suicidal behaviors.

Suicidal behavior occurs along a spectrum from thinking about suicide or suicidal ideation, planning, suicidal attempts, aborted suicides to completed suicide (3), all of which cause significant suffering and burden. While 90% of completed suicides occur in psychiatric patients (4), the majority of whom suffer from affective disorders where it may be expected and thus targeted, still quite a few nonpsychiatric subjects resort to suicidal behavior. While suicidal behaviors, especially attempts and completed suicides, cannot be predicted, one possible marker heralding approaching suicide may be the appearance of suicidal thoughts, which are often the threshold of the downward spiral leading to more lethal suicidal manifestations. While the frequency of suicide attempts is up to 20 times that of completed suicides with a lifetime prevalence of 2.7%, suicidal ideation has a 9.2% lifetime prevalence, with 29% of ideators (and 56% of ideators with a plan) proceeding to making a subsequent suicidal attempt (5). Thus, while there may be some heterogeneity not only in the manifestation but also in the neurobiology of suicidal behavior along the suicide spectrum (6, 7), due to completed suicide being a relatively rare event in the community other manifestations along the spectrum are used in studies to extrapolate and estimate suicide risk (3).

Also, due to the significant suffering and burden associated with suicidal behavior coupled with the impossibility to reliably and effectively predict suicide as declared by the American Psychiatric Association and the Institute of Medicine (8), there has been a surge to identify predictors, such as suicidal ideation as well as biomarkers including genetic variants that predict suicidality.

Family, adoption, and twin studies clearly show a substantial role of genetic factors in suicidal behavior, contributing to a heritability estimated between 30% and 55% in different studies (9, 10), with an average of 43%, which is in general comparable to the heritability of psychiatric illnesses (11, 12) but is at least in part independent of the genetic transmission of affective disorders (13). There is a ten-fold risk of suicidal behavior in relatives of suicide completers (14) and a 175-time relative risk for suicidal behaviors including attempts and completion in monozygotic twin pairs compared to dizygotic ones (15).

Due to initial findings of an association between low 5-HIAA levels in the cerebrospinal fluid (16, 17) of suicidal depressive patients and subsequent reports of lower serotonin transporter expression in various relevant regions of the suicidal brain (18, 19), the serotonergic system has been early implicated in suicidal behavior and subsequently genes in the serotonergic system have become prime candidates in the search for the genetic underpinnings of suicide. Already in the early era of psychiatric genetics, attention was focused on *5-HTTLPR*, a 44-base pair insertion-deletion polymorphisms (rs4795541), located upstream from the transcription start site in the promoter region and playing a role in the regulation of the serotonin transporter gene *SLC6A4*, located on chromosome 17 (17q11.2) and encoding a presynaptic transmembrane protein responsible for the reuptake of serotonin. The 14-repeat short variant (s allele) of *5-HTTLPR*, contributing to reduced expression compared to the 16-repeat long variant (l allele) (20, 21) has been found to be associated with several phenomena related to the appearance of suicidal behavior including depression (22), affective temperaments (23), aggression (24–26), and impulsivity (27–29), especially in the context of environmental stress. *5-HTTLPR* has also been implicated in the background of personality traits involved in increased risk of suicidal ideation, including for example alexithymia (30, 31), which could prove useful in prediction, screening and management of suicide risk (32–34). While there has been a large number of subsequent studies focusing on the role of *5-HTTLPR* in suicide and related risk factors,

there is a lack of agreement due to the contradictory findings of these studies.

In addition to the substantial heritable contribution to suicidal behavior, and in line with the commonly accepted diathesis-stress model of suicide (35), in addition to genetic factors there is also an equally substantial role for environmental components including both predisposing distal and precipitating proximal factors, which emphasises the role of both early and current adverse experiences (7), and plays a key role in modulating the genetic predisposition and triggering of suicide (36). In spite of this, suicidal behaviors have been less frequently studied in gene x environment models, although successful prevention of suicide would require understanding of how risk of suicide emerges in the presence of biological predispositions triggered by external influences. In spite of Caspi and colleagues' initial paper (22) on the interaction of serotonin transporter gene with life events involved not only in depression but also suicide, only a few studies approached the role of *5-HTTLPR* in suicidal behavior with gene x environment interaction models.

Thus, in our present study, we analyzed the impact of *5-HTTLPR* on previous suicide attempts, current suicidal ideation, and other suicide risk markers such as hopelessness and death-related thoughts in interaction with early childhood adverse experiences and recent negative life events in a large general European population.

MATERIALS AND METHODS

Participants

This investigation is part of the NewMood project (New Molecules in Mood Disorders, Sixth Framework Program of the EU, LSHM-CT-2004-503474). In total, 2,588 non-related, European white ethnic origin volunteer participants (1,808 female and 780 male) aged between 18 and 60 from Greater Manchester and Budapest recruited between 2005–2008 through general practices or *via* the internet (www.newmood.co.uk) were sent a questionnaire pack and a genetic sampling kit. Inclusion criteria included voluntary participation, signing of informed consent, providing genetic material and returning the questionnaire pack. Inclusion was independent of any positive psychiatric anamnesis. Subjects whose DNA sample was not successfully genotyped as well as subjects with missing questionnaire data were excluded from statistical tests. The present analysis was carried out in 2,358 subjects who provided eligible phenotypic data and could be genotyped for *5-HTTLPR*. More details about the population sample can be found in our previously published reports (37–39). The study has been conducted in accordance with the Declaration of Helsinki and has been approved by the local ethics committees. All subjects gave written informed consent prior to participation in the study.

Phenotypes

Previous suicidal attempts (SUIC) were recorded through self-report. Current markers of suicidal ideation were measured *via* relevant items of the Brief Symptom Inventory (40), including item 3, "Thoughts of ending your life" to indicate suicidal ideation (BSI03), as well as item 18, "Feeling hopeless about the future", to indicate hopelessness (BSI18), a well-established independent predictor of suicide risk, and item 21, "Thoughts about death and dying" to indicate death-related thoughts (BSI21) during the previous week using a scale of 0–4. Childhood adversities (CHA) were measured using a short form of the Childhood Trauma Questionnaire (CTQ) (41) and covered emotional and physical abuse and emotional and physical neglect. Recent negative life events (RLE) occurring over the previous 12 months were measured by the List of Threatening Experiences (42) which sums life events related to four validated subscales (43) previously used in gene-by-environment interaction models (GxE) (44, 45). The four subscales include financial difficulties (RLE-financial), personal problems (RLE-personal), intimate relationship problems (RLE-relationship), and social network disturbances (RLE-social). Intercorrelations between the subscales have also been previously reported and were found to be either nonsignificant (between RLE-social and RLE-financial; and RLE-social and RLE-relationship), or significant but negligible weak (44).

Genetic Data

The extraction of the DNA from buccal mucosa cells was based on previously applied protocol (46). For the *5-HTTLPR* genotype characterization we used Illumina CoreExom PsychChip as described elsewhere (38). The quality control and imputation steps are based on our previous paper (38). All laboratory work was performed under the ISO 9001:2000 quality management requirements and was blinded with regard to phenotype.

Statistical Analysis

IBM SPSS Statistics 25 was used to calculate descriptive statistics and to run univariate general linear models solely for visualization purposes. Plink v1.90 (https://www.cog-genomics.org/plink2) was used to calculate Hardy-Weinberg equilibrium and minor allele frequency (MAF), and to build dominant, recessive and additive linear and logistic regression models with age, gender, and population as covariates in all models. Analyses were supported by scripts individually written in R 3.0.2 (R Core Team, 2013). In case of each outcome variable including lifetime SUIC, current suicidal ideation (BSI03-Thoughts of ending your life), current hopelessness (BSI18-Feeling hopeless about the future), and current thoughts of death (BSI21-Thoughts about death and dying), first the main effect of *5-HTTLPR* was tested, followed by interaction analyses. Interaction analyses included interaction with CHA in case of SUIC, and interaction with CHA, RLE, and subtypes of RLE including recent relationship problems (RLE-relationship), recent financial problems (RLE-financial), recent personal problems (RLE-personal), and recent social network problems (RLE-social) in case of BSI03, BSI18, and BSI21. All analyses were run according to additive, dominant, and recessive models. Nominal significance threshold was $p < 0.05$. To correct for multiple comparisons in analyses for each of the above outcome variables, Benjamini-Hochberg false discovery rate (FDR) Q-values (without robust method) were calculated. Results with a Q-value ≤ 0.05 were considered as significant. Raw data comprising the basis of the presented analyses are available at https://doi.org/10.6084/m9.

figshare.12214748.v1 (47). Only in order to facilitate visualization in the general linear models, RLE scores were divided into three categories as described previously (44, 45) as 0 event, 1 event, 2 or more events.

RESULTS

Descriptive Data

The descriptive data of our study population are shown in **Table 1**.

5-HTTLPR was in Hardy-Weinberg equilibrium in our total sample (p=0.8942). Minor allele frequency was 0.4271 for the short (s) allele.

Gene-environment correlations, as calculated in linear regression models for RLE and its subscales and for CHA, are shown in **Table 2**. *5-HTTLPR* genotype had no significant effect on CHA, RLE, or on individual recent life event subtypes (**Table 2**).

Investigation of the Main Effect of *5-HTTLPR* on Lifetime Suicide Attempts, Current Suicidal Ideation, and Suicide Risk Indicators

No main effect of *5-HTTLPR* was detectable on previous SUIC in additive (Q=0.7134), dominant (Q=0.7134), or recessive models (Q=0.7134) (**Table 3**). *5-HTTLPR* had a significant main effect on BSI03 Thoughts of ending your life in the dominant (Q=0.0344) model with presence of s allele associated with higher scores, but not in additive (Q=0.0669) or recessive (Q=0.8532) models (**Table 4**). No main effect of *5-HTTLPR* on other current markers of suicidal risk including BSI18 Feeling hopeless about the future (Q=0.4320,

TABLE 1 | Description of the study population.

Demographics				
Gender	Males: 723 (30.66%) Females: 1635 (69.33%)			
Age	Minimum	Maximum	Mean	SEM
	18	60	32.80	0.2190
Phenotypes				
Previous suicide attempts	No: 2074 (88%) Yes: 284 (12%)			
Current suicidal risk factors				
L1BSI03 (thoughts of ending your life)	0	4	0.32	0.0199
L1BSI18 (feeling hopeless about the future)	0	4	0.90	0.0295
L1BSI21 (thoughts of about death and dying)	0	4	0.62	0.0262
Environmental stressors				
Childhood adversities	0	16	3.29	0.0694
Recent Life Events	0	8	1.22	0.0266
RLE-relationship	0	2	0.14	0.0080
RLE-financial	0	3	0.21	0.0106
RLE-personal problems	0	3	0.36	0.0128
RLE-social	0	3	0.41	0.0133
Genotypes				
Ss		438 (18.58%)		
Sl		1138 (48.26%)		
Ll		782 (33.16%)		
MAF (minor allele frequency)		0.43 (s)		

BSI, Brief Symptom Inventory; RLE-relationship, intimate relationship problems; RLE-financial, financial difficulties; RLE-illness, Illness/injury; RLE-social, social network disturbances.

TABLE 2 | Main effect of *5-HTTLPR* on the occurrence of environmental stressors.

	ADD		**DOM**		**REC**	
	p	**FDR Q**	**P**	**FDR Q**	**p**	**FDR Q**
CHA	0.3402	0.4862	0.5502	0.5502	0.2885	0.5709
RLE whole	0.1044	0.4534	**0.0343**	0.2058	0.3660	0.5709
RLE-relationship	0.7481	0.7481	0.5257	0.5502	0.5371	0.6445
RLE-financial	0.2267	0.4534	0.0868	0.2160	0.6905	0.6905
RLE-personal problems	0.4052	0.4862	0.2098	0.3147	0.3806	0.5709
RLE-social	0.2076	0.4534	0.1080	0.2160	0.2128	0.5709

CHA, childhood adversities; RLE, recent life events; p values for linear regression models are shown with FDR Q correction for multiple testing. ***Bold*** *type denotes nominally significant (p < 0.05) values prior to correction.*

TABLE 3 | Main effect of *5-HTTLPR* and interaction with childhood adversities (CHA) on previous suicide attempt (SUIC).

5-HTTLPR	ADD				DOM				REC			
	OR	SE	P	FDR Q	OR	SE	P	FDR Q	OR	SE	P	FDR Q
Main effect	1.049	0.0926	0.6058	0.7134	1.068	0.1405	0.6392	0.7134	1.062	0.1649	0.7134	0.7134
Interaction with CHA	1.178	0.1086	0.1312	0.4812	1.261	0.165	0.1604	0.4812	1.236	0.1964	0.2802	0.5604

CHA, childhood adversities; ADD, additive model; DOM, dominant model; REC, recessive model.

TABLE 4 | Main effect of *5-HTTLPR* and interaction with childhood adversities (CHA) on current suicidal ideation (L1BSI03 Thoughts of ending your life).

5-HTTLPR	ADD				DOM				REC			
	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q
Main effect	0.07152	0.03127	0.02229	0.0669	0.1293	0.0468	**0.0057**	***0.0344***	0.0451	0.0568	0.4266	0.8532
Interaction with CHA	0.0025	0.0386	0.9457	0.9580	0.0030	0.0573	0.9580	0.9580	0.0067	0.0699	0.9234	0.9580

CHA, Childhood adversities; ADD, additive model; DOM, dominant model; REC, recessive model.
Bold *type denotes nominally significant (p < 0.05) values prior to correction;* ***bold italics*** *indicate significant p values surviving correction for multiple testing (p < 0.05, FDR Q < 0.05).*

Q=0.4320, Q=0.4792 for additive, dominant, and recessive models, respectively) (**Table 5**) or BSI21 Thoughts about death and dying (Q=0.1872, Q=0.4083, Q=0.1872 for additive, dominant, and recessive models, respectively) emerged in any of the models (**Table 6**).

Interaction Effect of *5-HTTLPR* and Childhood Adversities (CHA) on Lifetime Suicide Attempts, Current Suicidal Ideation, and Current Predictors of Suicide Risk

5-HTTLPR had no significant interaction effect with childhood adversities on previous SUIC in any of the models (Q=0.7134, Q=0.7134, Q=0.7134, in additive, dominant, and recessive models, respectively) (**Table 3**). Similarly, there was no significant *5-HTTLPR* x CHA interaction effect detectable on current suicidal ideation (BSI03 Thoughts of ending your life) (Q=0.9580, Q=0.9580, Q=0.9580 for additive, dominant, and recessive models, respectively) (**Table 4**); on current hopelessness (BSI18 Feeling hopeless about the future) (Q=0.9216, Q=0.9216, Q=0.9524 for additive, dominant, and recessive models, respectively) (**Table 5**); or on current thoughts of death (BSI21 Thoughts about death and dying) (Q=0.1872, Q=0.2675, Q=0.1872, for additive, dominant, and recessive models, respectively) (**Table 6**).

Interaction Effect of *5-HTTLPR* and Total Number of Recent Life Events (RLE) on Current Suicidal Ideation and Current Predictors of Suicide Risk

No interaction effect was observed with total number of recent life events in case of current suicidal ideation (BSI03 Thought of ending your life) (Q=0.7455, Q=0.6052, Q=0.3540, for additive, dominant, and recessive models, respectively) (**Table 7**), current hopelessness (BSI18) (Q=0.3992, Q=0.2160, Q=0.7817, for additive, dominant, and recessive models, respectively) (**Table 8**), or current thoughts about death or dying (BSI21) (Q=0.2690, Q=0.6124, Q=0.3981, for additive, dominant, and recessive models, respectively) (**Table 9**).

TABLE 5 | Main effect and interactions of *5-HTTLPR* with childhood adversities (CHA) on current hopelessness (L1BSI18 Feeling hopeless about the future).

5-HTTLPR	ADD				DOM				REC			
	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q
Main effect	0.0608	0.0374	0.1041	0.4320	0.0818	0.0560	0.1440	0.4320	0.0797	0.0678	0.2396	0.4792
Interaction with CHA	-0.0134	0.0455	0.7680	0.9216	-0.0248	0.0678	0.7148	0.9216	-0.0049	0.0822	0.9524	0.9524

CHA, Childhood adversities; ADD, additive model; DOM, dominant model; REC, recessive model.

TABLE 6 | Main effect and interactions of *5-HTTLPR* with childhood adversities (CHA) on current thoughts of death (L1BSI21 Thoughts about death and dying).

5-HTTLPR	ADD				DOM				REC			
	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q	Beta	SE	P	FDR Q
Main effect	0.0489	0.0313	0.1188	0.1872	0.0388	0.0469	0.4083	0.4083	0.1035	0.0567	0.0681	0.1872
Interaction with CHA	0.0633	0.0382	0.0978	0.1872	0.0694	0.0569	0.2229	0.2675	0.1062	0.0692	0.1248	0.1872

CHA, Childhood adversities; ADD, additive model; DOM, dominant model; REC, recessive model.

TABLE 7 | Main effect and interactions of *5-HTTLPR* with recent life events (RLE) and RLE subtypes on current suicidal ideation (L1BSI03 Thoughts of ending your life).

5-HTTLPR	ADD				DOM				REC			
	β	SE	P	FDR Q	β	SE	P	FDR Q	β	SE	P	FDR Q
Main effect	0.0715	0.0313	0.0223	0.1337	0.1293	0.0468	**0.0057**	***0.0218***	0.0451	0.0568	0.4266	0.6399
Interaction with RLE	-0.0136	0.0419	0.7455	0.7455	0.0409	0.0613	0.5043	0.6052	-0.1242	0.0794	0.118	0.3540
Interaction with RLE-relationship	0.0483	0.0281	*0.0862*	0.2160	0.1212	0.0451	**0.0073**	***0.0218***	0.0071	0.0518	0.8907	0.9128
Interaction with RLE-financial	-0.0415	0.0390	0.2875	0.4312	0.0032	0.0594	0.9577	0.9577	-0.1440	0.0714	**0.0439**	0.2631
Interaction with RLE-personal	0.0427	0.0891	0.6322	0.7455	0.0923	0.1341	0.4914	0.6052	0.0180	0.1638	0.9128	0.9128
Interaction with RLE-social	0.1829	0.1132	0.1063	0.2126	0.2612	0.1683	0.1207	0.2414	0.2270	0.2122	0.2848	0.5696

RLE-relationship, intimate relationship problems; RLE-financial, financial difficulties; RLE-personal, personal problems; RLE-social, social network disturbances; ADD, additive model; DOM, dominant model; REC, recessive model. ***Bold*** *type denotes nominally significant ($p < 0.05$) values prior to correction;* ***bold italics*** *indicate significant p values surviving correction for multiple testing ($p < 0.05$, FDR $Q < 0.05$).*

TABLE 8 | Main effect and interactions of *5-HTTLPR* with recent life events (RLE) and RLE subtypes on current hopelessness (L1BSI18 Feeling hopeless about the future).

5-HTTLPR	ADD				DOM				REC			
	β	SE	P	FDR Q	β	SE	P	FDR Q	β	SE	P	FDR Q
Main effect	0.0608	0.0374	0.1041	0.3992	0.0818	0.056	0.144	0.2160	0.0797	0.0678	0.2396	0.7188
Interaction with RLE	0.0634	0.0494	0.1996	0.3992	0.1084	0.0726	0.1357	0.2161	0.0467	0.0928	0.6147	0.7817
Interaction with RLE-relationship	0.04728	0.0336	0.1592	0.3992	0.0962	0.0525	0.0671	0.2162	0.0278	0.0616	0.6514	0.7817
Interaction with RLE-financial	-0.0174	0.0423	0.6814	0.6814	-0.0455	0.0630	0.4702	0.5642	0.0104	0.0774	0.8934	0.8934
Interaction with RLE-personal	-0.0482	0.0662	0.4668	0.5602	-0.1452	0.0949	0.126	0.2164	0.0712	0.1181	0.5467	0.7817
Interaction with RLE-social	0.0615	0.0729	0.3988	0.5602	0.0216	0.1134	0.8487	0.8487	0.1719	0.1318	0.1922	0.7188

RLE-relationship, intimate relationship problems; RLE-financial, financial difficulties; RLE-personal, personal problems; RLE-social, social network disturbances; ADD, additive model; DOM, dominant model; REC, recessive model.

TABLE 9 | Main effect and interactions of *5-HTTLPR* with recent life events (RLE) and RLE subtypes on current thoughts of death (L1BSI21 Thoughts about death and dying).

5-HTTLPR	ADD				DOM				REC			
	β	SE	P	FDR Q	β	SE	P	FDR Q	β	SE	P	FDR Q
Main effect	0.0489	0.0313	0.1188	0.2690	0.0388	0.0469	0.4083	0.6124	0.1035	0.057	0.0681	0.3981
Interaction with RLE	0.0625	0.0417	0.1345	0.2690	0.1075	0.0613	0.0795	0.6124	0.0494	0.0786	0.5297	0.3981
Interaction with RLE-relationship	0.0780	0.02755	**0.0047**	***0.0281***	0.1364	0.0431	**0.0016**	***0.0094***	0.0761	0.0506	0.1327	0.3981
Interaction with RLE-financial	0.01612	0.0352	0.6469	0.7539	0.0243	0.0524	0.6436	0.6436	0.0183	0.0644	0.7762	0.9202
Interaction with RLE-personal	0.0173	0.0550	0.7539	0.7539	-0.0428	0.0788	0.5875	0.6436	0.1200	0.0982	0.2219	0.4438
Interaction with RLE-social	0.0532	0.0604	0.3786	0.5679	0.1365	0.0938	0.1460	0.2920	-0.0110	0.1093	0.9202	0.9202

RLE-relationship, intimate relationship problems; RLE-financial, financial difficulties; RLE-personal, personal problems; RLE-social, social network disturbances; ADD, additive model; DOM, dominant model; REC, recessive model. ***Bold*** *type denotes nominally significant ($p < 0.05$) values prior to correction;* ***bold italics*** *indicate significant p values surviving correction for multiple testing ($p < 0.05$, FDR $Q < 0.05$).*

Interaction Effect of *5-HTTLPR* and Different Subtypes of Current Life Events on Current Suicidal Ideation and Other Current Predictors of Suicide Risk

Interaction analyses for distinct recent life event subtypes showed a strong significant effect on current suicidal ideation (BSI03 Thoughts of ending your life) in case of recent intimate relationship problems (RLE-relationship) in the dominant (Q=0.0218) (**Figure 1**), but no effect in the additive (Q=0.2160 or recessive models (Q=0.9128). No significant interaction effect for *5-HTTLPR* with other recent life event subtypes, such as recent financial hardships (RLE-financial) (Q=0.4312, Q=0.9577, Q=0.2631 for additive, dominant, and recessive models respectively); recent personal problems (RLE-personal) (Q=0.7455, Q=0.6052, Q=0.9128 for additive, dominant, and recessive models respectively); or recent social network problems (RLE-social) (Q=0.2126, Q=0.2414, Q=0.5696 for additive, dominant, and recessive models respectively) emerged in any models (**Table 7**).

In the case of current hopelessness (BSI18 Feeling hopeless about the future), no significant interaction effect emerged with any types of recent life events in any models such as RLE-relationship (Q=0.39912, Q=0.2162, Q=0.7817 for additive,

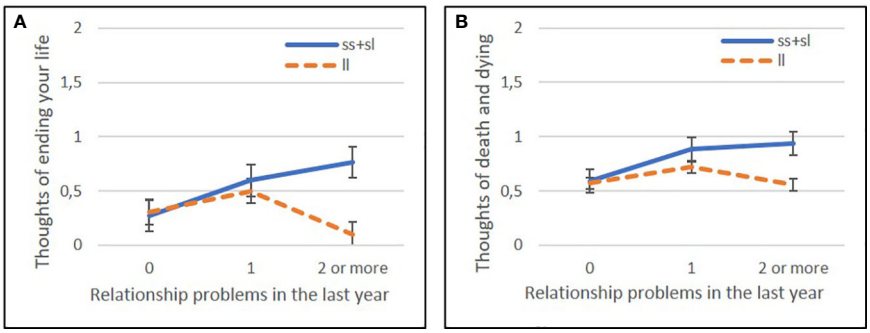

FIGURE 1 | Significant effect of *5-HTTLPR* genotype in interaction with recent life events related to relationship problems in the past year (RLEC-relationship) on current suicidal ideation and thoughts about death and dying in the dominant model (ss+sl vs ll genotype). Recent life events are categorized as 0 (no recent life events reported), 1 (1 life event reported), and 2 (2 or more life events reported in the last year). Mean ± SEM is displayed. Linear regression indicated a significant interaction between *5-HTTLPR* genotype and recent life events related to relationship problems (RLE-relationship) on current suicidal ideation (BSI03 Thoughts of ending your life) (Q=0.0218) **(A)** and on current thoughts of death (BSI21 Thoughts about death or dying) (Q=0.0094) **(B)** in the dominant model. Presence of the s allele is associated with increasing severity of suicidal ideation and thoughts about death with increasing number of relationship problem experiences in the previous year.

dominant, and recessive models respectively); RLE-financial (Q=0.6814, Q=0.5462, Q=0.8934 for additive, dominant, and recessive models respectively); RLE-personal problems (Q=0.5602, Q=0.2164, Q=0.7817 for additive, dominant, and recessive models respectively); or RLE-social (Q=0.5602, Q=0.8487, Q=0.7188 for additive, dominant, and recessive models respectively) (**Table 8**).

In the case of thoughts about death and dying (BSI21) a strong significant effect between *5-HTTLPR* and recent relationship problems (RLE-relationship) was found in the additive (Q=0.0281) and dominant (Q=0.0094) (**Figure 1**) but not in recessive models (Q=0.3981). In case of the other three recent life event subtypes, that is recent financial hardships (RLE-financial) (Q=0.7539, Q=0.6436, Q=0.9202 for additive, dominant, and recessive models respectively); recent personal problems (RLE-Personal) (Q=0.7539, Q=0.6436, Q=0.4438 for additive, dominant, and recessive models respectively); or recent social network problems (RLE-social) (Q=0.5679, Q=0.2920, Q=0.9202 for additive, dominant, and recessive models respectively) no significant interaction effect emerged in any models (**Table 9**).

The investigated effects including the significant results are shown in **Figure 2**.

DISCUSSION

Our study focused on the effect of *5-HTTLPR* on lifetime suicide attempts and current suicidal ideation and other predictors of current suicidal risk including hopelessness and thoughts of death, in interaction with childhood adverse experiences and distinct types of recent negative life events in a large general population sample. We found that *5-HTTLPR* genotype did not influence lifetime suicide attempts, but had a significant effect on current suicidal ideation, with no effect on current hopelessness or thoughts of death. In our present study, childhood adversities did not interact with *5-HTTLPR* either on lifetime suicide attempts, current suicidal ideation, or any current predictors of suicide risk. Recent life events in total also did not interact with *5-HTTLPR* on current suicidal ideation or other predictors of current suicide risk. However, when subtypes of recent stress were considered separately, *5-HTTLPR* showed a strong interaction with intimate relationship problems but not with other recent stressors on current suicidal ideation and on current thoughts about death or dying. In all cases, presence of the s allele (ss and sl genotypes) was associated with increased scores. No other types of recent life events, such us financial hardships, personal problems, or social network difficulties interacted with *5-HTTLPR* on current suicidal ideation or other predictors. Furthermore, no significant effect of *5-HTTLPR* or an interaction with early childhood adversities or recent negative life events emerged in case of hopelessness. Thus, our results suggest that *5-HTTLPR* is involved in current suicidal ideation directly and in interaction with current relationship problems.

Presence of the s Allele of *5-HTTLPR* Is Not Associated With Increased Risk of Lifetime Suicide Attempts, but Is Associated With Current Suicidal Ideation

5-HTTLPR emerged as a potential genetic marker associated with suicidal behavior in part because of its association with several potentially related neural, clinical, and personality characteristics including hippocampal volume (48), amygdala reactivity (49, 50), personality traits such as neuroticism (24), anxiety (21), affective temperaments (23), aggression (25), and a range of psychiatric disorders beyond depression including anxiety disorders, substance use disorders, ADHD, autism, eating disorders, and psychosomatic disorders suggesting that *5-HTTLPR* mediates a nonspecific vulnerability for mental and behavioral disturbances, and specifically plays a role in modulating the effects of environmental influences in the development of mental problems (51). Following a number of controversial results from individual studies, meta-analyses of *5-HTTLPR* in suicidal behavior have been carried out yielding

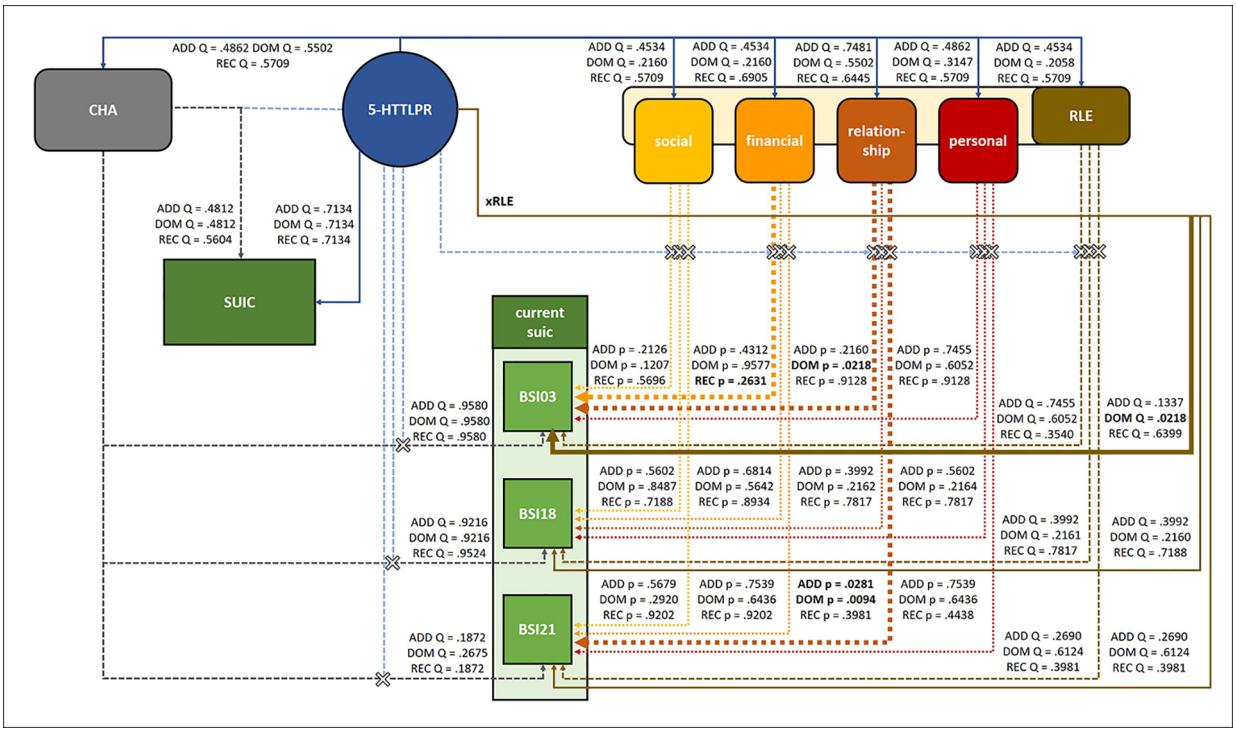

FIGURE 2 | Main effects and interactions of *5-HTTLPR* with childhood adversities (CHA), recent life events (RLE) and subtypes of recent life events on lifetime suicide attempts (SUIC), current suicidal ideation (BSI03 Thoughts of ending your life), current hopelessness (BSI18 Feeling hopeless about the future), and current thoughts of death (BSI21 Thoughts about death and dying). Of the main effect and interaction effects investigated in the present study, *5-HTTLPR* had a signifcant main effect on current suicidal ideation (BSI03 Thoughts of ending your life) in the dominant model, and significantly interacted with recent relationship problems on current suicidal ideation (BSI03 Thoughts of ending your life) in the dominant and on current thoughts about death (BSI21 Thoughts about death or dying) in the dominant and additive models. In all cases, presence of the short allele was associated with higher scores. Solid lines indicate main effects, dashed lines with "X" indicate interaction effects; significant effects are indicated by bold lines and significant Q values are shown in bold type. CHA, childhood adversities; SUIC, lifetime suicide attempts; RLE, recent life events; social, recent social network stressors; financial, recent financial hardships; relationship, intimate relationship problems; personal, recent personal problems; current suic, current suicidal risk markers; BSI03, Thoughts of ending your life; BSI18, Feeling hopeless about the future; BSI21, Thoughts about death and dying.

equally contradicting results, with no results reported in some (52), but positive findings in other studies (52–55). The most recent meta-analysis including 45 studies did not find a significant association in the whole sample possibly due to large clinical and sociodemographic differences between the individual studies, however, a positive association was reported between the s allele and increased risk of violent suicidal behavior among substance abusers (56). Our present findings which failed to identify an effect for *5-HTTLPR* on previous suicide attempts but show an association with current suicidal ideation reflects the contradictory nature of findings concerning the involvement of this variant in suicidal behavior. Our results specifically point to the possible heterogeneity underpinning different manifestations of suicidal behavior, especially considering that in case of predictors of current suicidal risk, only suicidal ideation (Thoughts of ending your life) but not hopelessness or thoughts about death or dying showed association with *5-HTTLPR*. These latter findings also indicate that distinct genetic factors and divergent pathways may be involved in subtle differences between multiple processes contributing to the evolving risk of suicide, and draw attention to the importance of carefully differentiating between risk factors and risk phenotypes in studies concerning the genetic underpinnings of suicidal behavior.

5-HTTLPR Does Not Interact With Childhood Adversities in Influencing Lifetime Suicide Attempts, Current Suicidal Ideation, Thoughts About Death, or Hopelessness

In the initial report concerning the role of the *5-HTTLPR* s allele in increasing sensitivity towards recent stressors and thus increasing the risk of depression, as well as suicidal ideation and attempts, in the face of stress exposure (22), a significant interaction between early childhood trauma during the first 10 years and *5-HTTLPR* genotype in predicting depression (but not suicide) has also been shown. Later it has been hypothesized that *5-HTTLPR* mainly mediates effects of early childhood stressors impacting neurodevelopment, leading to altered brain

functioning in regions involved in mood and emotion regulation and consequentially maladaptive cognitive and behavioral patterns contributing to the manifestation of depression and risk of suicide (57, 58). While a few studies specifically looked at the interactions between early childhood stressors and *5-HTTLPR* on risk of suicidal behaviors, results have been conflicting. A significant effect of *5-HTTLPR* was found in suicide attempters reporting childhood physical and sexual but not emotional abuse in depressed patients (59), while in another study in substance abusers, association of suicide attempts with an interaction between *5-HTTLPR* genotype and early childhood trauma was reported (58). Interaction between *5-HTTLPR* and early trauma on suicidal behavior has also been found in another study in major depressive patients, however, in this study the ll genotype was found to increase risk (60). Furthermore, specifically an association with suicidal ideation and interaction between *5-HTTLPR* and early maltreatment was reported in children (61). Our results contradict these findings in reporting no interaction effect between *5-HTTLPR* and childhood adversities on either lifetime suicide attempts or current suicidal ideation, hopelessness or thoughts of death, which may, at least in part, be due to different study samples.

5-HTTLPR s Allele Interacts With Recent Relationship Problems but Not Other Types of Life Events on Suicidal Ideation and Thoughts of Death

The initial results on the role of the *5-HTTLPR* short allele in increasing sensitivity towards recent stressors and its association with increased depression prevalence in the face of stress exposure (22) were followed by a large number of contradictory individual studies and meta-analyses, and the latest and largest such meta-analysis reported no significant effects (62). However, fewer studies aimed at replicating the results of Caspi and colleagues in the same study (22) reporting increased suicidal ideation and attempts in *5-HTTLPR* s allele carriers exposed to more severe recent stress. An interaction between recent stressors and *5-HTTLPR* was demonstrated in depressed patients on suicide attempts (63) with some other studies reporting negative results for suicidal ideation (64). A recent longitudinal study suggested a sex-dependent moderating effect of *5-HTTLPR* genotype of stressful life events in suicidal ideation with a strong but nonsignificant trend in female s carriers in *post hoc* tests (65). In another longitudinal study in adolescents a significant interaction between family support and *5-HTTLPR* genotype on suicidal behavior was found in boys together with a marginally significant effect in girls predicting a higher risk of suicidal attempts in s carriers with poorer social support (66). One important aspect of this study was that *5-HTTLPR* s allele increased sensitivity not only to negative environmental effects but also towards high quality positive environmental conditions, in line with the differential susceptibility theory (67). A similar study but in an elderly population reported a significant interaction between both stressful life events and deficits of social support and *5-HTTLPR* genotype on baseline prevalence and 2-year incidence of suicidal ideation (68). Finally, in a community sample of young people a significant association between non-suicidal self-injury and the interaction between s allele and interpersonal stress was reported (69).

In contrast to some of the above studies, we found no interaction between recent stress in general and *5-HTTLPR* on either suicidal ideation (thoughts of ending life), or other suicide risk factors such as hopelessness or thoughts of death. A significant interaction effect, however, emerged, in case of one specific type of recent life event. Namely, we saw a significant interaction effect with recent relationship difficulties in case of suicidal ideation and thought of death, where presence of the s allele was associated with more severe suicidal ideation when exposed to an increasing number of relationship problems.

Thus, our results implicate the involvement of *5-HTTLPR* in increasing sensitivity towards certain types recent stressful life events and impacting suicidal ideation and risk. In this sense, suicidal ideation could be regarded as a measure of the subjective impact of the difficulties which is modulated by serotonin. More importantly, our findings also support our previous hypothesis that the effect of distinct types of stressors are mediated *via* different neurobiological pathways and may contribute to the appearance of different phenotypes or clinical phenomena (44, 45, 70, 71). Previously, we reported a significant interaction with recent financial stress but not other types of life events on depressive symptoms in case of the *5-HTTLPR* (44), while in a younger subsample the s allele showed an opposite effect and was protective in case of recent social network stressors (70). In a similar model, but in case of variants in the *CNR1* gene encoding the endocannabinoid 1 receptor and the *GABRA6* gene encoding the alpha 6 subunit of the GABA-A receptor we found that not only the certain genes mediate only certain types of life events which is different in case of different genes, but also that in case of the same genetic variant, the affected outcome phenotype (in our study depression vs anxiety) may also be different in case of different types of recent stress (45). Namely, we found that *CNR1* rs7766029 in interaction with recent financial difficulties (RLE-financial) increased both depression and anxiety scores, however, *GABRA6* rs3219151 interacted with social network stressors (RLE-social) on anxiety scores and with recent personal problems (RLE-personal) on depression scores (45). Here, we extend our previous results on the *5-HTTLPR* s allele specifically mediating the effect of financial hardships on depression, with our novel findings that when exposed to recent relationship difficulties presence of the s allele leads to increased suicidal ideation and thoughts about death.

Altogether, our present results can be interpreted as a contribution to previous studies postulating a role for 5-HTTLR in suicidal behavior and risk, specifying that the existing effect may be obscured by the fact that *5-HTTLPR* has an impact only on certain phenotypes of suicidal behavior and mediates the effects of only certain types of stressors.

5-HTTLPR: No Effect on Hopelessness, an Independent Factor of Suicide Risk

Finally, we must mention that *5-HTTLPR* showed no effect either directly or in interaction with either childhood or current

stressors on hopelessness, which has long been established as an independent cognitive risk factor and predictor for suicide (72, 73) and specifically for suicidal ideation (74). This lack of association even as a main effect on the one hand contradicts a previous report of our group in an independent sample reporting an association between *5-HTTLPR* and hopelessness as measured by the Beck Hopelessness Scale (24), and a subsequent study where hopelessness was also associated with *5-HTTLPR* in men with cardiovascular disease (75), while on the other hand our present findings suggest that *5-HTTLPR* is involved in suicidal behavior and specifically ideation not *via* hopelessness but other processes or trait or state markers, such as for example increased aggression.

Limitations

There are several limitations of our study which must be mentioned. First, our assessment concerning recent life events and current suicidal ideation was cross-sectional, thus we could not evaluate the longitudinal effects of recent life events on suicidal behavior. Therefore, it is possible that suicidal ideation or behavior occurring in a longer time following very recent life events could not be identified in our study. Also, we did not determine the timing of recent life events relative to current suicidal ideation. Second, RLE and CHA were recorded retrospectively and are thus subject to recall bias. Third, we only subcategorized recent life events into four, although validated, categories, it is therefore possible that some categories should be further refined. Although correlations between different categories of life events reported in our previous studies were weak, it is also possible that in isolated cases these life events are not independent of each other, which may influence the results. Fourth, all our measures, including current suicide risk markers, previous suicide attempts as well as childhood adversities and current life events are based on self-report. Fifth, our study sample is a general, non-epidemiological and non-representative population sample based on volunteers, therefore may be subject to sampling bias. Sixth, we used two geographically different subsamples in our study, and ancestry was not assessed in the present study using molecular methods such as whole-genome SNP genotyping. Although to consider this, we used population as a covariate in all our statistical analyses, there may exist subtle genetic differences both between the two subsamples and also within each sample due to population stratification which may lead to spurious effects. Finally, we would like to emphasize the exploratory nature of our analyses and urge replication of the results presented here in other cohorts.

CONCLUSION

In summary, our present study supports the involvement of *5-HTTLPR* in suicidal behavior following previous conflicting results. Our findings show that *5-HTTLPR* is involved in only certain aspects of the suicide spectrum, namely suicidal ideation but not previous suicide attempts, and that it interacts with only with certain types of recent stress but not childhood adversities. This suggests that existing effects may be obscured in several studies not differentiating carefully between suicidal phenotypes and stressor types. Furthermore, our results also support our previous findings that specific genes and variants, such as the *5-HTTLPR* may only mediate the effect of certain types of stressors and may lead to the emergence of different phenotypes depending on the type of stressor. Thus, our results emphasize the importance of differentiating between types of stress in gene-environment studies to avoid obscuring existing associations, and also suggest that future sophisticated models of predicting and preventing suicide should include highly specific gene-environment interaction pathways. Further studies should focus on the prospective association between distinct types of current stressors and suicide attempts and completed suicides in relation to *5-HTTLPR* genotype, and should also attempt to investigate whether the current findings can be employed in preventive approaches to decrease suicidal ideation in short allele carriers after exposed to distinct types of stress.

DATA AVAILABILITY STATEMENT

Raw data comprising the basis of the presented analyses and supporting the conclusions of this article are available at https://doi.org/10.6084/m9.figshare.12214748.v1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Scientific and Research Ethical Review Board of the Medical Research Council. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG, GB, and GJ designed and conceptualized the study and collected the data. SK, DT, NE, ZG, and SS and participated in statistical analyses. All authors participated in interpreting the data. XG, JB, and DT wrote the first draft of the manuscript. DT and SS created figures. All authors participated in developing further and final versions of manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: BD has recently received fees for scientific advice from Autifony and he has share options in P1vital. IA has received consultancy fees from Servier, Alkermes, Lundbeck/Otsuka, and Janssen, an honorarium for speaking from Lundbeck and grant support from Servier and AstraZeneca.

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frontiers in Psychiatry

ORIGINAL RESEARCH
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Suicidal Ideation in Newly-Diagnosed Chinese Cancer Patients

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Objective: Suicide is one of the main reasons cited behind the death rate of cancer, and suicidal ideation (SI) is the first step toward it. This study aimed to investigate the prevalence and associates of suicidal ideation in newly-diagnosed Chinese cancer patients.

Methods: This multicenter study was conducted from January 2018 to September 2019. Eligible participants were asked to complete a Case Record Form (CRF), the Patient Health Questionnaire (PHQ-9), General Anxiety Disorder Questionnaire (GAD-7), Fear of Cancer Recurrence Questionnaire (FCRQ-7), and McGill Pain Questionnaire-Visual Analogue Scale (MPQ-VAS). Univariate analyses and multivariate logistic regression analyses were conducted for assessment.

Results: Out of 603 patients, 91 (15.1%, 95%CI: 12.23%–17.96%) reported suicidal ideation in the last 2 weeks. Physical comorbidities (OR=1.808, P=0.039), childhood adversity experience (OR=5.999, P=0.001), cancer pain (OR=1.828, P=0.047), depression (OR=2.811, P=0.013), and anxiety (OR=6.532, P<0.001) were significantly associated with suicidal ideation. It was also found that patients who regularly exercised were less likely to report suicidal thoughts (OR=0.172, P=0.007).

Conclusion: Physical comorbidities, body ache, and mood disturbances are possible risk factors for suicidal ideation that warrant further attention in clinical practice. Preventive measures, such as systematic screening and arrangement for regular check-ups, could be beneficial to lower the risk of suicide.

Keywords: cancer, China, factors, prevalence, suicidal ideation

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INTRODUCTION

Emotional distress is considered as the sixth vital sign targeting a cancer patient's well-being along with signs of respiration, body temperature, blood pressure, heart rate, and pain (1). With the growing awareness and pivotal attention being paid to mental health, a number of researchers in the field of oncology have focused on cancer patients' psychological wellbeing. These have then, subsequently reported a high prevalence of depression, anxiety, and suicidality as a part of it (2–6).

Suicide is one of the main reasons subscribed behind the death rate affecting cancer. Spoletini et al. found a higher risk of suicide in cancer patients compared to the general population (7), and Anguiano et al. reported that there is a "suicide peak" in the first year after initial cancer diagnosis (8). Newly-diagnosed cancer patients have unique biological and psychological needs. Therefore, more efforts should be made to provide better insights into this population's well-being. It is of significance to identify the pattern for suicidal ideation and its correlates in this population to further help clinicians adopt a more appropriate strategy and interventions to reduce the risk of suicide.

Suicidal ideation is commonly recognized as the first step, thought, and plan toward suicide (9, 10). A recent review reported a wider range of percentages between 0.8 and 71.4% of suicidal ideation in cancer patients, compared to a range of 1.1–19.8% in the general population (11). Another review, involving 44 relevant studies indicated that the prevalence of suicidal ideation ranged from 0.8 to 46.2% among cancer patients; with lowest figures being reported by an American study while the highest percentage was reported in Chinese samples (12).

There have been a variety of sociodemographic, clinical, and psychological variables found to be related to suicidal ideation. For example, advanced cancer stage, impaired physical functioning, cancer pain, depression, anxiety, hopelessness, existential distress, and limited social support were consistently proven to be risk factors for suicidal ideation in cancer patients (11). Gender, age, race, and treatment type were also reported to be associated with suicidal ideation, however, the findings have been often conflictive (12). A recent Chinese study reported that depression, anxiety, metastatic cancer, poor performance status, surgery, and palliative care were significantly associated with suicidal ideation, whereas, compared to demographic or clinical factors, psychological characteristics were more vital in predicting patient's suicidal ideation (13).

It has been shown that suicidal ideation could lead to suicidal behavior and a completed suicide as one of the factors contributing to the high mortality rate behind cancer (14). However, most existing studies on suicidal ideation have been performed in cancer samples with mixed-time since diagnosis. To the best of our knowledge, evidence-based assessments targeting newly-diagnosed cancer patients are scarce. Moreover, the first few months after a confirmed cancer diagnosis is a critical time-window for patients because of the changes in both their physiology and psychological well-being. Therefore, before developing preventive strategies and alleviating the negative outcomes of suicidal ideation for this vulnerable population, it is important to understand its epidemiology and its correlates. Thus, the current study aims to provide an evaluation of the prevalence and correlates of suicidal ideation among newly-diagnosed (time lapse since diagnosis ≤ 6 months) Chinese cancer patients.

METHODS

Participants and Study Procedure

This is a multicenter, cross-sectional study conducted in southern China. A consecutive sampling method was utilized to recruit patients from Guangdong Provincial People's Hospital (Cancer Centre), Guangzhou Women and Children's Medical Centre (Breast Cancer Centre), and Southern Medical University Nanfang Hospital (Department of Radiotherapy). Data was collected from January 2018 till September 2019. To be included in the study, participants needed to: 1) be above 18 years old; 2) have had a cancer diagnosis within 6 months; 3) be able to read and write Mandarin and/or Cantonese; and 4) provide written informed consent. Simultaneously, participants were excluded if they had disturbance of consciousness, or were blind or deaf.

All patients were approached in the waiting areas of these above mentioned facilities by trained research nurses who attempted to explain the study's aim and procedure. For those then found eligible, and could provide written informed consent form; a face-to-face interview was conducted by a senior physician who was responsible for on-site recruitment and assessment. Participants were assured that the total interview time would not exceed 10 min and that they would not have the appointments delayed with their oncologist either. Participants were asked to complete a personal information sheet and a set of standardized questionnaires for assessment. All participants were assured that their participation would be kept confidential, and they could withdraw participation at any given time. The recruitment process was supervised by a consultant oncologist (HMW). Ethical approvals were obtained from participating hospitals (ref No: NFEC-2018-038).

Measurements

Demographic and Clinical Data

A Case Record Form (CRF) was designed for this study to collect generic demographic and clinical information, such as gender, age, education level, marital status, employment status, personal monthly income, treatment/family history, physical comorbidities, lifestyle (smoking and exercise), and previous experience. Experience of adversity in childhood and experience of severe illness were assessed by two yes/no questions (15): 1) Have you ever experienced any childhood adversity, such as sexual abuse, bullying, traffic accident, or natural calamities? 2) Have you ever experienced any severe illness during childhood, such as childhood cancer, or traumatic injury? Consequently, stress was assessed by a single-item question (16): what is your current stress level? For which four responses were provided, namely: none, mild, moderate, and high level.

Depressive Symptoms

Patient's depressive symptoms were assessed by the Patient Health Questionnaire (PHQ). It is a nine-item self-report measure and is commonly used in medical settings. Its response anchors a range from 0 to 3, and a total score of 5 or more indicates a prevalence of depressive symptoms (17). The Chinese version of PHQ-9 shows good psychometric properties, of which the Cronbach's alpha is 0.89 (18).

Anxiety Symptoms

The General Anxiety Disorder Questionnaire (GAD) is a seven-item self-report scale used to measure an individual's anxiety

symptoms. Response options available are rated from 0 to 3; and a total score of 5 or more indicates a dominance of anxiety symptoms (19). The GAD-7 has been translated and well-validated in Chinese language. The Chinese version of GAD-7 has an internal consistency of 0.91 (20).

Fear of Cancer Recurrence

The seven-item Fear of Cancer Recurrence Questionnaire (FCRQ-7) is used to assess patient's recurrence fears and has been used with patients riddled with breast, colorectal, head, and neck cancer in a variety of clinical centers in the UK (21). The reliability of this questionnaire is good with an internal consistency of 0.92 (95%CI: 0.90, 0.94) with evidence for validity (22). The statistical 60th (score=17) and 90th (score=27) percentiles are regarded as levels for "moderate" and "high" reports of patient's FCR respectively. The Chinese version of FCRQ-7 shows good psychometric properties, of which the Cronbach's alpha is 0.87 (23).

Cancer Pain and Suicidal Ideation

The McGill Pain Questionnaire-Visual Analogue Scale (MPQ-VAS) is one of the most widely used tests for the measurement of pain, and it has been validated into the Chinese language in 2013 (24). The score of VAS ranges from 0 (no pain) to 100 (worst possible pain) (25). In the current study, participants were first asked: 1) Are you currently in any pain from cancer? (yes/no question), then a VAS was provided to further identify the exact pain severity thus reported. Patient's suicidal ideation was assessed by a standardized yes/no question adapted from Kessler's question (26, 27): Have you ever thought about killing yourself in the last 2 weeks? For those who answered "yes" to this question, they were classified under "Current Suicidality".

Statistical Analyses

All data analyses were performed by SPSS Version 24.0. Descriptive statistics were utilized to characterize all study variables. Normal distribution assumption was checked by one-sample Kolmogorov-Smirnov test. Sociodemographic and clinical variables between the two groups were investigated using independent sample t-test (for normally distributed continuous data), chi-square test (for categorical variables), or Mann-Whitney U test (for non-normally distributed continuous data). All variables that were found to be significant in the univariate analyses were further tested by multivariate logistic regression with "enter" method. Suicidal ideation was allocated as the dependent variable, while those with significant group differences in the above univariate analyses were entered as independent variables. Significance was set at 0.05, with two-tailed tests.

RESULTS

Patient Characteristics

A total of 603 patients agreed to participate, and completed the survey. The mean age of patients was 47.72 (SD=11.49) years. Simultaneously, around 90% (n=543) of the participants were female, and 78.5% (N=473) of the participants were specifically diagnosed with breast cancer. Most of the patients were married (85.2%), with low education level (high school or below=67.7%), had previously received surgery (92.9%), chemotherapy (86.1%), and radiation treatment (87.4%). Of the 603 patients, 91 (15.1%, 95%CI: 12.23%–17.96%) reported suicidal ideation in the last 2 weeks.

Univariate Analyses

In univariate analyses, suicidal ideation was significantly associated with patient's age (P=0.022), marital status (P=0.007), radiotherapy (P=0.025), cancer pain (P=0.038), physical co-morbidity (P=0.038), exercise (P<0.001), childhood adversity experience (P=0.001), and current stress levels (P<0.001). Those who were younger, single, had received prior radiation treatment, in current cancer pain, with antecedent childhood adversity experience, other physical co-morbidities and under high stress levels were more likely to have suicidal ideation than their counterparts. Depression, anxiety, and fear of cancer recurrence symptoms were also significantly associated with suicidal ideation (P all <0.001). Controversially, patients who kept routine exercise plans (more than 60 min/d) were less likely to report suicidal ideation than those without physical exercise (P<0.001). Patient's demographic, clinical, as well as psychological characteristics are presented in **Table 1**.

Multivariate Logistic Regression Analyses

Multivariate logistic regression analyses confirmed that physical comorbidities (OR=1.808, 95%CI: 1.030–3.172, P=0.039), childhood adversity experience (OR=5.999, 95%CI: 2.095–17.177, P=0.001), cancer pain (OR=1.828, 95%CI: 1.009–3.310, P=0.047), depression (OR=2.811, 95%CI: 1.238–6.382, P=0.013), and anxiety (OR=6.532, 95%CI: 2.911–14.657, P<0.001) were significantly associated with a patient's suicidal ideation. Additionally, patients who had routine exercise plans were less likely to report suicidal ideation (OR=0.172, 95% CI=0.048–0.619, P=0.007). Age, marital status, radiotherapy, stress level, and fear of cancer recurrence were no longer significant in multivariate logistic regression analyses (see **Table 2**).

DISCUSSION

For newly-diagnosed cancer patients, the first few succeeding months after diagnosis could be overwhelming, scary, and lonely. However, there is a paucity of evidence regarding the unmet mental health needs of newly-diagnosed cancer patients. To the best of our knowledge, this is the first study that examines the prevalence and correlates of suicidal ideation among newly-diagnosed cancer patients in China. Suicidal ideation in this current study was reported at an occurrence of 15.1%, which was similar to some; but not all studies. Zhong's study with 517 Chinese cancer inpatients showed that 15.3% of the patients reported suicidal ideation (13); while Tang's investigation

TABLE 1 | Factors associated with suicidal ideation (N=603).

