BIO-PSYCHO-SOCIAL INDICATORS OF SUICIDE RISK

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BIO-PSYCHO-SOCIAL INDICATORS OF SUICIDE RISK

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ORIGINAL RESEARCH
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Mood Symptoms, Suicide, and Associated Factors Among Jimma Community. A Cross-Sectional Study

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Background: The global burden of mental health problems is high and is predicted to rise. At present, mood symptoms are the foremost common psychological problems worldwide, yet little is known regarding their magnitude and associated factors in developing countries. Therefore, this study aimed to assess the magnitude and associated factors of anxiety, depressive, manic symptoms, and suicidal behavior among the rural Jimma community, Ethiopia.

Methods: A community-based quantitative cross-sectional survey was employed on 423 households selected through systematic random sampling. An adapted version of the Mini International Neuropsychiatric Interview tool was used for the structured face-to-face interview. The collected data were checked for completeness, coded, and inserted into Epi Data version 3.1 and exported to SPSS version 23 for analysis. Variables with $P < 0.05$ and odds ratio (OR) [95% confidence interval (CI)] on multivariate logistic regression analysis were considered as factors associated with the outcome variable.

Results: Overall, 185 (44.0%), 55 (13.1%), 44 (10.5%), and 23 (5.5%) of the respondents had anxiety, depressive, manic symptom, and suicide behavior, respectively. The odds of having anxiety symptoms were nearly 5 times higher among those who had perceived discrimination and racism experience compared to their counterpart [adjusted OR (AOR), 5.02; 95% CI, 1.90–13.26]. Likewise, recently bereaved participants had 4-fold higher odds of reporting depressive symptoms (AOR, 3.9; 95% CI, 1.4–10.4) than the non-bereaved ones. Furthermore, respondents who had depressive symptoms were almost four and a half times more likely to have manic symptoms compared to those who did not (AOR, 4.3; 95% CI, 1.71–11.02).

Conclusion: Anxiety, depressive, manic symptoms, and suicidal behavior were prevalent in the community and positively associated with multiple psychosocial factors. Implementing accessible and affordable community-based mental health services is recommended to mitigate the problems.

Keywords: mood symptoms, anxiety symptoms, suicide, community, Jimma, Ethiopia

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BACKGROUND

Mental health is vital to individual well-being, family bonding, and successful contributions to society. It is associated with the development of societies and countries (1, 2).

The global burden of mental health problems (mood, anxiety disorder, and suicide) is high and predicted to rise. At present, mood symptoms are the foremost common psychological problems worldwide, and it has been forecasted that unipolar depressive disorders will be the second leading cause of the burden of disease in 2030 (3–7).

Mental health problems are known to increase morbidity and mortality and are an important risk factor for adverse health outcomes. The social, economic, and health effects are extensive, where they are related to increased all-cause mortality, occupational disability, poor quality of life, and cardiovascular disease risk (8). Despite this, mental health is often ignored as public health priority (9).

Mental health problems such as mood disorders are associated with multiple factors such as gender, income (10), education level, socioeconomic conditions, medical illness (11, 12), age, substance use (13), stressful life events (14, 15), history of parental substance use (16), residence, marital status (17, 18), perceived racism and discrimination (19, 20), domestic violence (15), death of a close relative (21), birth order (22, 23), violence, migration, sexual abuse experience, life-threatening and physical injuries, difficulties with family relationships, and low emotional support at home during childhood (24, 25).

The World Health Organization (WHO) World Mental Health surveys show clearly that mental disorders are quite common in all the countries (26). However, developing countries, such as Ethiopia, are facing the impact of mental health problems while confronted with limited resources and inequities in access to mental health care (27).

More than three-quarters of people who have mental problems are residing in low- and middle-income countries (LMICs), with mental illness and substance use disorders presenting as an important cause of disease burden (28, 29). In many LMICs, there is typically a shortage of mental health professionals; with little or no multidisciplinary team and few regular drugs available, this can further worsen the impacts and burdens of the problems (30).

In Ethiopia, mental illness is the leading non-communicable disorder in terms of burden. Indeed, in a predominantly rural area of Ethiopia, mental illness comprised 11% of the total burden of disease. Severe mental illness is more often attributed to supernatural causes, rather than as a result of biomedical or psychosocial causes. The number of trained mental health professionals is inadequate for providing services to Ethiopians. There is only one dedicated psychiatric hospital in the entire country for more than 110 million population (31).

Evidence showed that in the rural context living conditions such as limited social and economic resources, stressful life events, poverty, and other demographic disadvantages pose a greater risk for mental health problems (32, 33). Also, various sociocultural factors such as deeply ingrained religious and inherited beliefs that all mental illnesses contribute to the existence and poor modern treatment for mental health problems in the country (34). In Ethiopia, in any ethnic or religious group, supernatural powers are given the attribute of controlling the well-being of the individual's mind. The traditional healing methods are used more by most people (35–37).

In Ethiopia, where undernutrition and preventable communicable diseases are very rampant, mental health problems, which are considered as non-fatal, are not given due consideration (38). Valid and inclusive epidemiological data on the magnitude and associated factor of mental health problems generated from community-based surveys have significant scientific and health policy implications (39). There are some research works documented in the literature regarding the magnitude and associated factors of anxiety, depressive, manic symptoms, and suicidal behavior among Ethiopians. However, in this study, variables such as migration history, perceived discrimination and racism experience, sexual abuse, and domestic violence were included. Furthermore, the studies on mental health problems are scarce in the sub-Saharan countries, and most studies were conducted in the cities. However, this study has tried to reveal the extent of mental health problems and associated factors in the neglected rural area of the country; this might help the local health planners and non-governmental organizations working in the area of mental health to investigate and design effective locally sound mental health interventions to avert the problems. Hence, this study aimed to assess the magnitude and associated factors of anxiety, depressive, manic symptoms, and suicidal behavior among the Jimma zone community, Ethiopia.

METHODS

Study Setting

The study was carried in the Jimma zone, Seka Chekorsa district. Jimma zone is administratively divided into 20 districts and one town administration. The total population of the zone was 2,986,957 in 2017 (40). Seka Chekorsa district is located 20 km from Jimma town, and the district has 30 kebeles (the lowest administrative division in the area) with a total population of 208,096 (41). This district has one primary hospital, nine health centers, and 35 health posts. The study was conducted from March 1 to 22, 2020.

Ethiopia is one of the 213 countries that have registered 2019 coronavirus disease (COVID-19) cases since March 13, 2020. In Ethiopia, several cases and deaths are identified (42). The study data were collected in the first couple of weeks of the virus detection in the country.

Sample Size Estimation

Single population proportion formula was used to obtain the desired sample size. We have assumed a 50% proportion of the magnitude of mood symptoms to get the maximum sample size, 95% confidence level, and 5% margin of error. Hence, $n = (z\alpha/2)^2$

Abbreviations: AOR, Adjusted Odds Ratio; CI, Confidence Interval; CORm, Crude Odds Ratio; OR, Odds Ratio; SD, Standard Deviation; SPSS, Statistical Package for the Social Sciences; US, United State.

$P(1-p)/d^2$; hence, $n = (1.96)^2 \times 0.5\ (1-0.5)/(0.05)^2 = 384$. With the addition of a 10% contingency for non-response, the final sample size was 423.

Study Design, Population, Sampling Technique, and Procedures

A community-based quantitative cross-sectional survey was carried out. First, Seka Chekorsa district was selected from a total of 20 districts in the zone through a simple random sampling lottery technique. Of the 30 kebeles in this district, nine were selected by lottery method based on the WHO sample size calculation guideline for the district health system (43). The number of sampled respondents from each kebele was determined by proportional allocation to the total number of households in each of the sampled kebeles. A systematic random sampling technique was used to select the study units, and periodic interval (K) was calculated using the formula $K = N/n$, whereby N is the total households in the selected kebeles (1,555), and n is the calculated sample size (423). Accordingly, every four households were included in the study. The first study unit was selected by lottery method between the first and fourth households. Finally, randomly selected household members 18 years or older in the selected household responded to the interview. The study participants were household members 18 years or older in the randomly selected households.

Eligibility Criteria

All the study community members 18 years or older were included in the study. The study community members who were acutely or chronically ill, which makes him/her difficult to participate in the study, were excluded from the study.

Measurements and Procedures

A face-to-face interviewer-administered structured questionnaire was used using an adapted version of the Mini International Neuropsychiatric Interview (M.I.N.I.). M.I.N.I. 5.0.0 was developed by Sheehan et al. and designed for assessing the major Axis I mental health problems in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) (researchers and clinicians working in non-profit or publicly owned settings can freely use for clinical and research use) (44). Validation and reliability of the tool have been done with good psychometric properties (45–47). The reliability, Cronbach α score, of the scales in this study was 0.76. This study has assessed the prevalence of *DSM-IV* criteria A symptoms of panic disorder (lifetime), social anxiety disorder (past month), generalized anxiety disorder (past 6 months), suicide characteristics (such as repeatedly consider hurting self, having a plan to kill self, repeatedly wish dead, and suicide attempt) (past month), a lifetime suicide attempt, major depression (current or 2 weeks), and manic episode (lifetime). The tool has also included questions to measure other family members with such symptom presentations. If the subject answers positive for any of the questions about symptoms included in M.I.N.I.'s anxiety, depressive, manic symptoms, and suicide module, it is considered to have the symptoms. For factors associated with the outcome variable, the questionnaire was developed after a thorough review of the literature that has been done on similar topics (32, 48–50); the presence or absence of these factors was measured using a structured question. Data were collected by 20 health extension workers after receiving training for 2 days on the components of the questionnaire, data recording, and the ethical principles of the data collection process. The English version of the questionnaire was translated into Afaan Oromo and back-translated to English to ensure its uniformity by blinded language experts. The translations were face validated by two independent external experts in the field. Moreover, the data collection tool was pilot tested on 5% of the population in another district to ensure its clarity and consistency. The pretest results showed the questionnaire was easily understandable, and the interview process was clear for the respondents. Afaan Oromo version of the questionnaire was used to obtain the desired data. Appropriate COVID-19 infection containment measures, which WHO recommended (keeping a 2-meter distance, wearing a face mask, and using alcohol-based hand sanitizers), were practiced during the data collection period.

Data Organization and Statistical Analysis

The collected data were checked for completeness, given code, and inserted into Epi Data version 3.1 and exported to SPSS version 23 for analysis. Descriptive statistics were done to summarize the variables. The logistic regression analysis model was used to identify the factor associated with the outcome variable. First, bivariate logistic regression analysis was done, and variables with $p < 0.25$ were selected as candidate variables for multivariate logistic regression analysis. After the model was tested for multicollinearity and Hosmer–Lemeshow test of model fitness, the final multivariate logistic regression analysis was carried out. Finally, variables with $p < 0.05$ and 95% confidence interval and odds ratio (OR) were considered as factors associated with the outcome variable.

Ethical Consideration

Ethical approval was obtained from the Institutional Review Board (IRB) of Jimma University (IHRPGD/584/2019). Additionally, a support letter was found from Oromia Regional Health Bureau, Jimma Zone Health Bureau, and a subsequent support letter was obtained from the Seka Chekorsa district health office before the commencement of data collection. Respondents were informed of the study objectives and were assured of the anonymity of their participation. Participation in the study was voluntary, and written informed consent was taken from the respondents. Respondents who had anxiety, depressive and manic symptoms, and suicidal behavior were advised to visit the nearby health facility for further mental health evaluation and management.