Variable	Suicidal Ideation					
	Total (%)	No (%)	Yes (%)	X^2/Z	df	P
Gender						
Male	60 (10.0)	51 (85.0)	9 (15.0)	0.001	1	0.983
Female	543 (90.0)	461 (84.9)	82 (15.1)			
Cancer site						
Breast	473 (78.4)	408 (86.3)	65 (13.7)	3.286	3	0.350
Lung	65 (10.8)	53 (81.5)	12 (18.5)			
Colorectal	49 (8.1)	39 (79.6)	10 (20.4)			
Nasopharynx	16 (2.7)	12 (75.0)	4 (25.0)			
Cancer stage						
Stage 1	43 (7.1)	38 (88.4)	5 (11.6)	2.871	3	0.412
Stage 2	264 (43.8)	225 (85.2)	39 (14.8)			
Stage 3	243 (40.3)	208 (85.6)	35 (14.4)			
Stage 4	53 (8.8)	41 (77.4)	12 (22.6)			
Marital status						
Single	47 (7.8)	32 (68.1)	15 (31.9)	12.137	3	**0.007**
Married	514 (85.2)	442 (86.0)	72 (14.0)			
Divorced	25 (4.1)	24 (96.0)	1 (4.0)			
Widowed	17 (2.8)	14 (82.4)	3 (17.6)			
Education level						
High School or below	408 (67.7)	350 (85.8)	58 (14.2)	1.297	2	0.523
Undergraduate	173 (28.7)	145 (83.8)	28 (16.2)			
Postgraduate or above	22 (3.6)	17 (77.3)	5 (22.7)			
Living condition						
Living Alone	27 (4.5)	23 (85.2)	4 (14.8)	0.093	2	0.955
Living with Families	560 (92.9)	475 (84.8)	85 (15.2)			
Living with Friends	16 (2.7)	14 (87.5)	2 (12.5)			
Employment						
Full Time	236 (39.1)	204 (86.4)	32 (13.6)	2.563	3	0.464
Part Time	36 (6.0)	30 (83.3)	6 (16.7)			
Unemployment	166 (27.5)	135 (81.3)	31 (18.7)			
Retired	165 (27.4)	143 (86.7)	22 (13.3)			
Monthly salary (Yuan)						
<3,000	260 (43.1)	216 (83.1)	44 (16.9)	3.181	3	0.365
3,000–5,000	166 (27.5)	143 (86.1)	23 (13.9)			
5,001–10,000	125 (20.7)	105 (84.0)	20 (16.0)			
>10,000	52 (8.6)	48 (92.3)	4 (7.7)			
Surgery						
No	43 (7.1)	36 (83.7)	7 (16.3)	0.051	1	0.821
Yes	560 (92.9)	476 (85.0)	84 (15.0)			
Chemotherapy						
No	84 (13.9)	70 (83.3)	14 (16.7)	0.189	1	0.664
Yes	519 (86.1)	442 (85.2)	77 (14.8)			
Radiotherapy						
No	76 (12.6)	58 (76.3)	18 (23.7)	5.011	1	**0.025**
Yes	527 (87.4)	454 (86.1)	73 (13.9)			
Family cancer history						
None	443 (73.5)	383 (86.5)	60 (13.5)	3.119	1	0.077
Yes	160 (26.5)	129 (80.6)	31 (19.4)			
Physical comorbidity						
None	383 (63.5)	334 (87.2)	49 (12.8)	4.324	1	**0.038**
Yes	220 (36.5)	178 (80.9)	42 (19.1)			
Current smoker						
No	575 (95.4)	489 (85.0)	86 (15.0)	–	-[a]	0.596
Yes	28 (4.6)	23 (82.1)	5 (17.9)			
Daily exercise time						
None	67 (11.1)	47 (70.1)	20 (29.9)	17.509	2	**<0.001**
<60 min	458 (76.0)	391 (85.4)	67 (14.6)			
>60 min	78 (12.9)	74 (94.9)	4 (5.1)			
Childhood adversity exp						
None	573 (95.0)	494 (86.2)	79 (13.8)	–	-a	**0.001**
Yes	30 (5.0)	18 (60.0)	12 (40.0)			

(Continued)

TABLE 1 | Continued

Variable	Suicidal Ideation					
	Total (%)	**No (%)**	**Yes (%)**	**X^2/Z**	**df**	**P**
Childhood severe illness exp						
None	550 (91.2)	468 (85.1)	82 (14.9)	0.162	1	0.687
Yes	53 (8.8)	44 (83.0)	9 (17.0)			
Current stress level						
None	186 (30.8)	173 (93.0)	13 (7.0)	24.997	3	**<0.001**
Mild	238 (39.5)	199 (83.6)	39 (16.4)			
Moderate	134 (22.2)	111 (82.8)	23 (17.2)			
High	45 (7.5)	29 (64.4)	16 (35.6)			
	M (SD)	**M (SD)**	**M (SD)**	**T/Z**	**df**	***P***
Age (years)	47.72 (11.49)	48.18 (11.07)	45.19 (13.44)	2.294	601	**0.022**
Cancer pain (VAS score)	23.55 (17.03)	22.95 (16.67)	26.92 (18.66)	–2.072	- [b]	**0.038**
Depression (PHQ score)	4.97 (4.80)	3.93 (3.61)	10.81 (6.27)	–10.306	- [b]	**<0.001**
Anxiety (GAD score)	3.76 (4.24)	2.89 (3.47)	8.63 (4.82)	–10.711	- [b]	**<0.001**
Fear of recurrence (FCR score)	19.85 (6.38)	19.07 (6.03)	24.22 (6.56)	–7.408	601	**<0.001**

in bold: P<0.05; a: Fisher's exact test; b: Mann-Whitney U test.

Exp, experience; VAS, McGill Pain Questionnaire-Visual Analogue Scale; PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Disorder seven-item scale; FCR, fear of cancer recurrence; M, mean; SD, standardized deviation.

TABLE 2 | Multivariate logistic regression of factors associated with suicidal ideation.

Variable	Category	OR	95% CI Lower	95% CI Upper	df	P
Age (years)		0.978	0.954	1.003	1	0.079
Marital status	Single	ref	-	-	-	-
	Married	0.724	0.254	2.062	1	0.545
	Divorced	0.293	0.027	3.230	1	0.316
	Widowed	2.755	0.379	20.046	1	0.317
Radiotherapy		0.874	0.376	2.032	1	0.755
Physical comorbidity		1.808	1.030	3.172	1	**0.039**
Daily exercise time	None	ref	–	–	–	–
	Less Than 60min	0.360	0.171	0.757	1	**0.007**
	More Than 60min	0.172	0.048	0.619	1	**0.007**
Childhood adversity exp		5.999	2.095	17.177	1	**0.001**
Current stress level	None	ref	–	–	–	–
	Mild	1.701	0.764	3.786	1	0.193
	Moderate	1.384	0.580	3.300	1	0.464
	High	2.526	0.907	7.032	1	0.076
Cancer pain		1.828	1.009	3.310	1	**0.047**
Depression		2.811	1.238	6.382	1	**0.013**
Anxiety		6.532	2.911	14.657	1	**<0.001**
Fear of recurrence		1.080	0.477	2.443	1	0.854

CI: confidence Interval; in bold: P<0.05; Exp, Experience.

indicated that the corresponding prevalence was 18.1% (28). However, Cheng et al. reported that 46.2% of the cancer participants reported suicidal ideation (29). The difference of estimates in suicidal ideation found could be partially explained by the differences in the study sample, measurement tools/questions, defined timeframe, and assessment method.

Our study showed a significant association between physical comorbidities and suicidal ideation. A previous research in prostate cancer patients reported that men with comorbidities tend to report more depressive symptoms and suicidal ideation compared to those without comorbidities (30). Similar studies also indicate that patients with more physical comorbidities reported elevated psychological disturbances as well (31, 32). It is possible that individuals with more comorbidities suffer from more physical discomfort, pain, fatigue, and psychological distress, which results in more suicidal ideation.

There is a plethora of evidence supporting the significant causational relationship between childhood traumatic experience and suicide in difference populations (33–35). It is possible that stressful traumatic experience could largely waste a patient's mental energy and resources, which makes them more vulnerable to mental disorders (36). From the perspective of Joiner's interpersonal theory (37), specific childhood trauma, such as severe neglect and rejection, can plant the seed for social isolation in an individual's mind. These individuals will then build up a belief that there is no one that they live for or belong to. This absence of a sense of belonging may result in higher risk of suicide in these individuals.

In accordance with previous findings in studies conducted, patients experiencing cancer pain are at higher risk of reporting suicidal ideation and/or behavior (38) than those otherwise. The reason for the same might be associated with the secondary psychological distress and depression raised by cancer pain (38). Researchers also indicated that most suicides by cancer patients who are suffering from pain at a terminal stage tend to be more rational than being driven by under-diagnosed depression (39). This study's finding highlighted the importance of providing adequate pain treatment which may help in better clinical advancements and a reduced suicide rate.

A strong association between depression and suicidal ideation has been identified in previous studies (2, 4, 29). Specifically, researchers found that having depression significantly predicted a higher risk of unnatural mortality, i.e. accident, and suicide in breast cancer patients (40). In fact, suicidal ideation has always been classified as one of the core diagnostic criteria and critical representations of major depressive disorder (41). Being female, having depression and suicidality are all closely connected (40, 42, 43), while even symptoms of depression; such as hopelessness, insomnia, loss of appetite, loneliness, fatigue, and low self-esteem greatly increase the risk of suicidal ideation, planning, and attempt (9). According to the interpersonal psychological model in suicidal behavior (37), traumatic feelings, such as painfulness, inconvenience, hopelessness, and feeling of burdensomeness can strengthen a patient's suicidal desire continually.

Regarding the association mapped between anxiety and suicidal ideation, inconsistent results were reported. For example, Xin et al. reported that compared to non-anxious group, patients with anxiety disorder were at a higher suicidality risk (44), while Xu et al. revealed that anxiety did not significantly predict cancer patient's suicidal ideation (45). Therefore, owning to this cross-sectional design, the causality between anxiety, depression, and suicidal ideation could not be determined in the current study. There is a need for further longitudinal investigation to better examine the link between them.

Our results show a significantly negative association between exercising frequency and suicidal ideation. Cancer patients with regular exercise plans are less likely to have suicidal thoughts. A previous review, including 14 studies indicated that exercise was negatively associated with suicidal ideation in adults (46). Asthenia, weakness, and reduction in motility are crucial indicators in a positive diagnosis of depression (41). The negative link between exercise and suicide ideation could be mediated by depression. In addition, the protective influence of exercise on suicidality might also be related to stronger immunity and positive attitude toward life brought on by scheduled exercise.

There are several limitations that should be acknowledged in the current study. First, although, there was a large sample scale, the distribution of sample; in gender and cancer type was uneven. Most of the participants were females, and diagnosed with breast cancer. These cases could be substantial enough to cause a bias in the data, thereby, affecting the research findings and making them non-generalizable for the entire Chinese cancer population. Second, the results of our study were all based on self-rated inventory; recall bias might exist. A single item question was used to assess patient's suicidal ideation. This item might be effective for assessment of explicit suicidal ideation but might fail to measure implicit ideation. Similarly, several factors, such as childhood adversity experiences and illness experiences were also assessed by single yes/no question, and these may not hold enough statistical power. Further studies with larger sample sizes, using validated objective instruments are warranted to further attest to these claims. Thirdly, other variables associated with suicidal ideation, such as time lapse since diagnoses, and pre-existing mental disorders, were not examined in this study. The mediation effect of emotional disturbances (such as, depression and anxiety) in determining suicidal ideation was not explored in detail either. Lastly, this was a cross-sectional study which could not draw any causal association between tested variables and suicidal ideation, hence, raising the need for further studies using longitudinal study design.

CONCLUSION

In conclusion, physical comorbidities, body ache, and mood disturbances are possible risk factors for suicidal ideation that warrant further attention in clinical practice. Considering the significant risk for suicide for cancer riddled population; preventive measures, such as regular screening and effective pain management, psychological supports should be performed widely. Health policy makers and health professionals should improve early identification of high risk patients and provide easy access to counseling and psychotherapy services for those in need.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nanfang Hospital Research Ethics Committee, Southern Medical University (ref No: NFEC-2018-038). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design: YZ, YY, and HW. Data collection, analysis and interpretation: YZ, HS, and WL. Drafting of the manuscript: YZ, WL, and ZZ. Critical revision of the manuscript: SG, YY, and HW. All authors contributed to the article and approved the submitted version.

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Learning From Artemisia's Lucretia: Embodied Suffering and Interoception in Suicide

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In the painting "Lucretia," Artemisia Gentileschi, one of the major painters of the 17th century, depicts Lucretia's suicide. This artwork empathic vision offers the spectator the apprehension of a unique phenomenon where psychological pain is transformed into self-aggression. To understand why the body becomes an object to attack, it is important to study the role of interoception and self-awareness in the suicidal process. This essay discusses how bodily representations are crucial for interacting efficiently and safely with the outside world and for establishing the sense of self. It presents some of the available evidence showing that alterations in the body representation and in the sensations perceived by it contribute to suicide. Indeed, neuroimaging studies show that social environmental factors and their biological consequences in the body (e.g., increased neuroinflammation) can alter the neural networks of suicidal behavior by increasing the sensitivity to psychological pain and the disconnection from self-awareness. Therefore, body image, sensations and awareness as well as psychological pain should be examined to improve the understanding of the dynamic interactions between body, brain, and mind that underly suicidal behavior. This conceptualization brings clinical and therapeutic perspectives in a domain where they are urgently needed.

Keywords: suicide, interoception, self-awareness, art, body

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INTRODUCTION

Artemisia Gentileschi (1593–1654 or later) is the most celebrated woman artist of the Baroque period in Italy. Her exceptional artwork "Lucretia's Suicide" questions the overlooked issue of the body in suicidal behavior (**Figure 1**). More precisely, this artwork gives some insights into a rather unique process in suicidal individuals where psychic pain translates into an aggression against their own body. In this essay, our objective is, by starting from this painting, to discuss, on a narrative basis and based on recent and relevant publications, the current advances and future research directions to understand the role of interoception and self-awareness in the suicidal process.

FIGURE 1 | Lucretia, Artemisia Gentileschi (1). Source: Wikipedia.org

"LUCRETIA'S SUICIDE" BY ARTEMISIA GENTILESCHI

"Lucretia's Suicide" (1) wonderfully illustrates the question of the embodied self in suicide. Lucretia was raped by the son of the Etruscan king of Rome. She then committed suicide to prove her innocence and to demonstrate her refusal to live with her honour tainted. Her rape and subsequent suicide led to the establishment of the Roman Republic. It is hard not to construe this act as an escape from social pain (e.g., fear of exclusion). Artemisia Gentileschi works have given rise to many discussions among art history experts, and brought a strong feminist perspective (2, 3). Indeed, it has been proposed that her work is a proof of her resilience because Artemisia also was a victim of rape. The depiction of Lucretia by Artemisia carries the weight of Caravaggio's characteristic pictorial style, particularly when the painting is compared with the masterpiece by Rembrandt on the same subject (4). The remarkable physical realism and the palpable emotional turmoil of Lucretia emerging from the darkness gives a nuanced and naturalistic representation of the human condition. This also echoes a well-known text by Cardinal Paleotti (*De sacris et profanis imaginibus*, 1582), who

tried to establish the Counter-Reformation doctrine on religious and secular art, where he advises painters to give in-depth instruction on the inner physiology of the human body in order to better represent the martyrs' torments. Lucretia's attire suggests that the rape was committed shortly before the scene depicted in the painting, and the close-focus composition accentuates the dramatic impact of the violent act. Lucretia is seized in a moment of deep contemplation, of decision making, between life and death. This is what the painting seems to tell the viewers: the dynamism in torsion that begins with the contrapposto, the Renaissance-style pyramidal architecture, the spiral drapery, and finishes with the crossed arm that goes as far as grasping the breast and indicates the dagger, which contrary to the other objects, is directed toward the sky, the same direction of her gaze. Everything in this painting leads the viewer to look at Lucrezia's face with its expression of anguish that is manifested by the frowning eyebrows and her gaze of suicidal terror. This suicidal contemplation is accentuated by the striking contrast between the breast (reminding of the breastfeeding Virgin) and the dagger (death), which was an important issue in the feminist reading of Artemisia's work in the 1970s. This painting captures the climax of the narrative in a simple, but deeply moving combination of facial expression, body posture, arm movements and the fateful dagger. Lucretia alone, her lonely decision made, resolved her inner conflict by ending her life. Then, why did she harm her body? Because it was harmed, as Livy told us: "But it is only the body that has been violated, the soul is pure; death shall bear witness to that." Thanks to the art of Artemisia, the important role of pain, interoception and self-awareness in suicide is more obvious.

PSYCHOLOGICAL PAIN AS CORE DIMENSION IN SUICIDE

The intense psychological suffering that leads people to consider killing themselves should not mask the fact that they have also a body. Indeed, people who have engaged in suicidal behavior also have somatic problems that may affect the way they see themselves (5–7). Moreover, suicidal vulnerability may be modulated by body signals. For instance, abnormalities in somatic markers (e.g., skin conductance) contribute to decision-making impairment, a cognitive trait of susceptibility to suicidal behavior, driven by the functioning of the orbitofrontal cortex (8–10).

In suicidal patients, activation of the orbitofrontal cortex is decreased during risky decision-making. This suggests that they might be more sensitive to negative emotional stimuli and short-term rewards, and consequently more prone to suicidal behaviors under the influence of pain (11). According to some prominent authors, suicide can be understood as a way to escape, through death, from a state of unbearable inner pain (12–14). Death will put an end to that pain because the *self* will disappear (15). Psychological pain is a core dimension in suicide and can predict future suicidal behavior, independently of depressive symptoms or suicidal ideation (16, 17). Psychological pain has been defined as "a lasting, untenable and unpleasant feeling that results from a negative evaluation of an incapacity or deficiency of the *self*" (18). Therefore, psychological pain can be interpreted as a "brokenness of the *self*" that induces a sense of injury, disconnection, and loss of control. Importantly, the neuroanatomy of suicide and pain involves some circuits associated with the *self*. Neuroimaging studies showed that experiences of social and psychological pain activate various important neurobiological substrates involved in suicidal vulnerability. Interestingly, some brain areas (notably insula, anterior cingulate cortex, and somatosensory cortex) are activated by psychological/social pain and also by physical pain (19), suggesting that psychological/social pain may be intimately related to bodily pain. Several studies in suicidal patients have detected difficulties in reading and interpreting emotional feedback and rewards, resulting in the activation of frontal areas upon presentation of angry faces or rewards (10, 20, 21). Altogether, the higher sensitivity to negative emotional stimuli and propension to risky decisions may lead to misinterpretations of the social environment, making suicidal patients more vulnerable to social exclusion (22). Indeed, brain activation is different in patients with and without history of suicide attempts in situations of social exclusion that induce the response of insula and anterior cingulate cortex (ACC), and therefore the response of the physical and psychological pain networks (23). Overall, as body signals modulate suicidal vulnerability, and as susceptibility to social exclusion involves a pain network, it could be hypothesized that suicidal patients have a specific neurobiology that makes them more vulnerable to attacks by their *self*.

THE ROLE OF INTEROCEPTION

Interoception is the ability to effectively perceive the physiological condition of the body, thus allowing detecting bodily sensations in a conscious way (24). Interoceptive deficits refer to a disconnection from the physical body that can cause difficulties in truly understanding and knowing their own body. Muehlenkamp & Brausch (25) theorized that interoception is an important component of body regard (how the body is perceived, cared for, and experienced). The disparity between expected and sensed interoceptive states may promote a wide range of maladaptive behaviors intended to change the internal milieu in order to match the anticipated state (26). Thus, people disconnected from their body may not feel protective and caring toward it, making easier to engage in behaviors that harm the body. Disconnection from the body may contribute to increase body objectification, which also facilitates self-harm of a body that is seen only as an object.

Various nerve pathways are responsible for detecting and mapping these homeostatic sensations (e.g., the degrees of visceral muscle contraction, the chemical composition of the

internal environment). In interoception, the vagus nerve is the most important afferent pathway, and the insula is one of the main cortical targets of the interoceptive system signals (27). Insula has a pivotal role in anticipating and processing sensations to guide behavior in close connection with the ventral striatum. This provides a mechanism for the integration of interoceptive stimuli in the emotional response that generates an action or a decision (28). The activation of these brain regions, which are also involved in suicide, in pain and in social exclusion, leads to investigate the mechanisms involved in their dysregulation. Peripheral inflammation and inflammatory interoception are among the recently postulated mechanisms. Studies combining imaging techniques and induction of peripheral inflammation showed the activation of various interoceptive pathways that are projected toward the insula (29). In this way, the peripheral inflammation status is transmitted to the central nervous system (CNS) through the vagus nerve and other autonomic nerves. Similarly, some peripheral inflammation factors have been detected directly in the CNS through the circumventricular sensory organs. Moreover, some of these inflammatory mediators (interleukin-6, interferon alpha, monocytes) can cross the blood-brain barrier in small quantities. The direct trafficking of monocytes to the CNS allows the amplification of behaviors related to the stress response, by involving also the microglia. Thus, changes in the insula induced by these inflammatory interception mechanisms can contribute to changes in the subjective experience and to various psychiatric disorders.

INFLAMMATION AND SUICIDAL BEHAVIOR

In suicidal behavior, growing evidence suggests the existence of a *ménage à trois* involving inflammation, social exclusion, and suicidal behavior. Social isolation, negative social interactions in daily life, and social defeat are common triggers of suicidal behavior and also strong inducers of inflammatory responses. For instance, Slavich et al. (30) reported that exposing humans to a laboratory social stress task leads to an increase in peripheral cytokines that is corelated with the activation of ACC and insula in functional magnetic resonance imaging (fMRI) during a social exclusion task. Many evidences indicate the involvement of peripheral inflammation and neuroinflammation in suicidal behavior (31). Therefore, it can be hypothesized that peripheral inflammation activates the insula *via* interoceptive pathways that in turn modify the brain pain pathways and self-consciousness, inducing psychological pain. In addition, inflammation induced by social stress, infections, or autoimmune diseases could chronically alter the functioning of various neuronal circuits by increasing the production of antineuronal auto-antibodies, promoting neuroinflammation and neurotoxicity through microglia activation, increasing the production of proinflammatory cytokines in the CNS, altering the blood-brain barrier permeability, increasing the activity of self-reactive T cells, and upregulating the transcription of proinflammatory genes (32). This might result in damage to neuronal networks and alteration of self-awareness that could make possible self-aggression.

INTEROCEPTIVE FEATURES IN SUICIDE

Studies in the general population and in clinical samples suggest the implication of interoception in suicidal behavior. A systematic review assessed satisfaction with body image, body experience and body ownership (i.e., feelings of detachment from their own body), body sensations and somatic complaints, and interoceptive awareness in adolescents with history of self-injury (33). The main conclusion was that the reported levels of body dissatisfaction, body detachment, somatic complaints, and interoceptive deficits were higher in self-injuring adolescents, especially those who recently attempted suicide. In addition, the longitudinal studies included in this review suggest that disorders in the interpretation of the body sensations are more easily associated with future self-injury compared with body dissatisfaction. Therefore, the association between body and self-injury is not limited to the emotional aspects of the body, but also to the sensation or perception aspects of the body. This is in line with studies suggesting that suicide attempters tend to ignore more their body sensations, and show lower self-regulation using body sensations, and greater interoception deficits (34).

The study of interoception in eating disorders also provides important insights. These patients are at very high risk of suicide (35), and they are chronically engaged in behaviors that harm the physical body, such as self-starvation and self-induced vomiting. Body image distortion and disturbances in interoceptive awareness are among the core symptoms of eating disorders, and interoceptive deficit prospectively predicts greater symptom severity 5–10 years later (36). Anorexia is associated with impaired ability to predict and interpret interoceptive signals, such as feelings of fullness and pain, but also pleasant stimuli, such as an affective touch (37). It has been demonstrated that feeling extraneous from their own body is the experience that discriminates most between people with and without eating disorders. Moreover, it has been proposed that the increased trend to perceive themselves from an external perspective is the way to cope with identity problems (38). Activation of brain regions known to be critical in interoception is increased in patients with history of bulimia nervosa (39). Therefore, interoceptive alterations may make particularly difficult to integrate expectations about homeostatic state changes, ultimately promoting maladaptive behaviors, such as binge eating and food restriction, and possibly self-injury. In people with eating disorders, interoceptive deficits are greater in patients with than without history of suicide attempts (40). In an 8-year longitudinal study, interoceptive deficits at baseline were greater among patients with eating disorders who then attempted suicide during the study (41). Dodd et al. (42) reported in eating disorders a connection between interoceptive deficits and suicide attempts, albeit largely through mediating variables,

such as non-suicidal self-injury, and pain tolerance. In patients who attempt suicide, detachment from the body is characterized by interoceptive errors, insensitivity to bodily sensations and a perceived lack of bodily control. Moreover, it is associated with a decreased sensitivity to pain, leading to self-neglect and facilitating self-destructive behavior. Thus, interoceptive deficits might be one of the key factors that increase suicide in these disorders.

Dissociation and depersonalization are experiences that give rise to a feeling of unreality or of being outside their own body and therefore, outside the self. A meta-analysis showed that patients with dissociative disorders were more likely to have attempted suicide or non-suicidal self-injury, compared with patients without dissociative disorder (43). In addition, the scores of dissociation were higher in patients with suicide attempt or with non-suicidal self-injury than in patients without these behaviors. One study examined adolescents with a recent suicide attempt or with a psychiatric disease without previous history of suicide attempt, and healthy controls (44), and found greater psychological pain, lower tolerance for psychological pain, and higher levels of physical dissociation and insensitivity to bodily sensations in suicidal patients. Therefore, in these patients, unbearable mental pain may trigger a process of physical dissociation that manifests itself in insensitivity to physical pain and indifference to the body. The authors concluded that blocking the body awareness and signals makes the body a lifeless object and an easier target for attack.

CLINICAL IMPLICATIONS AND AVENUES FOR FUTURE RESEARCH

Despite these evidences, studies on interoception and suicidal behavior are still in their infancy. Future works should integrate multidimensional assessments (e.g., heartbeat perception tests and specific self-report measures to assess a variety of interoceptive components) to thoroughly elucidate the nature of the associations between suicidal ideation/behavior, pain tolerance, and interoceptive deficits (e.g., attentional biases, distortions of physiological sensitivity, cognitive biases, and insight impairments) (45). Moreover, depression should be taken into account in these analyses because it has been associated with lower interoceptive accuracy (46). Assessing interoception deficits might be part of a multidimensional approach that would help to build suicide risk stratification models, as proposed by Orsolini and colleagues (47).

Focusing on the body and on the evaluation of interoception processes brings interesting perspectives in a field where treatments are lacking. In patients at risk of suicide, the assessment of body awareness and accuracy of interoceptive experiences may be useful to train patients with deficits to be more aware and mindful of their bodily signals (48). People with suicide ideation benefit from mindfulness-based cognitive therapy, an intervention that teaches how to deliberately direct attention to body sensations and to use body sensations to regulate the state of mind (49). It could be hypothesized that neurofeedback strategies (the use of a brain-computer interface to provide feedback about brain functioning) might enable self-regulation of the brain activity in suicide attempters. Indeed, Song et al. (50) recently reported that an event-related potential-based neurofeedback decreases psychological pain in suicide attempters. Similarly, real-time fMRI biofeedback deserves further investigation due to its interest for modulating pain and interoception (51).

Bodily representations are crucial for interacting efficiently and safely with the outside world and for establishing the sense of self as a distinct entity from the rest of the world. Therefore, alterations in the body representations and in the sensations perceived by the body contribute to suicide. Neuroimaging studies show that environmental factors (social stress, social defeat…) and their biological consequences on the body (increased inflammation, neuroinflammation…) can alter the suicide neural networks by increasing sensitivity to psychological pain and negative emotions and also by increasing disconnection from self-awareness. Thus, it is important to concomitantly study body image, body sensations, body awareness and psychological pain, through interoceptive measures to understand the dynamic interactions between body, brain and mind that underlie suicidal behavior.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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Further Insights Into the Beck Hopelessness Scale (BHS): Unidimensionality Among Psychiatric Inpatients

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Short versions of the Beck Hopelessness Scale have all been created according the Classical Test Theory, but the use and the application of this theory has been repeatedly criticized. In the current study, the Item Response Theory approach was employed to refine and shorten the BHS in order to build a reasonably coherent unidimensional scale whose items/symptoms can be treated as ordinal indicators of the theoretical concept of hopelessness, scaled along a single continuum. In a sample of 492 psychiatrically hospitalized, adult patients (51.2% females), predominantly with a diagnosis of Bipolar Disorder type II, the BHS was submitted to Mokken Scale Analysis. A final set of the nine best-fitting items satisfied the assumptions of local independency, monotonicity, and invariance of the item ordering. Using the ROC curve method, the IRT-based 9-item BHS showed good discriminant validity in categorizing psychiatric inpatients with high/medium suicidal risk and patients with and without suicide attempts. With high sensitivity (>.90), this newly developed scale could be used as a valid screening tool for suicidal risk assessment in psychiatric inpatients.

Keywords: hopelessness, inpatients, depression, Mokken analysis, unidimensionality

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INTRODUCTION

Hopelessness is an important psychological construct, defined as negative expectations regarding oneself and one's future life and a negative emotional state characterized by the lack of finding a solution for one's problems (1). In his research focused on depression mood and suicidal behavior, Beck (2–5) observed that patients diagnosed with depressive disorders shared common cognitive features—a negative view of the self, and of the self in relation to the world and in relation to the future. He paid special attention to one of these cognitive features—a negative view of the self in relation to the future, by introducing the construct of "hopelessness". Unlike depression, it is oriented towards the future as opposed to the present state (6).

According to Beck and his associates, hopelessness has substantial clinical utility for suicide risk assessment and prediction of future suicidal behavior. They produced empirical evidence for the

association between hopelessness and suicidality by arguing that severity of suicidal intent is more strongly related to hopelessness compared to depression (5, 7–11).

Subsequently, research showed that hopelessness could lead to suicidality (12–14). As a modifiable key psychological risk factor in suicidal behavior, with an impact that can be reduced by means of appropriate psychotherapeutic interventions, the recognition and assessment of hopelessness plays an important role in the prevention of suicidal behavior (15–17).

Measurement of Hopelessness: The Beck Hopelessness Scale

To investigate better the construct of the hopelessness, Beck (4), Beck, Weissman, et al. (6) constructed the Beck Hopelessness Scale (BHS). In its development, Beck grouped 9 items from an unpublished inventory assessing the attitudes about the future and 11 items drawn from a set of pessimistic statements formulated by patients with psychiatric diagnoses (6). The BHS scores were found to be strongly correlated with clinical ratings of hopelessness by Beck and colleagues in their validation study (6).

Several studies have indicated good predictive validity for the BHS (11, 14, 18–20). For instance, the BHS was found to predict suicidal thoughts and attempts among 289 psychiatrically hospitalized suicidal youth across a 1–6-month follow-up after hospital discharge (21, 22). Hopelessness, as measured by the BHS, was found a significant predictor of attempted suicides among psychotic patients at first admission to hospital (18).

The BHS performed similarly across inpatients and outpatients, for both psychiatric and medical samples (23–25), and can also be used for predicting social functioning and general status health in psychiatric samples (26).

Overview on Dimensionality BHS

In order to determine the dimensionality of the scale, Beck, Weissman, et al. (6) subjected the items of the BHS to a factor analysis. The factors were labeled "Feelings about the Future", "Loss of Motivation", and "Future Expectations", respectively. According to the authors, although the factor structure of the BHS made sense clinically, it can vary according to the type of clinical sample being studied and the type of factor-analytic methods conducted. Further studies analyzed this factor structure across different samples (27–30). According to the review by Aish et al. (31), factor structures found in the literature could be grouped as follows: (1) one-factor models (32); (2) two-factor models (33–38); (3) three factor models (27, 29, 30); and (4) models with four or more factors (28). In the reported studies, the emerging factors found differed from those identified by Beck et al.'s study in terms of the assigned factors' labels and their item composition.

In addition, some authors noted that some original items could fit models different from those proposed (31, 32, 36). For example, Aish and Wasserman (31) found that no strong evidence supported the multidimensionality of the BHS by the first CFA. In detail, 15 items tapped a single dimension of hopelessness, and so a reduced number of 4 items could summarize most of the information contained by the BHS. Thus, the dimensionality of the BHS remains an open issue of considerable interest. For example, Hill, Gallagher, et al. (27) found that only one component(giving up - the motivational component) was significantly related to suicidal intent. In this case, combining different dimensions into a composite scale (39) might reduce the predictive validity of the BHS.

Short Versions of the BHS

The length of the BHS could be discouraging for the respondents. Lengthy questionnaires reduce data quality and respondent willingness (21), especially in clinical populations (40, 41). In order to be useful in practical settings, an instrument should be sufficiently brief and easy to complete (42, 43), especially when multiple measurement scales are employed.

Previous methodological studies have suggested that a reduction by about 50–70% of the number of items could not compromise substantially the original psychometric functioning of a scale (44–47). This is also true for the BHS (31, 48). For example, some researchers have suggested that a single item, "My future seems dark to me" (item #7), could be sufficient to assess hopelessness. According to Aish and Wasserman (31), this sentence is ideal for summarizing the construct under investigation: the perception of a menacingly ambiguous and hopeless future. This suggestion was supported by Perczel Forintos et al.'s (13) study whose results showed that this item had the highest item-residue correlation (r = .75), that is the highest correlation with the total score of the BHS.

Other researchers have investigated the psychometric properties of different 3- or 4-item versions of the BHS. Based on confirmatory factor analysis, Aish and Wasserman (31) reported excellent fit for a 4-item version of the BHS (composed of items #6, 7, 9, 15). In a cross-sectional survey, Yip and Cheung (1) administered this shortened version to some 2,000 Chinese subjects. A significantly high correlation (r = .88, p <.001) of the shortened version with the original 20-item BHS was found, suggesting that the abbreviated scale can be reliably used in clinical studies. They also reported that the 4-item BHS was able to differentiate patients with and without suicidality, similarly to the original version of the BHS. Recently, Aloba, Akinsulore (48) introduced a new 4-item version of the BHS (composed of items 8, 9, 13, and 15) in a sample of 327 Nigerian adult psychiatric outpatients. The authors reported satisfactory reliability and validity, comparable to that of the long form of the BHS. Other researchers (28, 37) have also suggested that a three-item version of the BHS (items 7, 14, and 20)could represent the scale and be a valid measure of hopelessness.

Finally, some researchers have devised brief modified versions of the BHS. For example, Perczel Forintos, Sallai (13) proposed a three-item version of the BHS in their study on a clinical sample of 300 individuals. Three items with highest correlations with the BHS total score, plus an item # 2 from the Beck Depression Inventory (BDI), which refers to hopelessness, were included in this brief BHS. Scores on this scale were highly correlated with scores on the original scale (r = .88) and had relatively high internal consistency (Cronbach's α coefficient: r= .80). More recently, Fraser, Burnell, et al. (49) developed two short hopelessness measures by re-wording two items of the BHS

negatively (Brief-H-Neg) and items positively worded (Brief-H-Pos), and shifting the response format from "yes/no" to 5-point Likert scale (from "absolutely agree "to" absolutely disagree"). Nevertheless, no strong methodological evidence (i.e., construct validity) can be found in the literature for the Brief-H-Pos/Neg short forms. In addition, these two short forms could potentially be affected by the reverse-item bias, which is very common in scale with Likert response format (50).

Aims

Short versions of the BHS have all been created according the Classical Test Theory (CTT) (31, 48, 49), despite the fact that the use of CTT has been criticized (51–53). The Item Response Theory (IRT) approach to the refinement of measures of clinical constructs has many practical advantages (54). For example, IRT methods could: (i) detect subtile changes in patients' mental health that would not be recorded with the use of the mean or summed scores; (ii) overcome the sample dependence found in CTT; and (iii) produce invariant item/person statistics that allow optimal individual scores and comparison of individual scores across different tests (55, 56).In addition, applying item response models to the validation of psychopathology measures can help build a "*reasonably coherent unidimensional scale*" [(57), p.475] and treat symptoms as ordinal indicator of risk scaled along a single continuum. The unidimensional assumption was rarely met (58), especially using the CTT framework. The BHS, in this context, is not an exception. Thus, applying IRT models to the BHS could improve Beck's conceptualization of hopelessness as a unidimensional measure.

Therefore, the purposes of the current study were: (1) to investigate the psychometric properties of the individual items of the BHS; (2) to develop a reliable and valid version including a reduced set of items since time-effective instruments would be of great practical value both in clinical and research settings; and (3) to test the diagnostic performance of the proposed short version of the BHS in classifying psychiatric inpatients at higher risk of suicide, and to compare its performance with the original 20-item BHS and to other short versions proposed in the literature (31, 48). The versions proposed by Fraser, Burnell, et al. (49) were excluded in the comparison analysis due to their methodological weaknesses and the lack of studies in support of their psychometric validity.

METHODS

Participants and Procedure

The sample included 492 psychiatrically hospitalized, adult patients of whom 48.8% were males, with a mean age of 39.09 (SD = 13.13) years. Participants were recruited from January 2014 to December 2018 at psychiatric units situated in Sant'Andrea Medical Center, an affiliate of "Sapienza" University of Rome, Italy.

Inclusion criteria were to be inpatients aged 18 years or over with current psychiatric diagnosis performed according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Diagnoses were made by expert clinicians within the first 48 h of the psychiatric hospitalization. These were supported by means of an examination according to the Mini International Neuropsychiatric Interview criteria (59) and administered a psychological battery of tests, including the BHS, to assess the severity of psychopathology, and the presence of risk factors for suicide. The information was retrieved from clinical files for the indicated period of time. Participants with cognitive impairment and degenerative neurological disease were excluded from the study.

Primary psychiatric diagnoses included 174 (35.4%) patients with Bipolar Disorder type I (BD-I), 52 (10.6%) patients with diagnosis of Bipolar Disorder type II (BD-II), 58 (11.8%) patients with Major Depressive Disorder (MDD), 83 (16.9%) patients with Psychosis, 66 (13.4%) patients with schizoaffective disorder, 41 (8.3%) with other Axis I disorders, and 18 (3.7%) with no DSM-IV-TR diagnosis. In the total sample, 21 (4.3%) had a Personality Disorder (PD) as a secondary DSM-IV-TR psychiatric diagnosis.

The patients participated voluntarily and provided written informed consent. The study protocol was reviewed and approved by the local research ethics review board, with assurance that data would be reported anonymously and in aggregate form. All procedures were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Measure

Beck Hopelessness Scale (BHS)

The BHS is composed of 20 dichotomous "true/false" items that aimed to assess three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations. Total scores were created by first reverse-coding nine items (items 1, 3, 5, 6, 8, 10, 13, 15, 19) and then summing the item scores. Higher total scores indicate greater hopelessness (range 0–20). The Italian version of the BHS has been translated and validated by Innamorati, Lester, et al. (60) with the permission of Pearson Education (Upper Saddle River, NJ 07458, USA). A series of studies has shown that the BHS performed similarly across psychiatric inpatients and outpatients and medical samples (23–25, 36).

Data Analysis

The Mokken Scale Analysis (MSA) was carried out within the framework of Non-parametric Item Response Theory (NIRT), in order to (a) evaluate the fundamental measurement properties of the BHS; (b) address dimensionality issue problems raised from previous research; and (c) refine the scale by providing a unidimensional, brief and reliable measure. Compared to the parametric IRT models, the Mokken probabilistic approach does not required strict assumptions about the data, and persons are allocated to a finite number of discrete ability levels. Thus, the relationship between the latent variables and the probability for a response were not required to match a specific shape (61). For this reason, Mokken's model has been considered as less parsimonious than Rasch model. However, as pointed out by Emons, Sijtsma and Meijer (62) and Wind (63), the application of parametric IRT models (the Rasch model) might lead to inappropriate conclusions in: a) diagnosing psychological

latent variables that are not clearly understood, and b) assessing the monotonicity assumption when it does not hold for a particular item (63). In this view, Mokken non-parametric models represents a viable alternative to Rasch model (64).

The MSA for dichotomous response items includes the evaluation of two models: the Monotonic Homogeneity Model (MH) and the Double Monotonicity Model (DM) (61, 65–67). Briefly, the MH model entails an ordinal scale person measurement (68), which means that the relative ordering of psychiatric inpatients on the hopelessness latent variable is invariant across items. Data are found to fit the MH model if three underlying assumptions are satisfied: *Monotonicity*, *Unidimensionality*, and *Local independence*.

The DM model represents a special case of the MH model. In our case, assessing the DM model means that all the BHS items were ordered in the same way across the psychiatric inpatients. In addition to the MH assumptions, a fourth assumption is required for the DM model: the *Invariant Item Order* (IIO). Since the DM model provides evidence for invariant ordering of items and sample for dichotomous items, this model best represents the ordinal version of the Rasch model or the 1PL-IRT (69, 70).

Like other IRT models (e.g., the Rasch model), the MSA involves an iterative process in which an observed pattern of responses is refined in order to reach the overall fit to the model expectations.

Following Sijtsma, Meijer (71) and Sijtsma and Molenaar (65), a series of steps were carried out in order to assess both the MH and the DM models as well as the scale properties (i.e., the reliability). All analyses were performed using the *Mokken* package of R (72, 73).

- The *Unidimensionality* assumption was assessed by performing the Automated Item Selection Procedure (AISP) algorithm using consecutively different values of c (.30, .35, .40, .45, .50) (74). Once a scale was detected, the scalability coefficients for individual items (H_i), item pairs (H_{ij}), and for the total scale (H) were computed, along with the standard error. For H and H_i, values of H ≥.3 identify a "sufficient" scalability. For H_{ij}, values greater than 0 and positive identify good scalability (61).
- *Local independence* was investigated using the Straat, van der Ark (75) conditional association procedure and the W_1 and W_3 indices developed in the *Mokken* package. The procedure identifies locally dependent item pairs.
- The *Monotonicity* of the Item Response Function (IRF) was assessed using a non-parametric regression method (76). To evaluate if IRFs were non-decreasing and monotonic, we took into account the size of the violation of monotonicity (#vi/#ac) which should not exceed the value of .3; and the Diagnostic Crit Value (crit) which should not exceed the value of 80.
- The *Invariant Item Ordering (IIO)* assumption was investigated using the method MIIO (Manifest IIO) (77). Violations of the IIO were assessed by taking into account the size of "#vi/#ac" and the "Crit" indexes. When the IIO has been established, the coefficient H^T expresses the precision of the item ordering (from 0 "weak" to 1 "high precision", with a minimum value of .3).
- *Reliability* was assessed using the Moolenar–Sjitsma method (MS) (78). Cronbach (79) alpha and the Latent Class Reliability Coefficient (LCRC) (80) were also computed.
- Next, we compared the resulting unidimensional shortened version of the BHS with the Hungarian 4-item BHS models developed by Aish and Wasserman (31) and Aloba, Akinsulore (48), in order to assess which of the three competitive brief versions of the BHS performs better in measuring Beck's Hopelessness.

The diagnostic performance of the refined 9-item BHS was assessed using the Area Under (AUC) the receiver operating characteristic curve (ROC). The Youden (J) method was employed in order to detect the cut-off score of the final item set, and we also computed key predictive statistics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).ROC curve analysis was done using the MedCalc software package (MedCalc software, Mariakerke, Belgium) (81).

Optimal values of AUC ranged from 0 "weak performance" to 1"perfect performance" (82), with a recommended value of >.70 (83). The MINI Suicidal Subscale (59) cut-off score was employed to classify participants with high and moderate suicidal risk. We also computed a series of pairwise comparison of ROC curves to test whether the BHS long and short forms differed in performance across diagnoses. Finally, we tested the diagnostic accuracy of the 9-item BHS in discriminating between inpatients with and without prior suicide attempts.

RESULTS

Mokken Analysis

First, we re-coded all the BHS items written in a reversed format. Inadmissible scores as well as missing data were removed from the dataset. Next, we submitted the BHS items to a Mokken analysis to verify scalability and the unidimensionality assumption. As shown in **Table 1**, the individual item scalability (H_i) of the 20-item BHS was below the accepted cut-off of 30 for items #1, 3, 5 and 13. Several H_{ij} coefficients were found to be negative and below the .03 cut-off (e.g., the paired items 1-3; 3-5; and 13-2). The H coefficient of .323 (± .02) suggested a '*weak*' scale and, therefore, was likely multidimensional. As expected, the AISP, with different values of lower bound, suggested a three-scale structure. The main scale was composed of 16 items identified as the "Hopelessness" dimension, while the remaining scales were small and composed of two items for each (scale 2: item 8 and 13; scale 3: items 1 and 3). However, the results confirmed the BHS as a unidimensional scale since the typical outcome pattern was confirmed (65, 84) and was observed using the AISP algorithm with different values of *c*. Hence, four items were discarded from the full 20-item scale and the remaining items were submitted to a MSA to explore the fit both of the MH

TABLE 1 | Descriptive statistics of the items and the scale for the 20-item-BHS, the refined 9-item and the Aish et al. (31) and Aloba et al. (48) 4-item models.

	20-item BHS model			refined 9-item model			Aish et al. (31) 4-item model			Aloba et al. (48) 4-item model		
	Scale	Hi	SE	Scale	Hi	SE	Scale	Hi	SE	Scale	Hi	SE
BHS2	1	.363	.025	1	.459	.032						
BHS4	1	.350	.046									
BHS5	1	.283	.030									
BHS6	1	.403	.038	1	.459	.052	1	.500	.056			
BHS7	1	.399	.023				1	.402	.035			
BHS9	1	.308	.027				2	.298	.041	1	.166	.041
BHS10	1	.304	.028									
BHS11	1	.393	.025	1	.489	.031						
BHS12	1	.397	.029	1	.499	.034						
BHS14	1	.389	.045	1	.505	.053						
BHS15	1	.349	.025				1	.363	.038	1	.327	.035
BHS16	1	.327	.027	1	.475	.035						
BHS17	1	.346	.026	1	.497	.033						
BHS18	1	.491	.028	1	.566	.036						
BHS19	1	.383	.031									
BHS20	1	.393	.026	1	.551	.032						
BHS8	2	.221	.029							1	.259	.036
BHS13	2	.291	.042							1	.402	.052
BHS1	3	.061	.032									
BHS3	3	.088	.038									
H (SE)	.323 (.017)			.500 (.024)			.375 (.034)			.275 (.033)		
H^T	.37			.42			.34			.24		
MS	.87			.86			.64			.53		
α	.86			.86			.60			.51		
LCRC	.89			.89			.63			.56		

Hj, item scalability coefficient; SE, Standard Error of item scalability; MS, Molenaar–Sijtsma method; α, Cronbach's alpha; LCRC, Latent Class Reliability Coefficient.

(unidimensionality, monotonicity, local independency) and the DM (invariant item ordering, IIO) Mokken's model, as well as to measure the reliability of the scale.

For the 16 item-BHS scale, the H-coefficient was .42 (± .02), and H_i coefficients ranged from .323 (.034; item 5) to .554 (.029, item 18). All H_{ij} coefficients were non-negative, but some paired items showed scalability coefficients below the threshold (H_{ij} >.30). The conditional association procedure used to detect local independency suggested that the item pairs (4 with 7-11-12-14-18-19; 5-18; 6-18; and 14 with 14-18; 16-20; 19-18) were positively locally dependent. Next, the data analysis supported monotonicity, since no monotonicity violations were detected across all the items. Non-significant IIO was identified for items 12 and 6, and backward selection suggested removing item 7 (#vi/#ac = .20; crit = 73) and item 5 (#vi/#ac = .16; crit = 70), both of which showed signs of violating item ordering close to the recommended thresholds. The remaining items showed crit values <40, that indicated the violations reported were potentially due to sampling variations. The #vi/#ac values ranged from .9 to .2. H^T was .373 indicating low accuracy of the item ordering. Reliability estimates were satisfactory, with an MS index of .87, a Cronbach α of .86, and an LCRC of .89. Taken together, these results provided evidence for the weak unidimensionality of the Hopelessness scale, as it was composed at this stage. The MH and the DM Mokken's model requirements were partially meet since neither local independency nor IIO was reached at this stage.

Next, we removed in turn the items labelled as locally dependent through the conditional association procedure and with the lower H_i values, and the data set was iteratively reanalyzed. Then we removed items that showed the greatest violation of item ordering.

The Refined 9-Item Hopelessness Model

The refined Hopelessness scale resulted in a unidimensional set of nine items (items 2, 6, 11, 12, 14, 16, 17, 18, 20). The H-coefficient was .50 (± .02), all H_i coefficients were greater than .46, and all H_{ij} coefficients were non-negative. No violations of local independency and monotonicity were identified. A non-significant IIO was identified for all the items, and backward selection did not suggest removing any items. H^T was .42 indicating medium accuracy of the item ordering. These results suggested that the refined Hopelessness scale was unidimensional and met the requirements of a MH and DM Mokken scale, although the scale's ability to discriminate between levels of hopelessness severity among psychiatric inpatients was medium. Concerning the scale properties, reliability estimates were satisfactory with an MS index of .86, a Cronbach α of .86, and an LCRC of .89.

Comparison of Brief Versions of the BHS

Finally, the Aish and Wasserman (31) and Aloba, Akinsulore (48) 4-item versions were submitted to the MSA in order to test which of the brief version best measured hopelessness. Concerning the Aish and Wasserman (31) model, the AISP algorithm suggested a two-dimensional scale structure. The main scale was composed of items 6, 7 and 15, while item 9 loaded on a separate dimension. The H-coefficient was .37 (± .03), all H_i coefficients were greater than .23, and all H_{ij} coefficients were

non-negative, with item 6 (SE =.05) falling below the cut-off if the standard error was taken into account. No violations of monotonicity were identified, and no local dependence issue was observed. A significant violation of the IIO was identified for item 9, and backward selection suggested removing it from the model. H^T was .34 indicating poor accuracy of the item ordering. Reliability analysis suggested sufficient reliability for the scale, with an MS of .64, a Cronbach α of .60, and an LCRC of .63. Taken together, the brief version of BHS proposed by Aish and Wasserman (31) satisfied the monotonicity and item local independency assumptions of Mokken analysis, but failed to address unidimensionality and the invariant item ordering, but displayed a sufficient reliability score.

With regard to the Aloba, Akinsulore (48) 4-item version, the H-coefficient was .27 (± .03). Only two H_i coefficients were greater than .30, and all H_{ij} coefficients were non-negative, with all the items (SE ranged from .05 to .09) falling below the cut-off if the standard error was taken into account. No violations of monotonicity were identified, and a significant IIO was identified for items 9, 8 and 15. H^T was .24, indicating unacceptable accuracy of the item ordering. In addition, a local dependence issue was observed between item 15 with items 9–13. The reliability analysis also suggested poor reliability for the scale, with an MS of .53, a Cronbach α of .51, and an LCRC of .56. Thus, the Aloba, Akinsulore (48) model cannot be considered as a Mokken's reliable and valid measure of Beck's Hopelessness, and so we eliminated this scale from subsequently analyses.

In conclusion, the refined 9-item model proposed here best represents a reliable and Mokken's suitable measure of Hopelessness compared to the Aish and Wasserman's (31) brief version.

ROC Curve Analysis

A first ROC curve analysis was performed to compare the psychiatric inpatients with a high risk of suicide versus the low risk group. The results indicated that the 9-item BHS scale was able to discriminate between the two groups. The AUC for the 9-item BHS total score was .708 (95%CI =.665–.748), suggesting good discrimination between the groups. The Youden index of .39 for the 9-item BHS total score was observed at a score of 3 points, corresponding to a sensitivity of 68.56% and specificity of 64.43%. Positive and negative predictive power were 55.6% and 75.9%, respectively.

Similarly, a second ROC curve was performed to compare the psychiatric inpatients with a medium risk of suicide versus the low risk group. The results indicated that the 9-item BHS scale was able to discriminate the two groups with an AUC of .522 (95%CI of .477–.567). The Youden index of .13 for the 9-item BHS total score was observed at a score of 1 point, corresponding to a sensitivity of 90.91% and specificity of 22.22%. The positive and negative predictive powers were 7.8% and 97.1%, respectively. Thus, better accuracy was displayed by the 9-item BHS brief version in correctly diagnosing psychiatric inpatients at high risk of suicide compared to those with a medium risk of suicide.

When we compared the predictive validity of the total scores of the BHS long form and the brief 9 and 4-item models, the AUCs were identical, and the differences among them were not found to be significant for those with a high risk of suicide (ΔAUC ranged from .003 to .019) or for those with a medium risk of suicide (ΔAUC ranged from .008 to .046). Thus, results of the pairwise comparison revealed that proposed 9-item BHS brief version did not differ in diagnostic accuracy from the 20-item long form or the Aish et al.'s 4-item short form. Indicators of the predictive accuracy of the BHS scales are shown in **Table 2**.

Concerning the ability of the 9-item BHS into discriminate between subgroups of inpatients with or without suicide attempts, no differences were found in the AUC. The results indicated that the 9-item BHS brief version was able to detect with the same accuracy psychiatric inpatients with versus without any previous suicide attempt.

TABLE 2 | Area Under the Curve (AUC) of the Receiver Operating Characteristic Curve (ROC) Analyses for the different version of the BHS, and Comparison of independent ROC curves.

MINI Suicidality Subscale – cut-off	N	AUC	SE	(95%CI)	Sensitivity/ Specificity	Cut-off	PPV/NPV	Model	ΔAUC	SE	(95%CI)	z	p
High Risk	194												
20-item BHS		.724	.023	.682–.763	59.79/72.82	>8	58.9/73.6	BHS20 vs BHS9	.016	.011	–.005–.038	1.440	.150
9-item BHS		.708	.024	.665–.748	68.56/64.43	>3	55.6/75.9	BHS20 vs BHS4	.019	.013	–.006–.045	1.461	.144
4-item BHS		.705	.023	.662–.745	59.28/69.46	>1	55.8/72.4	BHS9 vs BHS4	.003	.017	–.032–.038	.181	.856
9-item BHS					N+	N-							
Inpatients with no attempt	55	.775	.078	.645–.875	11	46		with vs no attempt	.055	.135	–.209–.320	.409	.683
Inpatients with attempt	32	.720	.110	.527–.867	21	9							
Moderate Risk	33												
20-item BHS		.560	.047	.515–.604	81.82/32.90	>4	8.1/96.2	BHS20 vs BHS9	.037	.022	–.006–.081	1.674	.094
9-item BHS		.522	.047	.477–.567	90.91/22.22	>1	7.8/97.1	BHS20 vs BHS4	.008	.031	–.054–.072	.276	.782
4-item BHS		.569	.047	.524–.613	57.58/59.26	>1	9.2/95.1	BHS9 vs BHS4	.046	.043	–.039–.031	1.066	.286
9-item BHS					N+	N-							
Inpatients with no attempt	78	.529	.123	.393–.663	6	51		with vs no attempt	.081	.231	–.370–.533	.354	.723
Inpatients with attempt	9	.611	.195	.417–.783	3	27							

DISCUSSION

The BHS has been recognized as a powerful tool for predicting suicidal risk in patients diagnosed with depression mood (19, 85–87). The BHS has been used extensively under the assumption that it captures a single dimension, hopelessness, composed of three components: affective, motivational, and cognitive (6). However, international studies have reported that the BHS could consist of from one (31) to four dimensions (28). It should be noted that these differed for label and items composition.

In the current study, we submitted the BHS to a Mokken Scale Analysis (MSA) as a method to overcome the limitations of the CTT. The MSA allows the ordering of individuals on the basis of their raw scores and addresses the BHS unidimensional issue. Not surprisingly, we found that all the BHS 20 items did not tap a single unidimensional factor, but rather formed three dimensions.

The analysis did not support the original affective, motivational and cognitive model, or a clear single dimension of hopelessness. In line with a study by Aish and Wasserman (31), most of the item tapped a single dimension (Scale 1 with 16 items). Scale 2 contained items 8 (cognitive domain) and 13 (affective domain), while Scale 3 was contained items 1 (affective domain) and 3 (motivational domain). The H values were stable with respect to the scalability level for items in the Scale 1. Items that made up Scale 2 and 3 were found to be not scalable, suggesting that these scales were a weak indicator of hopelessness or that the item wording is poor. Likewise, local independency nor IIO assumptions were reached for several items at this step of the analysis. This implies that the individual's responses to BHS items were dependent on the individual's level of the latent trait being measured (88), as well as the ordering of the items according to its severity (or mean score) being different (not invariant) for individuals at different trait levels (89). Consistent with these results, both the MH and DM Mokken model assumptions have not been reached or met for the 20-item BHS version in the present sample of Italian psychiatric inpatients.

In order to obtain a conceptually clear measure of hopelessness, we removed items with low scalability, local dependency and a not invariant item ordering. After removing eleven items, the one-scale model maintained its psychometric viability. This was not at all obvious, given that removing items means obtaining less information for each individual and may impair construct validity and reliability (54, 62). The process resulted in a unidimensional set of nine items (items 2, 6, 11, 12, 14, 16, 17, 18, 20) and the assumptions of local independency and monotonicity for the MSA were satisfied, as well as the invariant item ordering feature. Six items corresponded to the motivational component of hopelessness, as conceived by Beck, Weissman, et al. (6), two items were drawn from the cognitive component and a single item from the affective component. All the items showed medium to high scalability coefficients, and the ability to discriminate between psychiatric inpatients with different levels of suicide risk.

Previously, some authors have proposed extremely short versions of the BHS [e.g., 2-item version by Fraser et al. (49) and 4-item versions by Aish et al. (31) and Aloba et al. (48)]. In our sample, Aish et al.'s (31) and Aloba et al.'s (48) competing models revealed psychometric weaknesses. The IRT refined short version of the BHS proposed in our study could represent a good compromise between time costs, and measurement precision.

The development and the use of short forms of measures has encountered contradictory views in the literature on clinical assessment (90). Overall, reasons why scores on short measures are likely to have less predictive validity than scores on longer inventories concern the poor sampling of the relevant behaviors (*construct underrepresentation bias*), and the lack of interest among researchers to improve the methodology of short-form development (i.e. *random measurement error issue*) (91).