RESULTS

Sociodemographic Characteristics

A total of 420 study participants were interviewed successfully, giving a response rate of 99.3%. Three respondents were not willing to participate in the study. The mean age of the respondents was 37.2 years (SD, ±11.9 years) with a range of 18

to 80 years. The majority of the study respondents were females [230 (54.8%)], married [345 (82.1%)], Oromo ethnic group [395 (94%)], Muslim [384 (91.4%)], and unable to read and write [168 (40.0%)]. The mean monthly income was 1,562.5 Ethiopian Birr (ETB) (SD, ±2,769.8) (approximately US $48.00) (**Table 1**).

Anxiety Symptoms

Twenty-eight participants (6.7%) had spells or attacks of sudden anxiety, frightened, uncomfortable, or uneasy, even in situations where most people would not feel that way on more than one occasion. Similarly, about 71 (16.9%) respondents were fearful or embarrassed by being watched including things such as speaking in public, eating in public or with others, writing while someone watches, or being in social situations in the past month. Nearly one-quarter [101 (24.0%)] of the participants were worried excessively or had been anxious about several things over the past 6 months. Overall, 185 (44.0%) seemed to have anxiety symptoms (**Table 2**).

Depressive Symptoms and Suicide Characteristics

Of the total respondents, 39 (9.3%) reported they have been consistently depressed, hopeless most of the day, nearly every day, for the past 2 weeks or more. About 31 (7.4%) participants could identify another family member who was tearful, hopeless, and complaining about emptiness for the past 2 weeks or more. About 40 (9.5%) of the respondents were less interested in most things or much less able to enjoy the things they were used to enjoy most of the time in the past 2 weeks or more. Additionally, 23 (5.5%) of the participants reported repeatedly wishing to be dead, and 5 (1.2%) attempted suicide. Overall, 55 (13.1%) of the respondents had depressive symptoms (**Table 3**).

Manic Symptoms

Among the total respondents, 11 (2.6%) had a lifetime period where they feel "up" or "high" or "hyper" or so full of energy or full of self that got into trouble, or other people thought they were not their usual self for 1 week or more. About 38 (9.0%) of the participants described persistently feeling irritable, had arguments or verbal or physical fights, or shouted at people for several days. Overall, 44 (10.5%) of the respondents were identified to have manic symptoms (**Table 4**).

Respondents' Psychological and Behavioral Characteristics

Among the respondents, 48 (11.4%) had a recent loss of a close family member. About 45 (10.7%) participants were reported being discriminated against. About 12 (2.9%) had confided about being sexually abused, and 118 (28.1%) described financial problems (**Table 5**).

Factors Associated With Anxiety Symptoms

Male participants had a 50% less risk of developing anxiety symptoms [adjusted OR (AOR), 0.50; 95% CI, 0.29–0.87]. The analysis results also showed rural residents were found to have a 75% less risk of having anxiety (AOR, 0.25; 95% CI, 0.14–0.44). The odds of having anxiety symptoms were ∼2 times higher among those who were on the first birth order than those on the third or more birth order. Those employed had 57% less risk of developing anxiety symptoms compared to the housewife counterpart (AOR, 0.43; 95% CI, 0.20–0.90). Respondents whose parents abuse substances had nearly twice increased odds of developing anxiety symptoms (AOR, 2.18; 95% CI, 1.12–4.22). The odds of developing anxiety symptoms were ∼5 times higher among those who had perceived discrimination and racism experience (AOR, 5.02; 95% CI, 1.90–13.26). Respondents who had reported stressful event had nearly 4 times' increase of having anxiety symptoms (AOR, 3.96; 95% CI, 1.53–10.24) (**Table 6**).

Factors Associated With Depressive Symptoms

The analysis result has shown depressive symptoms were three and a half times higher among respondents who were unable to read and write compared to primary school and above academic status (AOR, 3.5; 95% CI, 1.3–8.9). Respondents who were on the first birth order were nearly three and a half times more likely to have depressive symptoms compared to those on the third and above birth order (AOR, 3.6; 95% CI, 1.4–8.7). The study participants who had recent bereavement were nearly 4 times more likely to report depressive symptoms (AOR, 3.9; 95% CI, 1.4–10.4). Furthermore, respondents who had depressive symptoms were ∼5 times higher to have stressful events compared to their counterparts (AOR, 4.8; 95% CI, 1.7–13.5) (**Table 7**).

Factors Associated With Manic Symptoms

Respondents who had depressive symptoms were almost four and a half times more likely to have manic symptoms (AOR, 4.3; 95% CI, 1.71–11.02). Study participants with parental substance use history were 3 times more at risk of having manic symptoms (AOR, 2.8; 95% CI, 1.21–6.69). The result of the regression analysis has revealed respondents who had perceived discrimination and racism experience had 5 times more likely to report manic symptoms (AOR, 5.0; 95% CI, 1.96–12.77). Firstborn children had ∼4 times higher risk of developing manic symptoms compared to those on the third or more birth order (AOR, 4.1; 95% CI, 1.29–12.98). Study participants who perceived their economic status as a medium were two and a half times more likely to have manic symptoms than those who perceived low economic status (AOR, 2.3; 95% CI, 1.06–5.24) (**Table 8**).

DISCUSSION

The study aimed to assess the magnitude and factors associated with anxiety, depressive, and manic symptoms, and suicidal behavior among the Jimma zone community.

The finding of this study showed 55 (13.1%) of the respondents had depressive symptoms. Consistent findings were reported from the pooled prevalence of depression in Ethiopia (51), rural communities in Malaysia (11.30%) (10), Brazil (14%) (52), northwest Ethiopia (17.5%) (53), and Puerto Rico (17.8%) (54). The findings in all studies have shown that depression is a

TABLE 1 | Sociodemographic characteristics of respondents at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variables	Characteristics	Frequency	Percentage
Sex	Male	190	45.2
	Female	230	54.8
Age	37.2 (SD, ±11.9)		
	Range 18–80 years		
Residence	Urban	167	39.8
	Rural	253	60.2
Birth order	First	183	43.6
	Second	102	24.3
	Third	60	14.3
	Fourth or more	75	17.9
Ethnicity	Oromo	395	94.0
	Amhara	12	2.9
	Others*	13	3.1
Religion	Muslim	384	91.4
	Orthodox	24	5.7
	Others†	12	2.8
Monthly income	1,562.5 (SD, ±2,769.8)		
Educational status	Unable to read and write	168	40.0
	Able to read and write	81	19.3
	Primary school (grades 1–8)	112	26.7
	Secondary school (grades 9–12)	49	11.7
	Diploma	6	1.4
	Degree and above	4	1.0
Marital status	Single	30	7.1
	Married	345	82.1
	Divorced	12	2.9
	Widowed	33	7.9
Occupational status	Farmer	219	52.1
	Merchant	61	14.5
	Daily laborer	18	4.3
	Housewife	100	23.8
	Employed	22	5.3

Other ethnicities include Kefa, yem, Dawro, Gurage, and Silte.
†Other religions include Protestant, Catholic, and Wakefeta.

TABLE 2 | Anxiety symptoms characteristics of the respondents and their family at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variable	Characteristics	Frequency	Percentage
On more than one occasion; had spells or attacks; suddenly felt anxious, frightened, uncomfortable, or uneasy, even in situations where most people would not feel that way	Yes	28	6.7
	No	392	93.3
Other family members having these	Yes	18	4.3
	No	402	95.7
No. of family members having these	One	15	83.3
	Two	3	16.7
Experience of spells surge to a peak within 10 min of starting?	Yes	19	67.8
	No	9	32.2
At any time in the past, those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner	Yes	26	92.8
	No	2	7.2
Ever had one such attack followed by a month or more of			
Persistent concern about having another attack	Yes	22	78.6
	No	6	21.4
Worries about the consequences of the attack	Yes	23	82.1
	No	5	7.9
The significant change in your behavior because of the attacks	Yes	18	64.3
	No	10	35.7
Other family member having these	Yes	49	11.7
	No	371	88.3
No. of family members having these	One	45	91.8
	Two	2	4.1
	Three	2	4.1
In the past month, including things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations			
Fearful or embarrassed about being watched	Yes	68	16.2
	No	352	83.8
Being the focus of attention	Yes	71	16.9
	No	349	83.1
Fearful of being humiliated	Yes	43	10.2
	No	377	89.8
Other family member having these	Yes	22	5.2
	No	398	94.8
No. of family members having these	One	22	100
Being worried excessively or been anxious about several things over the past 6 months	Yes	101	24.0
	No	319	76.0
Worries present most days	Yes	61	60.4
	No	40	39.6
Difficult to control the worries	Yes	33	32.7
	No	68	67.3
The worry interferes with the ability to focus on what are doing	Yes	22	21.8
	No	79	78.2
Other family member having these	Yes	55	13.1
	No	365	86.9
No. of family members having these	One	50	90.9
	Two	2	3.6
	Three	3	5.5

global problem. However, this study finding is higher than the 4.4% WHO global and regional estimates of the prevalence of depression in 2015 (55). The current study was conducted 5 years later than the WHO study; various changes such as economic inflation, ethnic violence, increased Khat (local stimulant leaf), and other substance use in the area could be the probable contributing factors for the high prevalence of depression in the area. Yet, the result is lower than the studies done among adolescents living in the cities of Kenya (26.4%) (56) and South Brazil (35.4%) (11). The discrepancy could be explained by as follows: this study was conducted in the rural area of the country compared to the Kenya and Brazil studies. Concentrations of low socioeconomic status; low social capital, e.g., social support; and

TABLE 3 | Depression and suicidal behavior of the respondents and their family at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variable	Characteristics	Frequency	Percentage
Consistently depressed or down, hopples most of the day, nearly every day, for the past 2 weeks	Yes	39	9.3
	No	381	90.7
Other family members who were tearful, hopeless, complaining emptiness for the past 2 weeks	Yes	31	7.4
	No	389	92.6
No. of family members having this	one	25	80.7
	Two	4	12.9
	Three	2	6.4
In the past 2 weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	Yes	40	9.5
	No	380	90.5
In the past 2 weeks, other family members were less interested in most things or much less able to enjoy the things they used to enjoy most of the time	Yes	28	6.7
	No	392	93.6
No. of family members having this	One	23	82.1
	Two	4	14.3
	Three	1	3.6
In the past month repeatedly consider hurting self	Yes	17	4.0
	No	403	96.0
In the past month have a plan to kill self	Yes	28	6.7
	No	392	93.3
In the past month repeatedly wish dead	Yes	23	5.5
	No	397	94.5
Lifetime suicide attempt	Yes	5	1.2
	No	415	98.8
The family member having a suicide attempt	Yes	12	2.9
	No	408	97.1

TABLE 4 | Manic symptoms characteristics of the respondents and their family at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variable	Characteristics	Frequency	Percentage
Had a period feeling "up" or "high" or "hyper" or so full of energy or full of self that got into trouble, or that other people thought you were not your usual self for at least 1 week	Yes	11	2.6
	No	409	97.4
Other family members having these	Yes	39	9.3
	No	381	90.7
No. of family members having this	One	33	84.6
	Two	5	12.8
	Three	1	2.6
Ever been persistently irritable, for several days, had arguments or verbal or physical fights, or shouted at people	Yes	38	9.0
	No	382	91.0
Other family member having these	Yes	44	10.5
	No	376	89.5
Have you or others noticed that you have been more irritable or overreacted, compared to other people, even in situations that you felt were justified	Yes	53	12.6
	No	377	89.8
Other family member having these	Yes	43	10.2
	No	377	89.8
No. of family members having this	One	32	74.4
	Two	11	25.5

higher rates of pollution [e.g., air, water, and noise pollution in the cities might be the reason for the high prevalence of depression symptoms (57, 58)].

Manic symptoms were noted in 44 (10.5%) of the respondents; similarly, the US National Epidemiologic Catchment Area database showed that the prevalence of subthreshold bipolar symptoms was 5.1% (59). At present, no data exist that indicate how many patients there are with such subthreshold bipolar symptoms in the developing countries and community setting. The high prevalence of substance (Khat) use, socioeconomic pressure, and limited availability of mental health treatment centers in the area might contribute to the symptoms (39, 60).

The finding of this study has shown 185 (44.0%) of the respondents had anxiety symptoms. This finding is higher than those found in the studies done in Malaysia (8.2%) (15), from African cultures (7.3%) to Euro/Anglo cultures (10.4%) (61), rural communities of Northern India (22.7%) (62), and Kashmir valley (26%) (17). The worries and uncertainty resulting from living in poverty seem to be an important driver of mental health problems including anxiety, as do the effects of low income on childhood development and one's living environment (63).

In this study, 5.5 and 1.2% of the participants reported repeatedly wishing dead and attempting suicide, respectively. A consistent finding was reported from the study done in Addis Ababa, Ethiopia, in which the rates of suicidal ideation and attempt were 2.7 and 0.9%, respectively (64). Another population study in Ethiopia has shown 13.5% of the study participants had suicidal ideation, and 1.8% had suicide attempt (65). Additionally, a study was done in Nigeria that revealed 7.28% had suicidal ideation (66). A study done in rural communities in China reported 4.8% and 0.4% had suicidal ideation and attempt, respectively (67). However, our finding was lower than the findings of 17.1% for suicidal ideation and 2.8% for suicide attempts from Brazil (68). The discrepancy could be explained by the differences in the social control networks, extended family ties, religious, cultural practices differences, and different stressors in the study settings (7, 69).

The finding of this study has revealed that respondents with higher educational status had less risk of developing depression. This is consistent with the studies done in Iran (18) and Pakistan (70). This could be because education as a means enables people to gain success in life and may fundamentally contribute to the emotional well-being of the person (71). In the study area, an individual with higher education status usually has better work opportunities, health information, and living standards.

TABLE 5 | Respondents psychological and behavioral characteristics at Jimma Zone, Seka Chekorsa district Southwest Ethiopia, March 2020.

Variables	Characteristics	Frequency	Percentage
Any close family member who died recently and feel so bad	Yes	48	11.4
	No	372	88.6
Having any known medical illness	Yes	10	2.4
	No	410	97.6
Currently taking any medication/drug	Yes	7	1.7
	No	413	98.3
Migrated to another country	Yes	10	2.4
	No	410	97.6
Displaced from your home village	Yes	4	1.0
	No	416	99.0
Perceived economic status	Rich	14	3.3
	Medium	114	27.1
	Poor	292	69.5
Experience domestic violence with physical punishment	Present	18	4.3
	Absent	402	95.7
Experience difficulties with family relationships (parents and siblings)	Present	45	10.7
	Absent	375	89.3
Had low emotional support at home during childhood	Present	47	10.7
	Absent	373	88.8
Parent's abuse substance	Present	86	20.5
	Absent	334	79.5
Parents' divorce	Present	39	9.3
	Absent	381	90.7
Family financial problems	Present	118	28.1
	Absent	302	71.9
The low performance or school dropout	Present	113	26.9
	Absent	307	73.1
Perceived discrimination and racism experience	Present	45	10.7
	Absent	375	89.3
Suffered aggression and physical violence	Present	26	6.2
	Absent	394	93.8
Sexual abuse experience	Present	12	2.9
	Absent	408	97.1
Stressful events (relationship problems, separations, and unemployment)	Present	46	11.0
	Absent	374	89.0
Legal problems involvement	Present	11	2.6
	Absent	409	97.4
High frequency of exposition to community violence, theft, assault, and firearms uses	Present	4	1.0
	Absent	416	99.0
Access to mental health service	Present	19	4.5
	Absent	401	95.5
Current pregnancy	Present	14	3.3
	Absent	406	96.7
Currently in the post-partum period	Present	35	3.8
	Absent	385	91.7
Grow by caregiver/other than family	Present	21	5.0
	Absent	399	95.0
Physical and sexual abuse during childhood	Present	6	1.4
	Absent	414	98.6
Living arrangement	Alone	5	1.2
	With immediate family	141	33.6
	With extended family	270	64.3
	With friends	4	1.0

TABLE 6 | Factors associated with anxiety symptoms of the respondents at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variables	Category	Anxiety symptoms		COR (95 CI)	AOR (95% CI)
		No	Yes		
Sex	Male	122 (64.2)	68 (35.8)	0.53 (0.36–0.79)	0.50 (0.29–0.87)*
	Female	113 (49.1)	117 (50.9)	1	1
Residence	Rural	117 (70.1)	50 (29.9)	0.37 (0.24–0.56)	0.25 (0.14–0.44)*
	Urban	118 (46.6)	135 (53.4)	1	1
Birth order	First	93 (50.8)	90 (49.2)	1.59 (1.01–2.50)	2.20 (1.26–3.84)*
	Second	58 (56.9)	44 (43.1)	1.24 (0.74–2.11)	1.32 (0.70–24.8)
	Third or more	84 (62.2)	51 (37.8)	1	1
Occupational status	Farmer	116 (53.0)	103 (47.0)	0.69 (0.43–1.12)	0.64 (0.32–1.25)
	Employed	75 (74.3)	26 (25.7)	0.27 (0.15–0.49)	0.43 (0.20–0.90)*
	Housewife	44 (44.0)	56 (56.0)	1	1
Parents abuse substance	Yes	33 (38.4)	53 (61.6)	2.45 (1.51–3.99)	2.18 (1.12–4.22)*
	No	202 (60.5)	132 (39.5)	1	1
Perceived discrimination and racism experience	Present	9 (20.0)	36 (80.0)	6.06 (2.84–12.96)	5.02 (1.90–13.26)*
	Absent	226 (60.3)	149 (39.7)	1	1
Stressful events†	Present	14 (30.4)	32 (69.6)	3.30 (1.70–6.39)	3.96 (1.53–10.24)*
	Absent	221 (59.1)	153 (40.9)	1	1

*Variables significant at $P < 0.05$.
†Stressful events include relationship problems, separations, and unemployment.

TABLE 7 | Factors associated with depressive symptoms of the respondents at Jimma Zone, Seka Chekorsa district, Southwest Ethiopia, March 2020.

Variables	Category	Depressive symptoms		COR (95% CI)	AOR (95% CI)
		No (%)	Yes (%)		
Educational status	Unable to read and write	142 (84.5)	26 (15.5)	2.2 (1.1–4.4)	3.5 (1.3–8.9)*
	Read and write	65 (80.5)	16 (19.8)	2.9 (1.3–6.5)	5.3 (1.9–14.5)
	Primary school and above	158 (92.4)	13 (7.6)	1	1
Birth order	First	150 (82.0)	33 (18.0)	2.4 (1.2–5.1)	3.6 (1.4–8.7)*
	Second	91 (89.2)	11 (10.8)	1.3 (0.5–3.2)	1.1 (0.3–3.3)
	Third or more	124 (91.9)	11 (8.1)	1	1
Having a close family member who is died recently and feel so bad	Present	30 (62.5)	18 (37.5)	5.4 (2.7–10.6)	3.9 (1.4–10.4)*
	Absent	335 (90.1)	37 (9.9)	1	1
Stressful event†	Present	28(60.9)	18 (39.1)	5.8 (2.9–11.5)	4.8 (1.7–13.5)*
	Absent	337 (90.1)	37 (9.9)	1	

*Variables significant at $P < 0.05$.
†Stressful events include relationship problems, separations, and unemployment.

This could protect them against developing depression (72). Nevertheless, individuals with higher education backgrounds were comparatively more prone to mood disorders in the study done in the United States (10). This might be explained in that in Western culture highly educated people seek well-paid jobs and may have better socioeconomic expectations. In their race to meet these expectations, they could experience unmanageable stress, which predisposes them to mood disorders (73).

In the current study, respondents with first and second birth order status were more prone to have depression symptoms than those with third and above birth order status. This finding is in line with the study done in Nepal (74). However, no difference was observed in the study done in Egypt (75). Similarly, birth order was found to have an association with anxiety symptoms in this study. This finding was consistent with the study done in Kuwait (69). Birth order is one of the most significant life factors, and it is the best indicator of the kind of personality someone has. In the study area, the oldest child commonly has many responsibilities compared to the youngest child of the family. Studies also have shown that because of much expectations that are placed on the oldest child in a family, the eldest one experiences more emotional disturbance and struggles in coping with the stressful condition (76). In addition, the firstborns were considered as the smaller version of their parents; therefore, they have received much more control and attention from their parents. Hence, they tend to be over responsible, reliable, well-behaved, and careful. This might explain a higher level of emotional disturbances in this group (77).

TABLE 8 | Factors associated with manic symptoms of the respondents at Jimma Zone Seka Chekorsa district Southwest Ethiopia, March 2020.

Variables	Category	Manic symptoms		COR (95 CI)	AOR (95% CI)
		No	Yes		
Depressive symptoms	Yes	37 (67.3)	18 (32.7)	1	1
	No	339 (92.9)	26 (7.1)	6.3 (3.18–12.64)	4.3 (1.71–11.02)*
Parents abuse substance	Present	62 (72.1)	24 (27.9)	6.0 (3.16–11.67)	2.8 (1.21–6.69)*
	Absent	314 (94.0)	20 (6.0)	1	1
Perceived discrimination and racism experience	Present	28 (62.2)	17 (37.8)	7.8 (3.81–16.05)	5.0 (1.96–12.77)*
	Absent	348 (92.8)	27 (7.2)	1	1
Birth order	First	159 (86.9)	24 (13.1)	3.2 (1.28–8.17)	4.1 (1.29–12.98)*
	Second	88 (86.3)	14 (13.7)	3.4 (1.26–9.24)	4.7 (1.37–16.64)*
	Third or more	129 (95.6)	6 (4.4)	1	1
Perceived economic status	Medium	107 (83.6)	21 (16.4)	2.2 (1.21–4.32)	2.3 (1.06–5.24)*
	poor	269 (92.1)	23 (7.9)	1	1

**Variables significant at $P < 0.05$.*

In our study, respondents with self-perception of their economic status as a medium were at higher risk of having manic symptoms. In many studies, it was usually noted that bipolar disorder was relatively higher among those who have medium socioeconomic status than that of controls or the general population (78, 79). However, many current studies have failed to confirm such assumptions (12). The anticipation of economic shocks may cause mental illness such as mania. People living in poverty face substantial uncertainty and income volatility and complex financial portfolios, often without access to formal insurance; this might increase the risk of developing bipolar symptoms (80, 81).

In the current study, having depressive symptoms was associated with an increased risk of manic symptoms. This might be explained by bipolar disorders beginning with depressive episodes, and a significant proportion of individuals who had initial major depressive disorder will later be reclassified as having a bipolar disorder (82). Various precipitating factors, such as socioeconomic stress, poor control of depressive-manic symptoms through medication, and the nature of the illness by itself, might be the reason for manic-depressive cycle (83, 84).