In this view, this refined 9-item BHS has been developed using a sound item-development procedure: NIRT models. As suggested by Smith, McCarthy, and Anderson (90), the IRT based approach to short-form construction can lead to a shorter assessment without all the methodological issues that are often evident within CTT.

Similar, longer scales were likely to have greater content validity and higher reliability scores. To date, the overlap of content validity and scale length makes it difficult to determine "*whether the improved criterion validity of longer scales is the result of the improved reliability of measurement or the result of greater content validity*" (p. 884) (91). For example, the use of 1-item and 2-item measures has been found to increase both the Type 1-2 error rates, while slightly longer scales were found to increase the validity of study findings (92).

Similar to the content of long versions, our 9-item BHS tapped all the aspects of hopelessness: affective (item #6), motivational (item # 2–11–12–17–20), and cognitive (item #14–18) ones. Not surprisingly, the motivational aspect of this construct had greater weight, with five items that assess giving up (i.e. "*deciding not to want anything*"). As reported above, Hill, Gallagher et al. (27) found that only this was significantly related to suicidal intent. Indeed, "*loss of motivation has been found to represent the clinical picture of giving up, unpleasantness and darkness, which is a reality in suicide attempters*" (p. 142) (93).

The IRT-refined short version of the BHS also had good discriminant validity in categorizing psychiatric inpatients with high or medium suicidal risk, and patients with and without suicide attempts. Indeed, differences in diagnostic accuracy among the original 20-item version of the BHS, the four-item versions, and the IRT-refined nine-items short BHS were not significant. For high suicidal risk, a cut-off value scores >3 (with scores >1 for a moderate risk) for the refined nine-item short version of the BHS seem suitable, and this suggests that all patients with a total score of 3 should be referred for further risk assessment and management. Our IRT-refined short BHS had high sensitivity (>.90) and could be used as a valid screening tool for medium risk of suicide assessment across psychiatric inpatients.

Our results should be considered in light of four limitations. First of all, this sample consisted of a heterogeneous sample of adult psychiatric inpatients with and without suicidal attempts. Results using a more homogeneous sample of patients with mood disorders could differ, and the diagnostic accuracy of out IRT-refined nine-item short BHS reported in our study might be specifically related to the present population used. Authors of

study Reise and Waller (94) showed that items selected by NIRT models were able to discriminate within a particular range of the latent dimension or in a specific population of interest. This means that if one is interested into monitoring hopelessness in a population of healthy people, it is appropriate to have items that discriminate in the low-to-average trait range.

Second, for some authors, the Mokken analysis represents an explorative approach to the development and validation of clinical scales (95, 96). For example, Meijer and Baneke (97) recommended using NIRT models to investigate the data structure and to understand how items were functioning before applying parametric IRT. Future studies may apply parametric IRT models (e.g., two parameter [2PL] and four parameter [4PL] models) to test if the behavior of the specific responses may assume a specific logistic curve. For example, applying a 4PL model to the BHS items could reveal that the probability that individuals with severe hopelessness trait manifest a specific symptom less than the 100%.

Third, social desirability or other distortions in test responses could affect self-report measures and consequently our results. Fourth, we did not investigate the predictive validity, or further important aspects of validity of this IRT-refined 9-item short BHS. Establishing predictive validity between the self-report or screening tool and a criterion measure becomes mandatory (98). Future studies are necessary to test the present refined measure with an already well-established measure, i.e. to predict suicidal ideation and/or attitude in medical inpatients and outpatients.

CONCLUSIONS

Since its development, the Beck Hopelessness Scale was tested across different patient groups. Its shortening without a substantial loss of its predictive validity would be extremely useful in vulnerable patients, such as those to which it is addressed.

Nine best-fitting items of the Beck Hopelessness Scale satisfied the assumptions of local independency, monotonicity, and invariance of the item ordering when all the items were submitted to Mokken Scale Analysis in a large sample of adult psychiatric inpatients.

The IRT-based 9-item BHS showed good discriminant validity in categorizing psychiatric inpatients with high/medium suicidal risk and patients with and without suicide attempts, with high sensitivity (>.90). Thus, it could be used as a valid screening tool for suicidal risk assessment among psychiatric inpatients.

To our best knowledge, this study is the first focused on the application of the Item Response Theory approach to the refinement and shortening of the BHS. Previous short versions of this scale were developed within the Classical Test Theory. However, with the Item Response Theory it is possible to build a reasonably coherent unidimensional scale whose items/symptoms can be treated as ordinal indicators of the theoretical construct of hopelessness, scaled along a single continuum.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to MI, marco.innamorati@unier.it; MP, maurizio.pompili@uniroma1.it.

ETHICS STATEMENT

The study protocol was reviewed and approved by the local research ethics review board (Sant'Andrea Medical Center, an affiliate of the Sapienza University of Rome, Italy). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC and MB designed the study and conducted the statistical analyses. LC, MI, MP, and MB interpreted the data. LC, MB, MI, and DL drafted the manuscript. MP and MI recruited the sample and collaborated in editing the final manuscript. All authors contributed to the article and approved the submitted version.

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OPINION
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Suicidality Assessment of the Elderly With Physical Illness in the Emergency Department

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INTRODUCTION

Taking into account and evaluating the presence of a physical illness plays a crucial role in the clinical encounter with the elderly who may present suicidal ideation (SI) and suicidal behavior (SB) (1, 2).

On the one hand, physical illness is associated with greater suicidality risk in the elderly. This association has been inferred from both quantitative and qualitative findings based on population and registry cohorts (3–5), case-control studies (6–13), psychological autopsies (14, 15), coroners' reports (16, 17), and suicide notes (17, 18) [for reviews, see (19, 20)]. This applies to SI/wishes to die (20–22) and the entire span of SB, including suicide attempts (SAs) and completed suicides [for reviews, see (20, 23, 24)].

On the other hand, a physical illness may render the suicidality assessment of the elderly complex for multiple reasons (25): a) the possible presence of uncommon or masking clinical features of both SB (indirect or passive SB, e.g. self-starvation) and psychiatric disorders associated with SB (e.g. atypical depressive disorders with prevalent somatic or cognitive symptoms) (26–28); b) the risk of overlooking and missing SB when severe illnesses coexist (29); c) the frequent reticence among the elderly in externalizing SI as they place more emphasis on their physical conditions (30–33); and d) the eventual caregivers' representations of suicide as a more "understandable" act when facing greater physical fragilities and the intrinsic proximity of the end of life (34, 35). S. de Beauvoir wrote in the 1970s about the feeling of resignation or impotence of what may be considered an inexorable outcome: "Some suicides of elder people follow states of neurotic depression that one has not been able to heal; but most are normal reactions to an irreversible, desperate situation, experienced as intolerable" (36).

A large number of the elderly who died by suicide had had recent contact with primary healthcare professionals, including in emergency departments (EDs). Approximately 50 to 70% of individuals had consulted a healthcare professional in the 30 days preceding their death (32, 37), and more than 80% had done so in the six months prior to death (38). In most of these cases, the last consultation had focused on physical complaints in the absence of a psychiatric diagnosis (32, 37). Notably, affective disorders in the geriatric population can go undiagnosed by ED physicians (39).

The aim of this opinion paper is to point out the opportunity of assessing suicidality in the elderly when they present to the ED with physical illness. To this purpose, it could be useful to overview some both controversial and consensual key points on suicidality risk in the elderly, as discussed below.

DISCUSSION

Some Controversial Matters

When considering whether the presence of the physical disease is a significant risk factor for suicidality in older versus younger patients, a legitimate objection could be that the former has statistically higher somatic susceptibility. The same objection could be raised to the argument that an the increasing rate of SI/wishes to die (21), SAs (40), and completed suicides (5, 6, 8, 41) in the elderly has been observed in the presence of multiple somatic illnesses (a "burden of physical illness"). The answer to this question is probably addressed by qualitative studies, from which the subjective attributions of mental suffering as a consequence of one or more physical illnesses have emerged (14, 15, 17, 18).

Another debated point is the extent to which mental comorbidities contribute to the suicidality risk in the elderly (1). Psychiatric disorders such as major depressive disorder and substance use disorder have been shown to play a significant role in death by suicide among individuals older than 65 years (6, 42, 43). While some studies found that the effect of physical illness on suicidality risk persisted even after controlling for comorbid mental disorders (5, 9), others have relegated physical illness to a secondary contributing risk factor (16, 29). Major depressive disorder, in analogy with functional impairment or pain, could be considered as a possible mediating factor that partially explains the link between physical illness and suicidality risk (physical illness causes/contributes to the occurrence of depressive disease and the latter increases suicidality risk); similarly, substance use disorder (e.g., alcohol, benzodiazepine, or opioids abuse) may be included in this reciprocal link, initially interpreted as tentative of self-medication that eventually exacerbates both major depression and suicidality (4, 19, 28, 43–45).

And Some Common Clinical Features

In recent years, studies have highlighted the role of physical illness, especially among the oldest patients. Physical illness exerted a stronger motivational effect for suicide in old-old (≥75 years old) attempters compared to their young-old (65–74 years old) and middle-aged (64–50 years old) counterparts (46). One-third of those 70+ years of age who had attempted suicide attributed their act to somatic distress (47). Among those who had died by suicide, a greater incidence of physical illness was reported in the old-old compared to the young-old (38, 48) and middle-aged adults (38). Those in whom the reason for completed suicide was attributed to the presence of physical illness were older than those in whom the reason was attributed to the presence of mental illness (17). Hospitalization due to physical illness had the greatest influence on the risk of completed suicide among the old-old (41).

Contrary to findings in the general population, in the elderly non-lethal events seem to be more common in males (1), especially among the young-old where this has been attributed to so-called "elderly adolescentism" (49). Improvements to welfare and healthcare may have led to a rejuvenation of the 65–74 age group, which could be at the origin of certain behavioral patterns such as SA intended as a "cry-for-help" in response to environmental adversities (49). In this case, the stressful context could be represented by the occurrence of one or more physical illnesses (49). In studies that did not utilize the distinction between old-old, middle-aged, and young adults, the proportion reporting that SA was due to physical illness did not differ between males and females in the 70+ age group (47, 50). As far as completed suicides, the presence of physical illness should be considered as a warning sign, especially in males (15), in particular, those with serious and multiple illnesses (6). The risk of completed suicides has been shown to differ between males than females depending on the type of physical illness (4). In the old-old patients, hospitalization with a physical illness conferred a greater risk of completed suicides in males (41).

Globally, neurological diseases, pain, and oncological conditions occurred more frequently in the suicidal elderly. An association between neurologic diseases and SI, SA, and SB was observed (6, 12, 51–55), especially for stroke and hemiplegia (4, 11, 13, 56, 57), epilepsy (4, 8, 45, 58), and dementia (13, 59, 60). A greater rate of SI was documented in patients with Parkinson's disease (60, 61), and the role of sub-thalamic deep brain stimulation (DBS) on suicidality risk in patients treated for extrapyramidal movement disorders is still discussed [for a recent systematic review, see (62)]. The pain was significantly and independently associated with SI/wishes to die (21, 22, 63–66) and completed suicides (8, 10, 17). Oncological conditions in the elderly were shown to be associated with SI, and the entire span of SB (3, 4, 6, 7, 11, 13, 17, 67, 68).

CONCLUSIONS

The elderly who attend the ED with a physical illness are vulnerable individuals and the ED visit often represents a "sentinel event" that may signal a medical or psychosocial fracture in their established equilibrium (69, 70).

In addition to investigation and management of physical illness, attention needs to be paid to its psychic repercussion

on the elderly. This also includes addressing and assessing suicidality that, for the reasons synthesized in the introduction, is frequent in this population but can be missed by the clinician. In a specular way, recommendations on suicidality prevention measures in the elderly encourage a so-called "multi-faceted" approach, which emphasizes the in-depth consideration of aspects related to the presence of physical illness, considered among the most relevant determinants of the elderly's SI and SB (37, 71–74).

This opportunity involves both primary healthcare professionals and psychiatrists. The ED represents a clinical setting where the elderly with both physical illness and greater

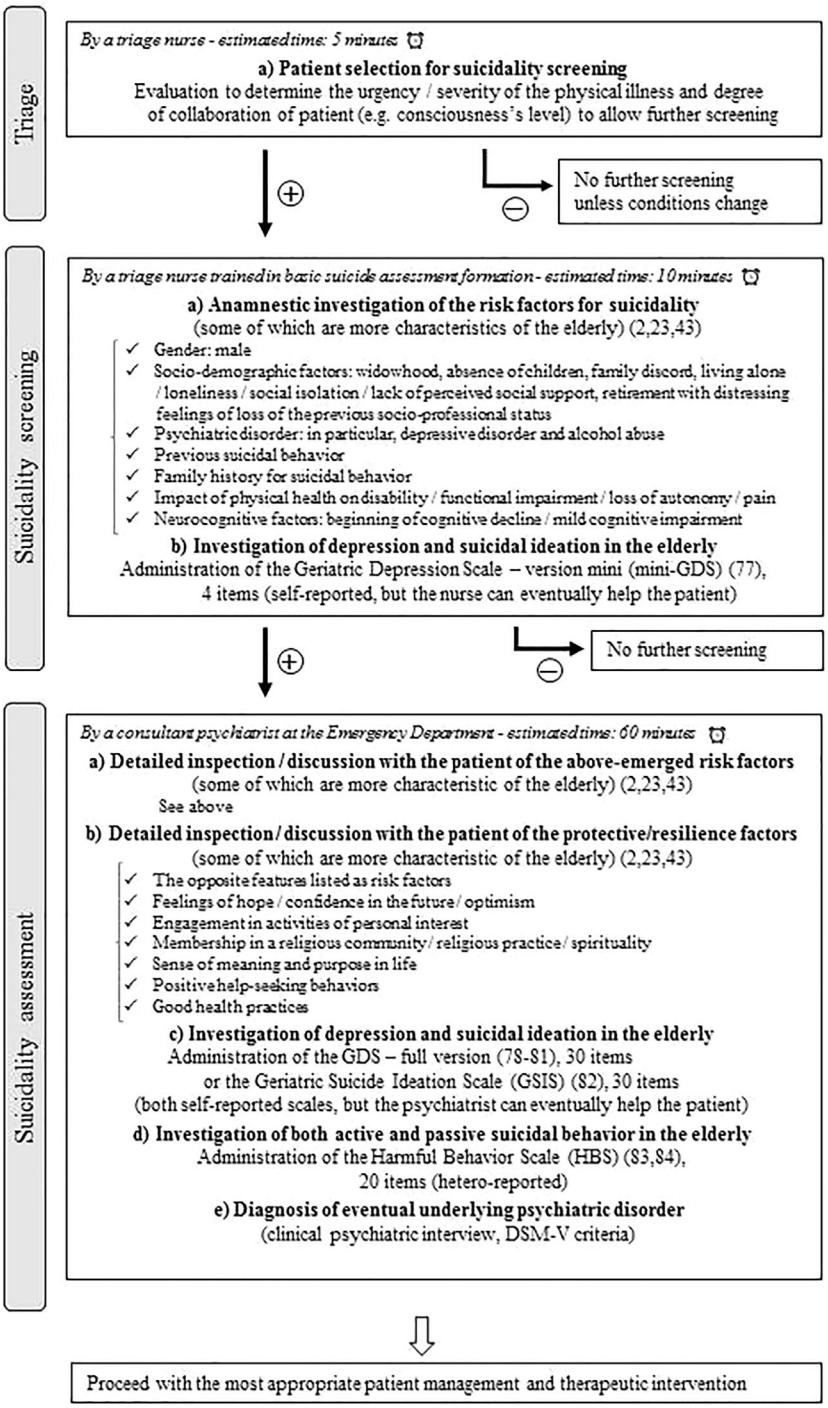

FIGURE 1 | A proposal for a potential tiered suicidality assessment in the elderly with physical illness attending an Emergency Department.

suicidality risk frequently converge. Conversely, the ED, by offering an integrated somatic/psychiatric approach, constitutes a precious resource for this complex and fragile population.

Not every elderly patient who arrives at the ED with physical illness can be screened for suicide. Thus, there are some pragmatic considerations, which would limit this approach in the clinical practice. They are dictated by the clinical condition of the patient (e.g. urgency/severity of the physical illness, consciousness's level) and the amount of resources, regarding both staff and time, which can be allotted for the suicidality assessment. To achieve a more balanced cost-benefit ratio, we propose —mainly on the basis of a previous Canadian work (75)— a potential example of a tiered assessment (2, 23, 43, 76–83) **(Figure 1)**.

The ED, the place of what cannot be deferred, may be finally at the center of the clinical and human encounter with the elderly who, confronted with the possibility of approaching the end of their existences (perceived as more concrete or urgent by the presence of physical illness), present a moral pain experienced as non-repairable. The dialogue with these patients in the ED can constitute the beginning of a therapeutic relationship aimed at trying to understand the individual meaning to the urgency of their days, and therefore to explore an alternative to suicide as unique possibility to avoid the unbearable psychache.

Future research is needed to refine the comprehension of the suicidality peculiarities in the elderly population and translate it into clinical practice through an eventual feasible, validated, and consensual screening.

AUTHOR CONTRIBUTIONS

AC, AAm, MR, and JA researched the literature and drafted the primary manuscript. SM, MPr, AAg, and GS carefully revised the manuscript. GS, MA, GB, LM, and MPo supervised all steps of the work and provided the intellectual impetus. All authors contributed to the article and approved the submitted version.

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REVIEW
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Non-Coding RNAs in Psychiatric Disorders and Suicidal Behavior

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It is well known that only a small proportion of the human genome code for proteins; the rest belong to the family of RNAs that do not code for protein and are known as non-coding RNAs (ncRNAs). ncRNAs are further divided into two subclasses based on size: 1) long non-coding RNAs (lncRNAs; >200 nucleotides) and 2) small RNAs (<200 nucleotides). Small RNAs contain various family members that include microRNAs (miRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs). The roles of ncRNAs, especially lncRNAs and miRNAs, are well documented in brain development, homeostasis, stress responses, and neural plasticity. It has also been reported that ncRNAs can influence the development of psychiatric disorders including schizophrenia, major depressive disorder, and bipolar disorder. More recently, their roles are being investigated in suicidal behavior. In this article, we have comprehensively reviewed the findings of lncRNA and miRNA expression changes and their functions in various psychiatric disorders including suicidal behavior. We primarily focused on studies that have been done in *postmortem* human brain. In addition, we have briefly reviewed the role of other small RNAs (*e.g.* piwiRNA, siRNA, snRNA, and snoRNAs) and their expression changes in psychiatric illnesses.

Keywords: major depressive disorder, schizophrenia, bipolar disorder, long non-coding RNAs, microRNAs

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INTRODUCTION

Non-coding RNAs (ncRNAs) are defined as RNAs that are not translated into protein. Protein-coding genes occupy only a small proportion (<3%) of the entire genome (1). However, the remaining non-protein coding genes are not a simple transcriptional noise (1, 2); instead, ~80% of them are transcriptionally active with elaborate regulatory roles. A majority of them are now considered non-coding RNA genes (3–6). Based on the size of the nucleotides, ncRNAs are divided into small ncRNAs and long ncRNAs (lncRNAs). ncRNAs that contain <200 nucleotides (nt) belong to small ncRNA family. On the other hand, those containing more >200 nt belong to long lncRNA family. Small RNAs include microRNAs (miRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs). ncRNAs function *via* interactions with RNA, DNA, and protein. They regulate the

transcription of mRNAs and participate in alternative splicing and epigenetic modifications such as chromatin and RNA editing (7, 8). These regulatory functions can target either neighboring transcripts (cis) or loci that are distant from their own transcription (trans). Collectively, ncRNAs constitute a unique layer of gene regulation where they function as key intermediate regulators in conveying the message from genotype to phenotype states (9).

A large number of ncRNAs are abundantly expressed in the brain (10–12). In addition, the expressions of ncRNAs are brain region- and cell type-specific (13–16). Several studies have shown the role of ncRNAs in brain evolution, development, homeostasis, stress response, and neuroplasticity (14, 17–25). Brain expressed ncRNAs can also influence the development of psychiatric disorders such as schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BD) as well as neurodegenerative disorders (11, 19, 23, 26, 27). More recently, their role in suicidal behavior has been postulated (28–30). The effects of ncRNA expression changes are not restricted to the type of psychiatric disorders but, to a large extent, to different brain regions. Recent evidence suggests the inability of brain regions to act independently. Instead, they act in a coordinated manner *via* functional networks. In various neuropsychiatric disorders, voxel based neuroimaging has demonstrated specific roles of brain regions such as cortex (prefrontal, anterior cingulate), hippocampus, and amygdala (31). Although each of these brain regions has important roles, such as amygdala and prefrontal cortex in emotion (32) and prefrontal cortex and hippocampus in stress response (33), these brain regions crosstalk to each other *via* complex gene networks which could be mediated *vis* ncRNAs.

Earlier published reviews have primarily focused on miRNAs in psychiatric illnesses (34–36). This review comprehensively summarizes the relationship between various ncRNAs. Although the emphasis is given to lncRNAs and miRNAs, a range of other ncRNAs are also included to provide a glimpse into where the field stands and what should be the course of direction for future research. The review is restricted to studies in human *postmortem* brain, given that the role of peripheral ncRNAs is not very well established. We have discussed a few peripheral blood cell studies which are relevant to suicidal behavior. The criteria for selecting literature search are as follows: Electronic search was done using PubMed with search terms ncRNAs (microRNA, small interfering RNA, piwi-interacting RNA, small nucleolar RNA, and small nuclear RNA) AND psychiatric disorders (schizophrenia, major depressive disorder, and bipolar disorder). Each combination was performed separately. Additionally, *postmortem* research for non-suicide studies, and both *postmortem* brain and peripheral tissue research for suicide studies, were included in the search criteria.

LONG NON-CODING RNAS

Long Non-Coding RNAs in Brain Functions

Long non-coding RNAs (lncRNAs) are defined as RNAs having >200 nucleotides with low (in the form of short peptide) or no protein coding potential (37). LncRNAs are transcribed by RNA Polymerase II and are processed to mature RNA by the same method as protein-coding mRNAs (38). LncRNAs' lengths span ~100 kilo base-pairs (bp) and are shorter than mRNAs but have longer exons (39–41). They were originally considered to be the products of heterochronic genes (4) that control the temporal dimension of development; however, there are limitations to fully understand the function of lncRNAs from this point of view. Interestingly, the genomic structure of lncRNAs is strongly related to their function (42). In the early nineties, the X-inactive specific transcripts (Xist) and H19 were first discovered as non-protein coding RNAs by exploring cDNA libraries (43, 44). Since then, over 100,000 lncRNA genes have been found and their number is still increasing (45). Recently, several lncRNA functions have been revealed. For example, they participate in chromatin modifications (46, 47); act as 'sponges' that prevent miRNA functions (48); act as scaffolds that provide docking sites for proteins (49); serve as activators and suppressors of mRNA transcription (50); and act as regulators of splicing patterns (50). The functions of lncRNAs are depicted in **Figure 1**.

In terms of functions in the brain, lncRNAs are strongly related to brain development (51). In this capacity, lncRNAs participate in spatiotemporal regulation of proliferation and differentiation of pluripotent stem cells (21, 52). High-resolution and high-throughput technologies, such as microarray and RNA-sequencing, have helped in examining the number and pattern of lncRNA expression in the brain. Microarray detects the expression of a large number of RNAs simultaneously, whereas RNA-seq detects both known and novel transcripts and quantifies a large dynamic range of expression levels with absolute rather than relative values. Ramos et al. (53) reported that more than 3,600 lncRNAs are expressed among three different brain regions: subventricular zone, olfactory bulb, and dentate gyrus. Clustering analysis revealed that lncRNAs have a tissue-specific expression pattern (39, 54). A study, using microarray analysis, investigated differential lncRNA expression in the temporal cortex ranging from infancy to adulthood (0.92–43.5 years old) and concluded that the expression pattern of lncRNA changes with age (55). At functional levels, several lncRNAs are involved in regulating neuronal development. This occurs through complex interactions between lncRNAs and other factors in transitioning neural stem cell to progenitors and eventually to differentiated neurons. Some of the lncRNAs that promote the differentiation of neural stem cells include Brn1b, RMST, and TUNA (56–58). EVF2, the first found central nervous system-specific lncRNA, regulates the differentiation of GABAergic neurons (18). The GABA system has been shown to be consistently involved in several psychiatric disorders such as SCZ (59–61), MDD (62), and BD (63). Another lncRNA, Pnky, promotes neural proliferation (64, 65). A recent study has shown that antisense lncRNAs also regulate key proteins related to psychiatric disorders. An inhibition of brain-derived neurotrophic factor (BDNF) antisense RNA (BDNF-AS) causes two- to sevenfold increase in BDNF protein level, which leads to neuronal outgrowth, differentiation, survival, and proliferation (66). An interaction between BDNF and neuropsychiatric disorders is well documented (67, 68). In addition, the mechanism of action of

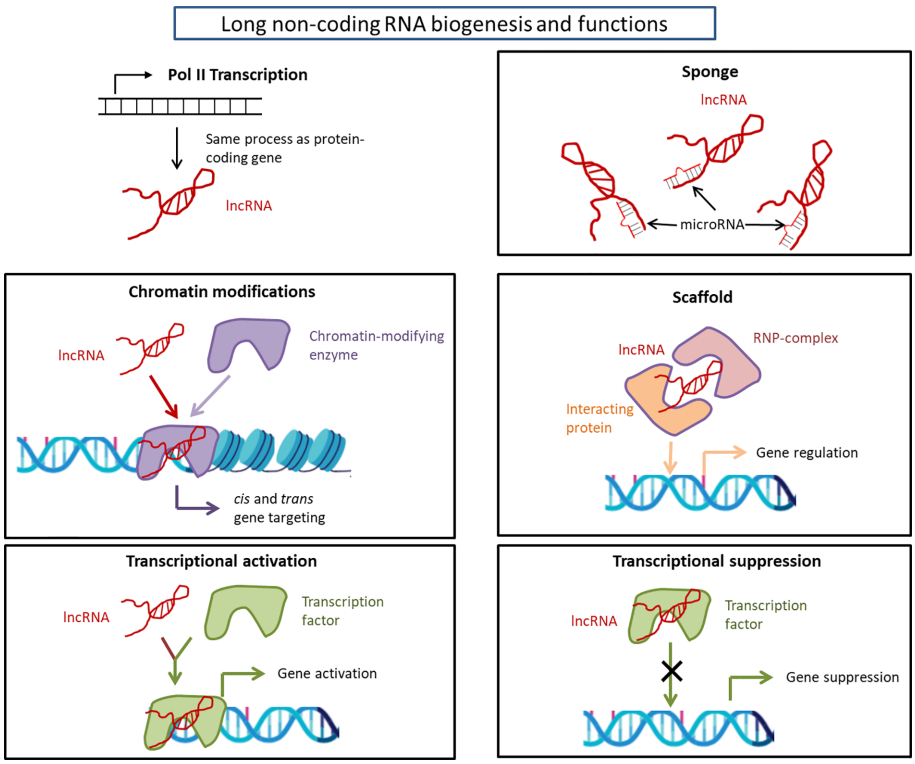

FIGURE 1 | Long non-coding RNA biogenesis and functions. Long non-coding RNAs are transcribed by RNA polymerase II and are processed to mature RNA by the same method as protein-coding mRNAs as detailed in the text. The considerable functions of lncRNAs are: chromatin modification, transcriptional activation/suppression, sponge, and scaffold. The functions of lncRNAs depend on the type of lncRNAs. lncRNA, long non-coding RNA; RNP, ribonucleoprotein.

antidepressants (69) and electroconvulsive therapy (70) also involve changes in the levels of BDNF, both centrally and peripherally. Not only do lncRNAs impact BDNF, but changes in the expression of a large number of lncRNAs have been shown following 1 h BDNF treatment in cultured neuronal cells (71). This shows that under neuronal environment, a feed forward and feedback loop might exist between neurotrophin signaling and lncRNA expression with the potential to develop effective therapeutic strategy in psychiatric conditions.

Long Non-Coding RNAs in Psychiatric Disorders

Examining the role of ncRNAs in psychiatric illnesses is an emerging field. Two recent studies used amygdala from SCZ subjects to decipher the role of lncRNAs in this disorder (**Table 1**). Tian et al. (72) examined lncRNA expression by RNA-seq using 21 SCZ and 24 healthy control subjects. They found alterations in the expression of 345 lncRNAs (104 up- and six downregulated) in SCZ subjects. Subsequently, they divided 21

TABLE 1 | LncRNA expression changes in psychiatric disorders based on *postmortem* brain studies.

Brain areas	Sample size	Methods	lncRNA expression changes		lncRNA functions and roles in disease conditions	Citations
			Upregulation	Downregulation		
Amygdala	21 SCZ and 24 Controls	RNA-seq	104 lncRNAs	AC140542.2, AP001347.6, LINC01011, SOCS2-AS1, AP003774.4, AC004540.5	Dysregulated lncRNAs were associated with protein synthesis, blood vessel development, nervous system pathways, and immune system pathways	(72)
Amygdala	22 SCZ and 24 Controls	RNA-seq	170 lncRNAs	80 lncRNAs	Two important lncRNAs (RP11-724N1.1 and RP11-677M14.2) located in the regions previously associated with SCZ based on GWAS are included	(73)

lncRNA, long non-coding RNA; SCZ, Schizophrenia.

SCZ subjects into nine undifferentiated, seven disorganized, and five paranoid. Individually, they found 155 up- and 17 downregulated lncRNAs in the undifferentiated SCZ group, 39 up- and six downregulated lncRNAs in the disorganized SCZ subjects, and no significant alteration in paranoid SCZ subjects when compared with control subjects. They performed gene set enrichment analysis to reveal the gene ontology terms associated with dysregulated lncRNAs (all SCZ *vs* control subjects) and found that dysregulated lncRNAs were associated with protein synthesis, blood vessel development, nervous system pathways, and immune system pathways. In another amygdala study, Liu et al. (73) used RNA-seq for detecting dysregulation of lncRNAs in 22 SCZ subjects and 24 healthy controls. Transcriptome data identified 250 lncRNAs that showed significant expression differences between SCZ and control subjects. The study further focused on two specific lncRNAs (upregulated RP11-724N1.1 and downregulated RP11-677M14.2), which were shown to be associated with SCZ based on previous genome-wide association study (GWAS). Additional analysis by dividing SCZ subjects into three subtypes revealed the dysregulation of RP11-724N1.1 in the undifferentiated subtype and RP11-677M14.2 in the paranoid subtype. RP11-724N1.1 overlaps the CNNM2 gene locus, which has a key role in the neurodevelopmental process (74). On the other hand, RP11-677M14.2 overlaps the neurogranin (NRGN) gene locus. Several SNPs of the NRGN gene have been associated with onset (75–77), intellectual disability (75), and anterior cingulate cortex (ACC) volume (78) in SCZ subjects. These amygdala studies suggest that not only are lncRNAs involved in SCZ pathophysiology, but they can also differentiate subtypes of SCZ.

lncRNAs and Suicidal Behavior

There are four studies that show a relationship between suicidal behavior and lncRNA expression changes. Of them, three studies explored lncRNA expression in the brain (one in ACC and two in the dorsolateral prefrontal cortex [dlPFC]), and one in the blood (**Table 2**). Zhou et al. (79) compared lncRNA expression levels in rostral ACC between 26 MDD suicide and 24 healthy control subjects by RNA-seq. After considering nominal p values ($p < 0.05$), without multiple testing, 364 out of 2,670 lncRNAs were differentially regulated; of them, 60% (217 lncRNAs) were downregulated. After genome-wide multiple testing, 15 upregulated and eight downregulated lncRNAs reached statistical significance. Potential cis-targets for significantly dysregulated 23 lncRNAs based on RNA-seq data showed that six lncRNAs (RP11-326I11.3 *vs* IRF2; RP11-273G15.2 *vs* LY6E; CTD-2647L4.4 *vs* HMOBX1; CTC-487M23.5 *vs* REEP5; RP1-269M15.3 *vs* PTPRT; RP11-96D1.10 *vs* NFATC3) were significantly correlated with one antisense or overlapping gene. All of them were found to be nominally differentially expressed

TABLE 2 | LncRNA expression changes in *postmortem* brain of suicide subjects.

Brain areas and blood source	Sample size	Methods	lncRNA expression changes		lncRNA functions and roles in disease conditions	Citations
			Upregulation	Downregulation		
ACC	26 MDD suicide and 24 Controls	RNA-seq and qPCR validation	SNORD3C, LLNLF-65H9.1, RP1-269M15.3, AC006003.3, AC012507.3, AC013460.1, C9orf106, DYX1C1-CCPG1, RP1-63G5.5, RP11-1186N24.5, RP11-1391J7.1, RP11-143K11.5, RP11-273G15.2, RP11-434C1.1 ZNF833P	RP11-453F18_B.1, RP11-96D1.10, AC004019.18, CTC-487M23.5, CTD-2647L4.4, RP11-326G21.1, RP11-326I11.3, RP11-326I11.5	The target genes Interferon regulatory factor 2 (IRF2, NM_002199), Lymphocyte antigen 6E (LY6E, NM_002346), and heme oxygenase (decycling) 1 (HMBOX1, NM_002133) (RP11-326I11.3, RP11-273G15.2, and CTD-2647L4.4) were successfully validated by qPCR	(79)
dlPFC	101 non-suicide, 50 non-violent suicide, 77 violent suicide (SCZ, MDD, and BD)	RNA-seq	LINC01268		Violent suicide group and aggressiveness group had higher expression of LINC01268	(28)
dlPFC	77 non-suicide, 13 non-violent suicide, and 16 violent suicide (SCZ)	RNA-seq			LOC285758 expression was associated with violent suicide	(80)
PBMC	63 MDD non-suicidal ideation, 57 MDD suicidal ideation, and 63 Controls	qPCR		TCONS_00019174, ENST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, NONHSAT142707		(30)

ACC, Anterior Cingulate Cortex; BD, Bipolar Disorder; dlPFC, dorsolateral prefrontal cortex; lncRNA, long non-coding RNA; MDD, Major Depressive Disorder; PBMC, Peripheral Blood Mononuclear Cell; SCZ, Schizophrenia.

except REEP5. With an additional qPCR approach, the authors validated three out of five genes (IRF2, LY6E, and HMBOX1). These genes are functionally related to interferon signaling, which plays a key role in CNS homeostasis and in psychiatric disorders (81).

Punzi et al. (80) revealed a correlation between violent suicide and lncRNA LOC28758 expression in dlPFC of SCZ subjects that included 77 non-suicides, 13 non-violent suicides, and 16 violent suicides. LOC28758 is located in the MARCKS gene, which was also found to be significantly highly expressed in violent suicides than non-suicides and non-violent suicides. In a recent study, the authors also examined lncRNA expression changes in dlPFC by RNA-seq (28). LINC01268 expression was significantly higher in suicide subjects compared to non-suicide subjects. Note that both suicide and non-suicide groups included three psychiatric disorders (SCZ, MDD, and BD). Subsequently, they divided the suicide groups into violent suicide and non-violent suicide (poisoning or asphyxia = nonviolent; others = violent). The violent suicide group had higher expression of LINC01268 than the non-suicide group, but the non-violent group did not show any change. Additionally, they explored quantitative trait locus (eQTL) of LINC01268 by genotyping 23 SNPs located within 100 kb up and downstream of the gene coordinates. Of those, only rs7747961 could regulate the LINC01268 expression (C-carriers > non-C-carriers). Based on the Brown–Goodwin questionnaire score, they revealed that LINC01268 expression was higher in the aggressive group than in the non-aggressive group. Lastly, weighted correlation network analysis (WGCNA) was performed with RNA-seq data to verify the relationship between LINC01268 and the co-expression gene set. WGCNA is a systems biology method for detecting the modules correlated with clinical traits by a soft-threshold algorithm. A module including 224 genes and LINC01268 was created. It was found that among 224 genes, P2RY13, a purinergic receptor present in both the peripheral immune system and in the brain, had a strong correlation with LINC01268.

One peripheral blood mononuclear cell (PBMC) study was conducted to identify change in lncRNAs in MDD suicide subjects (63 MDD no-suicidal ideation, 57 MDD with suicidal ideation, and 63 control subjects) by qPCR method (30). qPCR method identifies amplified fragments during the PCR process, but only a smaller number of genes can be measured at once compared to RNA-seq or microarray. Six lncRNAs (TCONS_00019174, NST00000566208, NONHSAG045500, ENST00000517573, NONHSAT034045, and NONHSAT142707), previously confirmed to be downregulated in MDD subjects, were selected for this study. All six lncRNAs were downregulated in MDD with suicidal ideation, compared with MDD no suicidal ideation and control groups. The authors concluded that six lncRNAs may possibly serve as biomarker for suicidal ideation among MDD patients. Another study showed that decreased expression of TCONS_00019174 was associated with depression and expression change was rescued by antidepressant treatment (82). Additionally, an *in vitro* experiment showed that TCONS_00019174 was negatively correlated with phosphorylated-GSK3β (p-GSK3β) protein and β-catenin. Further, the overexpression of NONHSAG045500 inhibited the expression of serotonin transporter (SERT), while siRNA interference of NONHSAG045500 induced the upregulation of SERT (83). These studies indicate that the peripheral expression change of lncRNAs can have functional relevance and may be worth pursuing in the brain.

microRNAs

MicroRNAs (miRNAs) are the best studied ncRNAs in terms of functionality and relevance to psychiatric illnesses. Averaging 22 nucleotides in length, miRNAs are synthesized *via* several enzymatic processes. Initially, primary miRNA (pri-miRNA) is transcribed from an encoded gene. Next, RNase III enzyme Drosha generates precursor miRNA (pre-miRNA) by removing the flanking segments and -11 bp stem region of pri-miRNA. Drosha requires DiGeorge syndrome critical region 8 (DGCR8) to complete this process. pre-miRNAs are then translocated to cytoplasm with the help of Exportin-5 (XPO5). In the cytoplasm, dicer, a double-stranded RNA endoribonuclease, converts pre-miRNA into double-stranded mature miRNA. Dicer requires TAR RNA-binding protein (TRBP) as a cofactor (84–88). Finally, one strand of miRNA/miRNA* duplex loads into Argonaute homologue protein (Ago) to make RNA-induced silencing complex (RISC). RISC/miRNA complexes mainly work as suppressors of mRNA expression (**Figure 2**).

Several miRNAs play a key role in modulating synaptic functions and neural structures. Overexpression of miR-125b can disrupt spine structure, whereas sponging of endogenous miR-125b can induce the prolongation of dendritic protrusions (89). Introduction of miR-132 in hippocampal neurons can induce dendrite morphogenesis, which is caused by the regulation of GTPase-activating protein (p250GAP) (90, 91). At the behavioral level, transgenic miR-132 mice show altered cognitive functions through repression of MeCP2 translation, which is implicated in Rett Syndrom and mental retardation (92). The role of miRNAs in various psychiatric illnesses has been studied extensively. A summary of the human *postmortem* brain miRNA findings in psychiatric illnesses is provided in **Table 3**. Below, we discuss miRNA studies in human brain pertaining to SCZ, MDD, and BD as well as suicidal behavior.

miRNAs and Schizophrenia

MiR-137 is a well-known miRNA in schizophrenia studies (110). The first report of the involvement of miR-137 came from a GWAS study which linked a risk variant rs1625579 within miR-137 to SCZ (111). A previous study had reported that target genes for miR-137 are associated with activation in the dlPFC (112). Guella et al. (102) subsequently examined miR-137 and its target genes in the dlPFC of SCZ and BD subjects. MiR-137 expression in the dlPFC was not different between diagnoses. Interestingly, when the genotype of rs1625579 was considered, significantly lower miR-137 expression was found along with higher expression of TCF4, a target gene of miR-137, in the homozygous TT subjects compared to TG and GG subjects within the control group. The miR-137 expression was region specific with amygdala and hippocampus having the highest levels. These results suggest that miR-137 and associated TCF4 gene may be risk factors for SCZ. Using miRNA-seq, one amygdala study

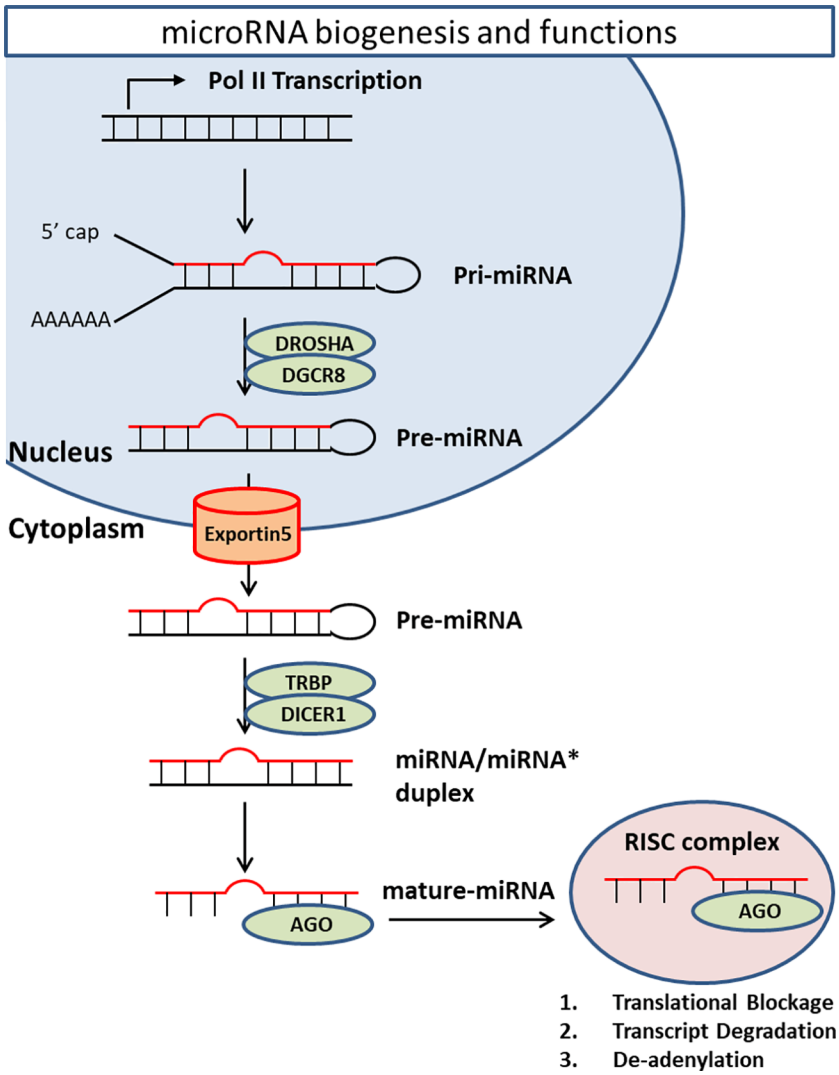

FIGURE 2 | MiRNA biogenesis and functions. Primary miRNA is transcribed from encoded gene. RNase III enzyme Drosha generates precursor miRNA by removing the flanking segments and -11 bp stem region of pri-miRNA. Drosha requires DiGeorge syndrome critical region 8 (DGCR8) to complete this process. pre-miRNAs are then transported from nucleus to cytoplasm by a transporter Exportin-5 (XPO5) in a Ran-GTP-dependent manner. In the cytoplasm, Dicer converts pre-miRNA into double-strand mature miRNA. Dicer requires TAR RNA-binding protein (TRBP) as a cofactor. Finally, one strand of miRNA/miRNA* duplex loads onto Argonaute homolog protein (Ago) to make RNA-induced silencing complex (RISC). RISC/miRNA complex mainly works as suppressor of mRNA expression through translational blockage, transcript degradation, and deadenylation.

showed seven upregulated and 11 downregulated miRNAs (73); of them, miR-1307 was located on a locus previously found to be associated with SCZ risk allele rs11191419 in GWAS (113).

Using custom microarray, Perkins et al. (93) studied miRNA expression in BA9 of subjects with SCZ or schizoaffective disorder and compared them with psychiatrically unaffected individuals. The study found 15 downregulated and one upregulated miRNA in these subjects. They further examined sequences in the pri-miRNA motifs of those dysregulated miRNAs and found that several miRNAs shared the same sequence. For example, miR26b, miR-30a, miR-30b, and miR-7-1 had UGAGNCUU upstream sequences, whereas miRNAs miR-9-1, miR-9-2, miR-9-3, miR-7-3, and miR-30e had GUCNCUUC upstream sequences in their corresponding pre-miRNAs. This suggests the possibility that the processing of pri-miRNA to pre-miRNA might be affected, which could eventually be related to miRNA expression changes. Moreau et al. (94) reported that 19% of miRNAs in BA9 were altered based on diagnostic classification among SCZ, BD, and control subjects. Interestingly, all of the downregulated miRNAs in SCZ were downregulated in BD subjects, supporting the similarity of the genetic background between SCZ and BD. Banigan et al. (95)

TABLE 3 | miRNA expression changes in psychiatric disorders based on *postmortem* brain studies.

Disease	Brain areas	Sample size	Methods	miRNA expression changes		Successfully validated miRNAs by qPCR	miRNA roles and other findings	Citations
				Up-regulation	Down-regulation			
SCZ	Amygdala	22 SCZ and 24 Controls	miRNA-seq	miR-196a-2, -1975, -34c, -451, -34a, -375, -144	miR-663, -639, -132, -124-2, -212, -483, -886, -585, -424, -520d, -1307		miR-1307 locus included rs11191419 previously reported in GWAS	(73)
	BA9	13 SCZ, 2 schizoaffective, and 21 Controls	Microarray	miR-106b	miR-26b, -30b, -29b, -195, -92, -30a-5p, -30d, -20b, -29c, -29a, -212, -7, -24, -30e, -9-3p	miR-26b, -30b, -92, -24, -30e		(93)
	BA9	35 SCZ, 33 BD, and 33 Controls	qPCR	19% of 234 miRNAs and 18 small nucleolar RNAs were changed due to SCZ or BD				(94)
	BA9	8 SCZ, 9 BD, and 13 Controls	Microarray	miR-497		miR-497	Exosome sample	(95)
	BA9	15 SCZ and 15 Controls	Microarray	Let-7d, miR-101, -105, -126*, -128a, -153, -16, -181a, -181d, -184, -199a, -20a, -219, -223, -27a, -29c, -302a*, -302b*, -31, -33, -338, -409-3p, -512-3p, -519b, -7		Let-7d, miR-128a, -16, -181b, -181a, -20a, -219, -27a, -29c, -7	Primary- and precursor-miR-181b and miRNA biogenesis-related enzymes were altered	(96)
	BA46	35 SCZ, 35 BD, and 35 Controls	TLDA	miR-34a, -132, -132*, -212, -544, -7, -154*				(97)
	BA46	37 SCZ/ schizoaffective and 37 Controls	Microarray	miR-519c, -489-3p, -652, -382, -532, -199a*, -17-5p, -542-3p, -199b, -592, -495, 487a, -425-5p, -152, -148b, -134, -150, -105, -187, -154, -767-5p, -548b, -590, -502, -452*, -25, -328, -92b, -433, -222	miR-512-3p, -423, -193a	miR-17, -107, -134, -328, -382, -652	miRNA biogenesis-related enzymes were upregulated	(98)
	BA46	35 SCZ, 32 BD, and 34 Controls	qPCR		miR-346			(99)
	BA46	34 SCZ and 109 Controls	miRNA-seq	miR-3162, -936			The correlation-based hierarchical clustering analysis made nine miRNA groups	(100)
	dlPFC	35 SCZ, 31 BD, and 34 Controls	Microarray		miR-132, -132*		miR-132 was downregulated by NMDA antagonist in mice study	(101)
	dlPFC and several regions	1st set (7 SCZ, 9 BD, and 10 Controls) 2nd set (35 SCZ, 34 BD, and 35 Controls)	qPCR	miR-137 was not significantly changed				(102)
	STG	15 SCZ and 15 Controls	Microarray	59 of 274 (21%) miRNAs		let-7e, miR-107, -15a, -15b, -16, -195, -181b, -20a, -26b, -19a		(96)
	STG	21 SCZ and 21 Controls	Microarray	let-7g, miR-181b		miR-181b	Visinin-like protein 1 (VSNL1, NM_003385) and Glutamate ionotropic	(103)

(Continued)

TABLE 3 | Continued

Disease	Brain areas	Sample size	Methods	miRNA expression changes		Successfully validated miRNAs by qPCR	miRNA roles and other findings	Citations
				Up-regulation	Down-regulation			
							receptor AMPA type subunit 2 (GRIA2, NM_000826) genes are potential target of miR-181b	
MDD	ACC	15 MDD, 8 BD, and 14 Controls	qPCR		miR-34a, -184			(104)
	BA44	14 MDD and 11 Controls	qPCR		miR-1202		miR-1202 regulates the expression of Metabotropic glutamate receptor 4 (GRM4, NM_000841) and predicts antidepressant response	(105)
	BA46	15 MDD and 15 Controls	qPCR	miR-124-3p				(106)
BD	ACC	15 MDD, 8 BD, and 14 Controls	qPCR		miR-34a, -132 -133a, -212		There was inverse correlation between nuclear receptor coactivator 1 (NCOA1, NM_003743) and miRNA-34a	(104)
	ACC	5 BD and 6 Controls	qPCR	miR-149			Glial cell derived exosome samples	(107)
	BA9	8 SCZ, 9 BD, and 13 Controls	Microarray	miR-29c		miR-29c	Exosome samples	(95)
	BA46	35 SCZ, 35 BD, and 35 Controls	TLDA	miR-22, -133b, -145, -145*, -154*, -504, -889	miR-29a, -32, -140-3p, -454*, -520c-3p, -573, -767-5p, -874			(97)
	BA46	35 SCZ, 32 BD, and 34 Controls	qPCR	miR-346 was not significantly changed				(99)
	BA46	1st set (7 SCZ, 9 BD, and 10 Controls) 2nd set (35 SCZ, 34 BD, and 35 Controls)	qPCR	miR-137 was not significantly changed				(102)
	dlPFC	35 SCZ, 31 BD, and 34 Controls	Microarray	miR-32, -188-5p, -187, -196b, -297, -383, -490-5p, -449b, -513-5p, -876-3p				(101)
	Hippocampus dentate gyrus granule cells	15 SCZ, 15 MDD, 15 BD, and 15 Controls	RNA-seq	miR-182 was not significantly changed			Genotype of rs76481776 affects the miR-1842 expression	(108)
	Cerebellum	29 BD and 34 Controls	qPCR	miR-34a			Upregulation was also confirmed in induced neurons from human fibroblast	(109)

ACC, Anterior Cingulate Cortex; BA, Brodmann area; BD, Bipolar Disorder; dlPFC, Dorsolateral Prefrontal Cortex; miRNA, microRNA; MDD, Major Depressive Disorder; SCZ, Schizophrenia; STG, Superior Temporal Gyrus; TLDA, TaqMan Low Density Arrays.

explored miRNA expressions in exosomes of BA9. Based on the microarray data, they validated the upregulation of miR-497. Several studies have shown that exosomes in the CNS may play a role in neuronal communications, nerve regeneration, synaptic plasticity, and immune response (114, 115).

Beveridge et al. (96) detected 25 upregulated miRNAs in BA9 of SCZ subjects; of them, 10 miRNAs (let-7d, miR-128a, miR-16, miR-181b, miR-181a, miR-20a, miR-219, miR-27a, miR-29c, and miR-7) were validated with qPCR. They also revealed that the biogenesis of miR-181b was perturbed in SCZ possibly due to the altered expression of pri- and pre-miR-181b and miRNA biogenesis-related enzymes DGCR8, DROSHA, and DICER1. Kim et al. (97) detected 7 upregulated miRNAs in another prefrontal cortical area BA46 of SCZ subjects. Of them, miR-132 was highly expressed in the forebrain and was regulated by cAMP response element-binding (CREB) and extracellular signal regulated kinase (ERK) signaling. Both CREB and ERK are targets of antipsychotic drugs (91, 116). On the contrary, Miller et al. (101) reported downregulation of miR-132 in dlPFC of SCZ subjects. The authors found that NMDA antagonist, when administered to adult mice, resulted in lower expression of miR-132 in the prefrontal cortex. Since miR-132 is highly expressed in the postnatal period, a period of synaptic pruning thought to be related to the mechanism of neurodevelopmental susceptibility to SCZ through NMDAR signaling (91), it was concluded that dysregulation in miR-132 and associated target genes may contribute to the neurodevelopmental and morphological abnormalities shown in SCZ.

Santarelli et al. (98) investigated miRNA expression in BA 46 of subjects with SCZ and schizoaffective disorder. They found differential regulation of 28 miRNA in the SCZ group compared to controls. Of them, six miRNAs (miR-17, miR-107, miR-134, miR-328, miR-382, and miR-652) were validated by qPCR. They also found increased expressions of miRNA biogenesis enzymes DGCR8, DROSHA, and DICER1 and concluded that miRNA changes may occur due to disruption in mRNA biogenesis. In another study, Zhu et al. (99) found lower expression of miR-346 in BA46 of SCZ subjects. Interestingly, miR-346 is positioned in intron 2 of the glutamate receptor ionotropic delta 1 (GRID1) gene, which was found to be downregulated in SCZ subjects. GRID1 is an important gene related to SCZ susceptibility (117). Recently, temporal dynamics of miRNA expression in dlPFC as well and their dysregulation was studied in SCZ subjects (100). It was found that miRNAs that were enriched in infants were upregulated, and those enriched in prepuberty were downregulated in SCZ. The targets of these miRNAs included genes encoding for synaptic proteins and were found to be altered in SCZ subjects. In addition, a significant upregulation in the expression of miR-3162 and miR-936 was noted. These results suggest the miRNAs may participate in the development of dlPFC. In addition, miRNAs that are enriched in infancy and prepuberty may be critical in the deployment of SCZ pathology.

Two other reports which used superior temporal gyrus (STG) also linked miRNA abnormalities to SCZ (96, 103). Both studies showed upregulation of miR-181b in SCZ subjects. Using reporter assay, one study revealed that miR-181b could regulate VSNL1 and GRIA2 genes (103). Expression changes in GRIA2 have been reported in BA46 (118) and the medial temporal lobe (119, 120) of SCZ subjects.

miRNAs and Major Depressive Disorder

A number of studies have linked miRNA changes to major depressive disorder (MDD) pathophysiology. Azevedo et al. (104) analyzed select 29 miRNAs by qPCR in ACC of subjects with MDD, BD, and control subjects. They found that miR-132, miR-133a, and miR-212 were differentially regulated in BD, miR-184 in MDD, and miR-34a in both MDD and BD. None of the miRNAs survived significance after multiple corrections. *In silico* analysis identified NCOA1, NCOA2, and PDE4B as a target of miR-34a, while NCOA2 and PDE4B were targeted by miR-184. Further qPCR analyses showed that NCOA1 had an inverse relationship with miR-34a in BD, while NCOR2 had a positive relationship with MDD. It is pertinent to mention that both NCOA1 and NCOR2 regulate the GR-mediated transcription of corticotropin-releasing hormone, a risk gene for stress-related psychiatric illnesses (121).

Lopez et al. (105) studied miRNA expression in the ventrolateral prefrontal cortex (vmPFC) of depressed individuals and found that primate-specific and human brain enriched miR-1202 was the most differentially regulated miRNA in MDD subjects. They found that miR-1202 regulated the expression of gene encoding metabotropic glutamate receptor-4 (GRM4). A recent report suggests that GRM4 3′ UTR variant (rs2229901) is associated with MDD risk (122). Interestingly, the antidepressant treatment induced miR-1202 expression and downregulated GRM4 expression (105). These results suggest that miR-1202 may be associated with MDD and may serve as target for new drug development.

It has been reported that miR-124-3p is highly expressed specifically in the brain (123), and has neuron-specific expression (124–126). Our group reported a significant upregulation in miR-124-3p expression in BA46 of depressed individuals (106). *In silico* prediction suggested that AMPA/NMDA receptors are major targets of miR-124-3p. Of them, expression changes for GRIA2 in dlPFC (127), GRIA3 in dentate gyrus (128) and PFC (129), and GRIA4 in PFC (129, 130) have been found in depressed individuals.

miRNAs and Bipolar Disorder

Compared to MDD, *postmortem* brain studies of miRNAs in bipolar disorder are limited. Azevedo et al. (104) reported downregulation of 4 miRNAs (miR-34a, miR-132, miR-133a, and miR-212) in ACC of BD subjects. miR-34a was correlated with PDE4B expression in BD. PDE4B expression changes have been found in several psychiatric disorders including SCZ (131, 132), MDD (133), and BD (134). Another ACC (BA24) study conducted by Choi et al. (107) explored expression changes in five miRNAs (miR-29c, miR-31, miR-15b, miR-497, miR-219, and miR-149) in glial exosomes. They found that miR-149 was significantly upregulated in BD subjects. Since miR-149 inhibits glial proliferation, an increase in miR-149 may be associated with previously reported reduced glial cell numbers in BA24 of patients diagnosed with BD (135).