Perception of prejudice and discrimination based on ethnicity increased the risk of presentation of manic and anxiety symptoms among the respondents. Stress associated with the experiences of perceived racial discrimination and prejudice has substantial negative effects on both physical and mental health and might precipitate mental health problems (85). Discrimination may contribute to psychological problems through numerous possible mechanisms including negative psychological and physical stress response, hypervigilance, and increased involvement in unhealthy behaviors (20, 86, 87). In Ethiopia, ethnicity-related violence in different parts of the country could be the reason for the death, and internal displacement of people from their living area can be considered as a serious stressor for manic symptoms eruption (88, 89).

In this study, respondents whose parents abuse substances were more likely to have anxiety symptoms. This could be because an individual who had parents with abusing substances were having problems including poor attachments, economic difficulties, legal problems, emotional abuses, and violence (90).

Most the studies conducted on depression, anxiety, mania, and suicide behavior in Ethiopia were among prisoners (91), substance users (92), university staffs and students (93, 94), women (95), pregnant women (96, 97), postpartum mothers (98), children (99), medically ill patients (100–103), epileptic patients (104), disorder threshold level (39, 105, 106), and in the context of common mental disorders (13, 107). Our study finding has a unique contribution as it has revealed the rural community mental health problems characteristics.

However, this article has presented psychiatric symptoms, not disorders. Additionally, some of the discussion comparisons were made with many countries that are culturally different from this study setting. So, the generalization and conclusions should be made cautiously. Moreover, as it is cross-sectional by nature, it does not show the cause-and-effect relationship between the outcome and explanatory variables. Ethiopia has registered the first COVID-19 cases on March 13, 2020, the period where this study was conducted. Even though the study was conducted in a rural part of Ethiopia, where the spread of the infection was gradual, this might affect the results of this study. The current study did not assess some of the anxiety symptoms in agoraphobia, posttraumatic stress disorder, and obsessive–compulsive disorder. Furthermore, the study tool to assess the variables of this study was not validated in the local, Afan Oromo, and Amharic languages. Additionally, the latest version of the M.I.N.I. questionnaire was not used because the study tool was restricted by the publisher for free use.

Future Directions

Based on this study's limitations, we recommend interested researchers in the field of mental health and public health to investigate further the magnitude of psychiatric disorders with the latest and validated tools in local languages with a larger sample size. Furthermore, longitudinal studies are recommended to explore the cause-and-effect association of the outcome and explanatory variables.

Clinical Implications of the Study

This study may have an immense contribution in improving the mental health service of the study area by revealing the magnitude of the problems and contributing factors. In the study setting, there were very limited mental health services, which do not match with the rates of mental health problems as found in this study. This study will further motivate the researchers to evaluate the study population's intention to use mental health services, and the presence of stigma on patients with mental health problems and services use that require effective locally sound education programs in the study setting.

CONCLUSIONS

The study has revealed that a significant proportion of the community members have anxiety depressive, manic symptoms, and suicidal behavior. Furthermore, various risk factors were identified to have an association with the problems. Therefore, appropriate community-based mental health services should be designed and implemented to address the negative impact of the problems.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Jimma University, Institute of health. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YT was the principal investigator of the study and was involved from inception to design acquisition of data, analysis, and interpretation, and drafting and editing of the manuscript. LA, SA, GT, ZB, GA, MG, and KY were involved in the reviewing of the proposal, tool evaluation, interpretation, and critical review of the draft manuscript. All authors read and approved the final manuscript.

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Association of Resting Heart Rate and Heart Rate Variability With Proximal Suicidal Risk in Patients With Diverse Psychiatric Diagnoses

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Objectively measurable biomarkers have not been applied for suicide risk prediction. Resting heart rate (HR) and heart rate variability (HRV) showed potential as trans-diagnostic markers associated with suicide. This study aimed to investigate the associations of resting HR and HRV on proximal suicide risk in patients with diverse psychiatric diagnoses. This chart review study used the medical records of psychiatric patients who visited the outpatient clinic at an academic tertiary hospital. A total of 1,461 patients with diverse psychiatric diagnoses was included in the analysis. Proximal suicide risk was measured using the Mini-International Neuropsychiatric Interview (MINI) suicidal score. Linear regression analyses with the MINI suicidal score as a dependent variable and binary logistic regression analyses with moderate-to-high suicide risk (MINI suicidal risk score $\geq$6) as a dependent variable were conducted to explore the effects of resting HR and HRV parameters on acute suicide risk after adjusting for age, sex, presence of major depressive disorder (MDD) and bipolar disorder (BD), severity of depression and anxiety severity. We found that 55 (34.6%) patients in the MDD group, 40 (41.7%) in the BD group and 36 (3.9%) in the others group reported moderate-to-high suicide risk. Linear regression analysis revealed that both resting HR and root-mean-square of successive difference (RMSSD) had significant associations with the MINI suicidal score ($P = 0.037$ with HR, $P = 0.003$ with RMSSD). In logistic regression, only RMSSD showed a significant association with moderate-to-high suicide risk ($P = 0.098$ with HR, $P = 0.019$ with RMSSD), which remained significant in subgroup analysis with patients who reported any suicide-related symptom (MINI suicidal score >0; $n = 472$; $P = 0.017$ with HR, $P = 0.012$ with RMSSD). Our study findings suggest the potential for resting HR and RMSSD as biomarkers for proximal suicide risk prediction. Further research with longitudinal evaluation is needed to confirm our study findings.

Keywords: suicide, resting heart rate, resting heart rate variability, root-mean-square of successive difference, biomarker

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INTRODUCTION

Suicide is a significant mental health problem. Extensive efforts have been made toward suicide risk prediction and prevention. In clinical practice, suicide risk assessment generally is based on clinical observation of the patient's current state and previous history. However, the validity, reliability, and utility of current suicide risk prediction systems are unknown (1). To increase the accuracy

of suicidal risk prediction, objectively measurable biomarkers that can discriminate patients in an "at-risk" state are needed.

Physiological biomarkers that can be measured when an individual is in an "at-risk" state are promising candidates for suicide risk monitoring. Heart rate (HR) and heart rate variability (HRV) can be used for this purpose. HRV refers beat-to-beat variations in HR. Both HR and HRV are produced by sympathetic and parasympathetic neural activity. Lower HRV is an indicator of dysregulation of cardiac autonomic function and a predictor of poor health status (2). Short-term power spectral analysis of HRV, which has been standardized since 1996 (3), has been developed as a reliable and non-invasive tool to probe the autonomic regulation of the heart. Several studies have reported that resting HR (4, 5) and resting HRV (6) showed associations with suicide attempts.

Despite the potential of resting HR and resting HRV as candidate biomarkers for "at risk" states, previous studies have limitations with respect to generalizing their results. First, aside from limited sample sizes, most studies have explored associations with suicide ideation (7–9) or lifetime suicide attempts (9, 10). To assess the potential of resting state HR and HRV as biomarkers to identify the "at-risk" state, an association with "proximal" suicide risk should be examined. Second, most studies included biased populations in terms of psychiatric diagnoses. Suicide is a complex phenomenon that can occur among individuals suffering from a range of diverse psychiatric conditions (11). Focusing on populations with certain psychiatric disorders can hinder generalization of study findings. In particular, patients with subthreshold disorder manifestations have not been included in previous studies. Considering the dimensional nature of suicidality, patients with subthreshold disorder manifestations that can involve significant distress and dysfunction (12) should be included in studies exploring potential biomarkers. In addition, resting HRV is a biomarker for various psychiatric conditions. Meta-analytic studies have shown that decreased HRV is associated with diverse psychiatric illnesses including major depressive disorder (MDD) (13), bipolar disorder (BD) (14), anxiety disorder (15), and schizophrenia (16), indicating a broad association of decreased HRV with psychopathology rather than with a single disorder. To determine the association between resting HRV and suicide risk, additional investigations that include diverse psychiatric populations are needed.

In the present study, we examined the association of resting HR and HRV with proximal suicide risk in patients with diverse psychiatric diagnoses. Using a large clinical population with diverse psychiatric conditions including subthreshold disorder manifestations, we investigated the associations of resting HR and HRV with proximal suicide risk.

METHODS

Study Population

Data were obtained from retrospective chart reviews of patients who visited the outpatient clinic of Samsung Medical Center between January 1, 2017 and December 31, 2019. As part of routine care, all patients who visited the outpatient clinic of the Department of Psychiatry at Samsung Medical Center underwent a standardized evaluation process including psychological and biological evaluations. Following an initial interview with a board-certified psychiatrist, patients between 18 and 65 years of age were referred for the evaluation process. The psychological evaluation was designed to confirm the clinical diagnosis of subjects based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR), and to evaluate symptom severity. The psychologist who conducted the evaluation had more than 2 years of clinical experience. Detailed psychological measures included in the evaluation process were described elsewhere (17). Patients suspected of psychosis or intellectual disability or those who required emergency admission were not referred for the evaluation. Because this study targeted trans-diagnostic features associated with emotional disorder, we also excluded any subject who were suspected to have schizophrenia and related disorders. In this study, we analyzed the test results of comprehensive psychological evaluations and resting HRV measures. A total of 1,461 subjects was included in the analysis.

The study protocol was approved by the Institutional Review Board of Samsung Medical Center (no. 2018-11-019). The study was performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. All identifying data were removed from the clinical database prior to analyses. The need for patient consent was waived because this was a retrospective chart review study.

Applied Measures

Psychiatric Diagnoses

The diagnoses of study subjects were evaluated using the Korean version of the Mini International Neuropsychiatric Interview (MINI) (18). MINI diagnostic modules for major depressive disorder, dysthymia, manic episode, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, alcohol dependence, schizophrenia, delusional disorder, generalized anxiety disorder, somatoform disorder, adjustment disorders and attention deficit hyperactivity disorder were included. When symptoms did not meet the full criteria, diagnoses with not otherwise specified were coded. Primary psychiatric diagnoses based on the DSM-IV-TR (19) diagnoses were included for the analysis.

Emotional Symptoms

The Hamilton rating scale for depression (HAM-D) (20) was adopted to evaluate current depressive symptoms in patients. The Hamilton rating scale for anxiety (HAM-A) (21) was used to evaluate anxiety symptoms.

Proximal Suicide Risk

The proximal suicide risk was measured using the MINI suicide-item modules. The MINI suicide module is a six-question, yes-or-no, interviewer-administered questionnaire used to evaluate suicidality. The MINI suicide module assesses experiences during the past month of recurrent thoughts of death (1 point), ideas of self-harm (2 points), presence of suicide ideation (6 points), plans for suicide (10 points), and suicide attempts (10 points).

In addition, lifetime history of suicide attempts (4 points) is assessed. The MINI suicidal score is calculated by adding the assigned points of the items checked as "yes" in the suicide module. We used the MINI suicidal score as a marker for proximal suicide risk. A previous study that examined the predictive validity of the MINI suicidal scale reported good sensitivity (0.61–0.75) and specificity (0.61–0.75) in predicting suicidal behavior. The suicide risk score is categorized as low risk (<6 points), moderate risk (6–9 points), or high risk (≥10 points) for future suicide attempts (22).

Resting HRV

Data collection and HRV analysis were completed using SA-6000 (Medicore Co., Seoul, Korea). HRV data analysis and signal processing followed guidelines defined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (23). The measurement was conducted between 9 A.M. and 4 P.M. Prior to undergoing measurement, patients were instructed to refrain from intake of alcohol, caffeine, and food and from smoking for at least 2 h before the test. After 5 min of rest, an electrocardiogram was recorded for 3 min with the patient in a sitting position. We calculated HR and three features based on R-R interval using time-domain analysis, standard deviation of average normal-normal intervals (SDNN), and root mean square of successive differences (RMSSD). The SDNN reflects both sympathetic and parasympathetic activities, while the RMSSD is sensitive to parasympathetic modulation (24). Frequency domain features indicate various spectral components, including low frequency (LF: 0.04∼0.15 Hz), high frequency (HF: 0.15∼0.4 Hz) and the LF/HF ratio. LF is modulated by sympathetic and parasympathetic activities, and HF is modulated by parasympathetic activities. The LF/HF ratio measures the balance between sympathetic and parasympathetic activities (25).

Statistical Analyses

We divided participants into three groups based on psychiatric diagnoses associated with high suicide risk: MDD, BD, and others. We compared demographic characteristics, depression and anxiety severity, frequency of each item of the MINI suicide module, resting HR, and HRV measures among the three groups. Analyses of variances (ANOVA) were used for continuous variables, and chi-square test was used for categorical variables. *Post-hoc* analyses were conducted using the Fisher's Least Significant Difference (LSD) method. We performed multivariate linear regression analyses to determine associations of resting-state HR and HRV measures with proximal suicide risk. The MINI suicidal score was entered as a dependent variable in linear regression analyses. Age, sex, diagnostic group (MDD, BD, and others), depression, and anxiety severity were entered as covariates. As most previous studies focused on suicidality in mood disorders, MDD and BD also were entered as covariates. To examine whether resting HR and HRV measures could differentiate patients with moderate-to-high suicide risk among patients who reported any kind of suicide-related symptom, multivariate logistic regression analysis was performed in a subgroup of patients with MINI suicidal score >0. The significance level was set at $P < 0.05$. All statistical analyses were performed using R version 4.02 (26).

TABLE 1 | Primary diagnoses of patients included in the analysis.

Diagnosis	*n* (%)
Major depressive disorder	448 (30.6)
Bipolar and related disorder	96 (6.6)
Others	917 (62.8)
Attention deficit/hyperactivity disorder	9 (0.6)
Adjustment disorder	126 (8.6)
Alcohol use disorder	16 (1.1)
Anxiety disorder	148 (10.1)
Depressive disorder other than major depressive disorder	124 (8.5)
Insomnia disorder	30 (2.1)
Obsessive-compulsive and related disorder	16 (1.1)
Panic disorder	222 (15.2)
Posttraumatic stress disorder and acute stress disorder	22 (1.5)
Somatic symptom and related disorder	102 (7.0)
Tic disorder	13 (0.9)
Others	16 (1.1)
Subthreshold diagnoses	73 (5.0)
Total	1,461 (100)

MDD, major depressive disorder.

RESULTS

A total of 1,461 patients (mean age of 42.05 years, 36.8% male) was included in the study analysis. **Table 1** lists the primary psychiatric diagnoses of the patients as determined by the MINI. Among the total 1,461 patients, 448 (30.7%) had MDD, 222 (15.2%) had panic disorder, 148 (10.1%) had anxiety disorder other than panic disorder, 102 (7.0%) had somatic symptom or related disorder, and 96 (6.6%) had bipolar disorder. Seventy-three (5.0%) patients did not experience psychiatric symptoms that met the DSM criteria for any disorder and were assigned as having a subthreshold diagnosis.

Among the total 1,461 patients, 472 (32.3%) responded "yes" to at least one item of the MINI suicide module (MINI suicidal score >0), while 229 (15.7%) showed moderate-to-high risk based on the MINI suicidal score. The primary psychiatric diagnoses of patients were diverse (**Figure 1**). The mean MINI suicidal score was highest in the BD group [6.49 standard deviation (SD) = 8.22)], followed by the MDD group [5.01 (SD = 7.42); **Table 2**]. Likewise, patients with moderate-to-high suicidal risk were most common in BD (41.7%) and MDD (34.6%) groups. Of patients with non-MDD, 19.2% ($n = 194$) responded "yes" to at least one item of the MINI suicide module, and 7.3% ($n = 74$) had moderate-to-high suicide risk.

In terms of demographic characteristics, females were more common in the MDD group. The BD group was youngest, followed by the MDD group and others. Depression and anxiety

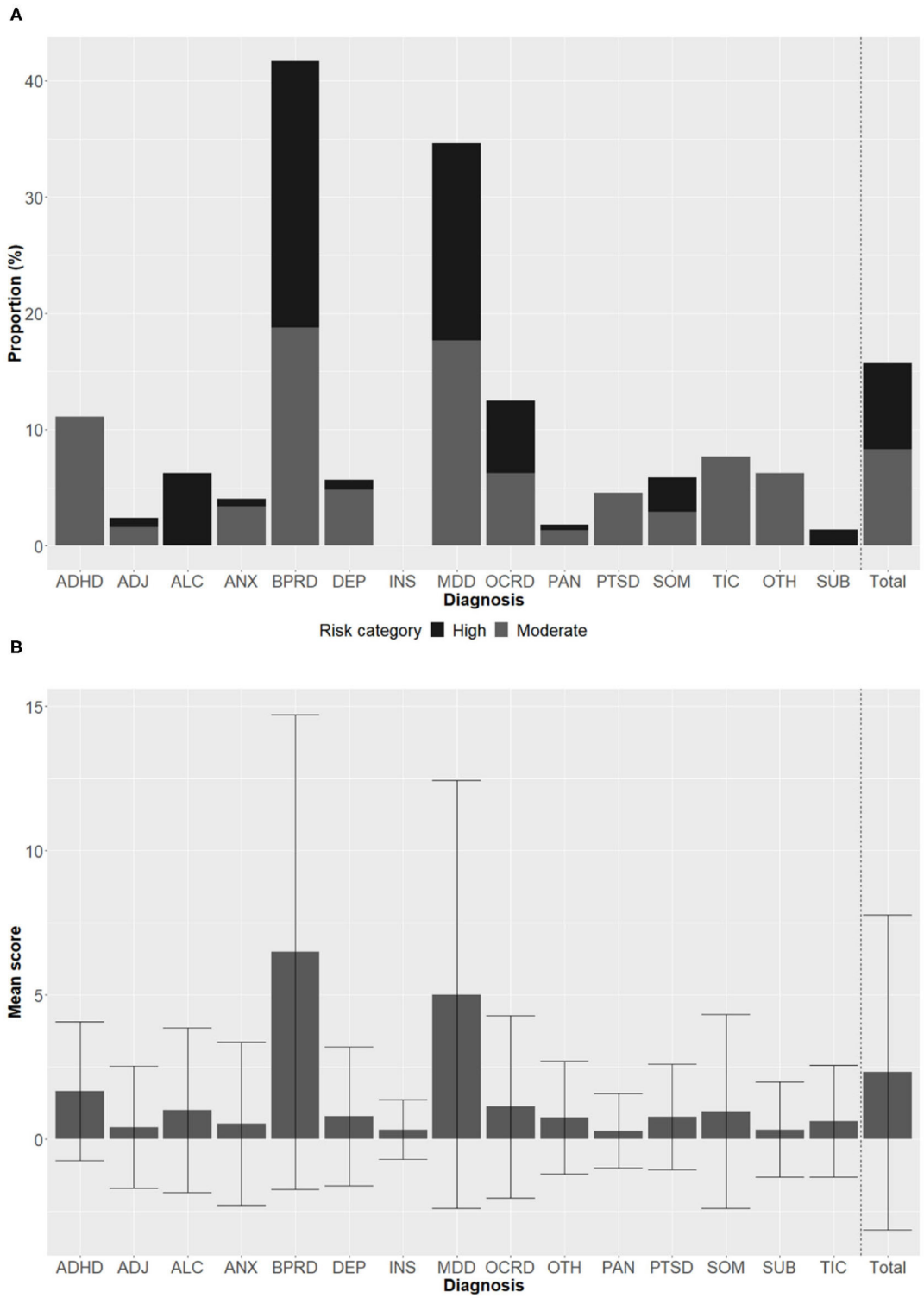

FIGURE 1 | Distribution of MINI suicidal scores across primary diagnoses. MINI suicidal score was categorized as low risk (<6 points), moderate risk (6–9 points), or high risk (≥10 points). Proportions of subjects with moderate risk and high risk in each primary diagnosis **(A)**. Mean MINI suicidal score in each primary diagnosis **(B)**. Error bars represent standard deviation. MINI, Mini-International Neuropsychiatric Interview; ADHD, attention deficit hyperactivity disorder; ADJ, adjustment disorder; ALC, alcohol use disorder; ANX, anxiety disorder other than panic disorder; BPRD, bipolar and related disorders; DEP, depressive disorder other than major depressive disorder; INS, insomnia disorders; MDD, major depressive disorder; OCRD, obsessive-compulsive and related disorders; PAN, panic disorder; PTSD, posttraumatic stress disorder or acute stress disorder; SOM, somatic symptom and related disorders; TIC, tic disorders; OTH, others; SUB, subthreshold diagnosis.

TABLE 2 | Comparisons of demographic, clinical characteristics and suicidal risk between major depressive disorder and other diagnoses.

	MDD[1] (*n* = 448)	BD[2] (*n* = 96)	Others[3] (*n* = 917)	X^2 or *F*	*P*	*Post-hoc* analysis		
						[1] *vs.* [2]	[2] *vs.* [3]	[3] *vs.* [1]
Demographic and clinical variables								
Age, mean (SD)	41.11 (13.85)	32.20 (10.51)	43.52 (13.04)	33.87	<0.001	<0.001	<0.001	0.001
Sex, male	125 (27.9)	46 (47.9)	368 (40.1)	24.50	<0.001	<0.003	0.405	<0.003
HAM-D score, mean (SD)	20.01 (6.01)	17.30 (7.19)	13.16 (5.90)	198.72	<0.001	<0.001	<0.001	<0.001
HAM-A score, mean (SD)	20.65 (6.34)	17.76 (7.88)	16.44 (6.92)	57.04	<0.001	<0.001	<0.001	0.071
MINI suicide module								
Recurrent thought of death, n (%)	257 (57.4)	55 (57.3)	116 (12.6)	33,036	<0.001	1.000	<0.003	<0.003
Idea of self-harm, n (%)	34 (7.6)	13 (13.5)	9 (1.0)	62.08	<0.001	0.180	<0.003	<0.003
Suicidal idea, n (%)	153 (34.2)	38 (39.6)	33 (3.6)	263.62	<0.001	1.000	<0.003	<0.003
Suicide plan, n (%)	39 (8.7)	12 (12.5)	5 (0.5)	75.48	<0.001	1.000	<0.003	<0.003
Recent suicide attempt, n (%)	26 (5.8)	7 (7.3)	3 (0.3)	FE	<0.001	1.000	<0.003	<0.003
Lifetime suicide attempt, n (%)	88 (19.6)	31 (32.3)	30 (3.3)	62.73	<0.001	0.021	<0.003	<0.003
MINI suicidal score, mean (SD)	5.01 (7.42)	6.49 (8.22)	0.58 (2.33)	155.8	<0.001	0.008	<0.001	<0.001

MDD, major depressive disorder; BD, bipolar disorder; HAM-D, Hamilton depression scale; HAM-A, Hamilton anxiety scale; MINI, mini international neuropsychiatric interview.

TABLE 3 | Comparison of HRV measures between MDD, BD, and others group.