Banigan et al. (95) explored exosomal miRNA expression in BA9 of patients diagnosed with BD and found that miR-29c expression was significantly increased. miR-29c regulates canonical Wnt signaling (136). Wnt signaling is linked to BD pathogenesis such that lithium impairs GSK-3β expression, a component of Wnt signaling system (137). Kim et al. (97) investigated the expression of 667 miRNAs in the PFC of individuals with SCZ and BD using Taqman Low Density Array system. They found downregulation of seven miRNAs in SCZ and 15 miRNAs in BD. These miRNAs targeted genes within the networks overrepresented for neurodevelopment, behavior, and SCZ and BD development (97).

Genetic similarities between SCZ and BD have been well documented (138). The overlapping miRNA changes between SCZ and BD may explain the genetic similarity. In the study by Kim et al. (97), miR-154* showed downregulation in PFC of both SCZ and BD subjects. Kohen et al. (108) investigated transcriptomic changes in the dentate gyrus (DG) granule cells of hippocampus in subjects with SCZ, MDD, BD, and nonpsychiatric controls. One miRNA that stood out was miR-182. MiR-182 is involved in several biological processes such as immune response (139), DNA repair (140), and the regeneration of peripheral nerves after injury (141, 142), which play key roles in BD pathogenesis. Carriers of different genotypes among subjects with SCZ and MDD had a loss of DG miR-182 signaling. Interestingly, carriers of high (C/C) *vs* low-expressing genotype (C/T or T/T) of rs76481776 in both controls and BD subjects, which is located in miR-182, had different levels of miR-182 target gene expression. This suggests that miR-182 may play a critical role in shaping the DG transcriptome based on genotype. Bavamian et al. (109) studied miRNA expression changes in cerebellum and reported an increased expression of miR-34a in BD subjects. In addition, they showed an upregulation of miR-34a in induced neurons derived from BD human fibroblast collected from another cohort. Subsequently, they validated the BD risk genes ankyrin-3 (ANK3) and voltage-dependent L-type calcium channel subunit (CACNB3) as direct targets of miR-34a with luciferase reporter assay. Functionally, enhanced miR-34a expression reduced neuronal differentiation and altered neuronal morphology as well as expression of synaptic proteins. On the other hand, reduced miR-34a expression improved dendritic elaboration.

The studies mentioned above suggest that BD patients have a distinct miRNA expression profile; however, there is a significant overlap with SCZ. This is quite relevant. In the future, miRNA profiling may be useful in identifying commonality and distinction between these disorders, both functionally and at pathophysiological levels.

miRNAs and Suicide

MiRNA studies related to suicide are summarized in **Table 4**. Using Taqman Low Density Array system, our group was the first to examine miRNA expression changes in BA9 of 18 MDD suicides and 17 nonpsychiatric control subjects (143). We found a global downregulation of miRNAs in MDD subjects. Altogether, we found significant downregulation in 21 miRNAs. Additional 29 miRNAs were also found to be downregulated by >30%; however, they did not reach statistical significance. When the regulation of these downregulated miRNAs was studied in detail, it was observed that many of them were encoded at the same or nearby chromosomal loci. In addition, they shared 5′-seed sequences. This suggests that miRNAs that were downregulated in MDD subjects had overlapping mRNA targets. Several instances were noted where miRNAs were found to be targeting the same genes. Some of the validated target genes included transcription factors, transmembrane and signaling proteins, growth factors, epigenetic modifiers, and apoptotic regulatory proteins. Predicted targets included ubiquitin ligases, CAMK2G, splicing factor NOVA1, and the GABA-A receptor subunit GABRA4. DNMT3b was another protein that was found to be targeted and further validated. DNMT3b is a key gene in epigenetic modifications and has been shown to be involved in MDD pathophysiology (152).

Gorinski et al. (144) examined whether 5-HT1A receptor (5HT1AR) palmitoylation is a mechanism involved in MDD and suicidality. They found that miR-30e expression was increased, while ZDHHC21 expression, which they identified as a major palmitoyl acyltransferase involved in palmitoylation of 5-HT1AR, was reduced in PFC of MDD suicide subjects, suggesting that 5-HT1AR palmitoylation may be key to MDD pathogenesis and treatment. Another mechanistic study by Torres-Berrio et al. (147) examined whether the expression of Netrin-1 guidance cue receptor DCC (deleted in colorectal cancer) gene was associated with resiliency or susceptibility to PFC dysfunctions in MDD suicide *via* miRNAs. They found a significant correlation between the decreased expression of miR-218 in BA44 of MDD suicide subjects and the elevated expression of DCC. By conducting an animal study, they concluded that miR-218 was associated with susceptibility *versus* resiliency to stress-related disorders through regulation of DCC expression.

Our group assessed miRNA expression in the synaptosome of BA10 from a cohort of SCZ, MDD, and BD subjects (145). Altogether, eight out of 14 BD subjects, seven out of 15 MDD subjects, and three out of 14 SCZ subjects had died by suicide. The result of comparison between all suicides (across diagnostic categories) and all non-suicide groups showed two upregulated miRNAs (miR-376a and miR-625) and six downregulated miRNAs (miR-152, miR-181a, miR-330-3p, miR-34a, and miR-133b). Based on significance values, miR-152 was found to be strongly associated with suicide. Distinct set of miRNAs were found in all three disorders; however, several miRNAs showed overlapping changes in SCZ and BD subjects. Discrete changes were also noted in MDD and suicide groups. Interestingly, downregulated miRNAs in SCZ group were enriched within the synapse. Follow-up studies in purified synaptosomes by deep sequencing in SCZ group suggested that there was a significant loss of small RNA expression in synaptosomes only for certain sequence lengths within the miRNA range. In addition, a large number of miRNAs (n = 73) were significantly downregulated and only one miRNA was upregulated. Remarkably, greater fold change of miRNAs in SCZ was associated with lower synaptic enrichment ratio in control subjects and vice-versa. Overall, synaptic miRNAs were generally downregulated in SCZ; however, highly synaptically enriched miRNAs showed greater down-regulation. It was concluded that there may be a deficit in synthesis, transport, or processing of miRNAs in SCZ; however, this

TABLE 4 | miRNA expression changes in *postmortem* brain and blood samples of suicide subjects.

Brain areas	Sample size	Methods	miRNA expression changes		Successfully validated miRNAs by qPCR	miRNA roles and other findings	Citations
			Upregulation	Downregulation			
BA9	18 MDD suicide and 17 Controls	TLDA		miR-142-5p, -137, -489, -148b, -101, -324-5p, -301a, -146a, -335, -494, -20b, -376a*, -190, -155, -660, -130a, -27a, -497, -10a, -20a, -142-3p		DNA (cytosine-5-)-methyltransferase 3 beta (DNMT3b) protein expression was significantly correlated with miR-148b expression	(143)
BA9	10 MDD suicide and 9 Controls	qPCR	miR-30a, -30e	miR-200a			(144)
BA10	15 SCZ (4 suicide), 15 MDD (7 suicide), 15 BD (9 suicide), and 15 Controls	TLDA	miR-376a, -625	miR-152, -181a, -330-3p, -34a, -133b	miR-17-5p, -145-5p, -219-2-3p	Synaptosome samples	(145)
BA10	38 suicide (4 SCZ, 23 MDD, 1 BD, and 6 subjects who did not have psychopathology) and 17 Controls	qPCR	miR-185*, 491-3p			TrkB-T1 (TrkB isoform) is a potential target of miR-185* validated by *in vitro* experiments	(146)
BA44	15 MDD suicide and 16 Controls	qPCR	miR-139-5p, -195, -320c, -34c-5p			There were significantly correlations (miR-34c-5p and miR-320c *vs* Diamine acetyltransferase 1 [SAT1, NM_002970]; miR-139-5p and miR-320c *vs* Spermine oxidase [SMOX, NM_001270691])	(105)
BA44	1st set (24 MDD suicide and 35 Controls) 2nd set (11 MDD suicide and 12 Controls)	qPCR		miR-218		Deleted in Colorectal Carcinoma (DCC, NM_005215) is a potential target of miR-218	(147)
BA46	12 MDD non-suicide, 14 MDD suicide, and 12 Controls	qPCR	miR-19a-3p			The upregulation of miR-19a-3p was also found in PBMC	(29)
LC	9 MDD suicide and 10 Controls	TLDA	miR-17-5p, -20b-5p, -106a-5p, -330-3p, -541-3p, -582-5p, -890, -99-3p, -550-5p, -1179	let-7g-3p, miR-409-5p, -1197			(148)
Edinger-Westphal nucleus	16 MDD suicide and 21 Controls	qPCR	miR-511			GDNF family receptor alpha-1 (GFRα1, NM_001145453) is a potential target of miR-511 validated by *in vitro* experiment	(149)
vPFC	32 MDD suicide and 20 Controls	qPCR	miR-425-3p, -146-5p, -24-3p, -425-3p			Four miRNAs are associated with MAPK/Wnt signaling pathways	(150)
Leukocytes	10 MDD with suicidal ideation, 22 MDD without ideation, and 32 Controls	qPCR	miR-34b-5p and -369-3p				(151)

ACC, Anterior Cingulate Cortex; BA, Brodmann area; BD, Bipolar Disorder; LC, Locus Coeruleus; miRNA, microRNA; MDD, Major Depressive Disorder; PBMC, Peripheral Blood Mononuclear Cells; SCZ, Schizophrenia; TLDA, TaqMan Low Density Arrays; vPFC, Ventrolateral Prefrontal Cortex.

process may be more selective for those miRNAs that are localized predominantly in the synaptic compartment.

Maussion et al. (146) examined miRNA expression changes in BA10 from 38 suicide subjects across SCZ, MDD, BD, and control subjects. miR-185* and miR-491-3p were found to be upregulated in suicide subjects compared to control subjects. TrkB-T1, one of the transcript variants of TrkB, expression was significantly lowered in suicide subjects and correlated with miR-

185* expression. This was specific only for TrkB-T1, but not for TrkB-T2 or TrkB-FL. TrkB has been shown to be involved in suicidal behavior as has been reported by us previously (67). In an effort to reveal the regulation of polyamine system and suicidal behavior, Lopez et al. (153) examined the expression of SAT1 and SMOX in BA44 and found them to be lower in MDD suicide subjects. They selected 10 miRNAs which were predicted to regulate SAT1 and SMOX genes. Of those, four miRNAs (miR-34c-5p, miR-320c, miR-139-5p, and miR-320c) were significantly upregulated and correlated with the polyamine stress response genes (miR-34c-5p and miR-320c with SAT1; miR-139-5p and miR-320c with SMOX). They concluded that polyamine stress response genes including SAT1 and SMOX may be linked to alterations in miRNA networks that are responsive to stress in MDD suicide subjects. In another study, Lopez et al. (150) noted upregulation of miR-425-3p, miR-146-5p, miR-24-3p, and miR-425-3p in ventrolateral prefrontal cortex (vPFC) of MDD suicide subjects. Resulting from *in silico* prediction and *in vitro* experiments, they concluded that all four miRNAs were related to the MAPK/Wnt signaling pathways. These signaling systems have been implicated in suicidal behavior (154).

In an effort to examine the regulation of pro-inflammatory cytokine genes in suicidal behavior, we examined the relationship between TNF-α and its regulatory miRNAs (29). We found an increased expression of miR-19a-3p in BA46 of MDD individuals who had died by suicide. The increased expression of miR-19a-3p was also found in PBMC of MDD subjects who had suicidal ideation. Mechanistically, we found that RNA-binding protein HuR helped in stabilizing TNF-α transcript. This occurred apparently by sequestering its 3′ untranslated region from miR-19a-3p-mediated inhibition. The study suggests that miR-19a-3p may be involved in cytokine dysregulation in suicidal individuals. Recently, we also explored miRNA changes in the locus coeruleus (LC) of MDD suicide subjects (148). A total of 10 upregulated and three downregulated miRNAs were detected in these subjects. Based on target gene prediction using the upregulated miRNAs, we narrowed our study to those genes with a strong neuropsychiatric background. We focused on RELN, GSK-3β, MAOA, CHRM1, PLCB1, and GRIK1 and found reduced expression levels for RELN, GSK-3β, and MAOA.

Maheu et al. (149) examined glial cell line-derived neurotrophic factor in MDD suicide subjects and found an isoform-specific decrease in GDNF family receptor alpha 1 (GFRA1) mRNA, which was associated with lower GFRα1a protein levels in basolateral amygdala. They found upregulation in several miRNAs that may target GFRA1 gene. One of them was miR-511. Under the condition of miR-511 overexpression in neural progenitor cells (NPC), they observed that protein expression of GFRα1 was significantly decreased and concluded that GFRα1 is regulated by miR-511 and may be associated with suicidality.

In terms of blood studies associated with suicidality, only one study is available. Sun et al. (151) reported downregulation of miR-34b-5p and miR-369-3p in MDD subjects with suicidal ideation compared to MDD without suicidal ideation. These changes were consistent with our previous *postmortem* study conducted in BA9 of MDD suicide subjects (143).

PIWI-INTERACTING RNAs

Piwi-interacting RNAs (piRNA) are the large small non-coding RNAs (26–32 nucleotide), which are preferentially expressed in nuclei and cytoplasm (155). Piwi proteins are recognized as one domain of argonaute (Ago) protein and bind to piRNA (156–159). The functions of Piwi/piRNA are unclear; however, they are highly expressed in germlines such as testes (156) and ovaries (160). Several studies show their role in epigenetic regulation of transposable elements in germlines (161–163). The existence of piRNA in mouse hippocampal neuron was reported by Lee et al. (164). In an *Aplysia* study, Rajasethupathy et al. (24) found that neuronal piRNA has a role in regulating memory-related synaptic plasticity. They found that the Piwi/piRNA complex may enable serotonin-dependent methylation of a CREB2 promoter CpG island in neurons, leading to the enhancement of long-term synaptic facilitation, learning-related synaptic plasticity and memory storage in *Aplysia*. More recently, Nandi et al. (165) reported that piRNA of Mili, the mouse ortholog of Piwi, exhibited behavioral deficits such as hyperactivity and less anxiety (165).

There is limited direct evidence of piRNA in psychiatric disorders. One study identified 37 piRNAs in ACC of SCZ subjects and one piRNA was correlated with antipsychotic medication (166). However, the authors did not mention the expression change between SCZ and control subjects because most of piRNAs were expressed only in a small number of samples.

SMALL INTERFERING RNAs

Small interfering RNAs (siRNA) are short (~20-24 nucleotide) double-stranded RNAs (dsRNAs) and interfere in the translation of proteins. Dicer enzyme cleaves long dsRNA and small hairpin RNAs into siRNAs (167, 168). SiRNAs have a role in mRNA cleavage by guiding RNA-induced silencing complex (RISC) to its complementary target mRNAs. Initially, siRNAs are loaded into Ago2 as duplexes. Subsequently, passenger strand of siRNAs is cleaved by Ago2; then, guide strand from siRNA duplex is liberated and produces active RISC, which has the capability to cleave target mRNAs (169, 170). Mainly, siRNAs are used for suppressing target genes as a scientific experimental method. To our knowledge, there is no report about siRNA expression changes in psychiatric disorders.

SMALL NUCLEAR RNAs

Small nuclear RNAs (snRNA), averaging about 150 nucleotides in length, are one of the components of spliceosomes. Five snRNAs (U1, U2, U4, U5, and U6) have been identified. snRNAs form ribonucleoprotein complexes (snRNPs) that can target and bind to specific sequences on pre-mRNAs (171). Spliceosomes have key roles in nuclear pre-mRNA splicing

that remove the pre-mRNA regions (intron) that do not code for functional molecules. Initially, U1 snRNA binds to its associated proteins at the 5′ splice end of the hnRNA (172). Subsequently, U2 snRNP is recruited to the spliceosome binding site for making complex A. Bai et al. (173) reported that unique U1 snRNP pathology is involved in abnormal RNA splicing in Alzheimer's disease (AD) that leads to the alteration in amyloid precursor protein (APP) expression and Aβ levels. Their group also showed U1 snRNP pathologic changes in *postmortem* brain of early onset AD (174). In addition, the small nuclear ribonucleoprotein U1-70K is aggregated in AD brain (175) and might contribute to neuronal toxicity in conjunction with N-terminal truncation (N40K) fragment derived from cleavage (176). In a mouse study, it is reported that dysfunction of U2 snRNA causes neurodegeneration through distortion of pre-mRNA splicing (177). A positron emission tomography study showed that amyloid accumulation is found in the brain of late-life MDD patients (178). At this stage, amyloid deposition may occur during the preclinical phase of dementia in patients who have depressive symptoms (179, 180), although MDD itself is a risk factor for the onset of AD (181). It is possible that Aβ changes through snRNAs may occur in late-life MDD patients even though the relationship between MDD and Aβ is unclear. One study, using ACC, found that 149 snRNAs were expressed in both SCZ and control subjects, and 35 snRNAs were expressed specifically for SCZ subjects (166). However, their biological impact on SCZ pathogenesis is unclear.

SMALL NUCLEOLAR RNAs

Small nucleolar RNAs (snoRNAs) are generally responsible for guiding modifications in rRNAs, tRNAs, and snRNAs. snoRNAs are divided into two main classes: 1) box C/D and 2) box H/ACA. Box C/D snoRNAs, averaging 60–90 nucleotides, have a role in catalyzing 2′-O-ribose methylation. Box H/ACA snoRNA, averaging 120–140 nucleotides, guide pseudouridylation (182, 183). In 2002, brain specific C/D box snoRNAs HBII-52 (SNORD115) and HBII 85 (SNORD116) and H/ACA box snoRNA HBI-36 were detected (184). Prader–Willi syndrome (PWS) is a neurodevelopmental disorder caused by imprinted gene clusters at human chromosome region 15q11q13. It was reported that SNORD115 and SNORD116 are partially responsible for the development of PWS (185, 186). Moreover, HBI-52 and HBI-36 snoRNAs are thought to regulate 5-HT_{2c} mRNA expression (184). 5-HT_{2c} has a role in MDD pathogenesis. Indeed, several antidepressants work as an antagonist to 5-HT_{2c} (187–189). In terms of schizophrenia, it is considered that 5HT-$_{2c}$ relates to SCZ pathogenesis through the dopaminergic pathway (190, 191) and by causing side effects to antipsychotic treatment (192). Actually, clozapine, a drug used for refractory schizophrenia, has high affinity to 5-HT_{2c} (192). SnoRNAs may influence psychiatric disorders directly or through 5-HT_{2c} receptors. Epigenetic changes have also been found in SNORD115 and SNORD116 in monozygotic twin study of SCZ. Hypermethylation in 12 regions on SNORD115 and five regions on SNORD116 regions were found in affected individuals (193).

In PFC synaptosomes from SCZ subjects, we noted ~50% decrease in a set of sequences that were derived from a C/D box snoRNA and SNORD85 (145). A 27-mer sequence TTCACTGAT GAGAGCATTGTTCTGAGC was the most abundant one that incorporated a C/D box and terminated four bases before the 3′ end of the host snoRNA. Our study, for the first time, showed that not only is this novel class of small ncRNAs expressed in humans, and more so in synaptosomes, but they may be significantly altered in a psychiatric disorders. Another study also showed expression change in snoRNAs in SCZ (166). A total of 343 snoRNAs were expressed in both SCZ and control subjects and six snoRNAs were expressed specifically in SCZ subjects. However, none of the snoRNAs were significantly changed in SCZ compared to controls.

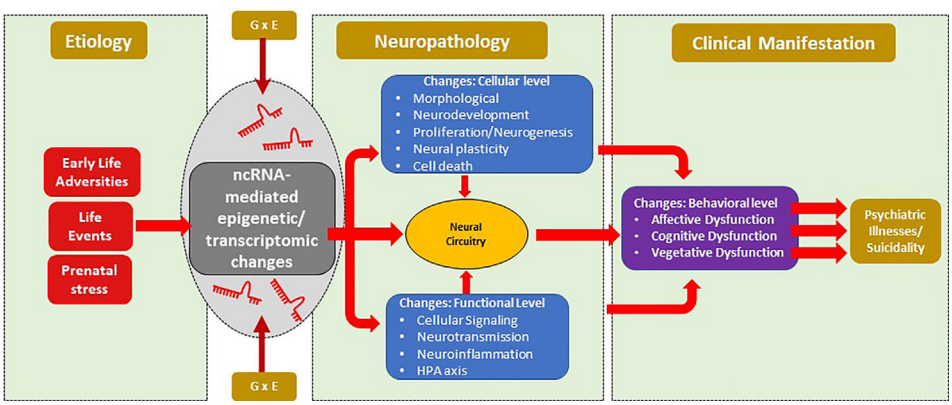

FIGURE 3 | Schematic diagram of the non-coding RNAs' impact on psychiatric illnesses and suicidality. Risk factors for mental illnesses include early life adversity, current or recurrent life events that along with gene environment interaction can lead to epigenetic modifications mediated by ncRNAs. These modifications can give rise to neuropathology mediated by changes at cellular and/or molecular levels, which can subsequently alter neural circuitry. Phenotypic changes can arise from circuitry changes that can mediate the development of psychiatric illnesses such as major depression, bipolar disorder and schizophrenia. Suicidal behavior could be a manifestation of psychiatric illnesses or may be independent of psychiatric illnesses. ncRNAs, non-coding RNA.

LIMITATIONS

There are a several limitations to ncRNA studies in neuropsychiatric disorders: 1) Several studies show changes in expression of expression lncRNAs and miRNAs; however, they are inconsistent even when studied in the same brain region with the same diagnosis. This could be attributed to several factors. For example, confounding variables such as PMI, brain pH, freeze–thaw cycle, age, and sex vary between studies. In addition, most of the studies use whole tissue. As mentioned earlier, the expression of lncRNAs and miRNAs are brain region and cell type specific. This cellular heterogeneity may affect ncRNA expressions. Thus, studying their expression patterns in neurons and glial cells (oligodendrocytes, astrocytes, and microglia) may delineate these discrepancies. Even within neurons, specific neuronal population needs to be studied. In this regard, single cell study will be helpful. 2) In recent years, many studies have focused on miRNAs and to a certain extent lncRNAs; however, the role of siRNAs, piRNAs, snoRNAs, and snRNAs are understudied. Given their important roles (*e.g.* epigenetic regulation of transposable elements; mRNA cleavage by guiding RISC), future research will be needed to explore their functional significance in psychiatric disorders. 3) Correct identification of new snRNAs and snoRNAs and their epigenetic roles needs to be studied (194, 195). New technologies like nanopore sequencing and structure prediction algorithms are emerging that can be helpful in this regard. 4) Although new members of ncRNA are being discovered regularly, the functions of these novel ncRNAs are not well understood. More *in-vivo* functional studies followed by high-throughput sequencing after chemical cross-linking or photoactivatable cross-linking and immunoprecipitation (PAR-CLIP) will be effective in probing the functional roles of novel ncRNAs at the cellular level (196). These assays can be also performed in human *postmortem* brain samples, but by minimizing the loss of tissue integrity and maximizing the likeliness of capturing the interaction at the molecular level. 5) Most of the studies have shown the temporal changes in ncRNA expression. Although it is very difficult to measure ncRNA expressions at different time points in *postmortem* samples, it is relatively easy to measure them in peripheral tissue samples. Using longitudinal studies, it will be possible to explore the diagnosis/therapeutic/disease state biomarkers for psychiatric illnesses.

CONCLUSIONS

ncRNAs are gaining traction for their role in various psychiatric illnesses. A schematic diagram of the non-coding RNAs' impact on psychiatric illnesses and suicidality is depicted in **Figure 3**. Both long-non-coding RNAs and miRNAs have been extensively studied in MDD, SCZ, and BD. As can be seen in **Tables 1–4**, a large number of miRNAs and lncRNAs have been implicated in SCZ, MDD, and BD. There were several miRNAs that showed overlapping changes between SCZ and BD, suggesting that these two disorders may share common susceptibility factors as has been demonstrated in several genetic studies.

The population-based studies have explored the expression changes of lncRNA and miRNA among psychiatric patients who have suicidal ideation. A couple of *postmortem* brain studies have also explored suicide associated ncRNAs. Interestingly, both lncRNAs and miRNAs were specifically changed in psychiatric patients who died by suicide even though the sample size and number of studies are quite small. The results are encouraging and need further exploration.

In terms of other small RNAs, the studies are quite limited; nevertheless, they appear to be promising. piRNAs and snoRNAs show interesting results in SCZ patients that may shed light on their role in regulating other RNAs and their role in this psychiatric illness. These studies need to be expanded in order to understand their precise role in regulatory mechanisms that can be involved in the pathogenesis of psychiatric disorders.

AUTHOR CONTRIBUTIONS

YD conceptualized, outlined, and edited the paper. YY reviewed literature and co-wrote the paper.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GLOSSARY

ncRNA	Non-coding RNA
lncRNA	Long non-coding RNA
Nt	Nucleotide
miRNA	microRNA
siRNA	Small interfering RNA
piRNA	Piwi-interacting RNA
snoRNA	Small nucleolar RNA
snRNA	Small nuclear RNA
SCZ	Schizophrenia
MDD	Major depressive disorder
BD	Bipolar disorder
bp	Base-pair
Xist	X-inactive specific transcripts
cDNA	Complementary DNA
Brn 1b	Brain-specific homeobox/POU domain protein 1b transcript
RMST	Rhabdomyosarcoma 2 associated transcript
TUNA	Tcl1 upstream neuron-associated transcript
Evf2	Erwinia virulence factor 2 transcript
GABA	Gamma aminobutyric acid
Pnky	Pinky
Bdnf	Brain-derived neurotrophic factor
BDNF-AS	Brain-derived neurotrophic factor antisense RNA
GWAS	Genome-wide association study
CNNM2	Cyclin and CBS domain divalent metal cation transport mediator 2
ACC	Anterior cingulate cortex
dlPFC	Dorsolateral prefrontal cortex
RNA-seq	RNA sequencing
IRF2	Interferon regulatory factor 2
LY6E	Lymphocyte antigen 6E precursor
HMOBX1	Homeobox containing 1
REEP5	Receptor accessory protein 5
PTPRT	Protein tyrosine phosphatase receptor type T
NFATC3	Nuclear factor of activated T cells 3
CNS	Central nervous system
MARCKS	Myristoylated alanine-rich C-kinase substrate
eQTL	Expression quantitative trait locus
WGCNA	Weighted correlation network analysis
P2RY13	Purinergic receptor P2Y13
PBMC	Peripheral blood mononuclear cell
qPCR	Quantitative polymerase chain reaction
p-GSK3β	Phosphorylated glycogen synthase kinase 3 beta
SERT	Serotonin transporter
pri-miRNA	primary microRNA
pre-miRNA	precursor microRNA
DGCR8	DiGeorge syndrome critical region 8
XPO5	Exportin-5
TRBP	TAR RNA-binding protein
Ago	Argonaute
RISC	RNA-induced silencing complex
p250GAP	p250 GTPase-activating protein
MeCP2	methyl CpG binding protein 2
TCF4	Transcription factor 4
BA	Brodmann area
CREB	cAMP response element-binding
ERK	Extracellular signal regulated kinase
NMDA	N-methyl-D-aspartate receptor
GRID1	Glutamate receptor ionotropic delta 1
STG	Superior temporal gyrus
VSNL1	Visinin like 1
GRIA2	Glutamate ionotropic receptor AMPA type subunit 2
GRIA3	Glutamate ionotropic receptor AMPA type subunit 3
GRIA4	Glutamate ionotropic receptor AMPA type subunit 4
NCOA1	Nuclear receptor coactivator 1
NCOA2	Nuclear receptor coactivator 2
PDE4B	Phosphodiesterase 4B
NCOR2	Nuclear receptor corepressor 2
GR	Glucocorticoid receptor
vmPFC	Ventromedial prefrontal cortex
GRM4	Glutamate receptor-4
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
DG	Dentate gyrus
ANK3	Ankyrin-3
CACNB3	Calcium voltage-gated channel auxiliary subunit beta 3
CAMK2G	Calcium/Calmodulin dependent protein kinase II gamma
NOVA1	Neuro-oncological ventral antigen 1
GABA-A	Gamma-aminobutyric acid type A receptor subunit alpha
GABRA4	Gamma-aminobutyric acid type A receptor subunit alpha 4
DNMT3b	DNA (cytosine-5-)-methyltransferase 3 beta
5HT1AR	5-Hydroxytryptamine receptor 1A
ZDHHC21	Zinc Finger DHHC-type palmitoyltransferase 21
DCC	Deleted in colorectal carcinoma netrin 1 Receptor
TrkB	Tropomyosin receptor kinase B
TrkB-T1	Tropomyosin receptor kinase B transcript isoform 1
TrkB-T2	Tropomyosin receptor kinase B transcript isoform 2
TrkB-FL	Tropomyosin receptor kinase B full-length isoform
SAT1	Spermidine/Spermine N1-acetyltransferase 1
SMOX	Spermine oxidase
vPFC	Ventrolateral prefrontal cortex
MAPK	Mitogen-activated protein kinase
Wnt	Wingless and Int-1
TNF-α	Tumor necrosis factor alpha
HuR	Human antigen R
LC	Locus coeruleus
RELN	Reelin
MAOA	Monoamine oxidase A
CHRM1	Cholinergic receptor muscarinic 1
PLCB1	Phospholipase C beta 1
GRIK1	Glutamate ionotropic receptor kainate type subunit 1
GFRA1	GDNF family receptor alpha 1
CREB2	Cyclic AMP response element-binding protein 2
Mili	Miwi like; Piwil2
dsRNAs	Double-stranded RNAs
Ago2	Argonaute 2
snRNPs	Small nuclear ribonucleoprotein complexes
AD	Alzheimer's disease
APP	Amyloid precursor protein
Aβ	Amyloid beta
N40K	N-terminal truncation fragment
HBII-52	C/D box snoRNA 52
HBII-85	C/D box snoRNA 85
HBI-36	H/ACA box snoRNA 36
PWS	Prader–Willi syndrome
5-HT2c	5-Hydroxytryptamine receptor 2C
PMI	*Postmortem* interval
PAR-CLIP	Photoactivatable cross-linking and immunoprecipitation

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ORIGINAL RESEARCH
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Exposure to Early Life Adversity and Interpersonal Functioning in Attempted Suicide

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Background: Early life adversity (ELA) may lead to an increased risk for mental health problems including suicidal behavior. ELA alters biological stress systems that affect behavior and control within the individual that in turn will affect interpersonal behavior. Strained relations and interpersonal conflicts leading to rejection and isolation have been shown to be factors for suicidal behavior. Difficulties in interpersonal relationships are a common reason for seeking help in psychiatric care. In the present study, we examined relationship between different types of interpersonal problems and adverse childhood experiences in patients with a recent suicide attempt.

Method: The study included 181 recent suicide attempters. We assessed early life adversity and specific interpersonal problems by using the Karolinska Interpersonal Violence Scale and the Inventory of Interpersonal problems respectively.

Results: Suicide attempters with high levels of early life adversity expressed a more socially avoidant, non-assertive, and exploitable personal style even after adjustment for comorbidities with personality disorder and substance use disorder.

Conclusions: Patients with a recent suicide attempt with high levels of early life adversity tend to isolate themselves, of being introvert, and having difficulties to open up and confide in others. They report low self-confidence and self-esteem and problems with feeling and expressing anger. These behaviors complicate interaction with others and make establishment of solid relationships more difficult. In regards to detection of suicidal communication and treatment of suicidal patients, this may lead to misinterpretations and difficulties to fully benefit from treatment given or for professionals to provide the appropriate treatment. Clinicians should closely investigate the presence of early life adversity in suicidal patients and pay attention to their personal style and their difficulties in interpersonal exchange.

Keywords: interpersonal problems, suicide attempt, early life adversity, adverse childhood experiences, Inventory of Interpersonal problems, Karolinska Interpersonal Violence Scale, suicide – attempted, mood disorder

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INTRODUCTION

According to data from the World Health Organization (1), suicide accounts for approximately 800,000 deaths each year. Moreover, the impact of suicide does not limit itself to the closest family and friends, in fact, many others in the society are affected, like health care providers, workplace colleagues, and neighbors (2). Suicide remains a true challenge for the world public health systems and should be a priority in every nation. Many mechanisms are involved in the development of suicidal behavior and a better understanding of these factors is crucial for successful suicide prevention.

Extensive research on risk factors both at the population and individual levels has been conducted and psychiatric disorders particularly have a strong impact on suicide rates as well as previous suicide attempt, a family history of suicidal behavior, and childhood sexual abuse. Precipitating factors in vulnerable individuals are considered to result in psychological changes, including feeling hopeless and burdensome, which may lead in turn to social isolation. One of the more widely studied risk factors for suicide is exposure to violence. Early experiences of both emotional and physical abuse are recognized as both biological and psychological risk factors leading to different negative outcomes in adulthood, including a higher suicide risk (3–6). In our previous study (5) focusing on the family history of suicide (FHS) and early life adversity (ELA) on suicide risk, we found that ELA was a predictor for suicide in women without regard to FHS. In men with both FHS and ELA, the risk for suicide was clearly heightened compared to those with only FHS. ELA was consequently a determinant for suicide in both men and women.

For individuals with fulfilled criteria for Posttraumatic Stress Disorder (PTSD), there is a strong association with suicidal behavior (7, 8). However, even in the subclinical population with PTSD symptoms, the association with suicidal behavior is strong (9). Furthermore, ELA is a known factor in interpersonal dysfunctional patterns expressed in personality and behavior (10–12) leading to a research focus on the individual predisposition for suicidal behavior (13). Several personality and psychological traits have been associated with suicidal behavior. For example, impulsivity and instability in interpersonal relationships are often found in the patients with borderline personality disorder (BPD) (14–16). Other interpersonal aspects, like lack of social connectedness, and the feeling of being a burden to others are known risk factors for suicide as they will increase the tendency of isolation (17, 18).

Problematic interpersonal behaviors are common among suicidal patients, (19) with shown deficits in active interpersonal problem solving (20). Interpersonal problems like avoidance, social isolation and submissiveness are common in patients with affective disorders, especially major depressive disorder (21). In fact, rejection and isolation related to interpersonal conflicts appeared as the main triggers of suicidal behavior in several studies on life events preceding a completed suicide (22–24).

To date, only few studies have investigated the relationship between early life adversity and interpersonal functioning, and to our knowledge very little research has been done so far with focus on attempted suicide (25). This study aims to investigate associations between early life adversity and interpersonal problems both assessed with structured instruments in patients with a recent suicide attempt.

MATERIALS AND METHODS

Study Setting

Patients having clinical follow-up after a suicide attempt at the Suicide Prevention Clinic at the Karolinska University Hospital, Stockholm, Sweden were invited to participate in two clinical studies which took place between the years of 1993–2005.

Participants

One hundred eighty-one suicide attempters (113 women and 68 men) were recruited according to following inclusion criteria: a recent suicide attempt, an age of 18 years or older and a command of Swedish language. Suicide attempt was defined as any non-fatal, self-injurious behavior with some intent to die (1). Patients with following diagnoses- schizophrenia spectrum psychosis, intravenous drug abuse, intellectual disability, and dementia were excluded. Trained psychiatrists diagnosed participants with the research version of SCID-I according to DSM III and DSM IV. To establish any occurrence of Axis-II diagnosis, the SCID-II interviews were performed by trained clinical psychologists. Almost all (91%) of the patients had at least one current Axis-I diagnosis. The most prevalent primary diagnosis was mood disorder (75%) while anxiety disorder and adjustment disorder each were present in 5% of patients. Substance use disorder as a primary Axis I diagnosis was present in 3%, one individual had anorexia nervosa and another had an unspecified psychiatric disorder. One third of the patients met criteria for a personality disorder. The most prevalent were a personality disorder not otherwise specified (39%) and borderline personality disorder (35%) followed by dependent personality disorder (11%), and avoidant personality disorder (9%). Six percent of the patients fulfilled criteria for antisocial personality disorder.

Assessments

The Karolinska Interpersonal Violence Scale (KIVS) subscale B "Victim of violence" in childhood 6–14 years was used to assess adverse childhood experience (26). Statements about being a victim of violence is rated between (0), no exposure to interpersonal violence, (1), occasional slaps, occasional fights of no importance, (2), bullied for short period of time, occasionally exposed to physical punishment, (3), repeatedly bullied and/or beaten in school and in home environment, (4), bullied throughout childhood, regularly beaten by parent or other adult, sexual abuse, and (5), repeatedly exposed to violent behavior that results in severe bodily harm, repeated severe sexual abuse. Trained professionals performed assessments using a semi-structured interview. A high inter-rater reliability of the scale has been reported (26) and KIVS has been used in suicide research (27, 28). The KIVS subscale B "Victim of

violence" in childhood has been validated using the Childhood trauma Questionnaire in a study of patients with hypersexual disorder (29). The KIVS exposure to interpersonal violence as a child showed a significant correlation with the CTQ-SF total score indicating that KIVS subscale measuring exposure to violence in childhood has validity as a clinical tool assessing early life adversity (29).

Inventory of Interpersonal Problems (IIP), a 64-item self-report inventory with a well-established validity and reliability (0.78), (30) was used to assess the most evident interpersonal problems (31). The IIP has been validated in Sweden (32). Eight subscales describing each different interpersonal problems (new denomination in parenthesis) are included in the IIP: Domineering (Domineering/Controlling); Vindictive (Vindictive/Self-centered); Cold (Cold/Distant); Social avoidant (Social inhibited); Non-assertive (Non-assertive); Exploitable (Overly Accommodating); Overly nurturant (Self-sacrificing), and Intrusive (Intrusive/Needy). The subjects respond to two forms of statements "it is hard for me to…" and "these are things I do too much or too often" of how they usually cope with distressing interpersonal behaviours. The answers are rated on a Likert scale ranging from 0 (not at all) to 4 (extremely).

The scale Domineering captures lack of control and aggressing others. "I try to change people too much" is an example of a statement in this scale. Scoring high in the scale Vindictive implies problems with vindictive thoughts, frustration and anger: "it's hard for me to put someone else's needs before my own". A high value in the scale Cold implies difficulties to connect to others with examples of items like "I keep other people at a distance too much" and "it's hard for me to get along with other people". The Social avoidant scale describes a rejective and introvert personal style with statements like "it's hard for me to show my feelings" and "it's hard for me to socialize with other people". High scores in the scale Social avoidant indicates feelings of anxiety, shame or shyness when interacting with other people. The Non-assertive scale reflects low self-confidence and low self-esteem. "It's hard for me to be firm when I need to be" is an example of a statement in the Non-assertive scale: Individuals with high scores in this scale doubt themselves and avoid expressing their needs for fear of criticism. High scorers in the Exploitable scale struggle to please others and report problems with anger expression. Examples of statements are "it is hard for me to let other people know when I'm angry" and "I let other people take advantage of me too much". In the scale Overly nurturant a characteristic is to have difficulties with boundaries. "I put other people's needs before my own too much" is one example of the inclination to try too hard. Finally, the scale Intrusive with items like "I tell personal things to other people too much" and "it's hard for me to stay out of other people's business" captures the individual's problems with boundaries.

The total score, translated to a normative T-score, reflects the individual's general level of interpersonal problems in relation to the normal population. The scores on eight scales describe the specific problematic domains and type of interpersonal problems. An ipsatized T-score that relates to the individuals' own problem level can also be used. The scores of IIP scale may thus be used to assess a patient's level of interpersonal problems, to compare different groups, or as a measurement of interpersonal problems before and after clinical treatment.

Statistical Methods

We used Shapiro Wilks test to evaluate skewness and kurtosis of the distributions. Correlational analyses were used to determine associations between the exposure to interpersonal violence as a child and the eight subscales of IIP. Pearson's r or Spearman rho were applied for parametric or non-parametric correlation analyses. Student's t-test and the Kruskal-Wallis' test were used to assess group differences (suicide attempters with and without comorbid personality disorder or substance abuse, respectively) in continuous variables.

Based on the results of the bivariate analyses, standard multiple regression analyses were conducted to determine whether early life adversity was associated with specific type of interpersonal problems adjusted for comorbidities with personality disorder and substance use disorder. All statistical tests were two-tailed.

The p value was set at <0.05. We used the Statistical Package JMP 9.0.3 software, SAS Institute Inc., Cary, NC, USA.

RESULTS

Level of Interpersonal Problems

The mean T-scores are shown in **Table 1** (n = 162; range for subscales 49–61). Patients with a comorbid personality disorder had significantly higher scores in all eight subscales (all p values < 0.01) compared to patients without a comorbid personality disorder. Comorbidity of substance use disorder was associated with significantly higher scores in domains Non-assertive (p = 0.042) and Social avoidant (p = 0.043).

Early Life Adversity and Interpersonal Problems in Adulthood

Patients with a comorbid personality disorder or a comorbid substance abuse disorder reported significantly higher exposure

TABLE 1 | IIP-ratings in suicide attempters (n = 162), T-score mean, standard deviation (SD), range.

Rating	IIP total	
	T score Mean (SD)	Range
Domineering	49 (12)	38–96
Vindictive	56 (16)	38–114
Cold	55 (13)	39–96
Social avoidant	56 (15)	35–104
Non-assertive	55 (16)	31–98
Exploitable	59 (15)	30–100
Overly nurturant	61 (15)	32–103
Intrusive	52 (12)	34–85

IIP, Inventory of Interpersonal Problems.

to interpersonal violence as a child compared to patients without comorbidity (Z = 4.12, p < 0.0001; Z = 3.99, p < 0.0001).

Table 2 shows correlations between exposure to interpersonal violence in childhood and interpersonal problems in adulthood in patients with a recent suicide attempt. The domains Social avoidant, Non-assertive, Exploitable, Cold, and Overly nurturant were significantly, positively correlated with exposure to interpersonal violence during childhood. Multiple regressions of the significant scales of IIP (Social avoidant, Non-assertive, Exploitable, Cold, and Overly nurturant) as a dependent variable, exposure to interpersonal violence as a child as well as comorbid personality disorder and substance use diagnosis as independent variables, were conducted.

The overall models were significant for three of IIP domains-Social avoidant, Non-assertive and Exploitable with adjusted R^2 = 0.05–0.09, meaning that the models explained 5–9% of the variance of these IIP subscales, **Table 3**.

The standardized values of t-ratio for exposure to interpersonal violence in childhood (between 2.61–3.10), indicated that higher scores in childhood interpersonal violence exposure were associated with higher scores of three IIP scales Social avoidant, Non-assertive and Exploitable. **Figure 1** shows correlation between exposure to interpersonal violence as a child and Social avoidance.

TABLE 3 | Exposure to interpersonal violence, comorbid personality disorder, and substance use disorder as predictors of IIP Social avoidance, Non-assertive, and Exploitable in suicide attempters.

Social avoidance	t ratio	*p* value
KIVS exposure as a child	3.10	0.0022
Comorbid Personality disorder	2.27	0.024
Substance use disorder	0.27	0.78
Non-assertive	t ratio	*p* value
KIVS exposure as a child	2.61	0.0097
Comorbid Personality disorder	1.47	0.14
Substance use disorder	0.81	0.42
Exploitable	t ratio	*p* value
KIVS exposure as a child	2.67	0.0081
Comorbid Personality disorder	1.23	0.22
Substance use disorder	0.02	0.98

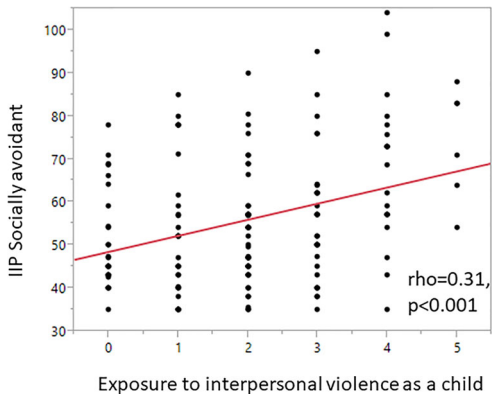

FIGURE 1 | Higher IIP ratings in the subscale Social avoidant were associated with higher scores of KIVS exposure to interpersonal violence as a child (rho = 0.31, p < 0.001).

DISCUSSION

In this study of patients in treatment after a suicide attempt, we wanted to investigate the relationship between early life adversity and interpersonal problems. The main finding was that suicide attempters with high levels of early life adversity expressed a more socially avoidant, non-assertive, and exploitable personal style even after adjustment for comorbidities with personality disorder and substance use disorder. Compared to the normative sample, the T-scores were higher for suicide attempters in all IIP-scales. However, none of the eight scales reached the level of severe interpersonal difficulties in IIP which is defined in the literature scoring two standard deviations above the mean score. Generally, the suicide attempters scored one standard deviation higher, and the scores varied more compared to the normative sample. In line with the hypothesis, patients with a comorbid personality disorder had higher scores in every domain of interpersonal problems, while a comorbid substance use diagnosis was associated to significantly higher scores in the domains Social avoidant and Non-assertive in group comparisons.

Patients with high levels of ELA had significantly higher scores on the scales Social avoidant, Non-assertive, and Exploitable when taking into account comorbidity with personality disorders and substance use disorder. These findings suggest an impaired ability in social interaction, and in how to express feelings and thoughts when with others. The difficulties may manifest as a tendency to keep to oneself. Further, patients who reported high levels of ELA scored lower self-confidence and self-esteem and reported problems with feeling and expressing anger in efforts to try hard to please other people. Behaviors like these may jeopardize establishment of strong relationships since they are often regarded as aversive by the environment. Furthermore, in regards to detection of suicidal communication and treatment of suicidal patients, this may lead to misinterpretations and difficulties to fully benefit

TABLE 2 | Correlations (Spearman's ρ) between the KIVS exposure to interpersonal violence as a child and IIP in suicide attempters.

	Overly nurturant	Intrusive	Domineering	Vindictive	Cold	Socially avoidant	Non-assertive	Exploitable
KIVS	0.16*	0.13	0.03	0.13	0.18*	0.31***	0.25**	0.22**

p, p-value; IIP, Inventory of Interpersonal Problems; KIVS, Karolinska Interpersonal Violence Scale.
**p < 0.05, **p < 0.01, ***p < 0.001.*

from treatment given or for professionals to provide the appropriate treatment. In clinical practice the patient may seem difficult to cooperate with, which leads to risk for disrupted contact. Stable and strong personal relationships may protect for suicidal crisis, during which the ability to seek and accept help from others is of importance (33). In long term, the patient may lose important relationships due to these interpersonal problems accentuating social isolation and feelings of hopelessness.

IIP has a negative correlation with The Hogan Personality Inventory (HPI) that is a measurement of normal personality qualities that describe how one relates to others when at one´s best (34). The total score on IIP has the highest correlation with the HPI scale Adjustment—with measures to which extent a person appears self-content and at ease as well as open to feedback from others. The IIP scale that has the highest negative correlation to Adjustment is Social Avoidant which then would suggest the opposite, a tense and self-critical person that resists to feedback.

When it comes to ELA, KIVS captures not only many types of maltreatment but also duration or repetitive exposures. However, due to the construct of the scale, it is not possible to investigate a specific type of victimization like sexual abuse which prior studies often have focused on. The KIVS subscale exposure to interpersonal violence in childhood has been validated using the Childhood trauma questionnaire, a gold standard instrument to measure early life adversity (29). CTQ total score as well as subscales measuring physical and emotional abuse showed significant correlations with KIVS exposure to interpersonal violence in childhood (29). However, many research studies have reported that multi-victimization is frequent among children and adolescents (35, 36). Bullying has been associated with suicidal behavior (37) and with depression and isolation (38). In connection to this, the subjective perception of social support has been shown to be a key element in suicidal behavior (10, 39, 40). Early risk factors play a role in attempted and completed suicide in epidemiological studies (41), as well as personality traits (42).

Isolation, either real or just the subjective experience of desolation, is an important factor in suicidal behavior, and a focus on social skills training in the suicidal patient is important. The specific interpersonal patterns related to ELA that appeared in suicide attempters in this study may have effect on their ability to have long-lasting, stable relationships.

Strengths of this study include the large sample of suicide attempters and the careful clinical characterization. A limitation is that we did not unfortunately have information concerning how many patients were eligible to participate during the whole study period.

Our results indicate that suicide preventive efforts should include programs at population level toward the detection and elimination of childhood abuse and broad support related to the issue, effective and thorough assessment of risk individuals in health care and their ability to connect to others and seek social support. Therapeutic interventions should consider the different aspects of patients' interpersonal functioning and aim to increase the individual´s ability to maintain positive relationships.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by: The Regional Ethical Review Board in Stockholm approved of the study protocols (Dnr 93-211 & Dnr 00-194). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Recruiting participants: JJ, MR. Performed the psychiatric interviews: JJ, MR. Formulating the problem and hypothesis: MR, JJ, TH, ER, and MÅ. Analyzed data: MR, JJ, TH. Wrote the paper: MR, JJ. Approved the final version of paper: MR, JJ, TH, ER, and MÅ.

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Association of Lipid Profile and Suicide Attempts in a Large Sample of First Episode Drug-Naive Patients With Major Depressive Disorder

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Several studies have reported a link between lipid disorders and suicidality. However, few studies have investigated the relationship between suicidal behavior and blood lipid profiles in patients with first-episode and drug-naive (FEDN) major depressive disorder (MDD). The main purpose of this study was to examine the relationship between plasma lipid profiles and suicide attempts in a large sample of FEDN MDD patients in the Chinese Han population, which has not been reported. A total of 1,718 MDD outpatients were recruited. Their clinical and demographic data as well as plasma lipid parameters were collected. We obtained suicide attempt data through interviews with patients and their family members. We rated the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) for all patients. The suicide attempt rate of MDD patients was 20.14%, of which 13.68% in the last month and 6.46% in the past. Further, compared with non-attempters, suicide attempters had significantly higher total levels of cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c), higher HAMA and HAMD scores, but significantly lower high-density lipoprotein cholesterol (HDL-c) levels. Logistic regression analysis showed that suicide attempts were correlated with higher TC, lower HDL-c, and higher HAMA and HAMD scores with the adjusted odds ratio (OR) of 1.35, 0.52,1.28, and 1.08, respectively (all $p < 0.05$). Our findings suggest that FEDN patients with MDD have a high rate of attempted suicide. In the early stage of MDD patients, certain blood lipid parameters and more severe symptoms of anxiety and depression are correlated with suicide attempts. However, due to the cross-sectional design of this study, it is impossible to draw a causal relationship between lipid profiles and suicide attempts. Moreover, an inverse correlation can also be considered, that is, high cholesterol may be the consequence of suicide attempts and depression.

Keywords: major depressive disorder, lipid, suicide attempt, clinical symptom, first episode

INTRODUCTION

In China, the suicide attempt rate of patients with major depressive disorder (MDD) is reported to be 7.3 to 48.4% (1), and in other countries, it is 16.9 to 33.7% (2–4). Moreover, more than 90% of people who die by suicide suffer from one or more mental illnesses, especially MDD, accounting for 59–87% of all suicides (1, 5). A systematic review suggests that many confounding factors may contribute to the risk of suicide in MDD patients, such as gender, family history of mental illness, more severe depression and comorbidities (6). In the past decades, many researchers have been trying to identify biomarkers that may be related to suicidal behavior. The role of lipid disorders in suicide has always been one of the researchers' focuses (7, 8). For example, a previous study found that the number of deaths among subjects treated with cholesterol-lowering drugs increased significantly, including suicide deaths (9). Subsequently, many studies have investigated the relationship between total cholesterol (TC) levels and suicide, but the results are conflicting (10–14). The association between low TC levels and suicide has been found in MDD (15–18), schizophrenia (19), personality disorder (20), anorexia nervosa (21), panic disorder (22), and bipolar disorder (23), or even in the general population (24), suggesting that low lipid metabolism, especially TC, may be a potential biomarker of suicidal behavior.

A large number of epidemiological and clinical studies have shown that MDD subjects with lower TC levels have increased suicide attempts (15–18, 25). For example, Papadopoulou et al. reported that psychiatric patients with a history of suicide attempts (including MDD) have lower TC levels. During their follow-up, the TC levels remained low (18). Moreover, in depression patients suffering from suicidal behavior, LDL-c, TC levels (26) and triglycerides (TG) levels (27, 28) were significantly lower. However, it has been reported that patients with depression who attempt suicide have higher HDL-c levels (27, 29). Further, some studies have shown that there is no relationship between the blood lipid levels and suicidal behavior in patients with depression (30–32), or even the opposite results in community populations (13, 33) and depression patients (15, 34). For example, Brunner et al demonstrated that in the past 12 months, there was a positive correlation between TC or TG and attempted suicide in patients with depression (34). A recent longitudinal study has found that both low and high TC levels can predict the incidence of suicidal ideation in the elderly, regardless of life stress, social support, alcohol consumption, depressive symptoms, and disability (35). Taken together, the relationship between suicidal behavior and blood lipid levels in MDD patients is still inconsistent.

Most of previous studies have had fewer clinical samples. Moreover, most of the subjects in previous studies were hospitalized or taking medication, which may affect diet and exercise habits, as well as subsequent lipid levels (15, 36, 37). Interestingly, it was reported that patients with first episode mental illness had a higher risk of suicide (38). Moreover, 60% of depressed patients completed suicide at their first episode (39). However, to our best knowledge, there is no study investigating the relationship between suicide attempt and lipid levels in first episode-depressed patients in a large sample. Moreover, it is unclear whether lipid level is either a state or a trait marker of suicide attempt.

In this study, we recruited a large sample of first-episode drug-naive (FEDN) MDD patients (n = 1,718) in a Chinese Han population. It is worth noting that the study of patients with first-episode MDD is helpful to understand the relationship between suicide attempts and lipid metabolism in MDD, which may minimize confounders, including drug treatment, course of disease, and related mental illness and medical complications. Therefore, the purposes of this study were (1) to investigate the prevalence and clinical features of attempted suicide in FEDN MDD patients, and (2) to identify contributors that are significantly associated with attempted suicide in these MDD patients.

METHODS

Subjects

This was a cross-sectional naturalistic study conducted in a psychiatric outpatient department of a general hospital in Taiyuan, Shanxi Province, China. 1,718 patients were recruited and met the following inclusion criteria: 1) Han nationality; 2) aged between 18 and 60 years; 3) meeting MDD diagnosis in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR; 4) at the first onset of MDD; 5) before entering the study, did not receive any drugs, including antidepressants, anti-anxiety drugs, antipsychotics, and other drugs that affect lipid levels, such as lipid-lowering drugs; 6) except for smoking, no alcohol or drug abuse disorders; 7) no pregnancy or lactation; 8) no major medical abnormalities, including central nervous system diseases and acute, unstable or life-threatening medical diseases such as cancer and infections.

The study was approved by the Institutional Review Board (IRB) of the First Clinical Medical College, Shanxi Medical University. All subjects signed an informed consent form to participate in this study.

Socio-Demographic Characteristics and Clinical Measures

Demographic and clinical data were collected by well-trained researchers. Each patient completed a detailed questionnaire, including general information and sociodemographic characteristics. We also collected other information from available medical records.

Suicidal behavior includes attempted suicide or suicide. Complete suicide (synonymous with suicide) is the act of deliberately causing one's own death. The definition of attempted suicide is a self-destructive behavior aimed at ending a person's life without causing death. In this study, the main outcome measure was attempted suicide. All participants were asked "In your entire lifetime did you ever attempt suicide?"

Abbreviations: MDD, major depressive disorder; FEDN, first-episode and drug-naïve; OR, odds ratio; BMI, body mass index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol.

If they gave an affirmative answer, they were coded as suicide attempter. They were then asked about their previous suicide attempts, including the following details: the number of suicide attempts, the exact date and method of each suicide attempt. If the answer was ambiguous, the researcher made additional visits with the patients' family members or clinical team for confirmation. The suicide attempters were further divided into two subgroup s: those who attempted suicide in the last month (recent suicide group), and those who attempted suicide in the past except for the last month (past suicide group).

The Hamilton Depression Scale (HAMD, 17 items) and Hamilton Anxiety Scale (HAMA, 14 items) were assessed by trained psychiatrists. In order to ensure the consistency and reliability of the scores throughout the study, two psychiatrists received training on the use of HAMD and HAMA before the study. After training, repeated evaluations showed that the inter-rater correlation coefficient of HAMD and HAMA total scores was greater than 0.8. Two psychiatrist assessors were blind to the patient's clinical condition.

Blood Sample

On the day when the clinical rating scale was measured, blood samples were collected between 6 am and 7 am after an overnight fast. All samples were sent to the laboratory center of the hospital immediately and measurements were taken before 11 am in the morning of the same day. The plasma TC, TG, HDL-c, and LDL-c levels were measured on the BECKMAN AU5800 system (Beckman Coulter, Brea, California, USA).