	MDD[1] (*n* = 448)	BD[2] (*n* = 96)	Others[3] (*n* = 917)	*F*	*P*	*Post-hoc* analysis		
						[1] *vs.* [2]	[2] *vs.* [3]	[3] *vs.* [1]
HR (bpm)	79.42 (13.12)	80.00 (12.88)	76.86 (12.24)	7.76	<0.001	0.679	0.549	0.386
RMSSD (ms)	20.73 (12.21)	23.94 (13.24)	21.42 (11.82)	−1.36	0.174			
SDNN (ms)	28.72 (13.29)	32.36 (13.83)	30.65 (13.93)	4.31	0.014	0.018	0.246	0.014
LF (ms^2/Hz)	234.82 (367.47)	366.63 (631.26)	274.48 (526.75)	3.031	0.049	0.017	0.081	0.162
HF (ms^2/Hz)	155.92 (197.06)	200.59 (237.62)	174.12 (244.50)	1.83	0.161			
LF/HF ratio	2.46 (3.22)	3.03 (4.69)	2.71 (5.68)	0.67	0.513			

MDD, major depressive disorder; BD, bipolar disorders; HR, resting state heart rate; RMSSD, root mean square of R-R interval of successive differences; SDNN, standard deviation of average normal-normal intervals; LF, low frequency (0.04∼0.15 Hz); HF, high frequency (0.15∼0.4 Hz).

severity, all items in the MINI suicidal module, and MINI suicidal score were highest in the BD group, followed by the MDD group and others.

Resting state HR and HRV measures were compared among the three groups (**Table 3**). Significant differences were observed in resting HR, SDNN, and LF between groups. In *post-hoc* analyses, the MDD group had lower resting HR, SDNN, and LF compared with the BD group and a lower SDNN compared with the others group.

In linear regression analyses, both HR ($P = 0.037$) and RMSSD ($P = 0.003$) showed significant association with the MINI suicidal score after adjusting for age, sex, primary diagnosis, and HAM-D and HAM-A scores (**Table 4**). The overall directions of the association were similar across MDD, BD and others groups (**Figure 2**). Other HRV measures did not show significant associations with the MINI suicidal score. In logistic regression analyses, only RMSSD showed a significant association with moderate-to-high suicide risk after adjusting for the aforementioned covariates ($P = 0.098$ with HR, $P = 0.019$ with RMSSD; **Table 5**). When we only included participants with any suicide-related symptom (MINI suicidal score >0), a total of 472 subjects with MINI suicidal score 0 was included in the analyses. Both HR ($P = 0.010$) and RMSSD ($P = 0.002$) showed significant associations with MINI suicidal score. In logistic regression analyses, HR ($P = 0.017$) and RMSSD ($P = 0.012$) showed significant associations with moderate-to-high suicide risk.

Of all patients included in the analyses, 738 (50.0%) completed the alcohol use disorders identification test (AUDIT) (27). An AUDIT score ≥8 suggests harmful alcohol consumption. When we adjust harmful alcohol consumption in regression analyses to determine the effects of HR and HRV on suicide risk, resting HR and RMSSD showed significant association with the MINI suicidal score in linear regression analyses (Standardized beta = 0.074, $t = 2.23$, $P = 0.026$ for HR; standardized beta = 0.070, $t = -2.073$, $P = 0.039$ for RMSSD), while none of them show significant associations with the moderate-to-high suicide risk in logistic regression analysis ($P = 0.170$ for HR; $P = 0.167$ for RMSSD).

TABLE 4 | Multivariate linear regression analysis of association of resting heart rate (HR) and root-mean-square of R-R interval successive difference with the MINI suicidal scale.

	Unstandardized beta	SE	Standardized beta	*t*	*P*
Model 1: HR as an independent variable					
HR	0.021	0.010	0.049	2.085	0.037
Age	−0.037	0.010	−0.090	−3.742	<0.001
Sex	0.431	0.264	0.038	1.634	0.102
HAM-D score	0.291	0.032	0.361	9.167	<0.001
HAM-A score	−0.063	0.028	−0.082	−2.254	0.024
Primary diagnosis, MDD	2.621	0.312	0.220	8.388	<0.001
Primary diagnosis, bipolar disorder	4.267	0.529	0.193	8.065	<0.001
Model 2: RMSSD as an independent variable					
RMSSD	−0.032	0.011	−0.070	−2.968	0.003
Age	−0.049	0.010	−0.120	−4.910	<0.001
Sex	0.392	0.264	0.0.35	1.486	0.138
HAM-D score	0.293	0.032	0.364	9.288	<0.001
HAM-A score	0.066	0.028	−0.085	−2.342	0.019
Primary diagnosis, major depressive disorder	2.611	0.312	0.220	8.367	<0.001
Primary diagnosis, bipolar disorder	4.271	0.528	0.194	8.086	<0.001

MINI, Mini-International Neuropsychiatric Interview; HR, resting state heart rate; SE, standard error; HAM-D, Hamilton depression scale; HAM-A, Hamilton anxiety scale; RMSSD, root mean square of R-R interval of successive differences.

DISCUSSION

Suicide is a major mental health problem that remains difficult to prevent. Finding objectively measurable biomarkers to detect proximal suicide risk could change the current approaches to suicide prevention. In this study, we examined whether resting-state HR and HRV measures showed significant associations with proximal suicide risk in patients with diverse psychiatric conditions. We found that resting-state HR and RMSSD were associated with proximal suicide risk, suggesting their potential as biomarkers for suicide risk prediction.

In our study, we included patients with diverse psychiatric conditions. The MDD group had more females compared with other diagnostic groups, which is consistent with previous findings that MDD is more commonly observed in females (28). Patients with diverse psychiatric diagnoses reported suicide-related symptoms. Approximately 4% of individuals in the others group showed a moderate-to-high suicide risk. A recent review suggested that a person with suicidal thoughts is at risk even if there are few overt symptoms of psychiatric diagnoses (29). Considering that suicidal behavior was observed trans-diagnostically, suicidal behavior disorder was suggested as a different psychiatric diagnostic entity in the DSM-5 (30).

Most previous studies on resting HRV focused on comparisons between patients with a single psychiatric disorder and healthy controls. Meta-analytic studies have shown that decreased HRV is associated with diverse psychiatric illnesses including MDD (13), BD (14), anxiety disorder (15), and schizophrenia (16), indicating an association of decreased HRV

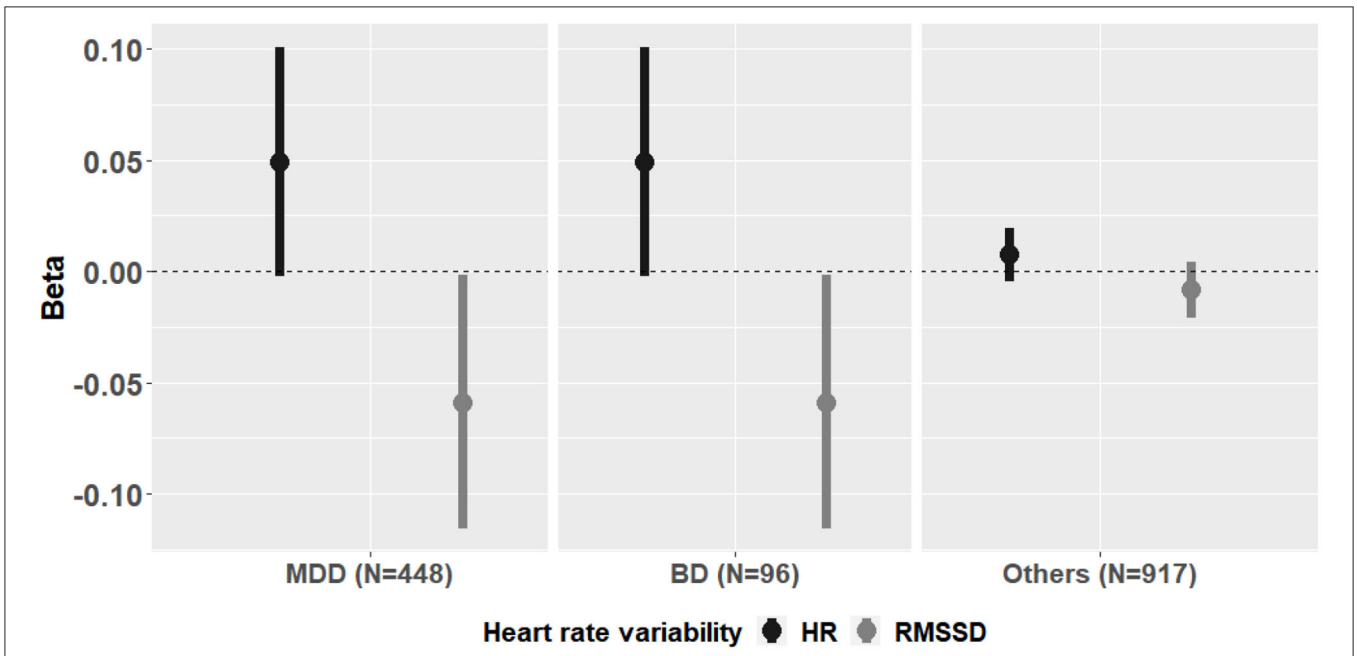

FIGURE 2 | Association between heart rate variability and MINI suicidal scale in two subgroups of major depressive disorder and other diagnoses. MINI, Mini-International Neuropsychiatric Interview; MDD, major depressive disorder; RMSSD, root mean square of R-R interval of successive differences; HR, resting state heart rate.

TABLE 5 | Multivariate logistic regression analysis of association of resting heart rate (HR) and root-mean-square of R-R interval successive difference with the moderate-to-high suicide risk.

	aOR	95% CI	*P*
Model 1: HR as an independent variable			
HR	1.012	0.998–1.026	0.098
Age	0.969	0.956–0.983	<0.001
Sex	0.844	0.582–1.225	0.372
HAM-D score	1.239	1.185–1.296	<0.001
HAM-A score	0.950	0.914–0.987	0.008
Primary diagnosis			<0.001
- Major depressive disorder	5.237	3.428–8.001	<0.001
- Bipolar and related disorder	8.037	4.436–14.563	<0.001
Model 2: RMSSD as an independent variable			
RMSSD	0.981	0.966–0.997	0.019
Age	0.962	0.948–0.976	<0.001
Sex	0.871	0.599–1.267	0.460
HAM-D score	1.241	1.186–1.298	<0.001
HAM-A score	0.949	0.913–0.986	0.008
Primary diagnosis			<0.001
- Major depressive disorder	5.237	3.427–8.005	<0.001
- Bipolar and related disorder	8.142	4.487–14.774	<0.001

MINI, Mini-International Neuropsychiatric Interview; HR, resting state heart rate; SE, standard error; HAM-D, Hamilton depression scale; HAM-A, Hamilton anxiety scale; RMSSD, root mean square of R-R interval of successive differences.

with psychopathology in general rather than with a single disorder. Whether there are diagnosis-specific differences in resting HRV measures remains unclear. Other factors including symptom severity could affect the differences between diagnostic groups. In our study, the overall directions of association were similar across diverse diagnostic groups (**Figure 2**), and the results remained significant even before adjusting for diagnostic groups.

Previous studies showed that a heightened autonomic state measured using HR and HRV (i.e., higher HR and lower variance of RR intervals) were associated with suicide (6). However, limited research has explored the associations of HR and HRV with proximal suicide risk. Most studies focused on lifetime suicide attempt or suicide ideation, which cannot be used to evaluate if an individual is an "at-risk" state. In our study, resting-state HR and RMSSD both showed significant associations with proximal suicide risk measured using the MINI suicidal score. In addition, the association remained significant in subgroup analysis with patients who reported any kind of suicide- related symptoms only (patients with a MINI suicidal score >0), indicating the potential of resting HR and RMSSD as a biomarker used for proximal suicide risk prediction.