Statistical Analysis

The prevalence of attempted suicide was expressed as a percentage. The demographic and clinical variables of the recent suicide group, past suicide group and non-suicide group were compared by using the analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Since there was no significant difference in lipid distribution between the recent suicide group and the past suicide group, we combined these two subgroups into one suicide attempt group. Then, we compared the demographic and clinical variables between suicide attempters and non-attempters by performing t-tests for continuous variables and chi-square tests for categorical variables. Whereas there was a significance in ANOVA test, analysis of covariance (ANCOVA) was then conducted to control for the influence of confounding factors. Finally, after controlling for the effects of age, gender, BMI, age of onset, duration of illness, severity of depression symptoms (HAMD) and severity of anxiety symptoms (HAMA), binary logistic regression analysis (enter) was performed to assess the factors associated with suicide attempts. Statistical analyses were performed using SPSS 22.0 for Windows. All statistical tests were two-tailed, and the significance level was set at ≤0.05.

RESULTS

A total of 1,718 patients included 588 men and 1,130 women. Among them, 346 (20.14%) had a history of attempted suicide, of whom 235 (13.68%) had attempted suicide in last month and 111 (6.46%) had attempted attempt in the past except for the last month. Their average age was 34.87 ± 12.43 years and the average course of disease was 6.31 ± 4.73 months, with a range of 5 to 28 months.

Table 1 shows the socio-demographic and clinical data of the recent suicide group, past suicide group, and non-suicide group. There were significant differences in sex (χ^2 = 7.92, p = 0.02), duration of illness (F = 6.87, p < 0.001) and BMI (F = 12.30, p < 0.001) between the three groups. Compared with the past suicide group, the recent suicide group had more women (p = 0.02), shorter duration of illness (p = 0.04), and higher BMI level (p < 0.001).

There were significant differences between the three groups, including TC (F = 52.61, p < 0.001), TG (F = 3.59, p < 0.001), HDL (F = 18.32, p < 0.001), LDL (F = 15.25, p < 0.001), HAMD (F = 107.17, p < 0.001), and HAMA (F = 184.67, p < 0.001). *Post hoc* analysis showed that TC and LDL levels, HAMD and HAMA scores of the recent suicide group and past suicide group were significantly higher than those of the non-suicide group (all p < 0.001). Moreover, HDL levels of the recent and past suicide groups were significantly lower than that of the non-suicide group (p < 0.001). However, there were no significant differences in lipid parameters and HAMD and HAMA scores between the recent and past suicide groups (all p > 0.001).

Since there were no significant differences in lipid parameters between the recent and past suicide groups, we combined them into one suicide group to compare the lipid profiles between suicide and non-suicide groups. **Table 2** shows the socio-demographic and clinical data of these two groups. Suicide attempters were significantly older (t = −2.10; p = 0.036), had a later age of onset (t = 0.66; p = 0.04), longer duration of illness (t = −2.83; p = 0.01), higher levels of TC (t = 10.19; p < 0.001), LDL-c (t = −5.51; p < 0.001) and TG (t = −2.68;p = 0.008), higher HAMA (t = −16.83; p < 0.001), and HAMD scores (t = −14.57; p < 0.001) but lower HDL-c levels (t = 6.05; p < 0.001) compared with non-attempters. After controlling for sex, age, and BMI, further ANCOVA showed that the following parameters between the two groups still remained significant: age of onset (F = 1.91; p < 0.001), TC (F = 1.47; p < 0.001), LDL-c (F = 1.51; p < 0.001) and TG (F = 1.27; p = 0.001), HDL-c (F = 1.45; p = 0.001), HAMA (F = 18.50; p < 0.001), and HAMD scores (F = 14.45; p < 0.001). In addition, there was no significant correlation between the number of suicide attempts and any lipid profiles (all p > 0.05).

Further binary logistic regression analysis showed that higher TC, lower HDL-c, and higher HAMA and HAMD scores were significantly associated with attempted suicide (**Table 3**), with the adjusted odds ratio (OR) of 1.28 (standardized β = 0.24; 95% CI: 0.12–1.35; df = 1, p < 0.01) for HAMA, 1.08 (standardized β = 0.08; 95%CI:0.11–1.16; df = 1, p = 0.01) for HAMD and1.35 (standardized β = 0.30; 95%CI: 0.11–1.59; df = 1, p < 0.01) for TC, and 0.52 (standardized β = −0.65; 95% CI: 0.33–0.83; df = 1, p < 0.01) for HDL-c.

In addition, we further conducted statistical analysis and provided results based on clinical reference values. The normal range of each index is as follow: 2.83–5.17 mmol/L for TC, ≤1.7 mmol/L for TG, ≥1.04 mmol/L for HDL-C, ≤3.12 mmol/L for LDL-C. Then we classified normal TC and decreased TC into one group for analysis because there were very few people (n =

TABLE 1 | Comparison of characteristics between recent and past suicide attempters and non-attempters (n = 1,718).

	Recent suicide attempters[1] (n = 235)	Past suicide attempters[2] (n = 111)	Never suicide attempters[3] (n = 1372)	χ2/F	*P*
Socio-demographic and clinical Characteristics (Mean ± SD)					
Age (years)	36.48(12.57)	35.36(11.90)	34.55(12.43)	2.51	0.08
Female (%)	170(72.34%)	64(57.66)	896(65.30%)	7.92	0.02[a]
Unmarried (%)	60(25.53%)	35(31.53%)	407(29.66%)	1.98	0.37
Education (years)	12.61(3.19)	12.43(2.84)	12.76(2.89)	0.79	0.45
Age of onset (years)	36.28(12.49)	35.06(11.79)	34.35(12.31)	2.51	0.08
Duration of illness (month)	6.53(4.84)	7.83(4.88)	6.15 (4.68)	6.87	0.00[b]
BMI	24.67(1.73)	23.58(3.13)	24.38(1.81)	12.30	0.00[c]
Scale assessment (Mean ± SD)					
HAMD	32.09(2.75)	32.55(3.14)	29.81(2.75)	107.17	0.00[d]
HAMA	24.22(3.55)	22.25(3.15)	20.09(3.08)	184.67	0.00[e]
Biological indicators (Mean ± SD)					
Total Cholesterol (mmol/L)	5.82(1.12)	5.67(1.08)	5.12(1.07)	52.61	0.00[f]
Triglycerides (mmol/L)	2.30(1.03)	2.29(0.98)	2,14(0.98)	3.59	0.00[g]
HDL cholesterol (mmol/L)	1.14 (0.28)	1.14 (0.30)	1.24(0.28)	18.32	0.00[h]
LDL cholesterol (mmol/L)	3.20 (0.92)	3.23 (0.88)	2.92(0.84)	15.25	0.00[i]

BMI, body mass index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; HDL, high density lipoprotein; LDL, low density lipoprotein.
All post-hoc analyses were done using Tukey;
[a]^{1}vs.^{2} p = 0.02,^{1}vs.^{3} p = 0.09, ^{2}vs.^{3} p = 0.23;
[b]^{1}vs.^{2} p = 0.04,^{1}vs.^{3} p = 0.48, ^{2}vs.^{3} p < 0.001;
[c]^{1}vs.^{2} p < 0.001,^{1}vs.^{3} p = 0.08, ^{2}vs.^{3} p < 0.001;
[d]^{1}vs.^{2} p = 0.33,^{1}vs.^{3} p < 0.001, ^{2}vs.^{3} p < 0.001;
[e]all post-hoc test p < 0.001;
[f]^{1}vs.^{2} p = 0.46,^{1}vs.^{3} p < 0.001,^{2}vs.^{3} p < 0.001;
[g]^{1}vs.^{2} p = 1.00,^{1}vs.^{3} p = 0.05,^{2}vs.^{3} p = 0.27;
[h]^{1}vs.^{2} p = 1.00,^{1}vs.^{3} p < 0.001,^{2}vs.^{3} p < 0.001;
[i]^{1}vs.^{2} p = 0.95, ^{1}vs.^{3} p < 0.001,^{2}vs.^{3} p < 0.001.

TABLE 2 | Characteristics of first episode drug naïve depressed patients with/without suicide attempts (n = 1718).

	All patients (n = 1,718)	Suicide attempt (n = 346)	Non-suicide attempt (n = 1,372)	t/χ2	P
Socio-demographic and Clinical Characteristics (Mean ± SD)					
Age (years)	34.87(12.43)	36.12 (12.35)	34.55 (12.43)	–2.10	0.036
Female (%)	1130(65.77%)	234 (67.60%)	896 (65.30%)	0.66	0.42
Unmarried (%)	502(29.22%)	95 (27.50%)	407(29.70%)	0.65	0.42
Education (years)	12.72(2.93)	12.55(3.08)	12.76(2.89)	1.14	0.25
Age of onset (years)	34.66(12.31)	35.89 (12.26)	34.35 (12.31)	0.66	0.04
Duration of illness (month)	6.31(4.73)	6.95 (4.89)	6.15 (4.68)	–2.83	0.01
BMI	24.37(1.93)	24.32(2.33)	24.38(1.81)	0.43	0.67
Scale assessment (Mean ± SD)					
HAMD	30.30(2.94)	32.24(2.89)	29.81(2.75)	–14.57	0.001
HAMA	20.80(3.47)	23.59(3.54)	20.09(3.08)	–16.83	0.001
Biological indicators (Mean ± SD)					
Triglycerides (mmol/L)	2.17(0.99)	2.29(1.02)	2.14(0.98)	–2.68	0.008
HDL cholesterol (mmol/L)	1.22(0.29)	1.14(0.29)	1.24(0.28)	6.05	0.001
LDL cholesterol (mmol/L)	2.98(0.86)	3.21(0.91)	2.93(0.84)	–5.51	0.001
Total Cholesterol (mmol/L)	5.25(1.11)	5.77(1.11)	5.12(1.07)	10.19	0.001

BMI, body mass index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; HDL, high density lipoprotein; LDL, low density lipoprotein.

11) with TC lower than 2.83 mmol/L. The chi-square test was used to compare the metabolic indicators between attempted suicide and non-suicide participants. Compared with those without attempted suicide, those who attempted suicide had significantly higher levels of TC and LDL-c but lower HDL-C levels (all $p < 0.05$). Binary logistic regression analysis indicated that in MDD patients, suicide attempts were associated with HDL-c, with an OR of 0.73 (95% CI: 0.54–0.97; df = 1, $p < 0.05$).

DISCUSSION

To our best knowledge, this is the first study to investigate the association between lipid profiles and attempted suicide in such a large FEDN MDD sample in China. Our study showed that the prevalence of suicide attempts in this large group of MDD patients was 20.14%. We did not find significant difference in lipid profiles between recent and past suicide attempts. However,

TABLE 3 | Predictors of suicide attempts within a binary logical regression model.

	Coefficients				95.0% Confidence Interval	
	β	Odds Ratio	*z* value	*p* value	Lower	Upper
Age	−0.37	0.69	−1.35	0.18	0.40	1.19
Gender	0.03	1.03	0.18	0.86	0.77	1.37
BMI	−0.06	0.94	−1.35	0.18	0.88	1.01
Age of onset	0.37	1.45	1.35	0.18	0.84	2.48
Duration of illness	0.05	1.05	1.72	0.09	0.99	1.11
HAMD	0.08	1.08	2.44	0.01	0.11	1.16
HAMA	0.24	1.28	9.72	<0.01	0.12	1.35
TC	0.30	1.35	3.54	<0.01	0.11	1.59
HDL-c	−0.65	0.52	−2.73	<0.01	0.33	0.83
TG	−0.07	0.93	−0.98	0.33	0.80	1.07
LDL-c	−0.11	0.89	−1.23	0.22	0.74	1.07

HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; TC, Total Cholesterol; HDL, high density lipoprotein; TG, Triglycerides; LDL, low density lipoprotein.

the lipid profiles of the two suicide groups were significantly different from those of the non-suicide group. Further analysis found that adjusting for gender, age and BMI, attempted suicide group had significant differences in demographic, clinical, and biochemical variables from non-suicide group. Further logistic regression analysis showed that higher TC levels, lower HDL-c levels, more severe anxiety and depressive symptoms were associated with suicide attempts, suggesting that these parameters may be important risk factors associated with suicide attempts.

Suicide is the most devastating result for patients with depression, with about one death in every 25 suicide attempts (40). In our study, the prevalence of suicide attempts (20.14%) was similar to that reported in other Asian countries, such as 16.9% in upper northern Thailand (4), and 19.8% in Korea (3). A recent epidemiological survey reported that the prevalence of suicide attempts was 1.3% in rural samples and 0.9% in urban samples in Beijing area (41). Therefore, our current findings indicate that the prevalence of suicide attempt in our MDD outpatients is nearly 20 times that in the general population, suggesting a dramatic increase in suicide attempt rate in first-episode MDD patients in the Chinese population. However, it is worth mentioning that most reports of suicide attempt rates in MDD patients in Western countries range from 27.5% in Europe to 36.3% in the United States (1), which is much higher than about 20% in Asian countries. Possible reasons for the different rates of suicide attempts among different ethnic groups include health resources, cultural traditions, political environment, access to psychiatric care, economic and sociocultural factors in different regions or countries (1, 42), as well as ethnic background, which is due to interethnic differences in the genotype frequency of suicide-related gene polymorphisms between Chinese and Caucasians (42).

One of the important findings in our current study is that high TC levels were associated with suicide attempts, which is consistent with several previous studies. For example, a case–control study compared psychiatric patients who attempted suicide (193 subjects) with those who did not attempt suicide (1,091 subjects) and found that high TC levels were associated with an increased risk of suicide in American men (43). A prospective follow-up study also showed that high cholesterol was associated with an elevated risk of suicide attempts in patients with depression (15). Also, similar results were found in population-based studies. For example, a previous study reported a positive association between TC levels and long-term suicide risk in a large sample of 7,309 middle-aged Japanese-American men (33). Tanskanen et al. reported that in a large general population, the adjusted relative risk of violent suicide in the highest TC group was twice that in the lowest TC group (13). Similarly, in a population-based study, Brunner et al reported higher cholesterol levels in suicide attempters than non-attempters (34). However, the reasons behind this association are still unclear. Some researchers speculate that patients with higher TC may have maladaptive nutritional behaviors, such as overeating, which may be associated to suicide attempts and suicidal ideation (34). Another possible reason is that elevated TC may be related to stroke, which is known to increase the risk of suicide (44). However, many previous studies have reported a negative or no association between TC and attempted suicide (14, 27, 45–47). Researchers have explored the possible mechanisms of this negative correlation. The hypothesis of cholesterol–serotonin–impulsivity has been proposed that low concentrations of cholesterol may reduce the exposure of serotonin receptors on the surface of brain cell membranes, and then reduce the function of serotonin receptors, thereby leading to impulsive or aggressive behavior in susceptible individuals (7, 10, 12, 48). However, studies have shown that the transmission of serotonin partly depends on brain cholesterol, but brain cholesterol is relatively isolated from changes in circulating cholesterol (19).

In our and previous studies, the possible reasons for the difference in the relationship between TC and the attempted suicide may be due to the clinical condition of the recruited samples. For example, the sample in our study was the first episode drug-naive MDD patients, while the samples in the previous studies were hospitalized MDD patients. The blood lipid levels of these hospitalized patients may be affected by drug treatment, including antidepressants (36) and second-generation antipsychotics (49). In addition, blood lipid levels may be affected by hospitalization, dietary intake, and weight loss after long-term depression (24). Other possible reasons include that the subjects in the previous study not only suffered from depression, but also

suffered from other mental disorders, such as accompanied by adjustment disorder (45) and psychotic symptoms (47), which are clinical confounders for suicide attempts. Interestingly, some researchers even suggest that changes in lipid metabolism in both directions may lead to changes in serotonergic function. For example, Kim et al reported that both higher and lower TC levels at baseline predicted the rate of suicidal ideation in the elderly. They stated that decreased serotonin activity was associated with lower TC levels, and that an atherogenic lipid profile was related to higher TC levels, and both may be associated with suicidality in later life (35). Taken together, the exact relationship between TC levels and suicide attempts remains unclear. In this study, the cross-sectional design, without long-term follow-up cholesterol data, limited the interpretation of the causal relationship between blood lipid levels and suicidal behavior, that is, the results of this cross-sectional study cannot differentiate whether high cholesterol may be a consequence of suicide attempts or the underlying pathological mechanisms that may result in suicide attempts. Although there is a positive correlation between high lipid levels and suicide attempts, the current results cannot lead to a causal relationship. Therefore, further prospective studies are needed to explore the correlation between high cholesterol and suicide attempts, which may also be confirmed by longitudinal data.

Generally, proatherogenic lipids (TC, LDL, and TG) and anti-atherogenic lipid (HDL) may have different roles in suicide. In this study, we also found a negative correlation between HDL-c and suicide attempts. However, previous studies are inconsistent, suggesting that higher or lower HDL-c levels were associated with suicide attempts in patients with depression (27, 29). The two most important findings of our study were the association between suicide attempts and high TC/low HDL-c levels. These findings are in line with the hypothesis that abnormal lipid profiles may be a sign of other metabolic abnormalities associated with increased risk of suicidal behavior. For example, omega-3 polyunsaturated fatty acids (PUFAs) may be a key mediator between lipids and suicide (34). There was an inverse correlation between PUFAs and the ratio of serum TC/HDL-c. As a result, subjects with high TC and low HDL-c have lower levels of PUFAs, and it has been reported that reduced PUFAs may be a strong risk factor for suicide and depression (50, 51), suggesting that lipid changes may be a surrogate marker.

It is worth mentioning that previous studies have found an association between the lipid profiles and either recent or lifetime suicide attempts in patients with depression (25, 27). However, whether lipid parameters are the state or trait markers for suicide attempts remain uncertain. In our current study, there was no significant difference in lipid profiles between recent suicide and past suicide attempters, suggesting that lipid parameters may be trait markers of attempted suicide. However, all patients in this study had their first onset, with an average ill duration of 7.8 months, and even those patients in the past suicide group attempted suicide in the past several months. Thus, the interval period of suicide attempts between recent and past suicide groups may not be sufficient to show differences in lipid profile. Therefore, whether the lipid profile is a state or a trait marker of the suicide attempt deserves further investigation.

Further, we found that the severity of depression was an important factor of suicide attempts, which is consistent with most previous studies (52). However, other studies have reported no correlation between suicide attempt and the severity of depression (2). The possible reason for this discrepancy may be due to the different time of assessing the severity of depression, rather than the time of attempted suicide (2). This may also explain why the Exp (β) value was only 1.08 in our current study.

Another finding of this study was that there was a significant association between anxiety and an increased risk of suicide attempts. Our results showed that the HAMA score was significant higher in suicide attempters than that in non-attempters, and the risk of suicide attempt for patients with high HAMA score was 1.28 times that of patients with low HAMA score. This result is consistent with previous reports showing that anxiety was an important factor for suicide in patients with depression (6). A previous study showed that depressed patients with higher levels of anxiety had more suicide attempts than those without anxiety before and after adjusting for the severity of depression (53). In addition, 79% of patients who committed suicide during hospitalization or immediately after discharge had severe anxiety/agitation symptoms before committing suicide (54). The possible biological mechanisms linking anxiety symptoms to suicide attempts may be explained by both anxiety and suicide associated with serotonergic dysfunction (55). This finding suggests that clinicians should pay more attention to those depressed patients comorbid with anxiety to prevent suicidality, and continue to assess and re-assess anxiety levels to reduce suicidal behavior.

There are several limitations to this study. First, in this study, lipid measurements were only collected at a time-point, but in general, these measurements may change over time. The association between lipid levels and suicide attempts may vary depending on the time points when lipid levels are tested. Moreover, the blood lipid levels of patients with first-onset depression are more likely to be influenced by their diseases. For example, patients do not want to eat and sleep poorly, so lipid disorders occur, leading to the association between lipids and suicide attempts, which is a symptom of depression. Hence, we may have a false lipid-suicide attempt association. We cannot exclude this possibility in this cross-sectional study, and should be further examined in further studies using a longitudinal design. Second, this is a cross-sectional study, with no long-term follow-up cholesterol data. Therefore, the causal relationship between lipid levels and suicidal behavior is still unclear. Third, we collected suicide information through research interviews with patients, family members, and clinicians, rather than using structured tools, which may introduce bias during the collection phase. Fourth, there are too many factors for attempted suicide, but we only included some variables as covariates. Important risk factors for suicide attempts, such as lack of social support, major physical conditions/pain, smoking and drinking, were not controlled in their adjusted analyses (18). Moreover, considering that both nutritional status and stress may affect blood lipid levels, the one time-point measurement of blood lipid levels at admission may not reflect the patient's baseline level (24). Sixth, there were more

female patients in this study, which may be a potential confounder, because the MDD and suicidality are more common in women than men (17). Finally, past suicide attempts may be due to depression or even a depressive episode. Therefore, the diagnosis of the first depressive episode may be questionable in some patients who attempted suicide.

CONCLUSION

In summary, our study showed that the prevalence of suicide attempts in FEDN MDD patients was 20.14%. Moreover, high TC and low HDL-c levels were significantly associated with suicide attempts in these patients, suggesting that abnormal lipid levels may be involved in suicide attempt in MDD patients at their early stage. Further, our finding provided further evidence that more severe symptoms of anxiety and depression were associated with suicide attempts in these MDD patients. Therefore, our findings have important implications for clinical care, because the understanding and treatment of depression and anxiety symptoms can provide better results for preventing suicide attempts in FEDN patients with major depression. Due to methodological limitations, longitudinal studies conducted under the control of related variables will more clearly determine the association and causality between abnormal blood lipid levels and suicide attempts in MDD patients in the early stage of the disease. Taken together, understanding the relationship between lipid profiles and suicide attempts in early stage of MDD will provide important implications for the prevention of suicidal behavior.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board (IRB) of the First Clinical Medical College, Shanxi Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

T-QL and X-YZ were responsible for the study design, manuscript preparation and revision. Y-JM and D-FW were responsible for statistical analysis, manuscript preparation and writing the protocol and the paper. Y-JZ, YL, and D-MW were responsible for data collection, lab experiments. All authors contributed to the article and approved the submitted version.

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Association of Existence of Third Places and Role Model on Suicide Risk Among Adolescent in Japan: Results From A-CHILD Study

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Objective: Low self-esteem among adolescents can be considered a risk factor for suicidal behavior in adolescents. Thus, the purpose of this study is to investigate the association between the existence of a third place and role model on self-esteem among adolescents in Japan, where low self-esteem is prevalent among adolescents.

Methods: We analyzed data from the 2016 Adachi Child Health Impact of Living Difficulty (A-CHILD) study, in which a school-based questionnaire was conducted among children in grades 4, 6, and 8 living in Adachi City, Tokyo ($N = 1,609$). Children self-rated their own levels of self-esteem. Low self-esteem was defined as lower 10 percentile group. The existence of a third place was defined as a place where children spent time after school other than the home or school campus, and role model was defined as having someone, other than a parent, who they looked up to, and these concepts were assessed via questionnaire.

Results: Adolescents without a third place and role model accounted for 10.5 and 6.1%, respectively. We found that children who lacked a third place also showed a significant association with low self-esteem (OR: 1.75, 95% confidence interval (CI): 1.09–2.81), and those who lacked a role model were 3.34 times more likely to have lower self-esteem (95% CI: 1.98–5.62).

Conclusion: The existence of a third place and a role model may be important to prevent low self-esteem among adolescents in Japan.

Keywords: self-esteem, adolescent, third place, role model, mental health, suicide, Japan

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INTRODUCTION

Low self-esteem among adolescents is an important marker for mental disorders. For example, adolescents with lower self-esteem are more likely to show signs of mental illness such as depression (1–4), anxiety (1, 4), and suicidal ideation and attempted suicide (5–7). Furthermore, adolescents with lower self-esteem are more likely to have physical health problems and limited economic prospects in adulthood (8).

Self-esteem among children in Japan is much lower than in the United States (US) or European countries, and is even lower than South Korea. Recent international surveys implemented as part of the International Sexuality Description Project among college students showed that Japan scored the lowest in terms of the Rosenberg self-esteem score (25.50; $SD = 4.37$) among 53 nations, which is markedly lower than Serbia which has the highest score (33.59; $SD = 4.99$) (9). Although cultural aspects such as individualism/collectivism (9) and performative pressure (10) play a major part in the level of self-esteem in Japanese, Japan is nonetheless a suitable setting to investigate the modifiable social determinants of low self-esteem.

Risk factors of low self-esteem among children have been reported in family-, school-, and community-levels in Japan using the ecological model (11). That is, poverty, poor parental mental health, and poor parental involvement (family level), poor school social capital (school level), and poor community social capital (community level) were found to contribute to low self-esteem among adolescents (10), suggesting a possible intervention target. However, income levels, parental mental health, parenting practice, and social capital in both school and community settings are difficult to modify in the short term through health policy.

To identify modifiable factors that contribute to low self-esteem, we hypothesized that the existence of a third place may be associated with low self-esteem among adolescents, based on the theory of the Third Place (12). The theory was first introduced by Oldenburg (1991), who defined it as "informal gathering places in which people gather between home and work," such as a café in France, a pub in the UK, or a hair salon in Brazil (12). By applying this theory, we hypothesized that the existence of a third place, i.e., a place where adolescents can spend time in other than home or school, such as the park, playground, or grandparents' house, may contribute to the prevention of low self-esteem among adolescents. In line with this hypothesis, previous studies have shown that having a third place is beneficial for the overall well-being in adolescents (13) by facilitating social inclusion (14).

In conjunction with third place, the existence of a role model, that is, having some adults in one's life who provide a positive influence, other than parents (assuming that the mother and father were the primary adults in adolescents' lives), may play a significant role in developing self-esteem, based on the mentoring theory (15). That is, a mentor, or role model, can be an example of how to regulate emotions to manage environmental stressors, as well as to provide attachment and uncover potential skills through praise and educational engagement, all of which could enhance self-esteem of adolescent (16, 17). Moreover, the existence of a role model may serve as a buffer for psychological distress caused by poor parenting style or peer pressure from schoolmates, which is known to be risk factor of poor mental health among adolescents (18). However, to the best of our knowledge, no previous study has explored the association between the existence of a third place or role model on low self-esteem among adolescents in Japan.

The purpose of this study is to investigate the association between the existence of a third place and role model on self-esteem among adolescents in Japan.

METHODS

Participants

This study is part of the Adachi Child Health Impact of Living Difficulty (A-CHILD) study conducted in 2016, which examined the living environment and health of elementary school and junior high school students and their parents in Adachi City, Tokyo. Self-reported questionnaires with anonymous unique identifiers were distributed to adolescents at schools in Adachi City, Tokyo, including 4th grade (age 9–10 years old, $N = 616$) and 6th grade (age 11-12 years old, $N = 623$) students in 9 elementary schools, and 2nd grade students in 7 junior high schools (i.e., 8th grade) (age 13–14 years old, $N = 755$). In Japan, children start elementary school starts from age 6 at the 1st grade, and graduate at age of 12 at the 6th grade. Following that, students will attend junior high school for 3 years (i.e., 7th to 9th grade). Both elementary school and junior high school are part of the compulsory education system. Most students will attend go on to high school (i.e., 10th, 11th, 12th grade). Students brought questionnaires home to their caregivers, both students and their caregivers responded, and then completed questionnaires were returned at school. A total of 1,773 participants returned the questionnaire [response rate = 88.9%, completed by mothers (90.3%), fathers (8.6%), and others (2.1%)], and 1,652 participants provided informed consent and submitted both the caregiver and child questionnaires (valid response rate = 82.9%). Written informed consent was obtained from all adult participants and the caregivers of children. We did not obtain written informed consent from children because it was granted by the children's caregivers, which is in line with Japan's ethical guidelines for epidemiological research. Of the valid respondents, 17 participants were excluded due to missing data from the main variables (self-esteem, role model, third place, sex, and school social capital) used in the analysis. Thus, the analytical sample was 1,635 participants (99.0% of valid sample). The A-CHILD protocol was approved by the Ethics Committee at the National Center for Child Health and Development (No. 1187) and the Institutional Review Board at Tokyo Medical and Dental University (M2016-282-02).

MEASUREMENTS

Self-Esteem

Children were asked about their self-esteem using one of the subscales from the Japanese version of the Children's Perceived Competence Scale (19), which was developed based on the Perceived Competence Scale for Children (20). Ten items were used (e.g., "Are you satisfied with the way you are now?" or "Do you think you have few good points?") and rated using a scale of 1 (*no*) to 4 (*yes*). A higher total score denoted a higher level of self-esteem. The Cronbach's alpha for the scale was 0.86 in this study. Low self-esteem was defined as lower 10 percentile group.

Third Places and Role Model

To assess the existence of a third place, we asked 4th grade children and 6th or 8th grade children in a different way. For the 4th grade children, we asked what is the place they spend the most time in after school, by selecting a list consisting of "my house," "grandparents," "friend's house," etc., and for up to three places. Those who selected items other than "my house" were regarded as having a third place. For 6th and 8th grade children, we asked what is the frequency of spending time at a place after school (i.e., "3 times or more per week," "1–2 times per week," "1–2 times per month," and "rarely or never"). Those who responded with items other than "rarely or never" for places other than "my house" and "at school for club activities" were regarded as having a third place.

As for role model, in the child questionnaire for 4th, 6th, and 8th grade children, the existence of a role model was assessed by asking if they have any adults aside from your parents whom they can trust, respect or provide care, etc., by listing several items, including "no one like that." We categorized those children who selected "no one like that" as not having a role model, and those who selected any other responses as having a role model (see details in **Appendix 1**).

Covariates

Covariates included family factors, lifestyle behaviors, and school factors. For family factors, poverty was assessed across three dimensions: income, existence of material deprivation, and experience of being unable to pay for things (see details of the response items in the **Appendix 2**). Based on these three variables, child poverty is defined in this study as a child who falls into any one of the following categories: (1) annual household income is <3 million yen; (2) household lacks one or more basic necessities, and (3) family lacks the capacity to pay for one or more types of lifeline utility cost. This definition is based on the deprivation theory about relative poverty, which focuses on the combination of monetary and non-monetary criteria (21, 22) and has been used in a previous study (23). We also assessed child's sex, marital status, parental mental health, existence of older sibling(s), younger sibling(s), and child maltreatment in the caregivers' questionnaire. Marital status was described as married, never married, divorced, widowed, or others, which was dichotomized into "married" or "single/divorced/widowed/others." Parental mental health was assessed using the Japanese version of the Kessler 6 (K6) (24). Child maltreatment was also assessed in the caregivers' questionnaire with the categories of physical abuse, psychological abuse, and neglect, using the Japanese child maltreatment scale (25), with cut-offs defined by experts on child maltreatment in Japan (23, 26). The children's questionnaire assessed lifestyle factors, including skipping breakfast (yes/sometimes vs. no), going to bed late (11 p.m. or later vs. before 11 p.m.), waking up late (7 a.m. or later vs. before 7 a.m.), and frequency of physical activity (3+, 1–2, <1 day per month).

Children's social capital at school, which is defined as intangible prosocial resources from social networks, including peer groups and teachers, in a school environment (27), was also assessed using seven items on a scale of 1 (*I do not agree at all*) to 5 (*I agree*). The items were: "I like the classroom atmosphere," "I like my homeroom teacher," "I think school is fun," "I greet my teachers and my classmates," "I trust my teacher," "I trust my classmates," and "I actively participate in school activities." The total score was calculated using the sum of seven items and ranged from 7 to 35, in which the score of each item was reversed (Cronbach's alpha = 0.88). Higher scores indicated that a child had poor school social capital. We calculated "school-level" school social capital, i.e., the aggregated school social capital score measured at the individual level as the mean. Further, individual-level school social capital was also calculated as centered by mean of each school-level school social capital.

Statistical Analysis

To adjust for school-level clustering, we applied multilevel analysis, which adjust for individual level and aggregated level simultaneously, using school grade as a unit in aggregated level in this study. First, the self-esteem score was used as a categorical variable (i.e., low self-esteem or not), thus applying multilevel logistic regression analysis, and we investigated an association with the existence of third places and role models, adjusted for age and grade as a crude model. Then, we adjusted for school social capital (both school- and individual-level) and family factors and lifestyle behaviors in multilevel model. As for sensitivity analysis, we conducted a similar analysis using self-esteem as a continuous variable. Significance level was set to 0.05. All analyses were conducted using Stata SE 14.0.

RESULTS

Characteristics of the sample are shown in **Table 1**. Sex distribution was almost equivalent, and adolescents with a third place and role model accounted for 90.5 and 93.9%, respectively. Among the caregiver sample, most were married (81.1%), and the proportion of families living in poverty was 27.7%. Parental psychological distress, which was measured by having a K6 score of 5+, was observed in 35.2% of caregiver participants, while child maltreatment was reported by 35.2%. Among the sample of adolescents, approximately half had older siblings and younger siblings. As for lifestyle behaviors, 12.5% of adolescents skipped breakfast, 16.1% went to bed later than 11 p.m., 44.3% woke up later than 7 a.m., and 23.7% exercised less than once a week. The mean self-esteem score (ranged 0–30) was 16.8 (standard deviation [SD] = 6.7), low self-esteem adolescents (n = 181, 11.1%) had a mean score of 4.24 (SD = 2.2), while the mean score of non-low self-esteem adolescents (n = 1,454, 88.9%) was 17.6 (SD = 5.5). Overall, adolescents with low self-esteem were more likely to be older, living in poverty and in a single-parent family, have a higher prevalence of parental psychological distress, as well as experience of child maltreatment, skipping breakfast, going to bed and waking up late, and being physically inactive (all $p < 0.05$).

Table 2 shows the characteristics of school social capital. The number of adolescents per school grade ranged from 20 to 170, with a mean of 65.4 (SD = 35.5). The grand mean of the school social capital score was 4.04 (SD = 0.30), and after categorization into low, middle, and high schools, the difference between each

TABLE 1 | Characteristics of sample (N = 1,635).

			Total (N = 1,635)		Low self-esteem (N = 181, 11.1%)		Non low self-esteem (N = 1,454, N = 88.9%)		p-value*
			N or Mean	% or SD	N or Mean	% or SD	N or Mean	% or SD	
Self-esteem score		Range 0–30	16.8	6.7	4.24	2.2	17.6	5.5	<0.001
Demographics	Grade	4th	523	32.0	31	17.1	492	33.8	<0.001
		6th	528	32.3	42	23.2	486	33.4	
		8th	584	35.7	108	59.7	476	32.7	
	Age	9-14	11.6	1.7	12.3	1.6	11.5	1.7	<0.001
	Sex	Male	795	48.6	70	38.7	725	49.9	0.005
		Female	840	51.4	111	61.3	729	50.1	
Social factors	Having third place other than home or school	Yes	1,480	90.5	147	81.2	1,333	91.7	<0.001
		No	155	9.5	34	18.8	121	8.3	
	Having role mode other than parents	Yes	1,536	93.9	146	80.7	1,390	95.6	<0.001
		No	99	6.1	35	19.3	64	4.4	
Family factors	Poverty	Yes	453	27.7	69	38.1	384	26.4	0.001
		No	1,182	72.3	112	61.9	1,070	73.6	
	Marital status	Married	1,326	81.1	133	73.5	1,193	82.1	0.006
		Single/divorced/widowed/other	255	15.6	43	23.8	212	14.6	
		Missing	54	3.3	5	2.8	49	3.4	
	Having older siblings	Yes	789	48.3	96	53.0	693	47.7	0.17
		No	846	51.7	85	47.0	761	52.3	
	Having younger siblings	Yes	774	47.3	82	45.3	692	47.6	0.56
		No	861	52.7	99	54.7	762	52.4	
	Parental psychological distress	K6 5+	575	35.2	79	43.7	496	34.1	0.04
		K6 <5	1,049	64.2	101	55.8	948	65.2	
		Missing	11	0.7	1	0.6	10	0.7	
	Child maltreatment	Yes	575	35.2	76	42.0	499	34.3	0.068
		No	1,048	64.1	105	58.0	943	64.9	
		Missing	12	0.7	0	0.0	12	0.8	
Life style factors	Skipping breakfast	Yes/sometimes	205	12.5	50	27.6	155	10.7	<0.001
		No	1,422	87.0	131	72.4	1,291	88.8	
		Missing	8	0.5	0	0.0	8	0.6	
	Late time go to bed (11 p.m. or later)	Yes	263	16.1	43	23.8	220	15.1	0.006
		No	1,358	83.1	138	76.2	1,220	83.9	
		Missing	14	0.9	0	0.0	14	1.0	
	Late time wake up (7 a.m. or later)	Yes	724	44.3	102	56.4	622	42.8	0.002
		No	904	55.3	79	43.7	825	56.7	
		Missing	7	0.4	0	0.0	7	0.5	
	Frequency of exercise	3 days+/week	735	45.0	58	32.0	677	46.6	<0.001
		1–2 days/week	498	30.5	49	27.1	449	30.9	
		<3 days/month	388	23.7	72	39.8	316	21.7	
		Missing	14	0.9	2	1.1	12	0.8	
School social capital	Individual-level school social capital, group centered, continuous		−0.002	0.8	−0.41	0.9	0.05	0.8	<0.001
	Individual-level school social capital, group centered, category	Low	551	33.7	105	58.0	446	30.7	<0.001
		Middle	544	33.3	50	27.6	494	34.0	
		High	540	33.0	26	14.4	514	35.4	

**P-value was estimated by t-test for continuous variables and chi-square test for categorical variables.*

TABLE 2 | Characteristics of school grade ($N = 25$).

		N	Mean	SD
Number of students per school grade	Range 20–170	25	65.4	35.5
School class social capital score, continuous	Range 0–5	25	4.04	0.30
School class social capital score, category	Low	9	3.80	0.26
	Middle	8	4.06	0.20
	High	8	4.30	0.17

category was 0.25, and the standard deviation of each category was similar (range 0.17–0.26).

Odds ratios for the existence of a third place and role models for low self-esteem are shown in **Table 3**. In the crude model adjusted for sex and grade, adolescents who did not have a third place or a role model were 2.13 and 4.73 times more likely to have low self-esteem (95% confidence interval (CI): 1.37–3.30 and 2.95–7.96), respectively. The association remained significant after adjustment for family factors, lifestyle behaviors, and school social capital at both the school and individual level, and after adjustment of both levels. That is, adolescents who did not have a third place or a role model were 1.64 and 2.75 times more likely to have low self-esteem (95% CI: 1.37–3.30 and 2.95–7.96), respectively. Post-estimation of the comparison between the odds ratio for the existence of a third place and a role model did not show a significant difference ($p = 0.16$). We also found that low and middle individual-level school social capital [odds ratio (OR) = 3.76 and 2.13, respectively], skipping breakfast (OR = 2.06), low frequency of exercise (i.e., OR = 2.02 for <3 days/month exercise), and late waking up time (OR = 1.64) showed significant positive association with low self-esteem, independent from existence of a third place and a role model. The OR of low individual-level school social capital, which was highest in the model, were not significantly different from having a role model ($p = 0.41$).

As for sensitivity analysis, the association of the existence of a third place and a role model with the self-esteem score as continuous variable was investigated (see **Supplementary Table 1**). In the crude model, adolescents who did not have a third place showed a significantly lower score of self-esteem (coefficient: −2.05, 95% CI: −3.02 to −1.09), and similarly, adolescents who did not have a role model showed a significantly lower score of self-esteem (coefficient: −4.92, 95% CI: −6.60 to −3.24). The association remained significant after the adjustment of covariates, school social capital at the school and individual level, and the adjustment of both levels. That is, adolescents who did not have a third place showed a significantly lower score of self-esteem (coefficient: −1.30, 95% CI: −2.13 to −0.46), and similarly, adolescents who did not have a role model showed a significantly lower score of self-esteem (coefficient: −2.71, 95% CI: −4.39 to −1.04). Post-estimation of the comparison of the coefficients for a third place and role model showed no statistically significant difference ($p = 0.19$).

DISCUSSION

As hypothesized, we found that adolescents in Japan who did not have a third place or a role model were approximately two times more likely to develop low self-esteem, regardless of family factors such as poverty or marital status, or school social capital. To the best of our knowledge, this is the first study showing the link between the existence of a third place and having a role model with low self-esteem among adolescents, which may induce mental illness (1–4) or even suicide (5–7).

Our findings were consistent with previous studies investigating the association between community social capital and self-rated health among adolescents. For example, high school students living in a neighborhood with higher levels of social cohesion and membership in community organizations showed better self-reported wellbeing in New Zealand (28). Further, it was reported that adolescents aged 14–18 years old who have higher community trust showed better self-rated health in Lithuania, adjusted for individual covariates as well as family and school factors (29). Although community trust and third places are different, it is likely that children with high community social capital may be able to access third places, because third places would be located in the community. In addition, such children would be able to meet with role models, who acknowledge, respect and interact with adolescents.

The following three pathways may explain the mechanism underlying the association of the existence of a third place and role model, and better self-esteem. First, when spending time at a third place, adolescents can relax by releasing psychological distress accumulated in the family home or at school, such as talking or spending time with friends, or by interacting with their role model, which would eventually induce better self-esteem. This is similar to the mechanism of positive influence of social capital on health (30) and adult mentoring on child development (15). Second, adolescents may feel that they can be included, or at least not excluded, by spending time in a third place, or with a role model. Experiencing a feeling of acceptance from someone can help to increase self-esteem, the fourth level in Maslow's hierarchy of needs (31). Third, although speculation, the information or skills acquired from third places and role models could actually improve the life skills of adolescents by eventually inducing better self-esteem through the experience of accomplishment or success. Further studies are needed to elucidate the mechanism underlying the association between third places and role models with self-esteem.

This study has several limitations. First, because the current study is cross-sectional, reverse causation is likely; that is, adolescents with low self-esteem may be reluctant to seek out third places or role models. Indeed, the association can be bi-directional. Further longitudinal studies to explore the causality of the association are warranted. Second, third places, role models and self-esteem were self-assessed by the adolescent participants, thus common method bias may inflate the association. Further research using an objective measurement of spending time in third places, such as using a GPS, and assessment of self-esteem by others, such as friends or professional researchers, may improve the quality of the study. Third, mental disorder was not

TABLE 3 | Odds ratios of existence of third places and role model for low self-esteem.

			Crude*		Adjusted	
			OR	**95% CI**	**OR**	**95% CI**
Social factors	Having third places	Yes	ref		ref	
		No	**2.13**	**1.37 to 3.30**	**1.64**	**1.01 to 2.67**
	Having role model	Yes	ref		ref	
		No	**4.73**	**2.95 to 7.96**	**2.75**	**1.64 to 4.59**
Family factors	Poverty	Yes	**1.68**	**1.20 to 2.34**	1.29	0.85 to 1.96
		No	ref		ref	
	Marital status	Married	ref		ref	
		Single/divorced/widowed/other	**1.59**	**1.08 to 2.34**	1.08	0.67 to 1.75
	Having older siblings	Yes	1.2	0.87 to 1.65	1.21	0.84 to 1.76
		No	ref		ref	
	Having younger siblings	Yes	0.92	0.67 to 1.26	1.04	0.71 to 1.51
		No	ref		ref	
	Parental psychological distress	K6 5+	**1.49**	**1.08 to 2.06**	1.2	0.83 to i.72
		K6 <5	ref		ref	
	Child maltreatment	Yes	**1.42**	**1.03 to 1.97**	1.26	0.87 to 1.81
		No	ref		ref	
Life style factors	Skipping breakfast	Yes/sometimes	**2.89**	**1.96 to 4.26**	**2.06**	**1.32 to 3.22**
		No	ref		ref	
	Late time go to bed (11 p.m. or later)	Yes	1.43	0.97 to 2.12	0.88	0.56 to 1.38
		No	ref		ref	
	Late time wake up (7 a.m. or later)	Yes	**1.79**	**1.29 to 2.48**	**1.64**	**1.15 to 2.34**
		No	ref		ref	
	Frequency of exercise	3 days+/week	ref		ref	
		1–2 days/week	**1.88**	**1,22 to 2.90**	**1.71**	**1.08 to 2.70**
		<3 days/month	**2.52**	**1.71 to 3.72**	**2.02**	**1.32 to 3.08**
School social capital	School-grade level	Low	**1.91**	**1.13 to 3.23**	1.76	0.98 to 3.15
		Middle	1.66	0.99 to 2.79	1.58	0.88 to 2.81
		High	ref		ref	
	Individual-level	Low	**5.23**	**3.30 to 8.29**	**3.76**	**2.32 to 6.09**
		Middle	**2.18**	**1.32 to 3.60**	**2.13**	**1.27 to 3.55**
		High	ref		ref	
ICC					0.027	0.005 to 0.128

**Adjusted for sex and grade in univariate model.*

Adjusted model was a multilevel model that includes social factors, family factors, lifestyle factors, and individual-level school social capital as level 1 and school-grade level school social capital as level 2.

Bold signified $p < 0.05$.

assessed, which can be a confounder of the association between existence of third place or role model and low self-esteem. Fourth, due to the limited sample size, further stratifications by type of third places or specific features of role models were not possible. Further stratification analysis using a larger sample is needed to investigate the association between a specific type of third place and role model with adolescents' self-esteem.

Based on these findings, it can be proposed that the provision of third places may prevent low self-esteem among adolescents. In Japan, a policy to prevent suicide includes providing a safe place for children and adolescents to stay (32). It is noteworthy that the current study provides a rationale for such a policy, and that the existence of a third place that is independent from family and school factors may be effective in enhancing greater self-esteem and feelings of self-worth. Further, we add to the current policy that not only place, but also having a good role model who acknowledges or interacts with adolescents would be effective to prevent low self-esteem. Further evaluation studies on this policy are warranted.

In conclusion, social environment such as the existence of a third place or role model may be important to prevent low self-esteem among adolescents in Japan. Further research is needed to investigate the causality and mechanism of the association, and to evaluate the effectiveness of health policy providing adolescents with "places to stay" to prevent low self-esteem.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tokyo Medical and Dental University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TF conceived the study, collected and analyzed data, and wrote first draft of manuscript. SD, AI, and MO collected data and revised the manuscript. All authors approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.529818/full#supplementary-material

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I Cannot Read Your Eye Expression: Suicide Attempters Have Difficulties in Interpreting Complex Social Emotions

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Background: The ability to differentiate emotions in social contexts is important for dealing with challenging social situations. Suicide attempters show some difficulties in emotion recognition that may result in hypersensitivity to social stress. However, other studies on the recognition of social complex emotions found that suicide attempters have similar performances as depressed non-attempters.

Objectives: To investigate differences in social emotion recognition in patients with current Major Depressive Episode (MDE) with and without history of suicide attempt.

Methods: Two hundred and ten patients with MDE were recruited among whom 115 had lifetime history of suicide attempt (suicide attempters, SA) and 95 did not (affective controls, AC). Recognition of complex social emotions was assessed using the Reading the Mind in the Eyes Test (RMET). Emotions were separated in three valence categories: positive, negative, and neutral. Verbal intelligence quotient (IQ) and attention were measured with the National Adult Reading Task (NART) and the d2 test, respectively.

Results: Mixed logistic regression models adjusted for sex, lifetime bipolar disorder, verbal IQ and attention showed that the RMET performance for neutral emotions was worse in the SA than AC group (OR = 0.87 [0.75, 0.99]). Furthermore, when violent/serious SA were compared to non-violent/non-serious SA and AC, the RMET neutral valence category showed a trend for group factor ($p < 0.059$) and RMET scores were lower in the violent/serious SA than AC group (OR = 0.79 [0.64, 0.96]).

Conclusion: Recognition of neutral emotions is poor in SA and this may complicate their daily life. Interventions to improve the understanding of complex emotions may be helpful to prevent suicidal risk in patients with depression.

Keywords: RMET, emotion recognition, suicide attempt, major depressive disorder, severity

INTRODUCTION

About 800,000 people commit suicide every year (1). People who complete or attempt suicide usually have psychiatric comorbidities, especially affective disorders, such as major depression (2). Suicide rate could be partially reduced by early detection of people at risk (2).

A recent meta-analysis in the framework of the Research Domain Criteria (RDoC) showed that disrupted social processes are a risk factor for suicide (3). Indeed, previous studies found that suicide attempters are more vulnerable to social stress (4). It is thus crucial to understand the mechanisms that make some individuals more vulnerable to suicidal acts in the presence of social adversity (5). Suicide attempters show decreased activation of the insula during a social exclusion paradigm (the Cyberball Game) compared with patients with history of depression without suicidal acts (6). Moreover, it has been hypothesized that deficits in social cognition are one of the mechanisms associated with hypersensitivity to social stress (4). Suicide attempters also show specific deficits in the interpretation of disgust, fearful (7) and angry faces (8). Some studies highlighted that emotion recognition depends on orbitofrontal cortex (9, 10). This region has been widely associated with suicidal vulnerability (11). Interestingly, suicide attempters showed an increased activation of the orbitofrontal cortex when viewing angry faces (8, 12). Difficulties in emotional recognition in suicidal patients may thus be related with a dysfunctional processing of emotional stimuli by orbitofrontal cortex.

Impairments in complex social emotion recognition can be evaluated using the Reading the Mind in the Eyes Test (RMET) (13). This widely used test can detect subtle impairment in positive, negative and neutral emotion recognition (14). A meta-analysis on RMET performance showed lower scores in patients with major depression and borderline personality disorder compared with healthy controls (15). However, studies in patients with suicide behavior are scarce. Patients with current major depressive episode (MDE), with and without history of suicide attempt, perform worse in all the RMET categories than healthy controls (16). RMET performance is worse in patients with depression and predominantly affective symptoms (including suicidal ideation) than in patients with depression characterized by predominance of somatic symptoms (17). Among elderly patients with current MDE and history or not of suicide attempts, the total RMET score was lower in lifetime suicide attempters than in healthy controls (18). The absence of differences between patients with depression with and without history of suicide behavior suggests that RMET performance impairment could be associated with a cognitive/affective dimension of MDE rather than with suicidal behavior. However, this lack of differences could also be explained by the small sample size of these studies and the different ages of the included patients.

The main aim of this study was to investigate whether social emotion recognition (RMET score) is impaired in suicide attempters compared with non-attempters in a sample of inpatients with MDE. We hypothesized that suicide attempters would perform poorly in recognizing negative emotions (7, 8). Moreover, we wanted to assess whether history of violent/serious suicide attempt or of repeated suicide attempts was associated with impaired RMET performance.

METHODS

Participants

For this study, 210 patients (69% of women), aged between 18 and 70 year (mean ± SEM = 41.22 ± 0.89) were recruited at the Department of Emergency Psychiatry and Acute Care, Montpellier University Hospital, France. Patients were admitted for a current MDE, according to the DSM-IV criteria. Exclusion criteria were: current psychotic features, lifetime history of schizoaffective disorder or schizophrenia, euthymic status (i.e., Montgomery-Åsberg Depression Rating Scale, MADRS, score ≤ 7) (19), lifetime history of cerebrovascular accident and head trauma.

Among the 210 patients, 95 patients had no history of suicide attempt (affective controls, AC) and 115 had lifetime history of suicide attempt (suicide attempters, SA) according to the Columbia-Suicide Severity Rating Scale (C-SSRS) (20). A suicide attempt was defined as a self-damaging act carried out with certain intention to die, and was distinguished from self-mutilation, the use of substances or non-compliance with medical treatment (5). In the SA group, 34 patients were serious or violent SA. Violent suicide attempt was defined according to the criteria by Åsberg et al. (21) (i.e., hanging, drowning, jumping from heights, and suicide attempts with firearms or knives). Serious suicide attempt was defined according to the medical damage associated with the suicidal act (i.e., patient required hospitalization in intensive care) (22). Moreover, 63 SA were re-attempters (≥2 suicide attempt during their lifetime). Detailed characteristics of suicide attempts are described in **Table 1**.

The study protocol was approved by the local research ethics committee (CPP Montpellier Sud-Méditerranée IV, CHU Montpellier) and was carried out according to the tenets of the Declaration of Helsinki. All participants signed a written informed consent.

TABLE 1 | Characteristics of suicide attempts.

Method of suicide attempt	Number of patients
Medical intoxication (serious)	*N* = 81 (18)
Cutting	*N* = 7
Jumping	*N* = 5
Hanging	*N* = 3
Firearm	*N* = 1
Number of suicide attempts	Number of patients
1	*N* = 52
2	*N* = 24
3	*N* = 20
>4	*N* = 19
Age at first suicide attempt	Mean ± SEM = 28.41 ± 1.33

Clinical Assessment

At admission, patients were interviewed to collect their demographic data: age, education level, number of children, professional situation, civil status, and smoking history. The French version of the Mini International Neuropsychiatric Interview (MINI 5.0) (23) was used by senior psychiatrists to assess current and lifetime Axis I psychiatric disorders. Depression symptomatology was evaluated with the MADRS (19), and manic symptomatology with the Young Mania Rating Scale (YMRS) (24). Current psychotropic medication and daily dosage were recorded to calculate a general index of medication burden. The dosage of each drug was coded from 0 to 4, as previously described (25). The total medication burden was calculated by summing all the individual drug codes for the same patient. Finally, history of childhood trauma was evaluated using the Childhood Trauma Questionnaire (CTQ) (26).

Cognitive Tasks

After clinical assessment patients performed several cognitive tasks.

Verbal IQ

Verbal IQ was evaluated using the French version of the National Adult Reading Test (NART) (27). The test comprises 50 irregular words in French violating grapheme-phoneme rules. Patients have to read the words with the correct pronunciation.

Attention

Sustained attention was evaluated using the letter-cancellation task of the d2 test (28, 29). d2 test consists of several series of letters. The patient have to double mark as fast as possible "d" in the middle of distractors.

Complex Emotion Recognition

The French version of the RMET (13, 30) was used to assess emotion recognition. In this test, 36 photographs of the eyes that express different complex emotions are presented. Participants were asked to choose among four adjectives the one that best describes each picture (three foil adjectives and one correct adjective). If necessary, the definition of each adjective was provided. The score was the total number of correct answers. The 36 images were also classified in three valence categories based on Harkness et al. (14): 8 positive (e.g., friendly), 12 negative (e.g., upset), and 16 neutral (e.g., reflective).

Data Analysis

For sociodemographic and clinical variables, qualitative/categorical variables (i.e., sex, civil status, professional activity, current psychiatric comorbidity, etc.) were compared with the Chi-square test and quantitative/continuous variables (i.e., MADRS score, YMRS score, NART score, etc.) with the *t*-test. Spearman correlations were used to identify the variables (depression, mania, medication burden, verbal intelligence, and attention) associated with the RMET scores.

Then, mixed logistic models were performed, using as dependent variable the correct/incorrect identification of each RMET image (Right = 1/Wrong = 0). Suicide status and adjusting covariates (sex, lifetime bipolar disorder, verbal IQ using the NART total score, and attention using the GZ-F score from the d2 test) were used as fixed effects. The patient random effects and time random slopes were added to take into account the intra-patient correlation structure. This analysis was performed for each RMET valence category (positive, negative and neutral) and for the total RMET score, separately. The likelihood ratio test and Wald test were used to test significance.

The alpha significance level was fixed at 0.05. All statistical analyses were performed using R 3.5.3.

RESULTS

Sample Characteristics and Correlations With the RMET Score

Compared with the AC group, current post-traumatic stress disorder ($\chi^2 = 4.47$, $p < 0.035$) and antipsychotic intake ($\chi^2 = 6.87$, $p < 0.009$) were more frequent, and suicidal ideation (item 10 of the MADRS) was higher ($t_{172} = -3.73$, $p < 0.001$) in the SA group. Similarly, the CTQ total score was higher ($t_{176} = -2.73$, $p < 0.007$) and history of physical abuse ($\chi^2 = 4.37$, $p < 0.036$) and of sexual abuse ($\chi^2 = 4.19$, $p < 0.041$) was more frequent in the SA than AC group. Sociodemographic data and other clinical variables, as well as verbal IQ and attention (d2) scores were comparable between groups (all $p > 0.050$; **Table 2**).

The RMET scores were positively correlated with verbal IQ and attention (d2) scores, and education level (**Table 3**).

RMET Score and History of Suicide Attempt(s)

First, computing the random effects for all tested variables showed that time random slopes did not significantly improve the model (all $p > 0.050$). Therefore, all models were computed using only the patient random intercept. **Figure 1** shows Mean ± SEM of the percentages. Comparison of the total RMET score and the scores for each valence category showed that only the RMET score for the neutral valence category was lower in the SA than AC group (OR = 0.87, 95% CI [0.75, 0.99]) (**Figure 1A**). Conversely, there was not significant difference between groups for the total RMET score and also for the positive and negative valence categories (all $p > 0.050$).

When SA were classified in patients with and without history of violent/serious suicide attempt, the RMET score for the neutral valence category showed a trend for the group factor ($\chi^2 = 5.63$, $p < 0.059$). Indeed, this score tended to be lower in the violent/serious SA group compared with the AC group (OR = 0.79, 95% CI [0.64, 0.96]), but not with the non-violent/serious SA group (**Figure 1B**). The positive and negative valence category scores and the total RMET score were not different among groups (all $p > 0.050$).

Comparison of the RMET scores in suicide re-attempters, in patients who attempted suicide only once, and in the AC group did not highlight any significant difference (all $p > 0.050$).

All the results for the fixed effects tested, including covariates, are shown in **Supplementary Materials**.

TABLE 2 | Descriptive characteristics of the sample.

	Lifetime SA	AC	*p*-values
N =	115	95	
Sociodemographic data			
Age, years	40.75 ± 1.20	41.80 ± 1.34	$p < 0.559$
Women, *n* (%)	83 (72.2%)	62 (65.3%)	$p < 0.281$
Years of education	13.72 ±0.29	14.01 ±0.27	$p < 0.469$
Sep./Div./Wid., *n* (%)	26 (23.0%)	21 (22.3%)	$p < 0.909$
Children, *n* (%)	64 (56.6%)	57 (60.6%)	$p < 0.561$
Professionally active/Student, *n* (%)	60 (53.1%)	45 (48.4%)	$p < 0.501$
Current smoker, *n* (%)	58 (51.8%)	38 (40.4%)	$p < 0.251$
Clinical variables			
Current anxiety disorder, *n* (%)	72 (68.6%)	52 (58.4%)	$p < 0.143$
Current eating disorder, *n* (%)	10 (8.9%)	3 (3.3%)	$p < 0.103$
Current alcohol abuse/dep., *n* (%)	17 (15.6%)	13 (14.3%)	$p < 0.796$
Current substance abuse/dep., *n* (%)	17 (15.3%)	9 (9.7%)	$p < 0.229$
Current PTSD, *n* (%)	18 (15.8%)	6 (6.4%)	$p < 0.035$
Current mixed episode, *n* (%)	9 (8.0%)	10 (10.5%)	$p < 0.536$
Lifetime bipolar disorder, *n* (%)	52 (45.2%)	40 (42.1%)	$p < 0.651$
Depressive symptomatology (MADRS)	28.14 ±0.92	26.18 ± 1.10	$p < 0.173$
Suicidal ideation (Item 10 MADRS)	3.17 ±0.20	2.10 ±0.20	$p < 0.001$
Mania symptomatology (YMRS)	1.71 ±0.42	1.53 ±0.35	$p < 0.756$
Medication			
Antidepressants, *n* (%)	72 (66.1%)	54 (65.9%)	$p < 0.977$
Anxiolytics, *n* (%)	75 (68.8%)	48 (58.5%)	$p < 0.142$
Antiepileptics, *n* (%)	28 (25.7%)	22 (26.8%)	$p < 0.859$
Antipsychotics, *n* (%)	58 (53.2%)	28 (34.1%)	$p < 0.009$
Lithium, *n* (%)	10 (9.2%)	10 (12.2%)	$p < 0.500$
Medication burden	3.82 ±0.22	3.54 ±0.26	$p < 0.405$
Neuropsychological variables			
Verbal IQ (NART)	20.53 ±0.51	20.98 ± 0.44	$p < 0.512$
Attention (d2)	349.15 ± 9.33	364.94 ± 10.12	$p < 0.254$
Childhood Trauma Questionnaire (CTQ) Low/Severe/Moderate			
Total	52.27 ± 1.99	44.73 ± 1.87	$p < 0.007$
Physical Abuse, *n* (%)	37 (38.5%)	21 (24.1%)	$p < 0.036$
Physical Neglect, *n* (%)	49 (51.0%)	36 (41.9%)	$p < 0.215$
Emotional Abuse, *n* (%)	69 (72.6%)	49 (59.0%)	$p < 0.056$
Emotional Neglect, *n* (%)	78 (80.4%)	59 (70.2%)	$p < 0.112$
Sexual Abuse, *n* (%)	40 (41.7%)	24 (27.3%)	$p < 0.041$

SA, Suicide attempters; AC, Affective controls; Sep./Div./Wid., Separated/Divorced/Widowed; PTSD, Post-traumatic stress disorder; MADRS, Montgomery and Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; IQ, Intelligence quotient; NART, National verbal learning task.

DISCUSSION

Our results showed that the interpretation of social complex emotions is impaired in depressed patients with history of suicide attempt. Suicide attempters performed worse than patients with depression without suicide history when interpreting neutral emotions. Our results are in agreement with studies reporting that suicide attempters have difficulties in the interpretation of facial emotions (7), and show alterations in brain activation during facial emotional processing (8, 12, 31). However, when considering the RMET scores, previous studies failed to show differences between patients with depression and history or not of suicide attempts (16, 18). Several reasons may explain these discrepancies. First, Szanto et al. (18) used a sample of elderly patients, and normal aging has been associated with worse emotional recognition (32). Moreover, they did not adjust for attention and verbal intelligence. Although the RMET does not require high executive demands (13), its performance is closely related to the verbal IQ score (33). Our detection of differences between SA and AC might be explained by the fact that we adjusted our analysis for these variables. Interestingly, our results showed that the RMET score for the neutral valence

TABLE 3 | Spearman correlations between Reading the Mind in the Eyes Test scores and sociodemographic, clinical and cognitive variables.

	RMET Positive	RMET Negative	RMET Neutral	RMET Total
Age	$r = -0.095$	$r = -0.104$	$r = -0.061$	$r = -0.120$
Years of education	***r* = 0.157***	$r = 0.075$	***r* = 0.314****	***r* = 0.268****
Depressive symptomatology (MADRS)	$r = 0.091$	$r = 0.064$	$r = 0.029$	$r = 0.071$
Suicidal ideation (Item 10 MADRS)	$r = 0.015$	$r = 0.146$	$r = 0.044$	$r = 0.094$
Mania symptomatology (YMRS)	$r = -0.016$	$r = -0.047$	$r = -0.103$	$r = -0.067$
Medication burden	$r = 0.006$	$r = 0.127$	$r = 0.076$	$r = 0.092$
Days between last SA and evaluation	$r = -0.001$	$r = -0.025$	$r = -0.101$	$r = -0.090$
Verbal IQ (NART)	***r* = 0.233****	$r = 0.118$	***r* = 0.243****	***r* = 0.275****
Attention (d2)	***r* = 0.297****	***r* = 0.136***	***r* = 0.165***	***r* = 0.272****
CTQ total score	$r = 0.010$	$r = 0.038$	$r = -0.015$	$r = 0.017$

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
RMET, Reading the Mind in the Eyes Test; MADRS, Montgomery and Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; SA, Suicide attempt; IQ, Intelligence quotient; NART, National verbal learning task; CTQ, Childhood Trauma Questionnaire.

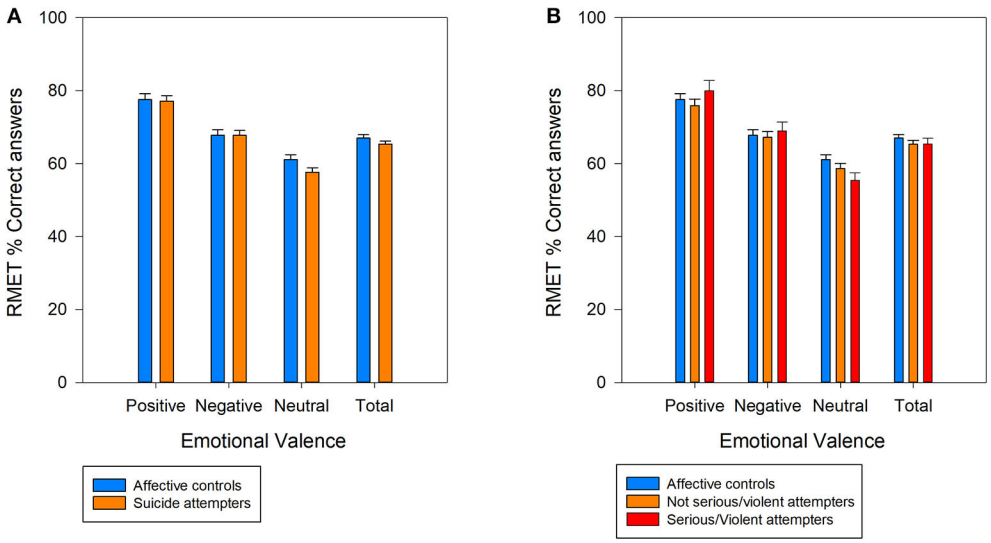

FIGURE 1 | Percentage (mean ± SEM) of correct answers for all photographs (total) and for each of three valence categories (positive, negative, and neutral) of the Reading the Mind in the Eyes test; **(A)** Comparison between patients with current major depressive episode (MDE) with and without (affective controls) lifetime suicide attempt history; **(B)** Comparison of patients with MDE without (affective controls) and with history of serious/violent suicide attempts, or history of non-serious/non-violent suicide attempts.

category tended to be worse in serious/violent suicide attempters. Similarly, Szanto et al. (18) found a negative correlation between suicide severity and total RMET score.

Conversely to our initial hypothesis, interpretation of negative emotions was not impaired in suicide attempters, only that of neutral emotions. Ai et al. (31) reported altered functions in the fusiform gyrus in suicide attempters compared with non-attempters during emotional processing of all kinds of emotional faces, including neutral faces. Fusiform gyrus is a key brain region in facial recognition, and systematically involved in prosopagnosia (34). During emotional faces recognition it has been shown that fusiform gyrus was highly interconnected with the orbitofrontal cortex and the amygdala (35), both areas impaired during emotional processing in suicidal patients (8, 12). Therefore, a possible mechanism to explain impaired emotion recognition in suicide attempters may be a disrupted connectivity between fusiform gyrus, prefrontal and limbic areas. Neutral expressions are inherently ambiguous, thus facilitating an overinterpretation of their valence (36). Maniglio et al. (37) showed that in the general population, people with more depressive symptomatology, death wishes and suicidal ideation and planning have difficulties in recognizing neutral facial expressions.

Our study has some limitations. Its cross-sectional nature limits causality inference; future studies should use a prospective design. Moreover, patients with psychosis who are characterized by impaired emotional recognition (38) were not included, thus preventing the result generalization to all

patients with suicidal risk. Finally, social functioning was not assessed, although it may provide insights into how emotion recognition impairment may affect the social daily life of suicidal patients.

In conclusion, our results show that recognition of neutral emotions is impaired in patients with depression and history of suicide attempt(s), particularly those with history of violent/serious suicide attempt. The development of programs to better identify and interpret neutral emotions may be considered to prevent suicidal risk in patients with depression.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP Montpellier Sud-Méditerranée IV, CHU Montpellier. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Recruiting participants: CG, MS, PC, and EO. Performed the psychiatric interviews: PC and EO. Performed the neuropsychological assessment: CG and MS. Reviewed the specific literature: IF, AA-C, AS, and EO. Formulated the problem and hypothesis: IF, AA-C, AS, PC, and EO. Analyzed data: AA-C and JD. Wrote the paper: IF, AA-C, CG, and JD. Approved the final version of paper: IF, AA-C, AS, CG, JD, MS, PC, and EO. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.543889/full#supplementary-material

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Do Suicide Attempts of Mood Disorder Patients Directly Increase the Risk for a Reattempt?

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Background: Preceding suicide attempts strongly predict future suicidal acts. However, whether attempting suicide *per se* increases the risk remains undetermined. We longitudinally investigated among patients with mood disorders whether after a suicide attempt future attempts occur during milder depressive states, indicating a possible lowered threshold for acting.

Methods: We used 5-year follow-up data from 581 patients of the Jorvi Bipolar Study, Vantaa Depression Study, and Vantaa Primary Care Depression Study cohorts. Lifetime suicide attempts were investigated at baseline and during the follow-up. At follow-up interviews, life-chart data on the course of the mood disorder were generated and suicide attempts timed. By using individual-level data and multilevel modeling, we investigated at each incident attempt the association between the lifetime ordinal number of the attempt and the major depressive episode (MDE) status (full MDE, partial remission, or remission).

Results: A total of 197 suicide attempts occurred among 90 patients, most during MDEs. When the dependencies between observations and individual liabilities were modeled, no association was found between the number of past suicide attempts at the time of each attempt and partial remissions. No association between adjusted inter-suicide attempt times and the number of past attempts emerged during follow-up. No indication for direct risk-increasing effects was found.

Conclusion: Among mood disorder patients, repeated suicide attempts do not tend to occur during milder depressive states than in the preceding attempts. Previous suicide attempts may indicate underlying diathesis, future risk being principally set by the course of the disorder itself.

Keywords: major depressive disorder, bipolar disorder, major depressive episode, suicidal act, suicide attempts

INTRODUCTION

Patients with depressive or bipolar disorder have a high risk for suicidal ideation, suicide attempts (1–3), and death by suicide (4, 5). Suicidal ideation occurs almost without exception with clinically significant depression (6, 7) and resolves with a decline in depressive symptoms (8–10). The differences in quality and intensity of partly overlapping factors influencing the formation of suicidal ideation and then risk for suicide attempts during mood episodes remain poorly understood (11).

Time plays a major role in suicidal behavior in major depressive disorder (MDD) and bipolar disorder (BD) (1). Over 70% of attempts occur during major depressive episodes (MDEs) and few (≤8%) during remission, while mixed states in BD constitute very high-risk periods (7, 12, 13). Although cross-sectional epidemiological surveys and meta-analytic categorical data have suggested that depression mainly influences suicidal ideation or challenges its clinical significance (14, 15), suicide attempts over time do accumulate among patients with the most severe, altering, and persistent symptoms (12, 13, 16).

Current theories on suicidal behavior are based on stress-diathesis models (17). The *stress-diathesis model* by van Heeringen and Mann (18) posits that external stressors, including the exacerbation of psychiatric disturbance, interact with the diathesis of suicidal behavior rooted in neurobiological dysfunctions. The *cognitive-behavioral theory* (CBT) recognizes three main constructs, including dispositional vulnerability factors, cognitive processes associated with psychiatric disturbance, and cognitive processes associated with suicidal acts (19). According to the CBT, transition from suicidal thoughts to action happens when an individual's tolerance for distress becomes overwhelmed. The cognitive processes associated with suicidal acts include suicide schemas that are postulated to strengthen with each suicide attempt, thus becoming more easily triggered in the future. Theoretical considerations also take into account the possibility of past suicide attempts lowering the within-individual threshold of tolerance (20). Three psychological theories termed to form ideation-to-action framework theories seek to explain suicidal thoughts and actions as separate processes. First, the *Interpersonal Theory of Suicide (ITS)* (21) postulates that suicidal desire results from an individual experience of thwarted belongingness and perceived burdensomeness (and related hopelessness). The model then separates the construct of the capability to engage in suicidal acts resulting from both hereditary and acquired components. According to Joiner et al. (22), a non-fatal suicide attempt may represent the most direct factor increasing this capability. Second, the *integrated motivational-volitional (IMV)* model (23) hypothesizes that motivational factors characterized by defeat and entrapment drive emergence of suicidal ideation, whereas acquired capability among other volitional factors contributes to suicide attempts. One of the key premises of the IMV model is that suicidal behavior intensifies suicidal ideation and intent so that over time this may lead to accelerated action. Third, the *Three-Step Theory (3ST)* (24) postulates that the experience of pain and hopelessness drives the emergence of suicidal ideation, which is intensified in the case of low connectedness. According to the 3ST, capacity and progression from ideation to suicide attempts is determined by an array of dispositional and practical factors and acquired capability. This commonly suggested acquired capability for suicide could be associated with a lowered threshold for acting and attempts during milder symptomatic levels, but this association remains to be investigated.

A clear consensus exists of a suicide attempt being a major risk indicator for a subsequent attempt (25, 26). However, the views on which mechanisms give rise to this association are divergent. Briefly, considering that the origins of suicidal behavior are multifactorial (27), a suicide attempt could index the interaction of dispositional and acute state-related factors. More severe and recurrent mood episodes could also predispose reattempts directly or among vulnerable individuals (1). In addition to marking a latent vulnerably factor, an attempt could directly increase the likelihood of a subsequent attempt or denote a mixture of both (28, 29). The stress-diathesis model (18) emphasizes the state and trait model, whereas the ideation-to-action theories (ITS, IMV, and 3ST) propose additional elements of acquired capability directly through past suicide attempts to increase the risks for reattempts. A lowered fear of death and an increased pain tolerance could contribute to this acquired capability (21), and repeatedly activated suicidal cognitions and behaviors could lead to their intense reactivation more readily (20, 23, 29). However, simple behavioral sensitization models hold uncertainties (30). The stress-diathesis model could be dynamic so that increasing capability could lead to a suicide attempt at lower levels of suicidal ideation, or vice versa (31).

The hypothesis of a suicide attempt directly increasing the likelihood of a subsequent suicide attempt has rarely been addressed in longitudinal clinical samples. Previous findings indicate that each past suicide attempt at baseline increases the risk for a next attempt by approximately a third (32–34). These findings include the shortening of the interval between subsequent suicide attempts as the number increases (35), which could also be accounted for by individuals with habitually short mood cycle lengths (36). Among patients with MDD and a non-fatal suicide attempt who eventually die by suicide, the attempts occur throughout successive episodes, whereas among survivors the attempts occur during earlier but not later episodes (37). Overall, data with individual-level repeated measures are necessary for estimating within-individual latent liabilities for attempting suicide. In addition, among patients with mood disorders individual-level data on the course of mood episodes are indispensable when drawing conclusions about the hypothesized effect of a suicide attempt directly increasing the risk of reattempt, for example, through a lowered threshold for acting.

Based on a large well-characterized prospective mood disorder cohort and life-chart methodology, we aim to examine within an individual whether sequential suicide attempts are associated with a lower level of depression severity. In addition, we explore whether an inverse association exists between the cumulative number of suicide attempts and the time between successive suicide attempts.

MATERIALS AND METHODS

Study Setting and Design

Altogether 597 patients within three representative screening-based mood cohorts were followed for 5 years [191 patients with BD in the Jorvi Bipolar Study (JoBS); 269 patients with MDD in the Vantaa Depression Study (VDS); and 137 patients with unipolar depressive disorder in the Vantaa Primary Care Depression Study (PC-VDS)]. The projects were collaborations between the University of Helsinki and Helsinki University Central Hospital, Department of Psychiatry; the Department of Public Health Solutions, Mental Health Unit, National Institute for Health and Welfare, Helsinki, Finland; and the Primary Health Care Organization of the City of Vantaa, Finland. The appropriate ethics committees approved the study design. The detailed methodologies of each cohort from baseline to the 5-year follow-up have been previously published (38–43).

Screening and Baseline Evaluation

A total of 3,555 primary or secondary care patients showing symptoms of a mood episode were screened for either bipolar disorder (JoBS), MDD (VDS), or unipolar depressive disorder (PC-VDS). Informed consent was requested after full disclosure of the study protocols. The DSM-IV axis I diagnoses were made by structured clinical interview for DSM-IV disorders, SCID-I/P (44) in JoBS and PC-VDS, and by schedules for clinical assessment of neuropsychiatry, SCAN (45) in VDS. The axis II diagnoses were made by structured clinical interview for DSM-IV personality disorders, SCID-II for DSM-IV (46) in JoBS and PC-VDS, and SCID-II for DSM-III-R in VDS. Most interviews were conducted by psychiatrists or psychiatric residents and two skilled clinical psychologists. The interrater agreements (kappa) ranged from 0.86 to 1.00. A detailed overview of the study methods, flow, and ratings is presented in **Table 1**.

Follow-Up and Life-Chart Methodology

Patients were re-interviewed at 6, 18 months, and 5 years in JoBS (SCID-I/P) and VDS (SCAN 2.0 at 6 and 18 months and SCID-I/P at 5 years), and at 18 months and 5 years in PCD-VDS (SCID-I/P). In addition, patients were extensively assessed with rating scales on clinical symptoms and suicidal ideation. A total of 407 patients (68.2%) were interviewed at the 5-year follow-up. Detailed information on the study design and follow-up procedures is presented in **Table 1**.

A graphic life-chart was created at all interviews based on DSM-IV criteria to depict the course of the mood disorder throughout the follow-up. This graphic life-chart was created by combining information from all available sources including the diagnostic interviews, study rating scales, and medical and psychiatric records. In addition, information from scales used in routine clinical practice was variably available. During these extensive interviews, a judgement was made of the course of the mood disorder during the follow-up. Changes in mood episodes or phases were timed both by combining all aforementioned information and by using probes of important life events to enhance the accuracy of the chart. The phases of depressive symptoms were classified based on DSM-IV criteria as (1) remission (no MDE criteria symptoms), (2) partial remission (one to four of the nine symptoms), and (3) full MDE (at least five criteria symptoms). In JoBS, in addition hypomanic, manic, mixed, mixed depressive, cyclothymic, or substance-induced phases and subsyndromal states of hypomania of BD were recorded. However, the minimum duration for hypomania was two instead of 4 days, and mixed depressive states were included.

Suicidal Behavior

A suicide attempt, by definition, was specified as self-injurious behavior involving at least some degree of intention to die (thus excluding self-harm without suicidal intention). At baseline, we examined the lifetime number of suicide attempts by combining the information from both interviews and psychiatric records. At follow-ups, the occurrence of suicide attempts was investigated by patient interviews and psychiatric and medical records. Mood episodes and their timing were assessed first and independently from suicide attempts to limit circumventing the evaluation of a mood state to be based on suicidal behavior, and vice versa.

Statistical Methods

Association Between the Number of Previous Suicide Attempts and MDE Status

We investigated the association between the number of previous suicide attempts and clinical MDE status at the time of a new monitored attempt. The number of previous suicide attempts at the time of an attempt formed a count variable, which can be modeled using Poisson regression (47). Note that lifetime suicide attempts prior to baseline were determined using medical records and interviews. The dependencies between observations (i.e., sequential suicide attempts of an individual during follow-up) were controlled using multilevel (a.k.a. random-effect) modeling as implemented in the "lme4" R package, version 1.1-12 in the R software, version 3.3.2 (47–49).

Specifically, the multilevel Poisson regression model assumes that the logarithm of the expected number of suicide attempts (Y) preceding the current one for patient i at attempt j is

$$\log(E\left[Y_{ij}|x_{ij}, f_{ij}, \eta_i\right]) = \beta_0 + \beta_1 x_{ij} + \beta_2 f_{ij} + \eta_i, \qquad (1)$$

where β_0 is the baseline rate (those in full remission), x_{ij} is a dummy indicator for partial remission, and β_1 is the associated effect difference to full remission, f_{ij} is a dummy indicator for full MDE and β_2 is its associated effect difference to full remission, and η_i is the patient-specific liability of patient i. If many preceding suicide attempts at the time of a new attempt are associated with higher proportions of partial remission and remission stages, negative β_1 and β_2 coefficients are expected. The null hypothesis is $\beta_1 = \beta_2 = 0$. Substantive interpretation of the random intercept (η_i) is complicated by the fact that it reflects both the deterministic condition that a second suicide attempt during the follow-up is preceded by $n + 1$ attempts if the first attempt was preceded by n attempts (etc.), and the stochastic condition of the overall higher n values in those with repeated attempts.

TABLE 1 | Materials and methods in the Jorvi bipolar study (JoBS), the Vantaa depression study (VDS), and the Vantaa primary care depression study (PC-VDS).

	JoBS	VDS	PC-VDS
Sampling period	Jan 1, 2002–Feb 28, 2003	Feb 1, 1997–May 31, 1998	Jan 2, 2002–Dec 31, 2002
Setting	Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital, Espoo, Finland (catchment area 261,116 in 2002)	Department of Psychiatry of Peijas Medical Care District, Helsinki University Central Hospital, Vantaa, Finland (catchment area 169,000 in 1997)	Primary Healthcare Organization of the City of Vantaa, Finland Three health centers and two maternity clinics serving two districts in the city of Vantaa on population basis (catchment area 63,400 in 2002).
Screening	All psychiatric in- and outpatients aged 18–59 years Seeking treatment Referred to treatment In an acute deteriorating clinical state among patients within secondary care	All psychiatric in- and outpatients aged 20–59 years Seeking treatment Referred to treatment In an acute deteriorating clinical state among patients within secondary care	Consecutive primary care patients aged 20–69 years in general practitioners' waiting room on randomly selected days, stratified for day of the week and month, and time of year.
Screening procedure	(1) Mood disorders questionnaire, 7/13 items positive, or (2) Clinical suspicion of BD ($n = 28$)	(1) One of five screening questions for depression from SCAN, or (2) Scale for suicide ideation, score $\geq$6	In two phases: (1) PRIME-MD: a positive item for depressive mood or anhedonia during the last month, and (2) telephone interview: confirmed presence of one main symptom of DSM-IV MDD (according to SCID-I/P)
Excluded in screening	ICD-10 schizophrenia	ICD-10 schizophrenia, or BD-I	Current psychiatric secondary care contact, primary psychotic disorder, bipolar and organic mood disorders, alcohol use disorders preventing 2 weeks' abstinence for interview, insufficient communication or Finnish language skills, poor general health status or medical emergency preventing screening
Total screened	1,630	806	1,119
Screened positive	546	703	402 (PRIME-MD), 375 telephone interview
Coverage of screening	46 (2.8%) declined from screening 49 (9.0%) with a positive screen declined from interview 7 not contacted	161 (22.9%) with a positive screen declined from an interview	8 declined from PRIME-MD screening 27 (6.7%) declined from telephone interview 10 (2.5%) declined from diagnostic interview
Interviewed	490 (SCID-I/P)	542 (SCAN)	175 (SCID-I/P)
Inclusion criteria	BD type I or II with a new DSM-IV depressive, manic, hypomanic, mixed, or depressive mixed episode.	DSM-IV MDD with a new depressive episode	DSM-IV MDD, dysthymia, or partial depression (two to four symptoms) with or without history of lifetime MDD
Eligible	201 (10 declined)	269	140 (3 declined)
Cohort	191 (65 inpatients and 126 outpatients) BD I: 90 BD II: 101 Men: 90 Women: 101 Age (mean) at baseline: 37.7 years (SD 12.2)	269 (46 inpatients, 223 outpatients) Men: 73 Women: 196 Age (mean) at baseline: 39.6 years (SD 11.1)	137 outpatients from primary care Current MDD: 91 Partial MDD: 46 (includes four patients with dysthymia) Men: 33 Women: 104 Age (mean) at baseline: 45.3 years
Patients at 6-month follow-up	176 (92.1%)	229 (85.1%)	–
Patients at 18-month follow-up	160 (83.8%)	207 (76.9%)	127 (93%)
5-year follow-up	113 (61.7%)	182 (67.7%)	112 (82.0%)
Number of patients Switch of diagnosis Participants vs. non-participants Follow-up time	1 schizoaffective disorder No difference in prevalence of suicide attempts before or during index episode at baseline. Median 62.2 months	29 BD, 1 schizophrenia, 2 schizoaffective disorder No difference in prevalence of suicide attempts or suicidal ideation before or during index episode at baseline. Median 62.4 months	6 BD No difference in age, gender, or baseline depression severity. Median 62.9 months
Diagnostic reliability at baseline	20 random videotaped diagnostic interviews; kappa coefficient for BD = 1.0	20 videotaped diagnostic interviews; Kappa coefficient for MDD = 0.86 (95% CI = 0.58–1.00)	20 random videotaped diagnostic interviews; kappa coefficient for current full and partial MDD = 1.0

(Continued)

TABLE 1 | Continued

	JoBS	VDS	PC-VDS
Symptom assessment	BAI, BDI, BHS, HAM-D, SSI, YMRS (baseline and at all follow-ups)	BAI, BDI, BHS, HAM-D, SSI (baseline and at all follow-ups), in addition BDI monthly for first 6 months	BAI, BDI, BHS (baseline, 3, 6, and 18 months, and 5 years), and HAM-D, SSI (baseline, 18 months, and 5 years)

BAI, Beck anxiety inventory; BD, bipolar disorder; BDI, Beck depression inventory; BHS, Beck hopelessness scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HAM-D, Hamilton rating scale for depression; ICD-10, International Classification of Disease, 10th edition; JoBS, Jorvi bipolar study; MDD, major depressive disorder; PC-VDS, Vantaa primary care depression study; PRIME-MD, primary care evaluation of mental disorders; SCAN, schedules for clinical assessment of neuropsychiatry; SCID-I/P, structured clinical interview for DSM-IV disorders; SSI, the scale for suicidal ideation; VDS, Vantaa depression study; YMRS, young mania rating scale.

Statistical Power

We studied our power to detect different effect sizes using a simulation procedure typical in multilevel modeling (47). Poisson-distributed observations were generated with an expectation equal to our empirically observed rate of previous suicide attempts at the time of a new attempt (4.35 on average, s.d. = 4.97, median = 3). Altogether 3,000 datasets equal in size to our sample (number of individuals and their repeated observations) were simulated for each studied effect size and level of random-effect variance. The proportion of significant tests among the 3,000 datasets characterizes the statistical power per effect size and random-effect variance.

Testing Acceleration of Suicidal Behavior

When studying cycle length acceleration in MDEs, over-representation of highly and consistently recurrent individuals among those with short inter-morbid intervals could result in the appearance of shortening of intervals between MDEs (36). To assess whether inter-morbid intervals truly declined as a function of the number of previous MDEs, Anderson et al. (36) subtracted within-individual averages from patients' inter-morbid intervals before investigating the association between inter-morbid interval and the cumulative number of MDE—lest the findings be confounded by stable individual differences in recurrence rates. In analogy, we took inter-suicide attempt intervals for patients with >2 attempts during follow-up ($n = 22$, having 99 repeat attempts), subtracted within-patient averages from time intervals of successive attempts, and investigated the association between the cumulative number of repeated suicide attempts and the time since a previous attempt. We estimated both ordinary correlation coefficients and a linear mixed model with patient-specific random intercepts, plus scatterplots.

RESULTS

Of the 597 patients included at the baseline, individuals with a suicide attempt during a mixed-state MDE ($n = 15$) or medication-induced hypomania ($n = 1$) during the follow-up were excluded. Of the remaining 581 patients included here, altogether 90 had a total of 197 suicide attempts during the follow-up (altogether 75 attempts among patients with BD, and 122 attempts among patients with unipolar depression). These attempts represent our sample of interest in this study. **Table 2** and **Figure 1A** describe the distribution of the lifetime cumulative number of attempts during follow-up (attempts preceding baseline included).

TABLE 2 | Distribution of lifetime cumulative number of attempts during follow-up†.

Cumulative number of attempts	Average MDD status	s.d. of MDD status	Group size
1	2.68	0.65	31
2–3	2.79	0.45	62
4–5	2.73	0.65	37
6–7	2.76	0.54	21
7–21	2.67	0.64	45

MDD values: 1 = remission, 2 = partial remission, and 3 = full MDE.
† includes attempts preceding baseline.

Is a Greater Cumulative Number of Past Suicide Attempts Associated With Successively Less Severe Depression at the Time of New Suicide Attempt?

In terms of an average MDE status (remission, partial remission, and full MDE), the data showed no clear association between the within-individual cumulative number of suicide attempts and the clinical status of depression at the time of each attempt. Instead, most attempts occurred in full MDE (**Table 2** and **Figure 1B**). An ordinary analysis of variance would support this conclusion [$F_{(4,191)} = 0.382$, $p = 0.821$], but is subjected to bias due to dependent observations and the possible dependence of MDE status on time since the MDD-based recruitment to study (baseline). The latter remains an unlikely confounder because the time from baseline to an attempt and MDE status at the time of an attempt were uncorrelated (polyserial $r = -0.006$). To model observation dependencies (trait-like differences in liability), we implemented a multilevel Poisson model predicting the number of previous suicide attempts at the time of a new attempt with (dummy) indicators of MDE status. Statistical power of the approach was first investigated.

Statistical Power in Multilevel Modeling

Figure 2 shows the statistical power (probability with repeated sampling) to detect an existing effect in the present sample, assuming a one-step lower, or less severe, MDE status at the time

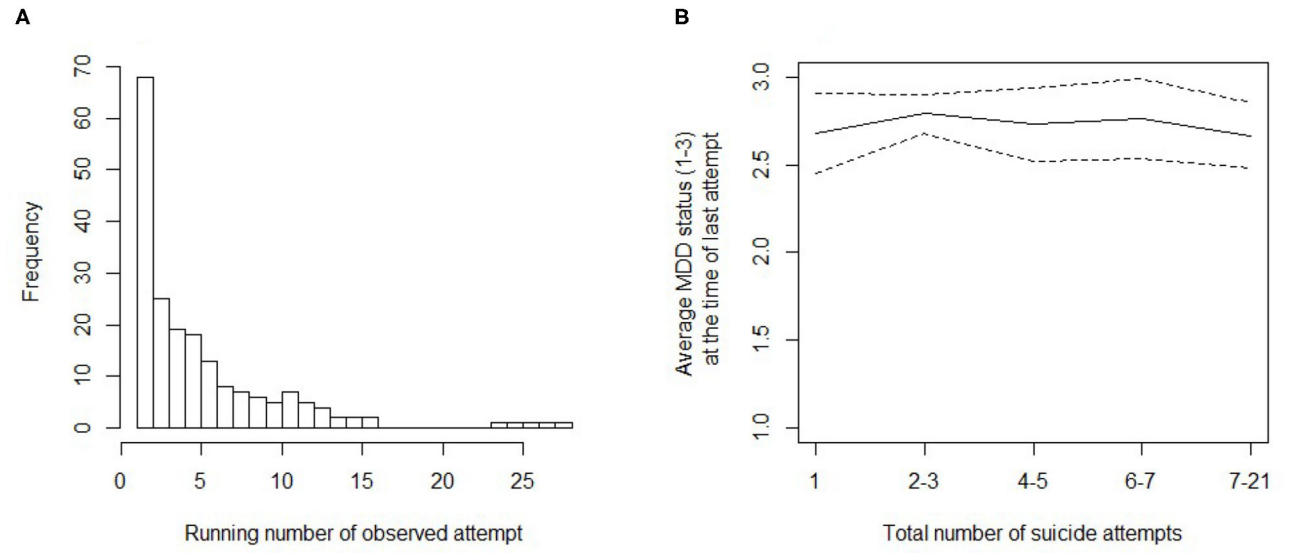

FIGURE 1 | Number of suicide attempts and status of major depressive episode (MDE). **(A)** Histogram of the lifetime running number of the attempt for each suicide attempt observed during the follow-up. **(B)** Average status of MDE (values: 1 = in remission, 2 = partial remission, and 3 = full MDE) at the time of the last attempt in patients with a different lifetime number of suicide attempts. The dashed lines give 95% Wald confidence intervals for the average (solid line).

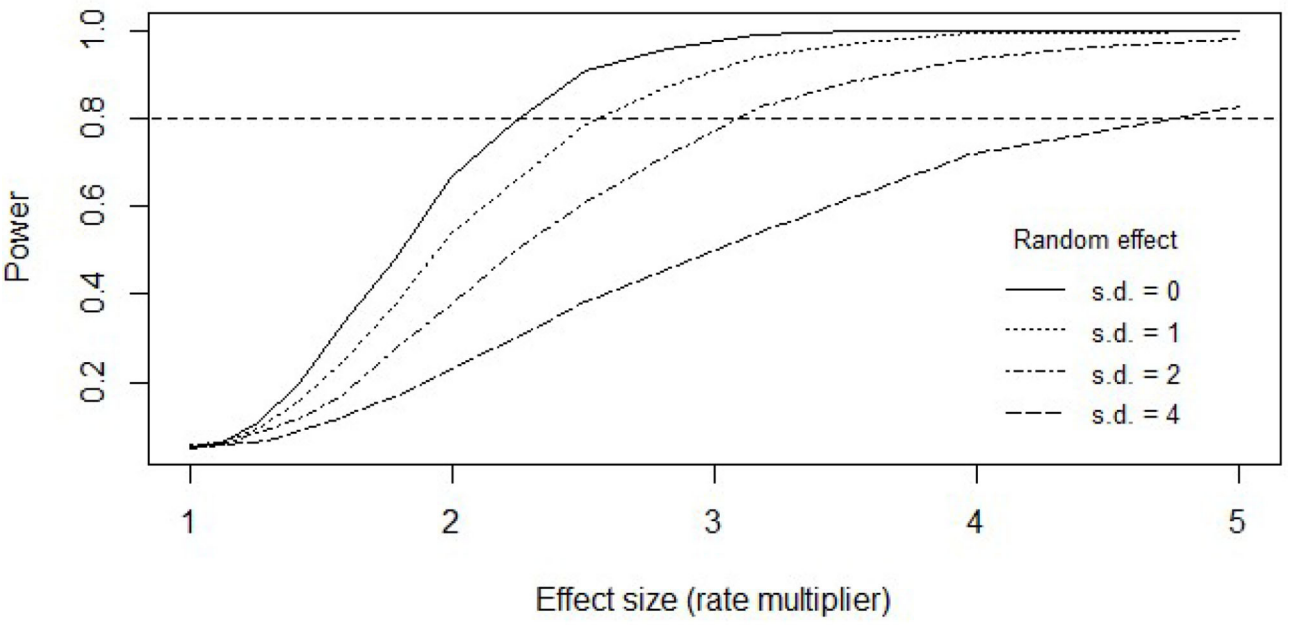

FIGURE 2 | Statistical power in the Poisson multilevel model test for the association between the status of major depressive episode (MDE) and the number of previous attempts at the time of a new attempt. As the effect of MDE status on suicide attempts increases (*x*-axis), chances to detect it increase too (statistical power; *y*-axis). The less the between-patient differences explain differences in suicidality, the more rapid the increase in our ability to detect an effect of MDE status. That is, power is a function of both attempt multiplier per depression-status difference (effect size) and between-individual differences in the overall numbers of suicide attempts (random effect standard deviance; greater the value greater the differences). Statuses of a major depressive episode can be "remission" (reference category), "partial remission," or "full MDE." Horizontal dashed line highlights the point of 80% chance to detect an existing omnibus effect in data like ours.

of an attempt is associated with a rate ratio (RR)-fold increase in the number of preceding suicide attempts. That is, the RR is the effect size. Statistical power was studied for four separate cases, assuming different amounts of individual differences in liabilities for attempting suicide. Normally distributed liabilities (η_i in Equation 1) with standard deviations 0, 1, 2, and 4 were

tested, corresponding to RRs of 1, 2.7, 7.4, and 54.6, respectively. The RR value of 54.6 represents a case of large between-individual differences in liability. With the smaller between-individual differences, we had a good power to detect 3-fold numbers of suicide attempts associated with a one-step decrease in MDE status; with large between-individual differences, only strong (5-fold) effects could be reliably detected. However, model estimates indicated that the data were in the smaller range of between-individual differences (i.e., $\sigma \approx 1$ in **Table 3**), suggesting reasonable statistical power for our analysis.

Real-Data Estimates in the Multilevel Model

Table 3 shows results from a multilevel Poisson regression model in predicting the number of previous suicide attempts at the time of a new attempt using MDE status and a random intercept as an independent variable. We found no evidence for dependence between the number of previous suicide attempts and MDE status at the time of a new attempt [**Table 3**; $\chi^2_{(2)} = 2.62$, $p = 0.270$ for likelihood-ratio test of difference between models with and without MDE status indicators, as in the power simulations]. Adjusting for fixed and random effects of time between the current attempt and the study baseline [$\chi^2_{(2)} = 1.40$, $p = 0.496$] did not change the situation.

TABLE 3 | Multilevel Poisson regression predicting the number of previous suicide attempts at the time of new attempt with MDE status (fixed effects) and individual-specific liabilities (random effect).

Effect type	Variable	β	RR	CI	*p*-value
Fixed	Intercept	0.536	1.708	1.08–2.63	0.018
Fixed	Partial remission	−0.191	0.826	0.58–1.18	0.283
Fixed	Full MDE	0.010	1.010	0.70–1.48	0.957
		σ_η	CI		
Random	Intercept	1.060	0.85–1.33		

β = regression coefficient, σ = random-effect (trait, or η in Equation 1) variance. MDE, major depressive episode; RR, implied rate ratio/multiplier; CI, confidence interval of left-hand value.

Does the First Lifetime Suicide Attempt Occur in More Severe MDE Than Repeated Attempts?

Altogether 31 first attempts occurred during the follow-up period. Contrary to the general supposition, on average first attempts occurred in less severe MDEs (average MDE status = 2.68, s.d. = 0.65) than repeat attempts (average MDE status = 2.74, s.d. = 0.56). By omitting observation dependencies, the difference (Cohen's $d = 0.11$) was statistically non-significant (Welch two-sample $t = -0.495$, $d.f. = 38.81$, $p = 0.623$). When considering observation dependencies by logistic multilevel regression, MDE status was still unassociated with an observed suicide attempt being either first or next in order [$\chi^2_{(2)} = 1.16$, $p = 0.559$].

Do Time Intervals Between Suicide Attempts Shorten as the Number of Attempts Grows?

The above analyses argued against the idea that the risk of a new suicide attempt grows with each attempt because repeat attempts occur in progressively less severe depression. The risk of repeating a suicide attempt could still grow by each attempt because depression or other triggers of suicidal behavior occur more often, in accelerating rapidity. Considering the unadjusted time intervals between successive suicide attempts, it may seem like the interval lengths are negatively associated with the cumulative number of repeat attempts during the follow-up (**Figure 3A**). However, adjusting for within-patient average intervals abolishes this impression (**Figure 3B**), suggesting it merely occurred because the patients with many suicide attempts had an overall higher rate of attempts than others, not because they underwent rate acceleration by attempt. Neither the correlation ($r = 0.06$, $p = 0.537$) nor fixed effect of a linear mixed model (b = 6.04, s.e. = 9.76, $p = 0.532$) was significant when looking for an association between attempt number and time between attempts. Although repeat attempts beyond 13 were lumped together in these data, their removal did not influence the conclusion ($r = -0.13$, $p = 0.224$, $n = 87$; b = −13.74, s.e. = 11.21, $p = 0.216$).

DISCUSSION

We used longitudinal one-of-a-kind individual-level data to investigate the widely held hypothesis that a suicide attempt directly increasing the risk for a reattempt. Specifically, we prospectively and by individual-level analyses examined whether successive suicide attempts occurred among patients with MDD or BD at increasingly lower levels of depression. The influence of the course and severity of depressive morbidity was considered using life-chart data. The main finding, with both theoretical and clinical implications, is that the data provided no evidence for a suicide attempt directly increasing the risk for a reattempt.

To our understanding, the study hypothesis was tested in a unique study design. The major strength was the availability of the longitudinal data on the course of the mood episodes by life-chart methodology, combined with the accurate timing of suicide attempts. Individual-level data enabled the modeling of within-individual differences in clinical status at the time of each sequentially monitored suicide attempt. The screening-based sampling yielded previously undiagnosed patients, assuring representativeness. Pooling data from the three representative cohorts to increase patient numbers was possible due to similar study methodologies. The study diagnostics were based on semi-structured interviews (SCID-I/P; SCAN) with high inter-rater agreement. The drop-out rate during long-term follow-up was relatively limited and only a few patients missed all follow-ups. Although we could have had a better statistical power for small effect sizes, the power was still good for moderate effect sizes. Data of this kind are rare, and we did not observe any indication that the null hypothesis should be rejected.

Although at the follow-ups, extensive information was gathered by interviews and scales, the main limitation of the study is the depiction of life-charts by three-step ordinary

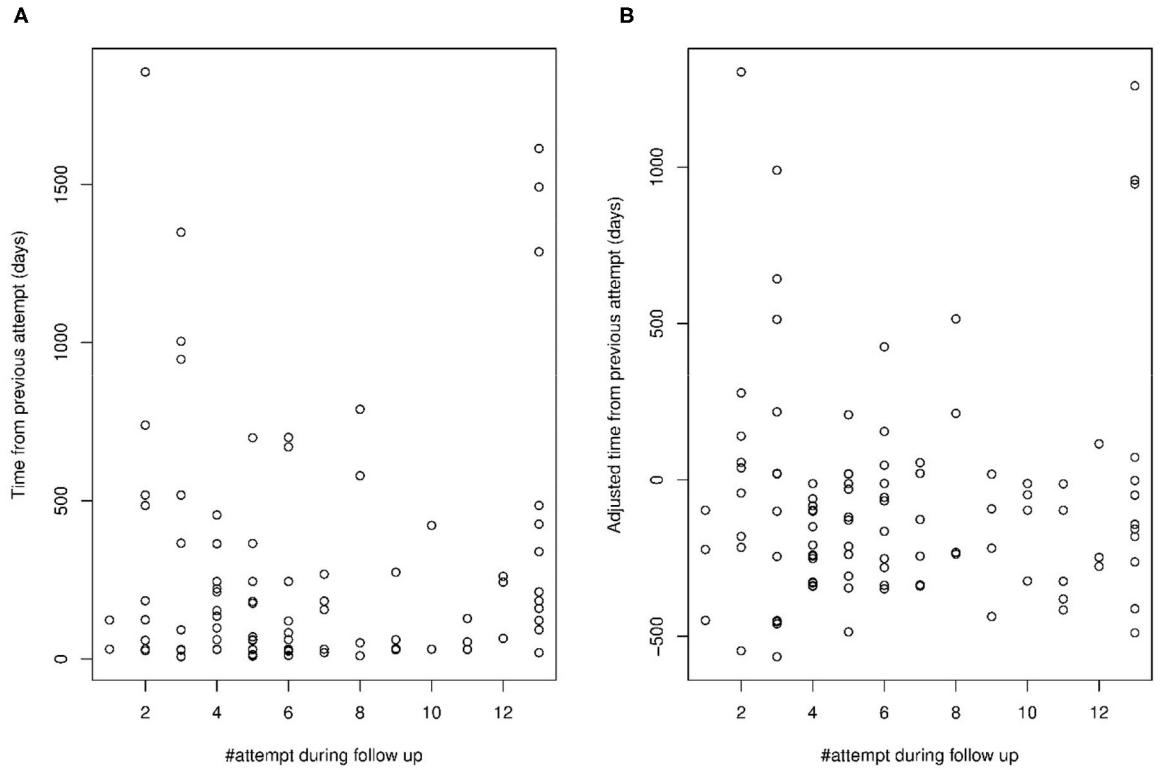

FIGURE 3 | Time intervals between suicide attempt during the follow-up per attempt number **(A)** unadjusted for within-patient average intervals, and **(B)** adjusted for within-patient average intervals.

scales of remission, partial remission, and full MDE. This restriction may have resulted in ceiling effects when severity above the diagnostic threshold at each attempt was neither measured nor modeled. However, this is a likely limitation for all prospective clinical studies until more detailed data on a daily basis become available, for example, through ecological momentary assessments. The intensity of suicidal ideation may have varied at the time of the attempt. Ambiguities remain pertinent to underlying the specific constructs of psychological theories of suicidal behavior, which remained unassessed with actual instruments. However, suicidal ideation was, by definition, present at the time of each attempt irrespective of possible theoretical constructs driving its formation. The constructs involving engaging in suicidal acts were implicitly modeled by examining the probability to attempt suicide one more time either at lower levels of depression, or at an accelerating rate from the previous attempt. Both outcomes are clearly defined and are of clinical and theoretical interest. Some circularity between the timing of suicide attempts and the course and severity of MDEs may be unavoidable. To minimize confounding, the life-charts were reconstructed first and independently from the timing of suicide attempts, and information on both was complemented with medical records. In addition, attempting suicide seldom determines whether the diagnostic criteria for an MDE are met (6). Recall biases over the last 3.5-year gap preceding the last follow-up may have resulted in some inaccuracies. Treatment received by the patients was as usual. About 42–78% received adequate treatment in the acute phase, whereas the adequacy of maintenance treatment was compromised as the follow-up progressed (50–54). Treatment received by a patient may have reduced the overall risk of attempting suicide, but to influence testing our study hypothesis, this should have had a direct moderating impact on the relationship between the level of depression severity and threshold for re-attempting suicide in a consecutive series of attempts. It is noteworthy that the findings pertain strictly to patients with depressive or bipolar disorder and may not be otherwise generalized. Lastly, in a sample of repeat attempters, the possibility of selection bias for low-lethality attempters exists and the interpretations for suicide deaths must be made carefully.

Patients with depressive or bipolar disorder are a high-risk group for suicidal behavior, accounting for over half of all suicides (55) and admissions for self-harm (56). Risk for suicide death is highest among those who have previously attempted suicide (57, 58). Clarifying the interrelations between mood episodes, suicidal ideation, and prior suicide attempts as risk factors for repeating acts is important. In this study, longitudinally monitored suicide attempts of an individual occurred with the same likelihood during an MDE as previous attempts. Conversely stated, a reattempt after a suicide attempt was not more likely

to occur during partial symptoms of depression, which would have been expected if a suicide attempt directly increases the risk for repetition at lower levels of distress. Neither did the data show a shortening of the inter-attempt interval as the number of suicide attempts increased, a result in line with similar null findings considering inter-episode intervals in MDEs (36). Those patients with a high number of suicide attempts had an overall high frequency of suicide attempts instead of rate acceleration. The findings of this study providing longitudinal and individual-level information agree with others (16, 59) on the importance of temporal and state-dependent understanding of suicidal behavior. Patients with depression and a history of a suicide attempt are at high risk for suicide (58) and form an important target group for suicide prevention (27, 60). Our findings are in alignment with this, but suggest that instead of direct (that is causal) effects, suicide attempts may index other more determinative factors such as more a severe course or characteristics of depression, or other individual factors belonging to the diathesis. While future studies will be needed to clarify the relationship, these may provide important targets for treatment and prevention.

Multifactorial state and trait-related factors, having origins both distally and proximally in time, contribute to suicidal ideation and attempts (27). Theoretically and congruent with stress-diathesis models of suicidal behavior, the data could be interpreted so that a past suicide attempt indicates multifactorial underlying vulnerability as a part of this diathesis. If so, predisposition to attempting suicide could be relatively stable, whereas suicidal ideation and intent vary temporally over the course of depressive episodes. The continuous interaction of these factors in time would then affect the probability for a suicide attempt. According to the interpersonal theory of suicide, acquired capability might also be formed through painful and provocative experiences other than suicide attempts such as childhood maltreatment and exposure to other suicidal behavior. After being formed, this capability could remain relatively stable over time (21). In this cohort, these acquired elements may have actuated *prior to the first attempt* and remained thereafter. Accordingly, childhood adverse experiences may be associated with specific current and definable clinical characteristics, such as borderline personality disorder traits, which may mediate their effects on predisposition to attempting suicide (61). Reduced distress tolerance, including emotional dysregulation and impaired impulse control, overall, contribute to the probability of acting on one's suicidal thoughts (27). Overall, hopelessness and depression contribute to suicidal ideation, whereas impaired self-control including cluster B and impulsive-aggressive traits to risk on acting on one's thoughts (11, 62, 63). However, the symptoms of these factors, commonly viewed as trait-like, actually show to a significant degree intensification along with concurrent depressive symptoms (16, 64–66). Whether diathesis of suicidal behavior could distally unfold during development or strengthen via acquired capability more proximally before the first attempt is open to future research. However, the data here provide no support for the direct within-individual influence of suicide attempts increasing the likelihood for suicide attempts during states below full MDEs. Differentiating and clarifying psychological and clinical characteristics operating at the time of a full mood episode for short-term risk should be an important aim for the field, albeit difficult to study.

To conclude, repetition of a suicide attempt may occur among vulnerable individuals with a concomitant, severe, and chronic course of a mood disorder. This study presented no convincing evidence that a suicide attempt could directly lower the within-individual threshold for a subsequent suicide attempt. While further research is warranted, these findings are informative both clinically and theoretically.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because dataset not publicly available due to restrictions imposed by the Finnish law and research permits. Requests to access the datasets should be directed to erkki.isometsa@hus.fi.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Helsinki and Uusimaa Hospital District (HUS). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KA reviewed the literature, drafted the initial version, and prepared the manuscript. IH, MH, PJ, SP, KR, KS, and MV were active researchers in the respective study cohorts. TR provided statistical expertise and conducted the analyses. EI created the project as the principal investigator. All authors participated in the study concept and design, critical interpretation of data, revisions of the paper, and approval of the final version for submission.

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Clinical Differences Between Single and Multiple Suicide Attempters, Suicide Ideators, and Non-suicidal Inpatients

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Single suicide attempters (SSAs) and multiple suicide attempters (MSAs) represent distinct subgroups of individuals with specific risk factors and clinical characteristics. This retrospective study on a sample of 397 adult psychiatric inpatients analyzed the main sociodemographic and clinical differences between SSAs and MSAs and the possible differences between SSAs, MSAs, and psychiatric patients with and without suicidal ideation (SI). Clinical variables collected included psychiatric diagnoses (Mini International Neuropsychiatric Interview), presence of substance use, current suicide risk status (Columbia Suicide Severity Rating Scale), Clinical Global Impression at admission, Global Assessment of Functioning improvement between admission and discharge, age at onset of psychiatric illness, duration of untreated illness in years, number of hospitalizations in psychiatric settings, and lethality of the most severe suicide attempt. A multinomial logistic regression model with groups showed that MSAs had a higher lethality of their last suicide attempt as compared to SSAs. In addition, MSAs had distinct sociodemographic characteristics compared to both SSAs and patients with SI. Although the study was limited by the relatively small sample size and retrospective nature, the present results suggest that identifying MSAs could be useful in predicting suicide risk and designing *ad hoc* prevention strategies.

Keywords: suicide, single suicide attempters, multiple suicide attempters, suicide ideators, lethality

INTRODUCTION

Suicide is a major public health issue, and nonfatal suicidal behaviors are lethal risk factors for suicide (1). World statistics indicate that for every suicide death, there are up to 25 suicide attempts (2). Bostwick et al. (1) found that ∼60% of individuals who completed suicide died on their index attempt (i.e., their first-lifetime attempt that required medical attention).

Among the 40% of suicide attempters who died as a result of their second or later attempt, more than 80% died within a year of the initial attempt. The study by Isometza and Lonnqvist (3) found that the majority of those who died by suicide (56%) died on their first attempt. In people who attempted suicide multiple times, Isometza and Lonnqvist also reported sex differences and a change in suicide methods, which likely increased the lethality of subsequent suicidal behavior. A high lethality of nonfatal attempts is an important predictor of later suicide, and multiple self-harm acts alone increase subsequent suicide risk (4). In successful final suicide attempts that involved hanging and gas poisoning (mainly charcoal burning), there was a tendency to adopt the same method as the last survived event, though this phenomenon is less marked for suicide attempters who survived jumps, overdoses, and cutting (5). Despite the above findings, the impact of suicide attempt frequency and level of lethality on suicide mortality remains unclear.

In comparison to single suicide attempters (SSAs), multiple suicide attempters (MSAs) likely represent a distinct subgroup of individuals with specific risk factors and clinical characteristics (6–11). For example, MSAs usually manifest borderline personality traits (8, 10, 12). Forman et al. (10) reported more severe depressive symptoms, suicidal ideation (SI), and hopelessness in MSAs than in SSAs, even after controlling for the diagnosis of borderline personality disorder. Furthermore, factors such as a family history of suicidal behavior, poor coping skills, and more severe psychopathology were more strongly associated with MSAs than SSAs (7).

As compared to SSAs, MSAs also seem to exhibit a greater number of suicide risk factors (e.g., a history of childhood emotional abuse and family suicide), increased psychopathology (e.g., depression and substance abuse), higher levels of suicidality (e.g., SI), and lower interpersonal functioning. As compared to SSAs, MSAs had significantly higher motor impulsivity, indicating spur-of-the-moment action (13, 14). MSAs also had a longer duration of bipolar illness, more frequently lived alone, had more than one psychiatric comorbidity, and were more likely to attempt suicide by self-poisoning (although this is also the most common suicide method in SSAs) (15). MSAs and SSAs presented higher levels of depression, hopelessness, aggression, hostility, impulsivity, borderline personality traits, and family history of major depression or alcohol use disorder as compared to psychiatric patients who were non-attempters (16). Despite these findings, some debate exists as to whether MSAs and SSAs have different clinical characteristics. Paashaus et al. (17) compared subjects with SI, MSAs, and SSAs in order to evaluate suicide capability, conceptualized by Joiner (18) as fearlessness about death, subjective pain tolerance, and objective pain persistence, and found no significant differences. Previous research also indicated differences and similarities between SSAs and subjects with SI (19).

In the present study, aimed to identify differences in sociodemographic factors and clinical features between SSAs and MSAs, we hypothesized that SSAs, MSAs and psychiatric patients with and without SI are a distinct population of patients.