Both HR and HRV are controlled by the autonomic nervous system. In particular, RMSSD is a marker of resting vagal tone. Cortical activity modulates cardiac activity via the vagus nerve (31). In addition, the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) tonically inhibit the amygdala via the vagal pathway (32). Thus, reduced vagal tone could reflect the activity of OFC and mPFC, which are associated with cognitive control in relation to suicide attempt (33). Prior studies have demonstrated the association between vagally-mediated resting state HRV and cognitive (34) and affective flexibility (35). Cognitive inflexibility can lead to suicidal behavior during a crisis, in which patients consider suicide the only way to escape their current distress (36).

In the Research Domain Criteria (RDoC) project that aims to identify trans-diagnostic dimensions of psychiatric illnesses, resting HR and HRV are affected by the arousal and regulatory system. This system is one of the least studied areas of the RDoC system in association with suicide (37). Unlike other risk factors, resting-state HR and HRV measures can be monitored on a real-time basis using recent technology (6). With this newly developed technology, clinicians might predict and prevent suicide in a more effective and timely manner. Additional study is needed to apply resting-state HR and HRV to evaluating acute suicide risk on a real-time basis.

The current study findings should be interpreted within the context of the study design. First, this study only included cross-sectional, single, and short-term evaluations. Therefore, we could not evaluate causal relationships. We also did not evaluate whether patients with high risk of suicide in our study actually showed suicidal behavior prospectively. However, as mentioned above, the MINI suicidal score showed good predictive validity in a previous study. Second, we could not control for several confounding factors of resting HRV including physical comorbidities, somatic symptoms, physical activity, current medications, body mass index, sleep profile, timing and smoking status. Third, the study did not include healthy controls.

Notwithstanding the abovementioned limitations, this study demonstrated the associations of resting-state HR and RMSSD with proximal suicide risk in patients with diverse psychiatric conditions. Across diverse psychiatric populations, including those with subthreshold disorder manifestations, we found that resting HR and RMSSD displayed significant associations with proximal suicide risk. In addition, we found that resting HR and RMSSD demonstrated significant associations with proximal suicide risk among patients with any suicide-related symptom (MINI suicidal score >0). Additional research with real time monitoring is needed to confirm the study findings.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Samsung medical center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JB developed the initial research idea. JB, DL, and YC conducted statistical analyses. JB and DL wrote the manuscript. DL and YC

constructed the table and figures. JB, DL, YC, and KH edited the finalized version. 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.2021.652340/full#supplementary-material

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ORIGINAL RESEARCH
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Predictive Factors Associated With Methods of Suicide: The Korean National Investigations of Suicide Victims (The KNIGHTS Study)

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Background: Because the suicide mortality depends on the lethality of suicide methods, the identification and prediction of suicide methods are important for suicide prevention.

Methods: Examination data of suicide decedents were collected based on police reports. Suicide decedents were divided into groups according to the suicide methods (hanging, gas poisoning, pesticide poisoning, jumping, drug poisoning, and drowning) they used. Predictive factors for each suicide method in comparison to other suicide methods were identified.

Results: Among 23,647 subjects, hanging was the most common method of suicide. Regarding gas poisoning, the history of previous suicide attempt was a risk factor and being age of 65 or older was a protective factor. Being age of 65 or older showed a highly strong association with suicide by pesticide poisoning. Being age of 18 or younger and the presence of schizophrenia were associated with jumping. A history of psychiatric outpatient treatment was a risk factor for drug poisoning. Regarding suicide by drowning, schizophrenia was a risk factor, while being age of 65 or older was a protective factor.

Limitations: Only eight out of a total of 17 regions in South Korea were examined and included in the data of this study. Also, the methods of suicide were defined as one method that directly caused the death, which could undermine other less fatal methods used.

Conclusions: There were differences in predictive factors according to the method of suicide. Predicting the method of suicide in people at high risk for suicide stands to be an important strategy for suicide prevention in clinical settings.

Keywords: method of suicide, suicide method, risk factor, suicide, suicide victims

INTRODUCTION

Suicide is a major cause of death worldwide, with ∼800,000 people dying by suicide every year. In 2018, the incidence of suicide in South Korea was 26.6 per 100,000 people (1), which is the highest national incidence among the Organization for Economic Cooperation and Development (OECD) countries (2). Although the government of South Korea has implemented suicide prevention policies, including the enactment of the Suicide Prevention Law, the positive effects of government actions are still insufficient.

The lethality of suicide methods affects suicide mortality. Therefore, the identification and prediction of suicide methods are important for suicide prevention. The process and mechanism of choosing a suicide method are complex and multidetermined, influenced by various factors, such as environment, culture, as well as individual characteristics. According to previous studies, the differences regarding methods of suicide appear between countries and regions (3–7). Trends in suicide methods may change with time (8, 9) as new methods of suicide emerge (10) and the diffusion occur between one population and another population (11). The selection of suicide method is also known to be affected by season or day of the week (7), media reports (12), genetic effect (13), and comorbid physical or psychiatric disorders (14, 15). High accessibility, such as specific drug use, household firearm ownership, occupational drug use, also acts as predictive factors for suicide methods (15–17). Moreover, previous studies have reported that sex, education, marital status, residential areas, leaving a suicide note, and experiencing interpersonal conflict are associated with the method of suicide (12, 18–20).

Nevertheless, the evidence on risk factors according to suicide methods has been established in small sample sizes in few countries, with known limitations that comparative analysis of suicide methods is insufficient. In this study, we aim to investigate the comprehensive risk factors of suicide methods using the examination data of police reports on people who have died by suicide in South Korea.

METHODS

Data Source and Study Population

This study used data from the Korean National Investigations of Suicide Victims (the KNIGHTS study) conducted by the Korea Psychological Autopsy Center (KPAC) (21). The KNIGHTS study was conducted by examining police investigation reports of people who died by suicide from January 1, 2013 to December 31, 2017. Trained investigators comprising mental health professionals (including certified psychiatric and mental health nurses), mental health psychologists, and mental health social workers with experience in psychiatric epidemiologic surveys were recruited for the study. The team visited a total of 254 police stations in 17 regions of South Korea. They examined police reports on people who had died by suicide and identified basic personal information, information related to the suicide, information on the causes of suicide, and information from informants' interview. According to the Korea National Statistical Office, the number of people who died by suicide during the study period was estimated to be ∼70,000. As of March 2020, KPAC had completed the examinations in eight regions (Seoul, Sejong, Daejeon, Gwangju, Jeju, Gangwon-do, Chungcheongbuk-do, and Chungcheongnam–do) of the 17 regions. At that time, data were publicly available on 23,648 deaths by suicide. The data of the KNIGHTS study were categorized into general disclosure, limited disclosure, and non-disclosure according to their characteristics, and we were able to include variables with general disclosure and limited disclosure in the analyses. The analyses of this data form the basis of the current study. Informed consent was waived by the Institutional Review Board of Samsung Medical Center because the study population is deceased.

Methods of Suicide

To identify the characteristics of suicide decedents according to the suicide method, we investigated the methods of suicide in the study population. Per KNIGHTS study protocol, the method of suicide was recorded as the one method that resulted in death. When two or more methods were used for suicide, the method of suicide was recorded as the direct cause of death based on police reports. When two or more direct causes of death were reported by police, the method with the higher fatality was recorded as the method of suicide.

Outcomes

We identified demographic, suicide-related, and psychiatric characteristics of people who died by suicide. The demographic characteristics included sex, age, employment status, and the presence of physical illness. The suicide-related characteristics included the location of suicide, drinking status, joint suicide, homicide-suicide, the presence of a suicide note, and major cause of suicide. The psychiatric characteristics included psychiatric symptoms, psychiatric diagnosis, psychiatric treatment, the history of previous suicide attempts, and the history of previous non-suicidal self-injuries. Regarding the potential risk factors, we investigated the association between potential risk factors and each method of suicide in comparison to other methods of suicide.

Statistical Analyses

We investigated the distribution of demographic, suicide-related, and psychiatric characteristics, of suicide decedents according to various methods of suicide. Comparisons between methods of suicide were conducted using chi-squared tests. The multivariate logistic regression analyses were used to calculate the odds ratios (ORs) for potential risk factors associated with each method of suicide in comparison to other reported methods of suicide. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Methods of Suicide in All Subjects

Among 23,652 people who died by suicide, 12,283 (51.93%) died by hanging, which was the most common method, followed by

jumping (15.81%), gas poisoning (13.73%), pesticide poisoning (8.00%), drowning (5.25%), and drug poisoning (2.10%). We subsequently analyzed the six methods of suicide including hanging, gas poisoning, pesticide poisoning, jumping, drug poisoning, and drowning. Four of the suicide cases by hanging were excluded due to insufficient personal information about the victims.

Demographic and Suicide Characteristics in Subjects

Table 1 shows the demographic characteristics and suicide-related information of the subjects. Males accounted for 69.7% of the sample. Although more males comprised the total sample, in cases of suicide due to drug poisoning, females accounted for 48.3% of deaths and the sex differences were small. The age distribution of the subjects also showed differences according to the method of suicide. Nearly half of the subjects aged 10–19 years died by jumping (49.8%), and the subjects aged 70 or older accounted for 54.9% of suicide deaths by pesticide poisoning. More specifically, 65.9% of subjects who died by pesticide poisoning and 51.7% of subjects who died by drug poisoning had physical illnesses.

Suicide characteristics also differed according to the method of suicide. More than half of the subjects who died in hospitals (51.5%) had selected jumping as the method. The status of drinking alcohol at the time of death was a common factor in a significant percentage of subjects who died by gas poisoning (44.2%) and in subjects who died by drug poisoning (43.3%). In the case of suicide by gas poisoning, the percentage of those who consumed alcohol (44.2%) was more than twice the percentage of those who did not drink at the time of death (20.7%). Of people who elected joint suicide, 76.8% died by gas poisoning. Of people who died by gas poisoning, 55.5% wrote suicide notes before death. In 54.5 and 56.7% of people who died by jumping and by drug poisoning, respectively, the major cause of suicide was mental health problems.

Psychiatric Characteristics of People Who Died by Suicide

Table 2 shows the psychiatric characteristics of people who died by suicide. Among 23,648 subjects, 84.0% had psychiatric symptoms and 68.3% had symptoms of depression. Psychiatric symptoms were present in 94.8 and 90.3% of people who died by drug poisoning and by jumping, respectively. Of subjects with psychosis, 43.9% died by jumping. Among the subjects who died by drug poisoning, 36.6% had insomnia, with this psychiatric symptom having the highest proportion in this group compared to those who died by other methods of suicide (**Figure 1**). Having a known history of psychiatric diagnosis was more frequent among subjects in the jumping group (50.1%) and in the drug poisoning group (64.0%), with 50.4 and 62.8% of the subjects having a history of psychiatric treatment, respectively. In these two groups, the most common psychiatric diagnosis was depressive disorders. 28.48 and 37.83% of subjects in the jumping group and the drug poisoning group, respectively, had been diagnosed with depressive disorders. Among the people diagnosed with schizophrenia, 49.51% died by jumping. Among the subjects in the drug poisoning group, there were more people with a history of attempted suicide (27.6%) than those without (18.9%).