MATERIALS AND METHODS

Participants

We enrolled 397 adult inpatients (202 men and 195 women) consecutively admitted to the University Psychiatric Clinic, Sant'Andrea Hospital, Sapienza University of Rome between 2017 and 2019. In the period of the study (2017–2019) the number of patients admitted to the hospital was 800. The mean age of participants was 40.41 years [standard deviation (SD) = 14.06; age range = 17–78 years]. Sociodemographic and clinical characteristics of the sample are summarized in **Table 1**. Inclusion criteria were: (1) Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for psychiatric disorders, and (2) informed consent for participation in the study. Exclusion criteria were: (1) severe neurological disorders (epilepsy, cognitive impairment, or genetic syndromes), and (2) the presence of cognitive deficits causing linguistic problems.

All patients participated voluntarily and gave their informed consent to participate in the study. The study analyzed baseline characteristics as part of a broader investigation on mental pain and suicide risk approved by the local institutional review board.

Measures

Two independent psychiatrists at the University Psychiatric Clinic, Sant'Andrea Hospital, Sapienza University of Rome analyzed each clinical record. Data were reported on a structured checklist created for this study by the authors. In cases of disagreement between the two evaluators, a third party was consulted. The k value for interrater reliability was 0.96.

Clinical variables collected included psychiatric diagnoses, the presence of substance abuse, current suicide risk status, Clinical Global Impression (CGI) (20) at admission, Global Assessment of Functioning (GAF) (21) improvement between admission and discharge, age at onset of psychiatric illness, duration of untreated illness (DUI) in years, number of hospitalizations in psychiatric settings, and lethality of the most severe suicide attempt (22).

Psychiatric diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (23) and supported bythe Italian translation of the Mini International Neuropsychiatric Interview (MINI). The MINI is a short, structured interview developed in France and the United States to explore 17 disorders according to the DSM-III-R (24). It has undergone many reliability and validity studies (25) and has been updated to map both DSM-IV, MINI 6.0 (version 10/10/10) and DSM-5, MINI 7.0.2 diagnostic criteria.

SI and suicide attempts were assessed using the Italian version of the Columbia Suicide Severity Rating Scale (C-SSRS) (26) administered by psychiatric residents in the first 2 days after admission to the psychiatric department. The C-SSRS was used to assess SI severity and intensity, types of suicidal behavior, and lethality of suicide attempts at time points and overtime periods. Use of the C-SSRS differentiated four different patient groups: SSAs, MSAs, and two control groups of non-attempters: a group of psychiatric patients with no recorded suicide risk and a group of psychiatric patients who reported SI but no current or lifetime suicide attempts. The C-SSRS begins with two items that assess the respondent's wish to be dead (e.g., "I wish I were dead")

TABLE 1 | Sociodemographic and clinical characteristics.

Variables	*N*	%
Sex		
Male	202	50.9
Female	195	49.1
Age—M|SD	40.41|14.06	
Marital status		
Married	110	27.8
Divorced or widowed	50	12.6
Single	236	59.6
Housing		
Living with family or others	303	76.5
Living alone	68	17.2
Other	25	6.3
Job		
Employed	167	42.1
Unemployed	201	50.6
Retired or other	29	7.3
Educational achievement		
≤8 years[a]	141	35.5
=13 years[b]	188	47.4
≥16 years[c]	68	17.1
DSM-5 diagnosis		
Major depressive disorder	47	12.1
Bipolar disorder	161	41.6
Schizophrenia or other psychoses	109	28.2
Personality disorder	39	10.1
Other	31	8.0
Comorbidity (yes)	28	7.1
Current admission for suicide attempt	123	31.0
Suicide risk		
Single attempters (current)	58	14.6
Multiple attempters	65	16.4
Suicide ideators	57	14.4
No attempts/ideation	217	54.7
CGI—M|SD	4.47	1.97
GAF improvement—M|SD	25.72	19.17
Age at onset—M|SD	26.48	12.64
Number of hospitalizations—M|SD	1.76	2.36
DUI—M|SD	3.45	7.22
Lethality of the most severe suicide attempt—M|SD	1.91	1.07

[a]*Middle school,* [b]*High school,* [c]*Master degree.*

and nonspecific active suicidal thoughts (e.g., "I've thought about killing myself"). If the participant responds affirmatively to either of these two items, they are presented with three additional items that assess active SI with any method but with no plan or intent to act; active SI with some intent to act but no plan; and active SI with a specific plan and intent. The assessment of active SI is therefore conditioned on the individual's endorsement of the wish to be dead and/or nonspecific active suicidal thoughts, based on the assumption that more severe forms of SI subsume less severe forms of SI. Given the difficulties in categorizing suicide attempts, we also referred to the revised nomenclature in suicidology (27, 28). We, therefore, referred to suicidal acts that were assessed in patients included in this sample as type-II suicide attempts, which may be described as self-destructive acts with some degree of intent to end one's life and some identifiable injuries.

Based on C-SSRS scores, we differentiated the lethality of suicide attempts as follows according to actual lethality/medical damage: 0: no physical damage or very minor physical damage (e.g., surface scratches); 1: minor physical damage (e.g., lethargic speech, first-degree burns, mild bleeding, sprains); 2: moderate physical damage, medical attention needed (e.g., conscious but sleepy, somewhat responsive, second-degree burns, bleeding of a major vessel); 3: moderately severe physical damage, medical hospitalization and intensive care likely required (e.g., comatose with reflexes intact, third-degree burns on <20% of the body, extensive blood loss but can recover, major fractures); 4: severe physical damage, medical hospitalization with intensive care required (e.g., comatose without reflexes, third-degree burns over 20% of the body, extensive blood loss with unstable vital signs, major damage to a vital area); and 5: death.

Statistical Analysis

All statistical analyses were performed with the statistical package for social sciences (SPSS 19.0). A series of ANOVAs and chi-square (χ^2) tests were used for bivariate analyses. Significant variables in bivariate analyses were included as independent variables in a multinomial regression analysis model with groups as a criterion. Odds ratios (ORs) and their 95% confidence intervals (CIs) were reported as measures of association. Tamhane's T2 *post-hoc* tests were used for group comparison. All tests were considered statistically significant if $p < 0.05$.

RESULTS

Group Characteristics

Fifty-eight patients had attempted suicide in the past few days (SSAs), 65 patients had attempted suicide in the last few days and had also attempted suicide in the past (MSAs), 57 patients reported lifetime SI but not behaviors, and 217 patients did not report either lifetime SI or behaviors (**Table 1**). Twelve percent of patients had unipolar major depression, 41.6% had bipolar disorder, 28.2% had schizophrenia or other psychoses, 10.1% had a personality disorder, and 8.0% had other specified disorders (mainly anxiety disorders). Twenty-eight patients also reported comorbidities with at least one other disorder (7.1% with mainly personality and anxiety disorders) and 23 reported substance abuse (7.0%) (**Table 1**).

Difference Between Groups

The four groups differed according to marital status ($\chi^2_6 = 19.77$, $p = 0.003$), diagnosis ($\chi^2_{12} = 31.39$, $p = 0.002$), GAF improvement during the last hospitalization ($F_{3;393} = 251.25$, $p < 0.001$), number of hospitalizations ($F_{3;393} = 3.70$, $p = 0.012$), and DUI (years) ($F_{3;393} = 4.25$, $p = 0.006$) (see **Table 2**). The four groups did not differ in terms of sex, age, job, educational achievement, housing, psychiatric comorbidities,

TABLE 2 | Differences between subgroups.

	Single attempters (current) $N = 58$	Multiple attempters $N = 65$	Suicide ideation, no attempt $N = 57$	No attempts/ideation $N = 217$	Test	*p*-value
Sex					$\chi^2_3 = 1.38$	0.71
Male	46.6%	47.7%	56.1%	51.6%		
Female	53.4%	52.3%	43.9%	48.4%		
Age—M|SD	42.95	40.51	37.60	40.43	$F_{3;393} = 1.40$	0.24
	14.96	14.60	12.30	14.03		
Marital status					$\chi^2_6 = 19.77$	0.003
Married	48.3%	26.2%	24.6%	23.6%		
Divorced or widowed	12.1%	20.0%	8.8%	11.6%		
Single	39.7%	53.8%	66.7%	64.8%		
Job					$\chi^2_6 = 4.61$	0.59
Employed	44.8%	40.0%	47.4%	40.6%		
Unemployed	43.1%	53.8%	49.1%	52.1%		
Retired or other	12.1%	6.2%	3.5%	7.4%		
Educational achievement					$\chi^2_6 = 5.27$	0.51
≤8 years	32.8%	40.0%	24.6%	37.8%		
13 years	46.6%	44.6%	52.6%	47.0%		
≥16 years	20.7%	15.4%	22.8%	15.2%		
Housing					$\chi^2_6 = 4.61$	0.60
Living with family or others	82.8%	72.3%	83.9%	74.2%		
Living alone	13.8%	20.0%	12.5%	18.4%		
Other	3.4%	7.7%	3.6%	7.4%		
DSM-5 Diagnosis					$\chi^2_{12} = 31.39$	0.002
Major Depressive Disorder	14.5%	17.7%	11.1%	10.2%		
Bipolar Disorder	34.5%	38.7%	37.0%	45.4%		
Schizophrenia and other psychoses	30.9%	24.2%	25.9%	29.2%		
Personality Disorder	20.0%	17.7%	11.1%	5.1%		
Other	0.0%	1.6%	14.8%	10.2%		
Comorbidities	6.9%	12.3%	5.3%	6.0%	$\chi^2_3 = 3.39$	0.34
CGI—M|SD	4.24	4.34	5.08	4.43	$F_{3;393} = 2.00$	0.11
	0.73	0.96	5.07	0.79		
GAF improvement—M|SD	49.17	48.52	13.00	15.96	$F_{3;393} = 251.25$	<0.001
	12.87	14.05	8.97	10.38		
Age at onset—M|SD	26.95	24.48	24.43	27.54	$F_{3;393} = 1.55$	0.20
	14.12	10.79	10.75	13.15		
Number of hospitalizations—M|SD	0.95	1.84	1.47	2.06	$F_{3;393} = 3.70$	0.012
	1.55	2.17	1.77	2.69		
Duration of Untreated Illness—M|SD	6.22	3.72	3.80	2.49	$F_{3;393} = 4.25$	0.006
	10.27	6.12	6.88	6.39		
Lethality of the most severe suicide attempt—M|SD	1.50	2.28	–	–	$t_{109.24} = -4.24$	<0.001
	1.11	0.89				
Methods					*χ2₄ = 6.805*	*0.147*
Cut/Pierce	23.3%	5.1%	–	–		
Drug ingestion	50.0%	51.3%	–	–		
Hanging	10.0%	7.7%	–	–		
Jump	13.3%	25.6%	–	–		
Poison by gas	3.3%	10.3%	–	–		

χ^2 = mean Chi square value; F = mean Fisher value; t = mean t test value.

substance abuse, CGI scores, or age at onset of psychiatric disorder (**Table 2**).

SSAs were more frequently married than other groups (48.3 vs. 26.2, 24.6, and 23.6%, respectively, for MSAs, patients with SI, and controls), and less frequently single (39.7 vs. 53.8, 66.7, and 64.8%, respectively, for MSAs, patients with SI, and controls). MSAs were more frequently divorced/widowed than other groups (20.0 vs. 12.1, 8.8, and 11.6%, respectively, for SSAs, patients with SI, and controls). SSAs and MSAs were more likely to have higher GAF improvement during the last hospitalization (49.17 ± 12.87 and 48.52 ± 14.05 vs. 13.00 ± 8.97 and 15.96 ± 10.38, respectively, for patients with SI and controls), and SSAs were more likely to have had fewer hospitalizations (0.95 ± 1.55 vs. 2.06 ± 2.69) and a longer DUI (years) (6.22 ± 10.27 vs. 2.49 ± 6.39) than controls. Suicide attempters also more frequently had a personality disorder diagnosis as compared to controls with no known suicide risk (20.7 and 18.5% for MSAs and SSAs, respectively, vs. 6.5% for controls when considering major diagnoses and comorbidities; $\chi^2_3 = 13.54$, $p = 0.004$).

Thus, MSAs and SSAs differed according to marital status and lethality of the most severe suicide attempt (evaluated with the C-SSRS), with higher lethality observed in MSAs (1.50 ± 1.11 and 2.28 ± 0.89 for SSAs and MSAs, respectively; $t_{109.24} = -4.24$, $p < 0.001$).

Suicide attempters differed from control groups according to marital status, GAF improvement during the last hospitalization, number of hospitalizations, and DUI (the latter differed only between SSAs and controls).

A multinomial logistic regression model with groups as a criterion that used significant variables at bivariate analysis as independent variables explained 66% of the between-group variance (Nagelkerke $R^2 = 0.657$; $-2LL = 522.69$; $\chi^2_{18} = 324.81$, $p < 0.001$) (not reported in the tables). Overall, GAF improvement ($\chi^2_3 = 285.64$, $p < 0.001$), number of previous hospitalizations ($\chi^2_3 = 8.39$, $p < 0.05$; not significant in single comparisons), and DUI ($\chi^2_3 = 8.45$, $p < 0.05$) were significantly and independently associated with group differences. Marital status ($\chi^2_6 = 4.64$, $p = 0.59$) and diagnosis ($\chi^2_3 = 1.91$, $p = 0.59$) were not associated with group differences. Compared to controls, SSAs were more likely to have higher GAF improvement (OR=1.20; 95% CI = 1.15/1.25) and a longer DUI (OR=1.09; 95% CI = 1.03/1.16). MSAs were more likely to have higher GAF improvement as compared to controls (OR=1.20; 95% CI = 1.15/1.25). Patients with SI and controls did not differ on any variables (**Figures 1**, **2**)

DISCUSSION

The present study sought to analyze the most relevant differences in sociodemographic and clinical characteristics between SSAs and MSAs. Comparisons were also made between suicide attempters and two subgroups of controls (patients with SI and psychiatric patients with no suicide risk). Overall, we found a few differences between MSAs and SSAs. MSAs were more frequently single and divorced/widowed, and less frequently married. These differences support existing data on the relationship between unmarried status and high suicide risk (29). In addition, MSAs had a higher lethality of the most severe suicide attempt. In MSAs, the absence of a stable relationship might represent a risk factor for the use of dysfunctional coping mechanisms in the presence of negative life events. For example, a previous study by Pompili et al. (14) found a high presence of at least one stressful life event both throughout childhood/adolescence and within the last 6 months in MSAs vs. SSAs (42.6 vs. 33.8%). Pompili et al. (14) did not find any differences between suicide attempters and non-attempters in terms of marital status but found that more SSAs (63.9%) reported low social support than MSAs (48.9%). However, these contrasting results can be attributed to the different samples analyzed, as well as to differences in research methodologies and designs between studies.

A higher lethality of the most severe suicide attempt in MSAs is also consistent with previous studies that have shown a positive correlation between the number of attempts and the lethality of attempts (30). The present study found that MSAs had higher suicide lethality than SSAs, which is in line with existing research supporting the hypothesis that MSAs constitute a subgroup of suicide attempters, particularly at risk of completing suicide, with a distinctive clinical phenotype and a higher lethality of attempts (31). In contrast, Michaelis et al. (6) reported higher suicide lethality in SSAs as compared to MSAs.

Previous studies also investigated clinical differences between SSAs and MSAs, focusing on patients sharing the same psychiatric diagnosis (6, 15). Boisseau et al. (32) found that Axis I disorders were not predictive of repeat suicidal behavior in a 10-year follow-up study. Notably, SSAs and MSAs differed only in terms of the diagnosis of borderline personality disorder.

In our study, only GAF improvement and DUI were independently associated with group differences after multivariate analysis. Suicide attempters generally reported higher GAF improvements than controls. This result could be associated with the scoring procedure of the GAF scale, which gives a score of 10–1 in the presence of a highly lethal suicide attempt while suggesting higher scores in the presence of severe psychopathology (e.g., hallucinations and delusions). In a naturalistic study, Altamura et al. (33) investigated factors associated with a longer DUI in 320 patients with bipolar disorders. The authors reported a higher frequency and number of suicide attempts in those with a longer DUI when compared to those with a shorter DUI. However, different results were reported by Dell'Osso et al. (34), who investigated sociodemographic and clinical variables characterizing patients with bipolar disorder and a prior suicide attempt. Furthermore, a longer DUI may negatively influence the clinical course and the response to treatment of several psychiatric diagnoses (35, 36) often associated to suicide risk. However, larger prospective studies are warranted to further investigate the role of the DUI within suicide risk. Suicide attempters had a higher rate of personality disorders than controls with no suicide risk. This finding is in line with previously published studies (15, 37) reporting an association between repeat suicidal behaviors and personality disorders, mainly borderline personality disorder. Of note is the fact that the proximal risk factor may play an important role in

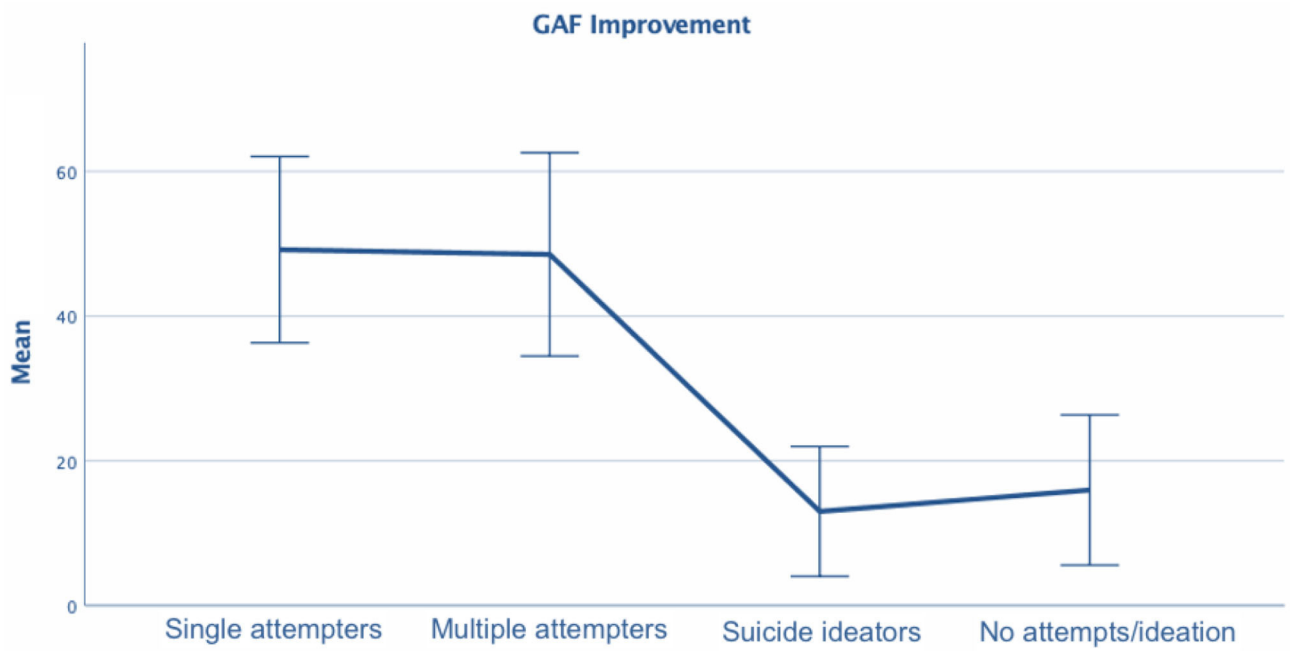

FIGURE 1 | One way ANOVA - global assessment of functioning among subgroups.

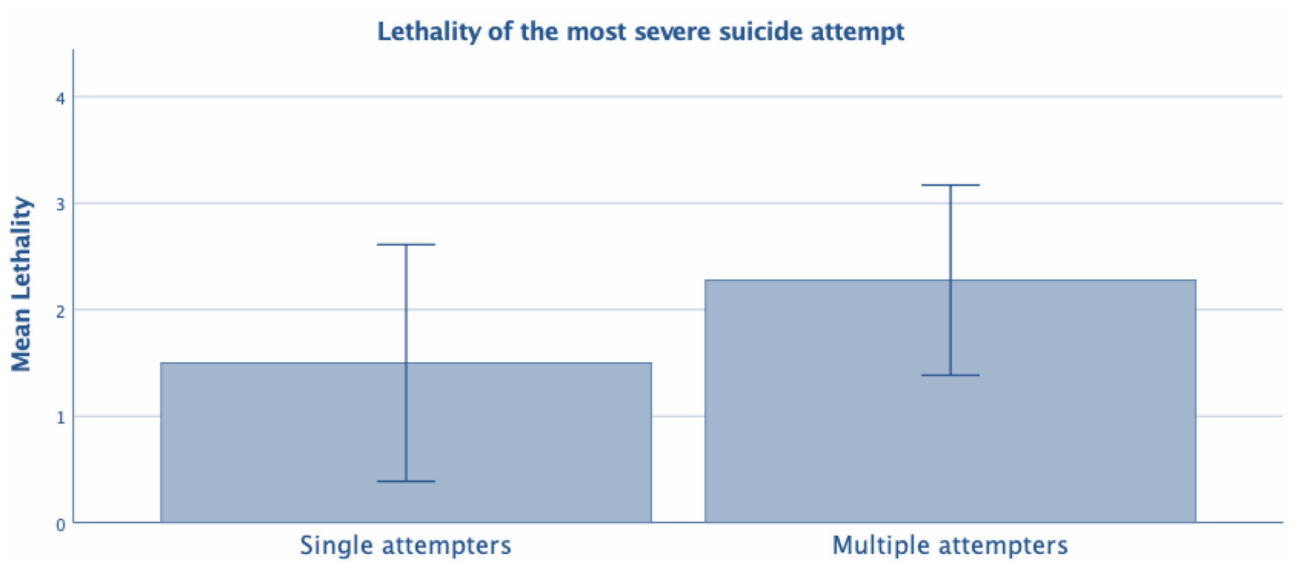

FIGURE 2 | Test *t* - Lethality of the most severe suicide attempt between single vs. multiple attempters.

the precipitation of suicide (38). Traumatic experiences, as in the case of natural disaster and health emergency as in the case of pandemics, may act as a major stress in the vulnerable individual and contribute to a higher risk of attempting suicide (39, 40).

The results of the present study indicated that patients with SI and controls did not differ on any variables. This might be related to the fact that SI seriousness was not assessed using distinct psychometric instruments (41). Unfortunately, SI, especially when manifesting with mild features, is common and it may not always be possible to distinguish ideators from controls. The present results, however, showed that ideators and attempters need to be considered as two distinct populations. More research is needed to

understand how and to what extent these sociodemograhic and clinical differences are able to characterize attempters and ideators (42).

LIMITATIONS

The present study needs to be considered in light of the following shortcomings that limit the generalizability of the present results. First, the sample size is relatively small and may not be representative of all SSAs and MSAs. Second, Italian law dictates that acute psychiatric patients admitted to an emergency department be hospitalized in a psychiatric ward, which is generally part of a public hospital. An array of clinical states and circumstances are commonly part of daily clinical practice, but a systematic assessment using psychometric instruments and a homogenous approach of psychiatrists working in the psychiatric unit are lacking. Finally, the subjects in this study were all inpatients and several suicide attempters who made non-lethal attempts might not be hospitalized; this may limit the generalizability of the study. Furthermore, we do not know whether there were differences between subjects who participated and subjects that did not participate in the study.

Finally, the cross-sectional nature of the present study design should be considered an additional caveat.

CONCLUSIONS

In the present study, MSAs showed higher lethality of their last suicide attempt as compared to SSAs. Moreover, MSAs had distinct sociodemographic characteristics as compared to SSAs and patients with SI. The present results suggest that identifying MSAs could help predict suicide risk and design *ad hoc* prevention strategies, including screening to identify at-risk individuals, public education campaigns, telephone helplines, easy access to psychiatric emergence units, treatment interventions, and follow-up care after suicide attempts.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

IB and AF wrote the article. MI provided statistical analysis. BI, BM, SS, ER, DE, GA, and MM collected data. GS, MA, and DL revised the manuscript. MP proposed the idea of the article and revised the entire manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Long-Term Suicide Risk of Children and Adolescents With Attention Deficit and Hyperactivity Disorder—A Systematic Review

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Background: Attention deficit and hyperactivity disorder (ADHD) is one of the most common mental disorders in childhood. Recently, several studies showed the high suicide risk of patients with ADHD; however, most of these studies had a cross-sectional design.

Aims: The aim of the current research is to complete a systematic review of published studies which investigate the suicide risk of ADHD patients with longitudinal design.

Methods: The systematic search was made on OVID Medline, PsychInfo, PubMed, Scopus, and Web of Science. The search terms were (ADHD OR attention deficit hyperactivity disorder) AND (suicide OR suicidal OR suicidality) AND (follow-up OR longitudinal study OR prospective study). The inclusion criteria were as follows: written in English; the participants were under 18 years at baseline; longitudinal, prospective studies; ADHD population at baseline and at follow-up; and suicide behavior as a primary outcome. The exclusion criteria were as follows: the study did not contain empirical data and reviews/meta-analyses and studies which aimed to investigate the drug treatment efficacy of ADHD.

Results: After the screening process, 18 papers were included in the systematic review. Ten articles were altogether published in the last 5 years. The range of follow-up periods varied between 2 and 17 years. Several different assessment tools were used to investigate the symptoms and/or the diagnosis of ADHD and the suicidal risk. Nine studies enrolled children aged under 12 at baseline, and three studies used birth cohort data, where there was no strict age-based inclusion criteria. A total of 17 studies found a positive association between ADHD diagnosis at baseline and the presence of suicidal behavior and/or attempts at the follow-up visits.

Limitations: The main limitation of this review is the methodological heterogeneity of the selected studies. A further limitation is the relatively low number of studies that examined a population with balanced gender ratios. Additionally, only one study published data about the treatment of ADHD. Finally, though we carefully chose the keywords, we still may be missing some relevant papers on this topic.

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Conclusions: In spite of the methodological diversity of the included studies, the results of the current systematic review highlight the importance of screening suicidality in the long term in patients with ADHD. Therefore, further studies that compare the suicidal risk of treated and untreated groups of ADHD patients in the long term are needed.

Keywords: ADHD, suicidality, follow-up, review, children, adolescent

INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) is one of the most common child and adolescent psychiatric disorders, with a prevalence rate of 3.4% (CI 95% 2.6–4.5) (1). The core symptoms are inattention, impulsivity, and hyperactivity, based on DSM-5 (2). There is growing evidence that ADHD has a significant negative effect on quality of life (QoL) as predicted by the symptom level and impairment. In connection with the QoL aspect, ADHD is associated with social–relationship problems (3), educational problems (4), and increased risk of substance abuse (5) and criminality (6). All these can reduce the effective treatment of ADHD (7). Several studies have suggested that long-term methylphenidate treatment in ADHD could reduce depression and suicidality (8). Numerous research studies have highlighted that comorbid conditions have an important role in the lower QoL of patients with ADHD (9). Children with ADHD had a significantly higher rate of comorbidities than individuals without ADHD (10). Among the most common comorbidities in ADHD are major depression, conduct disorder, anxiety disorder, and substance use disorder (11).

Suicide deaths are the second most common cause of death among females and third among males in the ages 15–29 years worldwide (12). Recently, several studies investigated the correlation between ADHD and suicidality, and even more reviews and meta-analyses were published with the inclusion of these studies (13–18). These reviews concluded a positive association between ADHD and suicidal behavior in all age groups compared; however, the relationship between suicide thoughts and behavior and ADHD is still unclear, i.e., the mediator and moderator factors, mainly the role of comorbidities.

All these previous reviews and meta-analyses focusing on the topic of ADHD and suicidality mainly included studies with a cross-sectional design. A very recent systematic review and meta-analysis by Septier et al. (17) collected cross-sectional and longitudinal data among child, adolescent, and adult studies. They focused only on the cross-sectional relationship, and baseline data were extracted from the longitudinal studies. The results found a significant association between ADHD and suicidal attempts, suicidal ideations, suicidal plans, and completed suicide.

The main aim of the current study was to identify all previously published studies which investigated the connection between ADHD and suicide thought and behavior with a longitudinal design, where the baseline data were available from age under 18 and that assessed ADHD participants. Furthermore, our aim was to provide a systematic overview about these identified studies according to findings, methods, and design.

METHODS

The literature search was made on the 24th of March 2019 on the following scientific electronic databases: OVID Medline, OVID PsychInfo, PubMed, Scopus, and Web of Science. The following search terms were calculated using a Boolean operator (to combine the categories, we used AND terms; to aggregate the subcategories we used OR terms): (ADHD OR attention deficit hyperactivity disorder) AND (suicide OR suicidal OR suicidality) AND (follow-up OR longitudinal study OR prospective study). To organize the articles and to manage the filtration, we used EndNote X8 software. The inclusion criteria of the systematic search were the following: written in English; the participants were under 18 years at baseline; longitudinal, prospective studies; a group of ADHD population at baseline and at follow-up; and suicide thought and behavior as a primary outcome. The exclusion criteria were if the study did not contain empirical data and reviews/meta-analyses and studies which aimed to investigate the drug treatment efficacy of ADHD. Using the inclusion and the exclusion criteria, we screened the titles and the abstracts of the articles found with the search terms. After this initial screening, the relevant full texts of the papers that passed were read, and the ones that met the inclusion criteria were collected. The title, abstract, and full text of the eligible studies were measured by the first author, a process which was carefully reviewed and supervised by the second author, i.e., all included and excluded articles were double-checked according to the inclusion and the exclusion criteria. In case of disagreement, the paper was carefully read again by both authors. The final selection of the relevant studies was based on the agreement of the two authors. The reference lists of the retrieved papers were screened, and papers that possibly met the inclusion criteria were retrieved and studied as well. After the systematic search method, the current literature was screened continuously for eligible studies to include in the review. The reporting of this systematic descriptive review follows the PRISMA statements. Due to the clinical and methodological heterogeneity of the included studies, a narrative approach to data synthesis and presentation was undertaken. To assess the methodology quality of the selected cohort studies, we used the Newcastle–Ottawa Scale Cohort Studies supplement (19), which was based on the agreement of the two authors.

RESULTS

After the systematic search, we found 360 articles in total, including duplicates. Additionally, one article was included manually (20). After the screening process, 18 papers were finally included in the systematic review (10, 20–36) (**Table 1**). The selection process is summarized in the PRISMA flowchart (**Figure 1**).

The 18 relevant articles (10, 20–36) are listed in **Table 1**. The included studies differ on several characteristics, such as the study populations, *e.g.*, the age range of the study population, the study design, e.g., the length of the follow-up period, and the measures of ADHD and suicidality. The quality assessment of the selected studies are listed in **Table 2**. The paper of Galéra et al. (24) and Goldston et al. (25) were not included to the cohort quality assessment due to different methodological study design.

Descriptive Analysis of the Included Studies

Based on geographical distribution, the articles investigated the following populations: 10 articles are from North America (21–23, 25–27, 31, 32, 34, 35), five are from Europe (20, 24, 30, 33, 36), two are from Asia (28, 29), and one is from South America (10).

Highlighting the significance of the topic, 11 of the investigated 18 articles were altogether published in the last 5 years (10, 20, 26–30, 32–35).

Eight papers reported data from a clinical sample, constituting the majority of the collected studies (22, 23, 25–27, 31, 32, 34); however, among these eight papers, five (26, 27, 31, 32, 34) were analyses from the same study population [for additional details, see Hinshaw et al. (37), Barbaresi et al. (21), and Yoshimasu et al. (35) who used data from the Rochester Epidemiology Project, Minnesota] (21, 35, 38). Although three studies used register-based data (28–30), among these studies, Huang et al. (28) and Lan et al. (29) used register-based data from Taiwan. Three studies recruited participants from a community sample (10, 24, 33), and birth cohort data were used by three studies (21, 35, 36).

Ten studies enrolled children aged under 12 years at baseline (10, 20, 23, 26, 27, 31, 32, 34–36). However, Barbaresi et al. (21) and Yoshimasu et al. (35) used birth cohort data, and there were no strict age-based inclusion criteria. The baseline age was calculated when the participants met the research diagnostic category; the mean age of the participants was 10.4 years (SD = n.a.) (21, 35). Huang et al. (28), Lan et al. (29), Ljung et al. (30), and Strandheim et al. (33) used a wide age range criterion including child, adolescent, and adult participants (28–30, 33).

Regarding gender distribution in the included studies, 12 studies recruited both male and female participants (10, 20, 21, 23–25, 28–30, 33, 35, 36); among them, eight studies investigated mainly male populations (more than 60% males in the population) (21, 23, 28–30, 35, 36), and four studies demonstrated an approximately balanced male–female ratio population (21, 23, 26). Six studies included only female participants (22, 26, 27, 31, 32, 34).

Follow-Up Period of the Included Studies

The follow-up period of the included studies varied in a wide range. Seven studies published data after more than a 10-years follow-up period (20, 21, 25, 30, 32, 35, 36). From 5 to 10 years of follow-up data were investigated by 10 studies (10, 22–24, 26–29, 31, 34). The mean follow-up period was <5 years in one study (33).

Nine of the 18 studies planned an exact number of follow-up visits (10, 22, 24, 26, 27, 31, 32, 34, 36). One follow-up visit was planned by Biedermann et al. (22), Caye et al. (10), and Galéra et al. (24). Hurtig et al. (36), Gordon and Hinshaw (26), Guendelman et al. (27), Miller et al. (31), and Swanson (34) planned two follow-up visits; three follow-up visits were accomplished by Owens et al. (32). The average number of research assessments for active participants was 12.8 (SD = 4.0) in the study of Goldston et al. (25).

The three register-based studies, the design of the studies, did not apply an exact number of follow-up visits where data were derived from (28–30).

Assessment of ADHD

The majority of the studies used structured interviews or medical records to establish the ADHD diagnosis. From these, 11 studies (22, 23, 25–29, 31, 32, 34, 36) used structured interview, and three of the studies used medical data to identify the participants with ADHD diagnosis (21, 30, 35). It was noted that four of the selected articles used a non-diagnostic tool to evaluate the hyperactivity–inattention trajectories and symptoms in the selected population (10, 20, 24, 33).

The NIMH Diagnostic Interview Schedule for Children (DISC) (39) was used to establish the ADHD diagnosis in six of the selected studies (23, 26, 27, 31, 32, 34). Four of these studies used DISC Version IV (DISC-IV) (40). DISC-IV is a highly structured interview addressed to evaluate more than 30 mental disorders, including ADHD. It was designed to be used in large-scale, epidemiological studies (40) using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (2) and the International Classification of Disorders (ICD-10) (41). In five studies (26, 27, 31, 32, 34), the ADHD diagnosis was based on the parents' responses about the unmedicated behavior of the participant girls at baseline evaluation (37). Chronis-Tuscano et al. (23) interviewed the mothers or the primary caregivers.

Barbaresi et al. (21) and Yoshimasu et al. (35) investigated a birth cohort. Enrollment to the baseline population, based on the documented school and medical records of the behavior symptoms of the participant, included the ADHD criteria of DSM-IV (2), (42).

Biederman et al. (22) collected a clinical sample based on medical records, but they used the Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (Kiddie-SADS-PL) (43). Kiddie-SADS-PL is a structured, diagnostic tool based on the diagnostic criteria of DSM-IV-TR diagnoses (2). The disorder was positive when either the participant's or his/her mother's information met the diagnostic criteria (22).

Goldston et al. (25) applied the Interview Schedule for Children and Adolescents (ISCA) (44) at baseline for children

TABLE 1 | Included relevant articles examining associations between ADHD and suicidal thought and behavior in a follow-up design.

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Barbaresi et al. (21)	Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study	2013	USA	Birth cohort	ADHD group: *N* = 232 (male ratio: 71.9%); control group: *N* = 335 (male ratio: 62.6%)	From birth; mean = 10.4 years (SD = n.a.) (when research diagnostical criteria were met)	n.a., mean age of the followed-up population = 30.0 years (SD = 1.9)	ADHD in childhood: medical and school records; positive ADHD questionnaire results; documented clinical diagnosis of ADHD; M.I.N.I ‹18 years	M.I.N.I.	Based on medical records	In the ADHD group, significantly more suicide deaths were reported than in the control group
Biederman et al. (22)	New insights into the comorbidity between ADHD and major depression in adolescent and young adult females	2008	USA	Clinical sample	ADHD female group *N* = 123 (ADHD only *N* = 43; ADHD + MD, *N* = 80), non-ADHD female group: *N* = 112 (controls, *N* = 89; controls + MD, *N* = 23)	Female subjects ages 6–18 years; control mean = 11.7 (SD = 2.8) ; control + MD mean=13.9 (SD =2.4); ADHD only MD mean = 10.0 8 (SD =3.3); ADHD + MD mean = 12.1 (SD = 3.2)	Follow-up: 5 years	ADHD/ MDD: K-SADS-PL ›18 years and the SCID ‹18 years	ADHD/MDD: K-SADS-PL ›18 years and the SCID ‹18 years	Not detailed	After the symptom-level analysis, the ADHD group and the control group only differed significantly in the rates of suicidal thoughts
Caye et al. (10)	Attention deficit/hyperactivity disorder trajectories from childhood to young adulthood: evidence from a birth cohort supporting a late-onset syndrome	2016	Brazil	Community	Childhood ADHD group: *N* = 393 (male ratio: 63.9%); non-ADHD group: *N* = 4,033 (male ratio: 47.9%)	11 years of age (SD = n.a.)	7 years (follow-up: 18 to 19 years of age)	Baseline: SDQ (parent and self-report); follow-up: ADHD, ASRS	M.I.N.I.	M.I.N.I—MDD supplement	Significantly higher number of self-reported suicide attempts in children and young adults with ADHD than without, what remained after excluding comorbidities
Chronis-Tuscano et al. (23)	Very early predictors of adolescent depression and suicide attempts in children with attention deficit/hyperactivity disorder	2010	USA	Clinical sample	ADHD group: *N* = 125 (male ratio: 85.6%), non-ADHD group: *N* = 123 (male ratio: 81.3%)	ADHD group: age 4–6 years (mean: 5.2 years; SD = 0.7); ADHD group: 4–6 years of age (mean: 5.2 years; SD = 0.8)	Approximately annual assessments during follow-up year 1 through 4, 6 through 9, and 12 through 14	DISC (for parents); Impairment Rating Scale (for teacher)	DISC for children (for parents); follow-up year 6 through 14 DISC for children (for youth)	Annually at follow-up, year 6 through 14: DISC (for parents and children)	The baseline 4–6 years ADHD group showed a greater risk for suicide attemps and emergence of MDD through reaching year 18 than comparisons. The risk for concrete suicide plans was higher in girls and participants with baseline ADHD-C subtype and baseline ADHD-C and ADHD-HI subtypes for suicide attempts

(Continued)

TABLE 1 | Continued

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Forte et al. (20)	Developmental trajectories of childhood symptoms of hyperactivity/inattention and suicidal behavior during adolescence	2020	Italy	Community	Community group, *N* = 1407 (male ratio = 47.2%)	5 months (mean age = n.a.)	Follow-up: 17 years (annually or bi-yearly assessment)	6, 7, 8, 10, and 12 years of age: BQ (for teacher)	Centre for Epidemiological Study Depression Scale; children depression symptoms (for teacher)	13, 15, and 17 years of age: item: "In the past 12 months, did you ever seriously think of attempting suicide?", if yes: "In the past 12 months, how many times did you attempt suicide?"	In boys, the high and the moderate ADHD trajectory groups showed a greater risk than the low-trectory group for suicide ideation; only high-trajectory group *vs* low-trajectory group was significant for suicide attempt. In girls, there were no significant differences among the trajectory groups
Galera et al. (24)	Hyperactivity–inattention symptoms in childhood and suicidal behaviors in adolescence: the Youth Gazel Cohort	2008	France	Community cohort	Total *N* = 916 (male ratio: 46.0%)	4–18 years (mean = n.a.; SD = n.a.)	Follow-up: 8 years	Baseline: CBCL (for parents); follow-up: a checklist of problems (derived from the CBCL and adapted for young adults)	CBCL	Follow-up: detailed questions about suicidal thought and behaviors (estimate lifetime, previous 12 months and 30 days)	Males with hyperactivity–inattention symptoms showed a significant association with lifetime suicide plans or attempts and nearly significant with 12-month plans/attempts. The association was not significant in the female group with hyperactivity–inattention symptoms. The association was not significant between any subgroups and lifetime and 12-month suicide ideation. Participants with childhood hyperactivity–inattention subtype had a greater risk for lifetime suicide plans/attempts
Goldston et al. (25)	Psychiatric diagnoses as contemporaneous risk factors for suicide attempts among adolescents and young adults: developmental changes	2009	USA	Clinical sample	Total *N* = 180 (male ratio: 49.4%), ADHD subgroup *N* = 29 (male ratio: n.a.)	12–18 years; mean = 14.8 years (SD = 1.6; 12.0–18.4)	Mean = 10,8 years (SD = 3.4); mean number of assessments for active participants: 12.8 (SD = 4.0)	Baseline: ISCA; follow-up: FISA	Baseline: ISCA; follow-up: FISA	Baseline: ISCA; follow-up: FISA	There was a significant relationship between simultaneous diagnosis (MDD, dysthimic disorder, GAD, panic disorder, ADHD, CD, SUD), including ADHD and the future suicide attempts. Strengthened relationship was observed to co-occur with psychiatric disorders (MDD, GAD, ADHD, SUD) and suicide attempts when the participants became older

(Continued)

TABLE 1 | Continued

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Gordon and Hinshaw (26)	Parenting stress as a mediator between childhood ADHD and early adult female outcomes	2017	USA	Clinical cohort	ADHD female group: *N* = 120, control female group: *N* = 81	ADHD female group: 6–12 years of age (Mean = 9.7; SD = 1.7), simply Hyperactivity ADHD type excluded; Control female group: 6–12 years of age (Mean = 9.3, SD = 1.6)	10 years (follow-up 1: 5 years, follow-up 2: 10 years)	Baseline: DISC-IV, CBCL, CDI (for parent)	Baseline: DISC-IV, CBCL, CDI (for parent), CDI, assessing maltreatment; follow-up 1: CBCL (for parent), CDI ‹18 years, ABCL, ASR, BDI ›18 years, Self-Injury Questionnaire; follow-up 2: CBCL (for parent) self-reported CDI ‹18 years, ABCL, ASR, BDI ›18 years, modified version of the Self-Injury Questionnaire	Follow-up 1, 2: The Barkley Suicide Questionnaire, FIP	In the female ADHD group, there were more suicide attempts than in the female controls (not detailed). The mother–daughter relationship showed a mediator role between childhood ADHD and young adult NSSI and an indirect effect between childhood ADHD and young adult depressive symptoms
Guendelman et al. (27)	Early-adult correlates of maltreatment in girls with attention deficit/hyperactivity disorder: increased risk for internalizing symptoms and suicidality	2016	USA	Clinical cohort	ADHD female group: *N* = 120 (ADHD-C, *N* = 93; ADHD-IT, *N* = 47)	ADHD female group: 6-12 years of age (Mean = 9.6; SD = 1.7), simply Hyperactivity ADHD type excluded	**10** years (follow-up 1: 5 years, follow-up 2: 10 years)	Baseline (for parents): DISC-IV	Baseline: DISC-IV, CBCL, CDI, SNAP-IV (for parent), CDI, assesing maltreatment; follow-up 1: CBCL (for parent), CDI ‹18 years, ABCL, ASR, BDI ›18 years EDI, EAT-26, WIAT-II, Self- Perception Profile for Adolescents, Self-Perception Profile for Adolescents, Self-Injury Questionnaire; follow-up 2: CBCL (for parent) Self-Reported CDI ‹18 years, ABCL, ASR, BDI › 18 years, modified version of the Self-Injury Questionnaire	Follow-up 1, 2: The Barkley Suicide Questionnaire, FIP	ADHD females with maltreatment experience before showed a greater number of suicide attempts (33%) than non-maltreated ADHD females (13%)

(Continued)

TABLE 1 | Continued

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Huang et al. (28)	Risk of suicide attempts in adolescents and young adults with attention deficit–hyperactivity disorder: a nationwide longitudinal study	2018	Taiwan	Register-based	ADHD group: *N* = 20,574 (male ratio: 78.8%), control group: *N* = 61,722 (male ratio: 78.8%)	Adolescents and young adults with ADHD Mean = 14.94 years (SD = 4.46) years, Controls Mean = 14.94 years (SD = 3.49)	Follow-up: 2-11 years; baseline: 01 January 2001–31 December 2009; follow-up: from baseline to 31 December 2011	Diagnosis of ADHD and psychiatric comorbidities was made by board-certified psychiatrists	Based on medical records	Based on medical records	The incidence of first and repeated suicide and the probability of suicide attempts were significanty higher in the ADHD group than in the control group, and the participants with ADHD were younger at first attempt. Medical treatment did not increase the risk of first/repeated suicide attempts. Long-term methylphenidate treatment showed a decreased risk of repeated suicide attempts in men
Hurtig et al. (36)	Suicidal and self-harm behavior associated with adolescent attention deficit–hyperactivity disorder—a study in the Northern Finland Birth Cohort 1986	2011	Finland	Birth cohort	ADHD group: *N* = 188, control group: *N* = 169 (male ratio: n.a.)	Participants from the same cohort	16 years (follow-up 1: age 7 to 8 years, follow-up 2: 16 years)	Screening of ADHD: SWAN; defining the clinical diagnosis: K-SADS-PL	K-SADS-PL	K-SADS-PL	The ADHD group showed a greater number of suicidal ideation, and the ADHD diagnosis had a strong effect of suicidal ideation after controlling other predictors. Female gender, comorbid depression and anxiety, and childhood emotional and behavioral problems were also associated with suicidal thoughts
Lan et al. (29)	Comorbidity of ADHD and suicide attempts among adolescents and young adults with bipolar disorder: a nationwide longitudinal study	2015	Taiwan	Register-based	ADHD + BP group: *N* = 500 (male ratio: 66.2%), BP only: *N* = 1,500 (male ratio 66.2%)	15–24 years; Group with Bipolar disorder and ADHD Mean=19.11 years (SD = 2.84); Group with Bipolar disorder Mean = 19.11 years (SD = 2.84)	Follow-up: 3–10 years; baseline: 01 January 2002–31 December 2008; follow-up: from baseline to 31 December 2011	Diagnosis of ADHD and psychiatric comorbidities was made by board-certified psychiatrists	Diagnosis based on the ICD-9-CM	Based on medical records	Bipolar adolescents and young adults with ADHD co-occurence associated a greater incidence of attempted suicide than the bipolar only group. After adjustment, ADHD was an independent risk factor for lifetime-attempted suicide later among adolescents and young adults with bipolar disorder

(Continued)

TABLE 1 | Continued

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Ljung et al. (30)	Common etiological factors of attention deficit/hyperactivity disorder and suicidal behavior: a population-based study in Sweden	2014	Sweden	Register-based	ADHD group: *N* = 51,707 (male ratio: 69.8%), control group: *N* = 258,535 (male ratio: 69.8%)	ADHD group: Age 3-40 years; Control group: matched 1:5 on sex and birth year.	n.a. (lifetime follow-up to age 40 years)	Register-based medical records	Based on medical records	Register-based data (suicidal behavior was allowed at age 12 years or older)	The group with ADHD diagnosis showed a greater risk for suicide attempt and suicide death after adjusting for comorbid psychiatric disorder. High risk of suicide attempts and suicide deaths was observed in first-degree relatives (parents, full siblings)
Miller et al. (31)	Childhood executive function continues to predict outcomes in young adult females with and without childhood-diagnosed ADHD	2012	USA	Clinical cohort	ADHD female group: *N* = 140 (ADHD-C, *N* = 93; ADHD-IT, *N* = 47), control female group: *N* = 88	ADHD female group: 6–12 years of age, simply hyperactivity ADHD-type excluded; control female group: 6–12 years of age (overall mean age = 9.6) (SD = n.a.); comparison sample matched on age and ethnicity	10 years (follow-up 1: 5 years, follow-up 2: 10 years)	Baseline: DISC-IV (for parent)	n.a.	The number of suicide attempts and the number of NSSI "episodes" that had occurred since their last visit were summed up	Elevated number of suicide attempts/NSSI was observed in the ADHD group compared to controls (only descriptive data were available)
Owens et al. (32)	Girls with childhood ADHD as adults: cross-domain outcomes by diagnostic persistence	2017	USA	Clinical cohort	ADHD female group: *N* = 140, control female group: *N* = 88	ADHD female group: 6–12 years of age; control female group: 6–12 years of age, overall mean age = 9.6 years (SD = 1.7); comparison sample matched on age and ethnicity	16 years (follow-up 1: 5 years, follow-up 2: 10 years, follow-up 3: 16 years)	Baseline: DISC-IV (for parent)	DISC-IV; BDI-II; SUQ; Self-Injury Questionnaire (follow-up 1, 2), follow-up 3: ABCL, ASR, SITBI (since follow-up 2)	Follow-up 1, 2, 3: The Barkley Suicide Questionnaire	The view of a persistent ADHD diagnosis through time as partial and persistent; ADHD females showed greater suicide attempts than comparisons after adjusting for covariates
Strandheim et al. (33)	Risk factors for suicidal thoughts in adolescence—a prospective cohort study: the Young-HUNT study	2014	Sweden	Community	Two-sample group: Young-HUNT1 (recruited 1995–1997) and Young-HUNT2 (recruited 2000–2001), *N* = 2399 (male ratio: 46.5%), attention problems subgroup: *N* = 448 (male ratio: 41.9%)	Two sample group: 13–19 years (Young-HUNT1) and 17–19 years (Young-HUNT2)	Mean follow-up time: 3.9 years (SD = n.a.)	ADHD symptoms: 14-item school-adjustment questionnaire	Questionnaire; pain and tension: headache, neck pain, muscle and joint pain, and palpitations during the past 12 months; alcohol use: number of reported alcohol intoxications; sleep disturbances: defined as difficulties in initiating sleep	Follow-up: item "Have you had thoughts about taking your own life?" (yes/no)	At baseline, comorbid conditions, including attention and conduct-associated problems, more than doubled the odds for suicidal thoughts in males and females. The odds decreased after stratifying by gender

(Continued)

TABLE 1 | Continued

References	Title	Year	Country	Sample	Population at baseline	Age of the population at baseline	Follow-up period (follow-up visits)	ADHD assessment	Measure of Comorbid conditions	Suicide outcome measure	Main findings
Swanson et al. (34)	Pathways to self-harmful behaviors in young women with and without ADHD: a longitudinal examination of mediating factors	2014	USA	Clinical cohort	ADHD female group: *N* = 140 (ADHD-C, *N* = 93; ADHD-IT, *N* = 47), control female group: *N* = 88	ADHD female group: 6–12 years of age; control female group: 6–12 years of age, mean age = 9.1 years (SD = n.a.); comparison sample matched on age and ethnicity	10 years (follow-up 1: 5 years, follow-up 2: 10 years)	Baseline: DISC-IV (for parent)	CBCL, Teacher Report Form, CDI, Self-Injury Questionnaire	Follow-up 1,2: The Barkley Suicide Questionnaire, FIP	The number of suicide attempts was significantly higher in ADHD-C subtype than the comparison group after adjustment. The persistent diagnosis of ADHD showed a higher rate of suicide attempts compared to the comparisons, but not to the transient ADHD participants. Data showed a significant positive correlation between baseline ADHD status and future suicide attempt, where the internalizing symptoms were estimated to play a partial mediator role
Yoshimasu et al. (35)	Psychiatric comorbidities modify the association between childhood ADHD and risk for suicidality: a population-based longitudinal study	2017	USA	Birth cohort	ADHD group: *N* = 232 male ratio: 71.9%; control group, *N* = 335 (male ratio: 62.7%)	From birth (when research diagnostical criteria were met)	n.a., mean age of the folllowed-up ADHD group = 27.0 years (SD = 2.6); mean ager of the followed-up non-ADHD group = 28.6 (SD = 2.2)	Mini International Neuropsychiatric Interview (M.I.N.I.)	M.I.N.I.	M.I.N.I.—Suicide thoughts and attempt section	A direct effect was identified between childhood ADHD and the criteria for suicidality. GAD had a significant synergic interaction effect for future suicide attempts in ADHD cases

ABCL, Adult Behavior Checklist; ADHD-C, ADHD combined type; ADHD-IT, ADHD inattentive type; ADHD, Attention Deficit Hyperactivity Disorder; ASR, Adult Self-Report; ASRS, World Health Organization Adult ADHD Self-Report Scale Screener; BDI-II, Beck Depression Inventory-II; BQ, Behavior Questionnaire; C, control; CBCL, Child Behavior Checklist; CD, Conduct Disorder; CDI, Children's Depression Inventory; DISC, Diagnostic Interview Schedule for Children; EAT-26, Eating Attitudes Test; EDI-2, Eating Disorders Inventory; FIP, Family Information Packet; FISA, Interview Schedule for Adults; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ISCA, Interview Schedule for Children and Adolescents; K-SADS-PL, Affective Disorders and Schizophrenia for School-age Children-Epidemiologic Version; M.I.N.I., Mini International Neuropsychiatric Interview; MD, major depression; SCID, Structured Clinical Interview for DSM-IV; SCL-90R, Symptom Check-List 90R; SITBI, Self-Injurious Thoughts and Behaviors Interview; SNAP, Swanson, Nolan, and Pelham rating scale; SUD, Substance Use Disorder; SUQ, Substance Use Questionnaire; SWAN, Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors; WIAT-II, Wechsler Individual Achievement Test, Second Version.

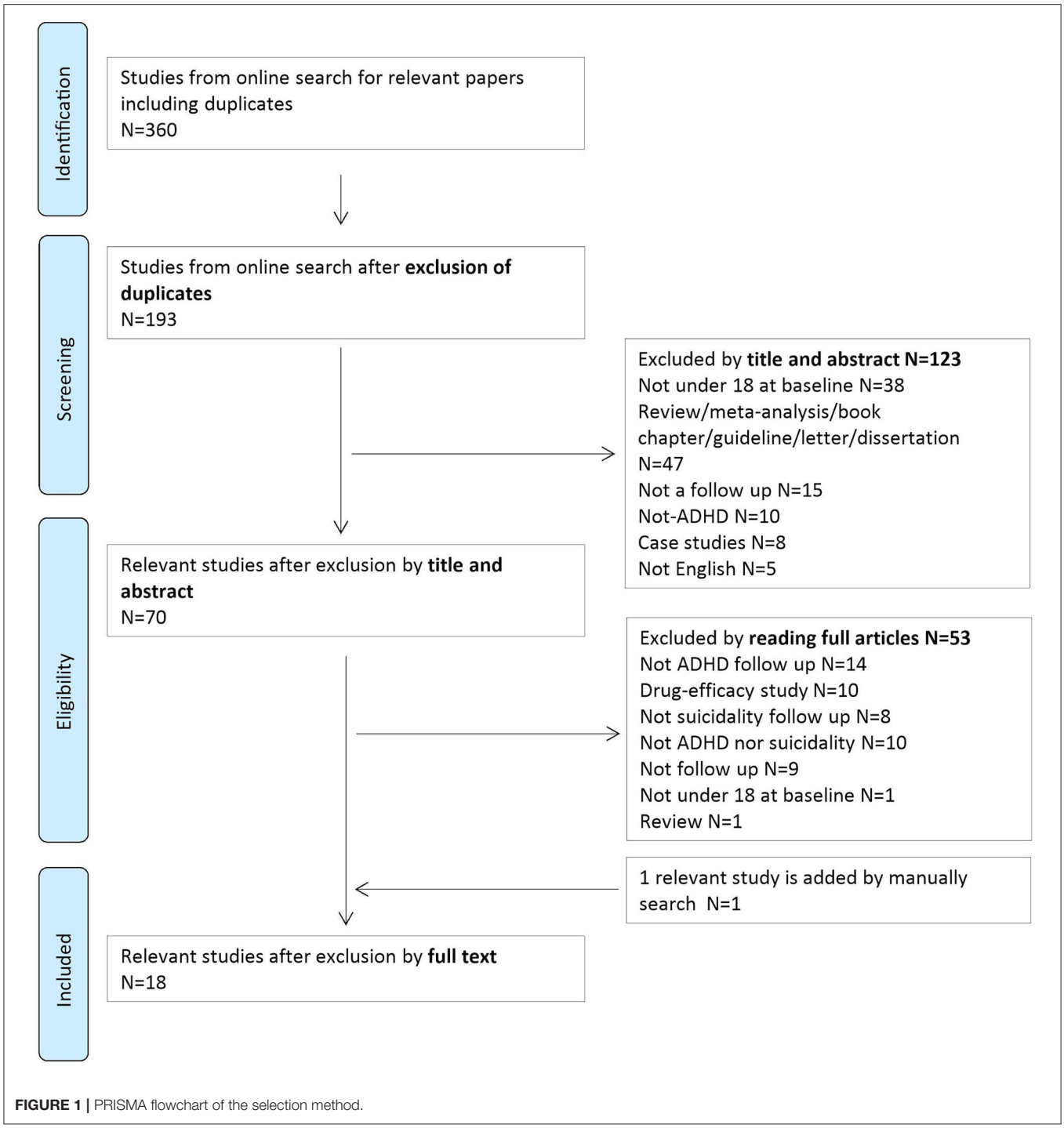

FIGURE 1 | PRISMA flowchart of the selection method.

and the adult version of ISCA, the Follow-Up Interview Schedule for Adults (FISA) (45), at the follow-up phase. Both the ISCA and the FISA are highly structured interviews to estimate the severity, duration, and functional impairment of the symptoms (44, 45).

Ljung et al. (30) identified the ADHD cases from register-based medical records.

Hurtig et al. (36) used a two-step identifying procedure for ADHD participants. They used the parents version of the Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors (SWAN) (46) to evaluate the continuum from attention problems to attention skills with a seven-point rating scale. After screening, the ADHD diagnosis was defined by Kiddie-SADS-PL (43). The ADHD diagnoses were made by board-certified psychiatrists based on their clinical interview and judgement in two studies (28, 29).

TABLE 2 | Methodological quality assessment of the selected studies-based on Newcastle-Ottawa Scale. In this scale each item could be awarded with a star per section. The number of the stars means the number of the awarded items.

References	Selection	Comparability	Outcome
Barbaresi et al. (21)	***	**	***
Biederman et al. (22)	***	**	**
Caye et al. (10)	***	*	*
Chronis-Tuscano et al. (23)	***	**	**
Gordon and Hinshaw (26)	***	Not available[a]	**
Guendelman et al. (27)	***	**	**
Huang et al. (28)	***	**	***
Hurtig et al. (36)	**	**	**
Lan et al. (29)	****	**	***
Ljung et al. (30)	***	**	***
Miller et al. (31)	***	**	**
Owens et al. (32)	***	**	**
Strandheim et al. (33)	**	**	*
Swanson et al. (34)	***	**	**
Yoshimasu et al. (35)	***	**	**
Forte et al. (20)	**	**	*

[a] *Only descriptive data were available for the suicide attempts (outcome).*

In the study by Forte et al., the teacher version of the Behavior Questionnaire (BQ) was used to evaluate ADHD symptoms. The BQ was developed with the incorporation of items from the Child Behavior Checklist (CBCL) (47), the Ontario Child Health Study Scales (48), and the Pre- school Behavior Questionnaire (49). The BQ contains four items for hyperactivity and three items for inattention symptoms.

Galéra et al. (24) used the CBCL (50) for the measurement of ADHD symptoms. CBCL is a self-reported questionnaire that mainly measures the internalizing and the externalizing dimensions, including attention problems (50). Caye et al. (10) used parent and self-report data of the Strengths and Difficulties Questionnaire (SDQ) (51, 52). The SDQ is a 25-item self-report questionnaire that evaluates behavioral problems and prosociality (51, 52). To define the child ADHD cases, they used a threshold of eight points associated with impairment (10). The SDQ contains four problem scales: emotional problems, conduct problems, hyperactivity problems, and peer problems (52). Strandheim et al. (33) assessed the participants with a 14-item school-adjustment questionnaire to evaluate attention and conduct symptoms.

Measurements of Suicidality

The assessment of suicidality focused on suicidal thoughts, suicidal attempts, or both. Two articles investigated suicidal thoughts (22, 33), six studies assessed only suicidal attempts (10, 21, 28–31), and nine studies investigated both phenomena of suicidal thought and behavior (20, 23–27, 32, 34, 35).

Suicidal Thought

Only two studies investigated on suicide thoughts exclusively. Strandheim et al. (33) used only one screening question ("Have you had thoughts about taking your own life?") to identify the participants with suicide thoughts at the follow-up visit. However, the article by Biederman et al. (22) did not detail the measurements of suicidal thoughts; they used the Kiddie-SADS (43). The suicide ideation and behavior screening interview contains items about thoughts of death, suicidal ideation, presence of suicide attempts, non-suicidal self-harming behavior, and medical lethality and intent associated with a possible suicide attempt (43).

Suicide Attempts

Majority of the selected articles, which investigated only suicide attempts, obtained data from medical records (21, 28–30).

Huang et al. (28) and Lan et al. (29) used a Taiwanese National Health Insurance Research database which includes demographic data, date of visit, disease diagnoses, and medical interventions (28).

By contrast, Barbaresi et al. (21) used medical records to identify the mortality of the participants, including suicide attempts. The infrastructure and the medical data of the study were based on the Rochester Epidemiology Project (38).

In another study, several Swedish nationwide registers were used in the research of Ljung et al. (30); among these, the Swedish National Patient Register (53) was used for the medical records and the Swedish cause of death register (54) to identify the causes of deaths.

Beyond the medical record-based studies, Caye et al. (10) investigated suicide attempts at age 11 years as part of the Pelotas (Brazil) Birth Cohort Study (55) and at 18 age of years as part of the assessment of Major Depression Disorder (MDD), which included the Mini International Neuropsychiatric Interview MDD supplement (56). It was noted that this measurement was based on a self-report setting.

Miller et al. (31) did not calculate an independent number of suicide attempts but created a non-suicidal self-injury (NSSI)/suicide attempt count by summing up the number of NSSI and suicide attempts since the last visit. The questionnaire which measured the suicide attempts was not detailed in the article.

Suicide Thoughts and Suicide Attempts

Gordon and Hinshaw (26), Guendelman et al. (27), Owens et al. (32), and Swanson et al. (34) used the Barkley Suicide Questionnaire (57). This is a self-reported questionnaire which includes the following three questions: "Have you ever attempted suicide?," "Have you ever considered suicide?," and "Have you ever been hospitalized for an attempt?" to evaluate suicide thoughts and attempts. Additionally, the Family Information Profile was used in the follow-up phase, which contains a suicide attempt sub-questionnaire reported by caregivers.

Chronis-Tuscano et al. (23) used the DISC-IV (40) to evaluate suicide attempts at the assessment in year 9 of the follow-up. Through the 6–14 years of the follow-up period, at every annual assessment, the participants and the parents were asked to report suicide attempts or suicidal ideation in the previous 6 months.

In the study of Forte et al. (20), a two-step questionnaire was used to detect suicidal thought and attempts: "In the past

12 months, did you ever seriously think of attempting suicide?" and "In the past 12 months, how many times did you attempt suicide?" if the first answer was positive.

Hurtig et al. (36) evaluated suicidal thought and behavior by the mood disorders section of K-SADS-PL (43), which includes five items for measuring suicidality and self-harm. To maximize the sample size, the authors included "recurrent thoughts of death" and "suicidal ideation" and the items "suicidal acts—medical lethality" and "non-suicidal physical self-damaging acts."

In the study of Galera et al. (24), information was collected from the participants about suicide thoughts or attempts in the follow-up phase. They used a detailed questionnaire about the presence and the frequency of suicidal ideations, suicide plans, and suicide attempts in the previous 30 days/12 months and lifetime.

Goldston et al. (25) investigated suicide attempts, thoughts, and behaviors at baseline and the follow-up period. Suicide attempts, thoughts, and behaviors were assessed by the ISCA (44) interview, and additional information was obtained from treatment/medical records and the parents about the suicide attempts at baseline. In the follow-up period, the ISCA (44) and the FISA (44, 45) were used to evaluate suicide attempts, thoughts, and behaviors since the last visit. Additional information about the dates of suicide attempts was collected from the medical treatment, school, and legal records. In the follow-up period, they used the Lethality of Suicide Attempt Rating Scale (58) to rate the medical lethality of the suicide attempt using a 0–10 scale.

Yoshimasu et al. (35) used the Mini International Neuropsychiatric Interview (59) to evaluate suicide behavior (thoughts and plan) and attempts. Five items rate the suicide thoughts and plan in the previous 1 month, and one item is about the lifetime suicide attempts. They created groups based on the severity of the suicide questions as none (0), low (1–5), moderate (6–9), or high (10+) risk groups (35) where 10 points was calculated in the case of suicide attempts in the last month.

Long-Term Association Between ADHD and Suicidality

Although the number of follow-up visits varied in a wide range among the selected studies, the vast majority of the studies collected data after more than a 5-years follow-up period.

Firstly, we present the articles which investigated the long-term risk of suicidal thoughts (22, 33), after that those ones which investigated suicidal attempts (10, 21, 28–31), and finally studies which measured the presence of both phenomena in children and adolescents with ADHD (23–27, 32, 34–36).

Long-Term Association Between ADHD and Suicidal Thoughts

Strandheim et al. (33) followed up an adolescent cohort population to investigate the presence of suicide thoughts, where 18.7% of the population showed attention problems ($N = 448$). After 17 years of follow-up, the gender-adjusted odds ratio was 1.3 (CI = 1.0–1.7). This odds ratio was lower compared to the anxiety/depressive, conduct problems, and insomnia subgroups.

In an adolescent and young adults female sample, Biedermann et al. (22) investigated the association between ADHD and major depression (MD). They measured the suicide thoughts in four groups: control, ADHD only, MD only, and ADHD + MD. After analyses of the symptom level, there was a significant difference between the ADHD only group and the control group in the rates of suicidal thoughts (68 vs. 43%, respectively; $p < 0.05$).

Long-Term Association Between ADHD and Suicidal Attempts

In a large birth cohort study, Barbaresi et al. (21) focused on the mortality and psychosocial functioning of the adult ADHD population who were diagnosed with ADHD in childhood. Among the mortality rates, there was a significant difference between the number of suicide deaths of the ADHD individuals ($N = 3$ from 367) and the controls ($N = 5$ from 4,946) (standardized mortality ratios for suicide = 4.83, 95% CI, 1.14–20.46; $p = 0.032$).

Another birth cohort study by Caye et al. (10) followed up children with ADHD and controls for more than 7 years. A significantly higher number of self-reported suicide attempts was found in children with ADHD than those without [35 (10%) vs. 213 (6%), $p = 0.003$] and in young adults with ADHD than in young adults without ADHD [75 (15.2%) vs. 180 (5.1%), $p < 0.001$).

Huang et al. (28) focused on the suicide attempts as well of ADHD adolescent patients and age- and gender-matched controls in a population-based, longitudinal cohort study, where the data were derived from health insurance records. The incidences of a first and repeated suicide attempts were significantly higher (0.5 and 0.1%, respectively, both $p < 0.001$) in the ADHD group than in the controls, similarly to the results of Caye et al. (10). At their first suicide attempt, the ADHD patients were significantly younger (19.35 vs. 20.77 years, $p < 0.001$) than the control group. The ADHD patients showed a higher probability to attempt suicide ($p < 0.001$), and the data showed that the ADHD diagnosis was an independent risk factor for any suicide attempt (hazard ratio = 3.84, 95% CI = 3.19–4.62) and repeated suicide act (hazard ratio = 6.52, 95% CI = 4.46–9.53) regardless of the gender and the age subgroup. An interesting finding was that long-term methylphenidate (MPH) treatment showed a significant association with a decreased risk of repeated suicide attempts in the case of ADHD men (hazard ratio = 0.46, 95% CI = 0.22–0.97). By contrast, MPH and atomoxetine did not show a significant association with the first suicide attempts and the repeated suicide attempts.

With a sophisticated register-based design, Lan et al. (29) focused on adolescents and young adults with bipolar disorder and a comorbidity of ADHD. They found the ADHD diagnosis as an independent risk factor for suicide after further adjustment for anxiety disorder (HR: 2.82, 95% CI: 1.38–5.77) and adjustment for disruptive behavior disorders, alcohol use disorders, and substance use disorders (HR: 2.38, 95% CI: 1.13–5.00).

Another register-based study (which used patient and prescribed drug register data) by Ljung et al. (30) assessed the genetic and environmental risk factors of patients with ADHD and their relatives for suicide attempts and completed

suicide. They found suicide attempts of 0.2 vs. 0.02% who had completed suicide, which meant a relatively high risk for suicide attempts [OR = 3.62 (95% CI, 3.29–3.98)] and completed suicide [OR = 5.91 (95% CI, 2.45–14.27)] among patients with ADHD, and this risk remained after adjusting for comorbid disorders.

Miller et al. (31) followed-up pre-adolescent girls with and without ADHD for 10 years and collected data about the number of suicide attempts and the NSSI which were summed for analysis. Limiting the evaluability of the results, only descriptive data were published with regard to the number of suicide attempts. The mean continuous number of the follow-up suicide attempts and NSSI in the comparison group (n = 71–86) were 0.38 (range 0–8; SD = 1.24) and 1.12 (range 0–12; SD = 2.33) in the ADHD group (n = 107–137).

Goldston et al. (25) focused on the relationship between suicide attempts and psychiatric disorders, including ADHD, in an adolescent population who were followed up for 13 years after recruitment following an inpatient admission. Altogether 14.3% of the first suicide attempters and 25.0% of repeated suicide attempters had a diagnosis of ADHD. From adolescence through young adulthood, patients with ADHD showed a greater risk for suicide attempts ($\chi^2 = 6.91$, $p = 0.009$; hazard ratio 2.41). For a broader view, the most prominent risk for suicide attempts was shown by patients with MD, panic disorder, conduct disorder, and substance use. It was noted that, in the multivariate model, the association in the case of ADHD did not remain significant ($\chi^2 = 1.53$, $p = 0.216$; hazard ratio 1.52). A very interesting finding is that the relationship between ADHD and suicide attempts strengthened with the age of the patients.

Long-Term Association Between ADHD and Suicidal Thoughts and Attempts

Regarding those studies, which assessed both suicide thoughts and attempts, Chronis-Tuscano et al. (23) investigated the risk for depression and suicide thought and behavior in children diagnosed with ADHD who were 4–6 years of age and in control participants without ADHD. They followed up the 4–6-year-old children with seven assessments in assessment years 6 to 14 (9–18 years of age). During the follow-up phase, 12.0% of children with baseline ADHD and 1.6% of children without baseline ADHD reported a concrete suicide plan ($\chi^2 = 5.38$, $p < 0.03$; hazard ratio 5.79). In the case of suicide attempts, 18.4% of patients with ADHD and 5.7% of the control group had a suicide attempt ($\chi^2 = 8.26$, $p < 0.005$; hazard ratio 3.60). For subgroups, only the combined subtype of baseline ADHD (ADHD-C) had a greater risk for concrete suicide vs. the controls ($\chi^2 = 6.52$, $p < 0.02$; hazard ratio 7.19); however, the hyperactive–impulsive (ADHD-HI) subtype ($p < 0.06$) and the inattentive (ADHD-IT) subtype ($p = 0.99$) had no greater risk for concrete suicide ideation than the participants without ADHD. Baseline ADHD-C ($\chi^2 = 6.42$, $p < 0.02$; hazard ratio 3.20) or ADHD-HI ($\chi^2 = 4.12$, $p < 0.05$; hazard ratio 3.37) also had a greater risk for suicide attempts than the control group. Consistent with the findings of Biedermann et al. (22), children with ADHD diagnosis at ages 4–6 years have a greater risk for MD through adolescence. Additionally, the maternal depression of the group having ADHD at baseline showed a greater risk for concrete suicide ideation during the follow-up ($\chi^2 = 9.55$, $p < 0.05$; hazard ratio 2.57).

Galéra et al. (24) followed up a 7–18-year-old community sample after 8 years. It was noted that the participants were measured with a hyperactivity symptoms scale; no ADHD diagnostic tool was used. In total, based on a multiple logistic regression model, the childhood HI-s had a greater risk for lifetime suicide plans or attempts (OR = 3.25, 95% CI = 1.26–8.40) and 12-months suicide plans or attempts (OR = 5.46, 95% CI = 1.16–25.81). The correlation was independent of both externalizing and internalizing problems and regular cannabis smoking as well.

As mentioned before, Gordon and Hinshaw (26), Guendelman et al. (27), Owens et al. (32), and Swanson et al. (34) conducted analyses taken from the same study population [for details, see Hinshaw et al. (37)], where the participants were pre-adolescent girls diagnosed with combined and inattentive-type ADHD and assessed without ADHD at baseline while unmedicated.

Gordon and Hinshaw (26) focused on parenting stress as a possible mediator between ADHD and young adult outcome in a 5- and 10-years follow-up setting. There were more suicide attempts in the ADHD group than in the control group after a follow-up [17.1 vs. 5.1%, χ^2 (1, N = 199) = 6.30, $p < 0.05$]. The data assessment did not show a correlation between the number of suicide attempts and parental distress ($p = 0.13$) or stress-inducing dysfunctional parent–child interactions ($p = 0.11$).

Guendelman et al. (27) investigated the role of maltreatment experience (physical abuse, sexual abuse, or neglect) in childhood and/or adolescence in the future outcome of internalizing symptoms and suicidality. The authors found a greater risk for suicide in the ADHD group, where maltreatment was experienced [33 vs. 12.8%; χ^2 (1, N = 124) = 6.59, OR = 1.85, 95% CI = 1.14, 3.00; $p = 0.01$]. Additionally, this group showed a greater impairment in internalizing symptomatology (anxiety and depression), eating disorder symptomatology, and self-esteem. The analyses of covariance (age, socioeconomic status, prenatal risk, adopted, or in foster care, baseline depression/dysthymic disorder, or anxiety disorder) revealed that the difference between maltreated and non-maltreated suicide attempts was significant (Wald = 5.55, $p = 0.02$).

Owens et al. (32) performed a wave three follow-up period to 16 years to evaluate the functional and symptomatological outcome of the female participants diagnosed with ADHD in childhood in 10 domains including self-injury. The baseline ADHD group was divided into three subgroups based on the persistence of the ADHD diagnosis at the follow-up visits: "desisters," "partial," and "persisters." The number of attempted suicides was less frequent among participants in the control (6.1%) and the desister groups (3.4%) than in the partial (23.7%) or the persisters groups (27.4%) (df = 3, 197; $F = 17.01$; $p < 0.001$). In the pairwise comparisons, the partial (OR = 5.0) and the persistent (OR = 5.8) groups showed higher rates in suicide attempt than the comparisons. However, a relatively large odds ratio showed in partial vs. desisters (OR = 9.0) and persisters vs. desisters (OR = 10.6); there was no significant difference because of the small sample size.

Swanson et al. (34) assessed the dates derived from the previously mentioned follow-up population and focused on the possible mediating factors between ADHD and NSSI or suicide attempts. The authors divided the participants in two ways of grouping: firstly, ADHD-C, ADHD-IT, and comparisons; secondly, transient ADHD group, persistent ADHD group, and lifetime non-diagnosed group. The rates of suicide attempts were significantly higher in the ADHD-C group (22%) than in the ADHD-IT group (7%, OR = 3.5) and comparisons (6%, OR = 4.5). In the case of longitudinal grouping, the persistent ADHD group (22%) reported more suicide attempts than the comparison group (4%, OR = 6.7), but not the transient group (13%, OR = 2.0). In the bootstrap mediator analyses, the data showed a significant positive correlation between baseline ADHD status and future suicide attempts [$b = 0.28$, standard error = 13, $t_{(195)} = 4.12$, $p < 0.001$, $R^2 = 0.08$] and in the 5-years follow-up. The authors reported the internalizing symptoms as a partial mediator between baseline ADHD status and future suicide attempts (indirect effect = 0.11, SE = 0.05, 95% CI = 0.03–0.25).

In another longitudinal study, Hurtig et al. (36) investigated suicide thoughts and acts in a birth cohort population with and without ADHD after a 16-years follow up. In this population, the ADHD diagnosis of the participants was associated with suicidal thoughts ($n = 53/104$ vs. n = 40/169), with 6.1 OR (95% CI 2.34–16.0). On the other hand, the number of suicidal acts was low in both groups, without a significant difference (6/104 vs. 4/169, $p = 0.855$).

Finally, Yoshimasu et al. (35) followed up an ADHD birth cohort through adulthood. They found a significantly higher rate of suicidality in the group of childhood ADHD (22%) than in non-ADHD participants (10.4%) ($p < 0.001$, OR = 2.42; 95% CI = 1.51–3.86).

Gender Differences in the Association Between ADHD and Suicidality

Regarding gender differences, we overviewed the included studies which investigated a mixed-gender population.

The objective of the study by Forte et al. (20) focused on the sex differences in the context of suicidality and ADHD symptoms with a 17-years follow-up design. Regarding the symptoms, the authors identified low, moderate, and high ADHD trajectories. After the comparison of the trajectories, only boys showed a prominent risk for suicide ideation (moderate vs. low, OR 4.4, 95% CI 1.3–15.1; high vs. low, OR 3.9, 95% CI 1.0–14.9); however, only higher trajectories showed differences vs. low trajectories regarding suicide attempts (OR 4.5, 95% CI 1.1–17.9).

By contrast to these findings, in the study of Strandheim et al. (33), the odd ratios of having suicide thoughts did not show robust differences between genders (boys aOR = 1.3, 95% CI = 0.8–2.1; girls aOR = 1.2, 95% CI = 0.8 to 1.8) among the ADHD participants; however, the follow-up period was only 4 years, compared with that of the previous study which was 17 years (19).

Chronis-Tuscano et al. (22) reported no gender differences ($p = 0.17$) in the case of a concrete suicide plan, but the girls showed a greater risk ($\chi^2 = 3.89$, $p < 0.001$; hazard ratio 7.37) for suicide attempt than the boys in the same group at 1-year follow-up period in a Cox modeling method. It was notable that the participants were only 5–7 years old at the first year of follow-up.

In the study of Galéra et al. (23), the HI-s boys showed a higher risk of suicide plans or attempts ($p = 0.02$) in a lifetime period than HI-s girls. Neither in male nor in female groups was there a higher risk of suicide ideation in the lifetime and the 12-months period. It was noted that the authors measured just the presence of hyperactivity symptoms; the participants had no established ADHD diagnosis.

Following was a register-based study of Ljung et al. (29), where female patients showed almost twice as much risk for suicide attempts than males [OR = 5.41 (95% CI, 4.60–6.36) vs. OR = 2.93 (95% CI, 2.60–3.29), $\chi^2 = 1{,}271.0$; $p < 0.001$)].

Role of Comorbidity in the Association Between ADHD and Suicidality

In our review, we found that four of the selected studies included measures of comorbidities in the data analysis.

Biedermann et al. (22) investigated the association of ADHD and MD in adolescent and young adult females. Females with ADHD had a greater risk for MD than the control group [65% ($n = 80$) vs. 21% ($n = 23$)]. The ADHD group showed more than double the risk (HR = 2.5, 95% CI 1.5–4.2; $p < 0.01$) for lifetime MD than the control group after adjustment for comorbid conditions. Following a symptom-level analysis, the ADHD group had a higher rate of suicidal ideation (68 vs. 43%, respectively; $p < 0.05$). For a broader view, MD combined with ADHD showed a greater duration of MD, with more severe MD-related impairment than in controls with MD only.

In the study by Lan et al. (29), data showed that the patients with ADHD and bipolar disorder had a significantly higher incidence of suicide attempts (3.0 vs. 1.1%, $p = 0.005$) than the group with bipolar disorder. Based on the Kaplan–Meier survival analysis, the risk of suicide attempts is greater ($p = 0.002$) in the group of patients with ADHD and bipolar disorder than in patients with bipolar disorder only.

The effect of the psychiatric comorbidities in relation to childhood ADHD diagnosis and suicide thought and behavior was the objective of the study of Yoshimasu et al. (35). In observing the effect of childhood ADHD on suicidality, they found a significant direct effect between the two phenomena ($p < 0.001$, OR = 2.58, 95% CI = 1.54–4.31). Based on the data, the three most prominent comorbid disorders that have a direct effect as a percent change of the total effect were as follows: MDD (25.7%), hypomanic episode (18.3%), and dysthymia (18.1%). They also calculated an expected joint effect to evaluate the synergic (OR exceed the expected OR) or independent effect of ADHD and other psychiatric comorbidities. The data showed a significant synergic effect between generalized anxiety disorder (expected OR = 4.86, OR = 10.94; 95% CI, 4.97–24.08), hypomanic episode (expected OR = 2.66, OR = 7.40; 95% CI, 3.48–15.77), and substance-related disorder (expected OR = 3.02, OR = 6.62; 95% CI, 3.15–13.91).

Finally, Caye et al., in their birth cohort study, reported a higher rate of comorbidities in young adulthood in those participants who had an ADHD diagnosis in childhood. A

significantly higher number of self-reported suicide attempts was found in children with ADHD than those without [35 (10%) vs. 213 (6%), $p = 0.003$] and in young adults with ADHD than in young adults without ADHD [75 (15.2%) vs. 180 (5.1%), $p < 0.001$]. These differences remained significant after excluding the comorbidities from young adults with and without ADHD [17 (6.6%) vs. 101 (3.5%), $p = 0.01$].

DISCUSSION

To our knowledge, this is the first systematic review on the topic of ADHD and suicidality including studies with follow-up design exclusively. By this method, our objective was to summarize the current literature findings to provide an additional perspective and a better understanding of the long-term cause–effect relationship between ADHD and suicidality.

In spite of the methodological heterogeneity of the included studies, which limits conclusions about the suicide risk of ADHD patients, there have clearly been major advances in the available studies with follow-up design. Based on these studies, there is now strong evidence that there is a positive association between the presence of ADHD diagnosis at baseline and having suicidal thoughts and/or attempts at follow-up visits.

In our systematic review, we could identify 18 studies with follow-up design which investigated the suicidal risk of ADHD patients (10, 20–36). The methodology of the selected studies shows a wide heterogeneity. From the 18 selected studies, 14 used a standardized method to establish the diagnosis of ADHD, including standardized measurement or reliable medical data (21–23, 25–32, 34–36). The other four studies measured ADHD symptoms in a dimensional approach without an established ADHD diagnosis, which limits the interpretation of these results.

For suicide measuring instruments, only half of the studies investigated both suicide thoughts and attempts (20, 23–27, 32, 34, 35). After excluding one study based on medical records, only five studies (10, 23–25, 35) used a detailed questionnaire for identifying suicide thoughts, ideation, or attempts. Suicide behavior can be interpreted along a continuum, as it consists of passive ideation, active intent, and specific plan (60). Measuring these elements together could elevate the interpretability of the data in the future.

Regarding our descriptive findings, the majority of the studies (10/18) are from North America; however, four of them collected data from the same population sample. The selected studies investigated only 10 separate populations. The data were derived from clinical samples (22, 23, 25–27, 31, 32, 34), register-based data (28–30), data from community samples (10, 20, 24, 33), and data from birth cohorts (21, 35, 36); however, the majority of the samples were derived from clinical samples (8 of 18). Five of these eight studies (26, 27, 31, 32, 34) from a clinical population followed up the same study population (37). The two register-based prospective studies assessed children from the same birth cohort (38).

The majority of the studies (12/18) assessed population from both sexes (10, 20, 21, 23–25, 28–30, 33, 35, 36); however, we found a relatively low number of studies that examined a population with balanced gender ratios (10, 20, 24, 25, 33).

Although ADHD is more prevalent among boys than girls, none of the selected studies investigated a male population only; however, one-third (6 of 18) of the studies followed up female participants only (22, 26, 27, 31, 32, 34).

Although the age of the study populations at baseline was mostly (10/18) under 12 years, the included studies covered a wide age range at the final follow-up visits.

Although the higher retention rate in child or adolescent longitudinal studies challenges the long-term design and an eligible sample size, except for one study (33), the followed-up period was longer than 5 years; moreover, the majority of the studies had a 5- to 10-years follow-up period.

In the case of measurement of suicidality, the most assessed domain was suicide attempt. Altogether 14 of the selected 18 articles assessed suicide attempts, of which 13 of them reported a significant association with baseline ADHD symptoms. Despite the fact that, among these studies, 12 used available data from detailed statistical probes, our results highlighted the growing evidence of the elevated risk of ADHD for later suicide attempt.

Regarding suicidal thoughts and plans, six studies published data, of which five reported a significant risk context of the baseline ADHD symptoms. Childhood ADHD diagnosis is deemed to be a significant risk factor for future suicide deaths; however, only a few (21, 30) longitudinal studies in child and adolescent populations are available in the current review on this topic.

These results are consistent with the recently published systematic reviews and meta-analyses, which mainly focused on a wide range of population of adults, adolescents, and children with ADHD and a cross-sectional design, and found a positive correlation between ADHD and suicidality (15, 17).

The selected studies showed a significant range in terms of the heterogeneity of different methodologies. However, the majority of the studies used standardized ADHD diagnostic tools or medical data (21–23, 25–32, 34–36); a majority of the selected articles investigated ADHD symptom severity scales (10, 20, 24, 33). The differences between the interpretation of the categorical and the dimensional symptom estimation could complicate the understanding of the results.

A selective review by Giupponi et al. (18) suggested a correlation between ADHD and an increased risk of suicidal ideation and attempts in adolescent and child populations, although they found a controversial direct connection between ADHD and suicidal thought and behavior (18). The non-systematical review of James et al. (13) focused on psychological autopsy studies and long-term follow-up studies of ADHD children, children, adolescents, and young adults. The data suggest an association between ADHD and completed suicide, especially for younger males. Impey and Heun (16) found that ADHD diagnosis is more frequent in "suicidal groups" than in controls, and suicide thought and behavior were more common in prediagnosed groups than in controls. A current systematic review by Balázs and Keresztény (15) concluded a positive association between ADHD and suicidal thought and behavior in all age groups and in both sexes.

Among the risk factors of suicidality, in this review, we focused on psychiatric comorbidities in two ways: We evaluated the risk for developing comorbid disorders in ADHD population. Two studies (22, 35) reported an elevated risk for the development of MD in ADHD. These data delineate the predictor role of ADHD for future MD and suicide thought and behavior, which is consistent with two other previous reviews (61, 62). These findings suggest some overlap between ADHD and MD and support the possible mediator role of MD between ADHD and suicidality.

However, there are no clear data on the role of comorbidities in suicide in ADHD population. James et al. (13) estimated that having the ADHD diagnosis may increase the risk of suicide in males by increasing the severity of comorbid conditions, particularly conduct disorder and depression. Balázs and Keresztény (15) conclude the mediator role of comorbid conditions between ADHD and suicidality.

Among the selected articles of the current review, two studies investigated the effect of comorbid conditions in suicidal thought and behavior in an ADHD population. Yoshimasu et al. (35) evaluated a direct effect between ADHD and suicidality and other comorbidities, i.e., GAD, hypomanic episode, and substance use disorder had a synergic effect for future suicidality. In contrast, Swanson et al. (34) identified a partial mediator role of the internalizing disorders in the context of suicide in ADHD patients. We should highlight that these two studies differ in the gender ratio, which can be a possible explanation of the co-occurring disorders with ADHD.

A further important topic among the objectives of this review was to investigate the risk of suicide in patents with symptoms of ADHD in the context of sex differences. Previously, Nigg et al. (14) reported an association between ADHD and an elevated risk of suicide attempts (particularly in girls) and lethal suicide attempts (particularly in boys). Among the selected articles of the current review, four studies published data on sex differences in suicide thought and behavior. The results by Ljung et al. (30) showed a nearly doubled risk of suicide attempts for ADHD girls than boys. Forte et al. (20) and Galera et al. (24) also conclude a significant risk for suicide thoughts and attempts only in boys with ADHD symptoms, but there was no established ADHD diagnosis. However, the former authors reported an elevated risk for suicide attempts only in ADHD males with more severe symptoms. In contrast, Chronis-Tuscano et al. (23) evaluated a greater risk for suicide attempts for girls after the first year of follow-up with Cox modeling, when the participants were only 5–7 years old. This limited finding raises the question on the severity of symptoms and the number of suicidal thoughts that may vary at different rates during the course of growing up. In our results, the importance of monitoring suicidal thought and behavior emerges, especially in individuals with ADHD in both genders. However, there are methodological differences between these studies, especially in terms of the sex ratio and the methodology of ADHD diagnosis vs. symptoms monitoring.

Focusing on the persistence of ADHD, two studies were included in our review (32, 34); however, the data of both studies were derived from the same female population (37). Interesting findings suggest that patients with persistent ADHD symptoms showed a greater risk for suicide thought and behavior. However, as these studies included only female participants and did not include ADHD participants only with hyperactivity symptoms, further studies are needed in the future.

In the case of ADHD subtypes, Chronis-Tuscano et al. (23) found a greater risk for suicide in the combined ADHD group only. Surprisingly, the HI and IT subtypes showed no elevated risk for future suicide thought and behavior. Consistent with this finding, Swanson et al. (34) reported an elevated suicide risk only in ADHD-C type, although the sample did not include ADHD-HI participants and boys.

These limited findings raise the possibility that children with ADHD may form an inhomogeneous group as a possible suicide risk factor. Our findings suggest that ADHD comorbidities, especially MD, combined type of ADHD, and persistence of the symptoms play a significant role in future suicide thought and behavior.

Long-term data about the effect of ADHD treatment on suicidality in childhood or adolescence are limited. Only one study (63) examined the effect of ADHD drug treatment and medication (methylphenidate and atomoxetine) on suicidality and found that it did not increase the risk of a suicide attempt. Our limited results also highlighted the importance of early detection and adequate treatment of ADHD cases.

Based on our review, we have the following methodological suggestions for future studies: (1) monitoring the ADHD symptom persistence and severity, (2) using more sophisticated suicidal thought and behavior (including thoughts, intentions, plans, and attempts) measurement tools, (3) monitoring the treatment of ADHD at a longitudinal setting, and (4) identifying the comorbidities, especially of MD, in participants.

LIMITATIONS

Among the selected studies, only one published data about the treatment of ADHD highlighted the importance of ADHD treatment which could even decrease the symptoms of depression and the number of harmful outcomes (64), including suicide thought and behavior. Our results are limited for us to be able to evaluate the effect of ADHD treatment on suicidality.

Further limitations are derived from the method of the study selection. Firstly, among the search terms that we used, the ADHD terms to find the relevant articles with participants who met the ADHD diagnosis did not minimize the symptoms-only related articles. Secondly, we performed the database search with terms of suicidal behavior. We did not add the terms "self-harm" or "self-injury" to focus on suicidal topics and minimize the articles that investigated non-suicidal self-harm or self-injury. These limitations are the cause that we may be missing some relevant studies on this topic.

CONCLUSION

In conclusion, our results, based on follow-up studies, underline the growing evidence of higher later suicidal risk of children and adolescents with ADHD. In the future, there is an additional need to clarify the role of treatment, comorbidities, subtypes, and persistence of ADHD in suicide thought and behavior. We would like to highlight the importance of the early diagnosis and treatment of ADHD, and during treatment, we need to pay special attention to comorbid conditions, especially anxiety and depression symptoms in boys.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

PG: article selection process, presentation of the results, and discussion. JB: supervising the selection process and the presentation of the results and discussion. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Detecting Suicide and Self-Harm Discussions Among Opioid Substance Users on Instagram Using Machine Learning

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Background: Suicide and substance use disorder (SUD) pose serious public health challenges among young adults in the United States. Increasing social media use among these populations can be leveraged as an alternative method to detect characteristics of suicide-related topics and behavior among substance users.

Objective: To detect and characterize suicide and self-harm related conversations co-occurring with SUD posts and comments on the popular social media platform Instagram.

Methods: This study used big data and machine learning approaches to collect and classify Instagram posts containing 632 controlled substance-related hashtags. Posts were first classified for online drug diversion topics and then filtered to detect suicide and mental health discussions. Posts and comments were then manually annotated for SUD and mental health co-occurring themes. Associations between these characteristics were tested using the Chi-square test.

Results: We detected 719 Instagram posts/comments that included user-generated discussions about suicide, substance use and/or mental health. Posts self-reporting SUD and mental health topics were also more likely to discuss suicide compared to those that did not discuss SUD and mental health topics, respectively ($p < 0.001$). Major themes observed included concurrent discussions of suicide ideation and attempts and low self-esteem.

Conclusions: Our study results provide preliminary evidence of social media discussions about suicide and mental health among those with SUD. This co-occurrence represents a key health risk factor on a platform heavily utilized by young adults. Further studies are required to analyze specific patterns of suicide and self-harm ideations for the purposes of designing future suicide prevention campaigns through digital channels.

Keywords: suicide, substance abuse, social media, Instagram, opioids, machine learning

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INTRODUCTION

The recent National Vital Statistics Reports (1) has ranked suicide as the second most common cause of death in 10–24 year olds, equating to 47,173 deaths in 2017 (1). In this age group, young adults (18–25 years old) had the highest prevalence of suicide attempts and have also been identified as the largest group of prescription opioid abusers (2). The human toll of the opioid epidemic is also apparent, with more than 70,000 deaths due to drug overdose reported in the U.S. in 2017, out of which more than 65% were related to opioids (3). Importantly, the probability of suicide ideation and attempts were higher in those with increased prescription opioid misuse (4).

Substance use tends to coexist with mental health illnesses and different co-occurrence of mental health issues. For example, individuals attempting suicide can have past or current experiences with substance use disorder (SUD) while also suffering from underlying mental health problems. This includes important interaction points between SUD and mental health status, such as experiencing depression following a failed attempt at successful drug treatment or going through withdrawal (5, 6). In fact, prior studies have reported a 2–3-fold higher risk of suicide associated with substance use among populations who also have mental health illnesses (7). Non-suicidal self-harm, cannabis use, and other illicit substance use have also been reported as the strongest predictors behind the transition from suicide/self-harm ideation to suicide attempts (8).

Concomitantly, according to the Pew Research Center, social media use is widespread among young adults, including for the popular picture and video sharing site Instagram owned by Facebook (67% of 18- to 29-year olds report use of Instagram) (9). These social networking sites have emerged as platforms for sharing thoughts, beliefs or behaviors related to both suicide ideation and SUD, with several high-profile cases leading Instagram to implement reporting tools for content related to suicide or self-injury (10). This includes reports of a Malaysian teen attempting suicide after posting a poll on Instagram of whether to choose life or death (69% of respondents suggested death) and the case of 14-year-old Molly Russell from the United Kingdom who attempted suicide after viewing content about suicide on Instagram in 2017 (10, 11). In response to these events, Instagram has pledged to remove images and drawings related to suicide from its platform and blocks searches for certain suicide-related hashtags (12).

Despite growing debate regarding suicide and self-harm activities posted to social media, young adults also use these platforms to self-report other mental health problems such as depression, anxiety, and bipolar disorder, separate from suicide and self-harm discussions, while also discussing SUD topics, such as opioid abuse (13). This user-generated content can help researchers identify latent and emerging behavioral themes at the intersection of SUD and mental health, which may not otherwise be detectable or reported in a timely manner through other survey instruments. In response, this study aims to detect and characterize suicide and self-harm related conversations associated with opioid discussion among Instagram users using big data and machine learning to better understand the interaction between these two crucial public health challenges.

METHODS

This study was conducted in three phases: (1) data collection; (2) supervised machine learning classification; and (3) text filtering and manual content analysis. Each phase is described below.

Data Collection

A web scraper was developed in the Python programming language to collect data from the Instagram platform. Instagram posts were then filtered for 632 hashtags related to opioids and other controlled substances with posts collected between July–October 2018. Data was collected as part of a prior published study examining illicit online drug diversion and dealing (14). This dataset yielded user-generated social media conversations about SUD (e.g., users seeking access to drugs, discussing experiences with drug use, etc.) and posts containing illegal drug dealing and selling activities. The original purpose of the published study was to identify and characterize illicit sellers of opioids, other controlled substances, and illicit drugs, but also contained SUD behavioral-related posts and comments of interest. These posts and comments were used in this study for the purpose of identifying and characterizing topics related to SUD and mental health. Data cleaning and processing of our dataset included removing duplicate results of posts and eliminating posts and comments with special characters (except # which represents hashtags), hyperlinks and stop words.

Supervised Machine Learning

The prior study's dataset that was used in this study employed a supervised machine learning classification approach to detect Instagram posts associated with illegal opioid drug selling and diversion. Specifically, the study used the package Pytorch in Python to develop a deep learning algorithm deploying Long-Short Term Memory (LSTM) and achieved a high accuracy of classification for the detection of illicit drug sellers (i.e., user accounts offering the direct sale of a controlled substance to consumers) (14). A manually annotated set of data was divided into a training set and a validation set to evaluate the performance of the deep learning model along with three other supervised machine learning models. The deep learning model yielded the highest performance among the models evaluated, resulting in a final dataset of 1,228 posts that were confirmed as involved in illegal online drug selling (14). The area under the curve (AUC) was calculated for: (i) text with hashtags; (ii) hashtags only; and (iii) text without hashtags in order to evaluate model performance. The highest AUC was observed for texts without hashtags (99.12%) followed by text with hashtags (98.12%) and only hashtags (94.32%) (14). These posts classified by our deep learning model formed the basis for further exploration of mental health and suicide topics that might be co-occurring in this population of drug sellers and the users they interact with per the aims of this study.

Keyword Filtering and Content Analysis

Based on the machine learning approach described above, all posts and comments interacting with user accounts identified as engaged in illegal online drug selling were further filtered for specific keywords associated with suicide including: "suicide," "suicides," "#suicide." After this additional keyword filter was applied, all posts and comments were then manually annotated by first and second authors based on the descriptive language, hashtags and/or images contained in the post or comment. An inductive coding scheme was used for content analysis and also served as our inclusion and exclusion criteria. The coding scheme included a binary classification of whether the post/comment discussed self-reported substance use behavior, suicide and/or self-harm or other mental health discussions (see **Supplementary Material** for detailed description of coding schema). The posts were also manually annotated for specific co-occurring SUD and mental health themes. For inconsistent results, authors reviewed and conferred on the correct classification. Content analysis was followed by Chi-square tests to examine if the proportion of posts containing suicide discussions varied among: (i) substance use related and non-substance use related posts; and (ii) mental health related and non-mental health related posts. Statistical analysis was conducted using Rstudio version 3.6.1 and a p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 56,464 Instagram posts and comments were collected for analysis over a 4-month period from July 2018 to October 2018. Using the machine learning approach described above, 1,228 illegal drug diversion posts were first identified. Further text filtering for suicide-related keywords/hashtags yielded 719 posts that were characterized using manual annotation for the following primary study areas of interest: (1) self-reported substance use behavior; (2) suicide and/or self-harm; and (3) other mental health discussions. The posts were also annotated for discrete as well as concurrent conversations (i.e., substance use in combination with suicide, substance use in combination with mental health discussions, suicide in combination with mental health discussions). Forty-three percent ($n = 315$) were confirmed as "signal" content (i.e., related to at least one study area of interest) with 107 posts 34% discussing suicide either discretely (see **Table 1**) or concurrently with substance use or other mental health discussions (see **Table 2**).

In relation to concurrent substance use, suicide and mental health discussion, 52 messages (16.5%) discussed suicide and substance use, 66 messages (21%) included suicide co-occurring with mental health, and 43 messages (13.7%) had simultaneous discussion of substance use and other mental health-related problems (see **Figure 1** for examples). Thirty-two messages (10.2%) discussed suicide, substance use and mental health problems concurrently. A chi-square-test of independence showed that there was a significant association between (a) suicide and substance use; and (b) suicide and mental health discussions. Posts containing signal for substance use were more likely to have positive signal for suicide compared to non-substance use related posts, $X^2\ (1, N = 660) = 131.39, p < 0.001$. Posts containing signal for mental health discussions were more likely to have positive signal for suicide compared to non-mental health related posts, $X^2\ (1, N = 660) = 161.14, p < 0.001$.

The common prevailing themes that were observed based on the text of the user-generated posts/comments included concurrent discussion of the struggles of addiction leading to mental health challenges, self-harm or suicide ideation with substance use mention along with discussion about depression, concerns regarding lack of substance use treatment efficacy, low self-esteem, and lack of needed social support for mental health care. Posts specific to signal for mental health problems most commonly discussed depression, anxiety and panic attacks with the majority of posts discussing depression along with anxiety. The majority of the signal related to discrete posts on suicide included self-reported attempts of suicide or self-harm or ideations toward the same. Posts with concurrent signal for suicide and substance use discussed intended as well as inadvertent overdosing along with suicide ideation. Posts with concurrent signal for suicide and mental health problems revolved around the social stigma associated with mental health and a lack of peer support leading to a feeling of hopelessness and suicide ideations. Other concurrent discussions on substance use and mental health problems reflected a vague dependence on substance use and lack of belief in seeking professional help for mental health problems.

DISCUSSION

The results of this study serve as a preliminary evidence about the existing themes around suicide/self-harm ideations concurrent with substance use and mental health illnesses as expressed by users on Instagram, an extremely popular social media platform with a large population of young adult users. While preliminary, the study evidences interaction of these themes in the digital community of Instagram users, adding important insight to current lack of robust data on the interaction between SUD behavior and suicide ideation, which can serve as a starting point in developing surveillance and prevention approaches that more specifically address this co-occurrence. Evidencing the lack of available data on suicide, the World Health Organization reports good quality vital registration data in only 80 member states that can be used to assess suicide rates (15). Hence, innovative surveillance strategies are important to augment existing data and monitor suicide and suicide/self-harm attempts, including methods leveraging technology, "infoveillance," and similar syndromic surveillance approaches (16). Specifically, data mining of self-disclosed conversations on social media can help in understanding the relationship between suicide and SUD that is not apparent in data available from traditional survey and national health registries.

However, rising social media interaction and exposure to information and peers relating to SUD, suicide, and other mental health issues remains an understudied topic. Other studies found social media advertisements on sites such as

TABLE 1 | Number of posts related to substance use behavior, suicide and/or self-harm, other mental health discussions (text of posts have been modified to de-identify from user, no user information reported).

Theme[a]	Posts[b]	Example conversation[c]
Suicide/self-harm	107 (34.0)	*"i was attempting to die last night lived through suicide last night"*
Substance Use	89 (28.3)	*"I can't hold on till summer so that I can get fked up and do cocaine or whatever 💔 #antixanax #lilxan #xanarchy #diegoleanos #heartbreaksoldier #cocaine @xanxiety"*
Mental health discussion	119 (37.8)	*"I want to kill myself . . . . . depression#destroying #anxiety #suicide #messedup #sorry #acting #crying #world #hate #notfine #tired #left #broken #falling #self-harm #neverenough #scars #empty #unloved #imperfections #drug #sober #recovery #disorder #smoking #drunk #ciggarettes"*

[a] *Discrete or concurrent signal.*
[b] *Number of posts and the percentage of total signal posts that contained the theme.*
[c] *Instagram posts/comments with signal.*

TABLE 2 | Number of posts with co-occurring discussions related to substance use behavior, suicide and/or self-harm, other mental health discussions (text of posts have been modified to de-identify from user, no user information reported).

Theme[a]	Posts[b]	Example conversation[c]
Suicide concurrent with substance use	52 (16.5)	*"I'm trying to get the most high I can get before I overdose and stop living . . . . #polishgirl #pills #drugaddict #drugs #xanax #xanaxfamily #death #sad #sadgirl #depression #sadness #alone #dank #perscriptiondrugs #junkie #addicted #suicide #suicidal #aesthetic #psycho #goth #emo #killme #ftp #satan #hell #praisethedevil"*
Suicide concurrent with mental health discussion	66 (21.0)	*"I had another difficlut night, Panic Attack, Depression, Tinnitus so loud!, veins in front of face hurt me so much, Anguish is rip me a part, Nightmare on my parents, Screaming out, little Seizure! Singing in Dreams, Heartbeat so faster, Anxiety so back! As Stress!! Suicide mode, tears out but stuck it! And I am stuck at house with not having courage to get out of my room, Almost seven months out of Drugs such as Xanax, and 14 months out of Zyprexa, and yet this sickness, like being the first months out of Drugs! And not seem Improvements, seem not possible to get back to normal life, maybe I didn't having one. So gotta live with or Drugs or gotta Die this winter? Why can see the the light of this Tunnel? I love u, but pain is so much that I to do something, Drugs? Or Death? And not see others nice"*
Substance use concurrent with mental health discussion	43 (13.7)	*"I took 17 different psychiatric drugs over 25 years and life sucked too much/ ignorance is bliss? Not so. But I believed the doctors knew better. I got off all those meds last August and now use only weed as medicine. Sooooo much cheerful and healthier as a consequence and greatly lowered my risk of Alzheimer's dementia depression suicide impotence oversleeping weight gain lethargy.... #bigpharmakills #bigpharmasucks #psychmedskill #antidepressants #zoloft #zyprexa #adderrall #ativan #wellbutrin #klonopin #weed #marijuana #cannabisismedicine #weedismedicine #psychiatry"*

[a] *Discrete or concurrent signal.*
[b] *Number of posts and the percentage of total signal posts that contained the theme.*
[c] *Instagram posts/comments with signal.*

Instagram and Twitter increase the odds of teens being exposed to drug use and thereby influence risky behaviors such as self-harm and suicide ideations (17). The preliminary findings of this study indicate that concurrent discussion of substance use and suicide or mental health problems are taking place on Instagram, despite the platform's pledges to remove such content in the wake of real-world tragedies involving its users. Though a controversial topic, conversations on social media sites can also aid in monitoring and identifying suicide among high-risk groups on a larger scale when combined with machine learning approaches. Further, the underlying characteristics of social media conversations on suicide ideation and SUD can be translated into targeted offline and online suicide prevention strategies that are more nuanced to SUD population and those engaged in online activity. Identifying co-occurrence of substance use disorders, suicide/self-harm and mental health problems can also help in designing future prevention tools that can be targeted for addressing co-morbidities of SUD and suicide simultaneously, while also stratified for the needs of different user populations. Other studies have provided evidence of this potential, with social media serving as a potential platform for designing suicide prevention strategies (18) and using social media data to help develop mobile health technology interventions for suicide, both approaches that can potentially benefit from our study results (19).

LIMITATIONS

This study has some limitations. The results of this study are not generalizable as the user characteristics have not been defined and the data collection was limited to a short period of four months (July–October 2018). Although the results reflect upon a specific set of social media users associated with

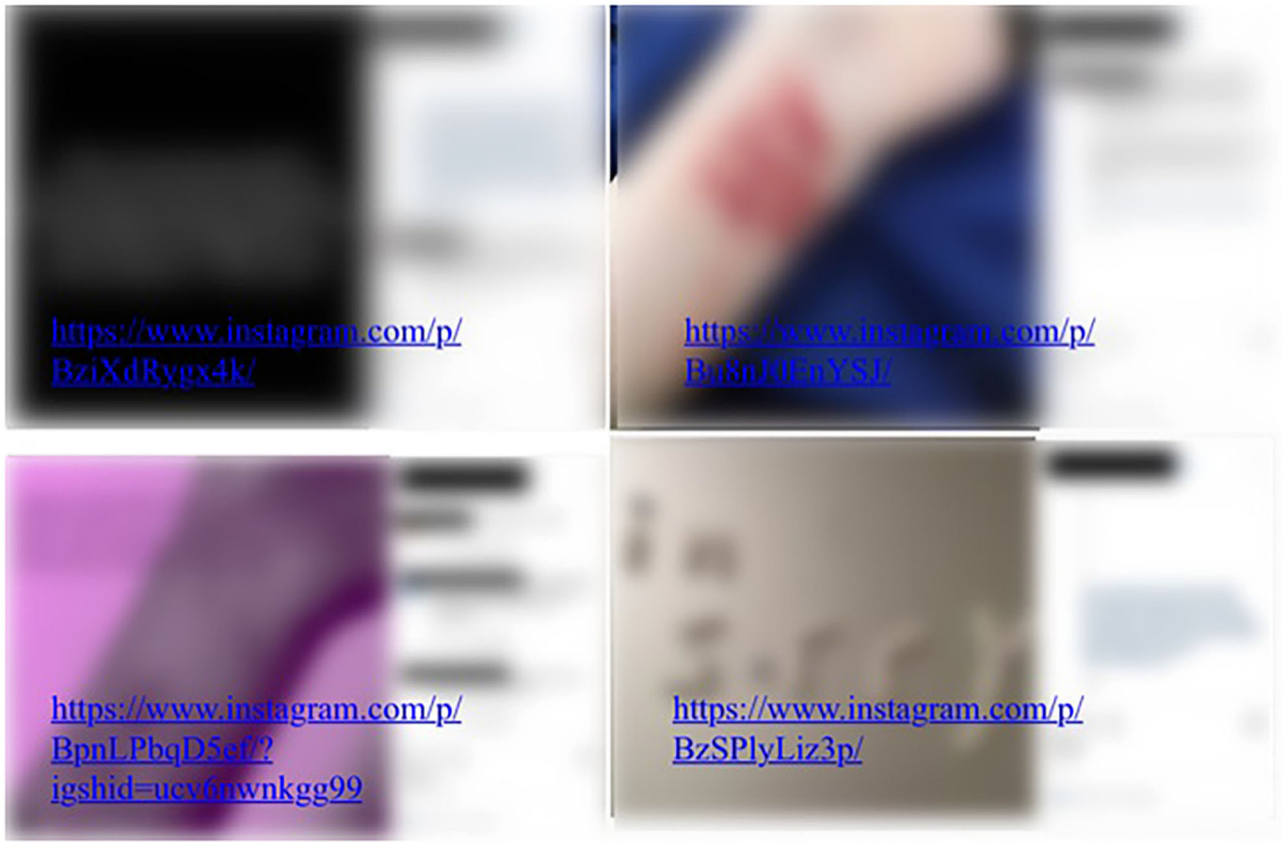

FIGURE 1 | Instagram posts with signal for suicide/self-harm, mental health problems and drug abuse (user information concealed and images blurred). If you're thinking about suicide, are worried about a friend or loved one, or would like emotional support, please contact the National Suicide Prevention Lifeline at 1-800-273-TALK(8255). Available 24 h (https://suicidepreventionlifeline.org/).

drug diversion posts on Instagram, lack of demographic data restricts their generalizability. User privacy and confidentiality issues also make any risk estimation difficult. The drug dealer data collected and analyzed in the 4-month study period were manually annotated to verify validity of results and model performance. This time lag between data collection and manual annotation may have resulted in deletion of some posts by users relevant to this study. Since text filtering was used on the drug diversion posts that were manually annotated, any discussions about suicide and mental health in the deleted posts could have been inadvertently lost. Further, social media data can rapidly change due to potential platform policy changes, including blocking or preventing searches of suicide-related posts, which can also coincide with changes in a user's real-world environment, such as growing concerns about a rise in substance abuse and mental health issues due to the COVID-19 pandemic (20). Future studies should be designed such that data collection and analysis is closer to real-time in order to better identify emerging trends and enable data-driven substance abuse and suicide prevention programs. It is also important to recognize that there are a wide range of mental health problems with diverse clinical presentations. For the purposes of this study, these conditions were grouped under an overall mental health category partially due to user description of multiple mental health challenges and also to emphasize the co-occurrence of substance use disorder, suicide and overall mental health problems. This study merely identifies the co-occurrence, but further research is needed to better characterize and disentangle the complexity of these co-morbid conditions and their interactions in the context of social media discussions. Also, this study was unable to validate the results using a prospective data sample. Future research should explore the use of prospective samples of social media users associated with opioid use disorder in order to identify and validate progression of possible suicide/self-harm attempts or other co-occurrent mental health issues. Future studies are needed to better elucidate the broader trends, characteristics and scope of discussions converging around SUD, suicide and mental health in this specific population of social media users as well as measuring user reactions and sentiment to these conversations. Also, recognizing patterns of suicide/self-harm behavior across different substance use characteristics such as types of drugs used and polydrug use, can provide insights on priority sub-groups within substance user communities.

CONCLUSION

In addition to the importance of these findings in the context of infoveillance for suicide and SUD, it will be critical to identify an ethical means of utilizing these results for targeted prevention and treatment for this at-risk population. Media-based messages targeting substance use population should be designed in such a way that they encourage seeking help from health professionals, without the fear of being judged or being stigmatized. In spite of increased number of mass media campaigns for suicide prevention, studies report limited efficacy (21). This may be due to poor adherence in a mistargeted population. For example, a broad suicide prevention campaign which does not address the factors specific to substance use may have low impact. Hence, the results of this study can help focus on the substance use specific risk factors and comorbidities that can be gathered by analyzing unstructured self-reported data communicated on these platforms which are highly populated by youth and young adults, a critical priority population in need of help, empathy, and intervention, particularly in the digital sphere.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

All information collected from this study was from the public domain and the study did not involve any interaction with users. User indefinable information was removed from the study results.

AUTHOR CONTRIBUTIONS

VP, JL, and TM jointly collected the data, designed the study, conducted the data analyses, and wrote the manuscript. All authors contributed to the formulation, drafting, completion, and approval of the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.551296/full#supplementary-material

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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