Adjusted Odds Ratios of Potential Risk Factors for Each Method of Suicide

Table 3 shows adjusted odds ratios of potential risk factors for each method of suicide in comparison to other methods of suicide. Regarding hanging, in comparison to subjects aged 19–34 years, being 18 years of age or younger (OR 0.49, 95% CI: 0.33–0.71) and having schizophrenia (OR 0.38, 95% CI: 0.30–0.47) were protective factors. Being 35–49 years of age (OR 1.43, 95% CI: 1.27–1.61), 50–64 years of age (OR 1.60, 95% CI: 1.41–1.81), and 65 years of age or older (OR 1.50, 95% CI: 1.31–1.72) were risk factors for suicide by hanging in comparison to being 19–34 years of age. Regarding gas poisoning, being 65 years of age or older (OR 0.19, 95% CI: 0.15–0.24) was a protective factor, while having previously attempted suicide was a risk factor (OR 1.62, 95% CI: 1.33–1.98). Compared to being 19–34 years of age, being 35 years of age or older showed a strong association with pesticide poisoning. Odds ratios for subjects in age groups of 35–49, 50–64, and 65 years or older were 2.81 (95% CI: 1.55–5.11), 10.43 (95% CI: 5.92–18.38), and 22.97 (95% CI: 12.97–40.67), respectively. Being self-employed (OR 2.16, 95% CI: 1.76–2.66), having schizophrenia (OR 2.31, 95% CI: 1.49–3.57), and having alcohol use disorders (OR 2.63, 95% CI: 1.86–3.71) were also risk factors for suicide by pesticide poisoning. Being a housewife was a protective factor for suicide by pesticide poisoning (OR 0.48, 95% CI: 0.32–0.72). Regarding suicide by jumping, being 18 years of age or younger (OR 3.71 95% CI: 2.63–5.22) and having schizophrenia (OR 2.39, 95% CI: 1.96–2.93) were risk factors, while being self-employed was a protective factor (OR 0.46, 95% CI: 0.37–0.57). Regarding suicide by drug poisoning, alcohol use disorders (OR 2.19, 95% CI: 1.49–3.24) and psychiatric treatment in outpatient clinics (OR 2.86, 95% CI: 1.92–4.26) were risk factors, while being 65 years of age or older (OR 0.49, 95% CI: 0.31–0.77) was a protective factor. Regarding suicide by drowning, having schizophrenia (OR 1.69, 95% CI: 1.21–2.36) was a risk factor and being 65 years of age or older (OR 0.32, 95% CI: 0.24–0.42) was a protective factor.

Table 4 presents the risk factors of each method of suicide in a descending order of ORs and protective factors of each method in an ascending order of ORs. Being 35 years of age or older, having alcohol use disorders, having schizophrenia, and being self-employed were strong risk factors for suicide by pesticide poisoning. Being 18 years of age or younger and having schizophrenia were strong risk factors for suicide by jumping. Treatment in psychiatric outpatient clinics and alcohol use disorders were strong risk factors for suicide by drug poisoning.

DISCUSSION

This study demonstrated that more than half of people who died by suicide chose hanging as the method of suicide. Strong risk factors for pesticide poisoning were being 35 years of age or

TABLE 1 | Demographic and suicide characteristics of people who died by suicide.

	Total people who died by suicide (n = 23,648)		Method of suicide												p
			Hanging (n = 12,279)		Gas poisoning (n = 3,248)		Pesticide poisoning (n = 1,893)		Jumping (n = 3,739)		Drug poisoning (n = 497)		Drowning (n = 1,241)		
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Sex															<0.0001
Male	16,485	69.71	8,762	71.36	2,602	80.11	1,298	68.57	2,125	56.83	257	51.71	932	75.1	
Female	7,163	30.29	3,517	28.64	646	19.89	595	31.43	1,614	43.17	240	48.29	309	24.9	
Age (years)															<0.0001
10–19	508	2.15	132	1.08	41	1.26	1	0.05	253	6.77	3	0.6	73	5.88	
20–29	2,212	9.35	910	7.41	408	12.56	8	0.42	534	14.28	38	7.65	265	21.35	
30–39	3,682	15.57	1,856	15.12	874	26.91	44	2.32	546	14.6	76	15.29	212	17.08	
40–49	4,443	18.79	2,363	19.24	926	28.51	133	7.03	548	14.66	113	22.74	218	17.57	
50–59	4,660	19.71	2,663	21.69	622	19.15	310	16.38	585	15.65	104	20.93	203	16.36	
60–69	3,011	12.73	1,673	13.62	238	7.33	358	18.91	430	11.5	72	14.49	116	9.35	
70–79	3,207	13.56	1,702	13.86	102	3.14	612	32.33	507	13.56	64	12.88	94	7.57	
≥ 80	1,925	8.14	980	7.98	37	1.14	427	22.56	336	8.99	27	5.43	60	4.83	
Employment status															<0.0001
Employed	5,007	21.17	2,755	22.44	998	30.73	159	8.4	585	15.65	78	15.69	271	21.84	
Self-employed	2,985	12.62	1,721	14.02	517	15.92	366	19.33	207	5.54	37	7.44	71	5.72	
Student	806	3.41	241	1.96	99	3.05	1	0.05	329	8.8	8	1.61	114	9.19	
Housewife	1,146	4.85	649	5.29	55	1.69	54	2.85	279	7.46	28	5.63	39	3.14	
Unemployed	11,943	50.5	6,026	49.08	1,251	38.52	1,199	63.34	2,139	57.21	292	58.75	610	49.15	
Other	1,761	7.45	887	7.22	328	10.1	114	6.02	200	5.35	54	10.87	136	10.96	
Physical illness															<0.0001
Yes	9,427	39.86	5,024	40.92	753	23.18	1,247	65.87	1,442	38.57	257	51.71	354	28.53	
No	7,721	32.65	4,007	32.63	1,345	41.41	309	16.32	1,254	33.54	122	24.55	491	39.56	
Unknown	6,500	27.49	3,248	26.45	1,150	35.41	337	17.8	1,043	27.9	118	23.74	396	31.91	
Physical disability															<0.0001
Yes	1,304	5.51	657	5.35	118	3.63	154	8.14	236	6.31	31	6.24	48	3.87	
No	11,702	49.48	6,170	50.25	1,675	51.57	806	42.58	1,840	49.21	235	47.28	632	50.93	
Unknown	10,642	45	5,452	44.4	1,455	44.8	933	49.29	1,663	44.48	231	46.48	561	45.21	
Location of suicide															<0.0001
Home	13,087	55.34	7,875	64.13	1,604	49.38	1,469	77.60	1,283	34.31	361	72.64	8	0.64	
Home of acquaintance	334	1.41	154	1.25	64	1.97	22	1.16	72	1.93	10	2.01	0	0	
School/work place	804	3.40	608	4.95	74	2.28	50	2.64	42	1.12	7	1.41	2	0.16	
Public place	6,416	27.13	2,106	17.15	1,135	34.94	216	11.41	2,125	56.83	47	9.46	652	52.54	

(Continued)

TABLE 1 | Continued

	Total people who died by suicide (n = 23,648)		Method of suicide												p
			Hanging (n = 12,279)		Gas poisoning (n = 3,248)		Pesticide poisoning (n = 1,893)		Jumping (n = 3,739)		Drug poisoning (n = 497)		Drowning (n = 1,241)		
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Accommodations	1,112	4.70	650	5.29	272	8.37	42	2.22	45	1.20	53	10.66	0	0	
Suburbs/hill	865	3.66	691	5.63	65	2	59	3.12	14	0.37	11	2.21	3	0.24	
Hospital	301	1.27	117	0.95	1	0.03	10	0.53	155	4.15	2	0.4	0	0	
Other	729	3.08	78	0.64	33	1.02	25	1.32	3	0.08	6	1.21	576	46.41	
Drinking status															<0.0001
Drinker	6,619	27.99	3,234	26.34	1,435	44.18	570	30.11	669	17.89	215	43.26	292	23.53	
Non-drinker	7,666	32.42	3,943	32.11	673	20.72	644	34.02	1,670	44.66	148	29.78	281	22.64	
Unknown	9,363	39.59	5,102	41.55	1,140	35.1	679	35.87	1,400	37.44	134	26.96	668	53.83	
Joint suicide															<0.0001
Yes	327	1.38	28	0.23	251	7.73	18	0.95	13	0.35	1	0.2	10	0.81	
No	23,220	98.19	12,237	99.66	2,996	92.24	1,873	98.94	3,726	99.65	495	99.6	1,148	92.51	
Unknown	101	0.43	14	0.11	1	0.03	2	0.11	0	0	1	0.2	83	6.69	
Homicide-suicide															<0.0001
Yes	92	0.39	41	0.33	4	0.12	11	0.58	13	0.35	1	0.2	4	0.32	
No	23,286	98.47	12,116	98.67	3,197	98.43	1,861	98.31	3,710	99.22	491	98.79	1,183	95.33	
Unknown	270	1.14	122	0.99	47	1.45	21	1.11	16	0.43	5	1.01	54	4.35	
Suicide note															<0.0001
Yes	8,576	36.27	4,626	37.67	1,804	55.54	399	21.08	923	24.69	235	47.28	340	27.4	
No	12,706	53.73	6,486	52.82	1,236	38.05	1,239	65.45	2,372	63.44	218	43.86	748	60.27	
Unknown	2,366	10.01	1,167	9.5	208	6.4	255	13.47	444	11.87	44	8.85	153	12.33	
Major cause of suicide															<0.0001
Occupational	1,080	4.57	600	4.89	149	4.59	28	1.48	179	4.79	5	1.01	93	7.49	
Economic	4,410	18.65	2,419	19.7	1,207	37.16	152	8.03	271	7.25	51	10.26	224	18.05	
Family-related	2,500	10.57	1,443	11.75	307	9.45	259	13.68	276	7.38	48	9.66	99	7.98	
Interpersonal	1,154	4.88	639	5.2	205	6.31	45	2.38	148	3.96	16	3.22	65	5.24	
Physical health	4,235	17.91	2,298	18.71	233	7.17	677	35.76	672	17.97	76	15.29	120	9.67	
Mental health	9,018	38.13	4,265	34.73	938	28.88	661	34.92	2,037	54.48	282	56.74	511	41.18	
Other	397	1.68	193	1.57	76	2.34	21	1.11	58	1.55	2	0.4	31	2.5	
Unknown	854	3.61	422	3.44	133	4.09	50	2.64	98	2.62	17	3.42	98	7.9	

TABLE 2 | Psychiatric characteristics of people who died by suicide.

	Total people who died by suicide (n = 23,648)		Method of suicide												p
			Hanging (n = 12,279)		Gas poisoning (n = 3,248)		Pesticide poisoning (n = 1,893)		Jumping (n = 3,739)		Drug poisoning (n = 497)		Drowning (n = 1,241)		
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Presence of psychiatric symptoms															<0.0001
Yes	19,872	84.03	10,261	83.57	2,607	80.26	1,574	83.15	3,377	90.32	471	94.77	956	77.03	
No	674	2.85	378	3.08	66	2.03	45	2.38	91	2.43	3	0.6	72	5.8	
Unknown	3,102	13.12	1,640	13.36	575	17.7	274	14.47	271	7.25	23	4.63	213	17.16	
Psychiatric symptoms															
Psychosis	1,495	6.32	436	3.55	69	2.12	76	4.01	656	17.54	49	9.86	135	10.88	<0.0001
Mania/hypomania	531	2.25	229	1.86	55	1.69	17	0.90	151	4.04	29	5.84	32	2.58	<0.0001
Depression	16,154	68.31	8,534	69.50	2,105	64.81	1,235	65.24	2,716	72.64	389	78.27	700	56.41	<0.0001
Anxiety	4,173	17.65	2,196	17.88	569	17.52	165	8.72	857	22.92	105	21.13	153	12.33	<0.0001
Insomnia	2,985	12.62	1,439	11.72	309	9.51	175	9.24	648	17.33	182	36.62	114	9.19	<0.0001
Cognitive impairment/behavioral problem	978	4.14	416	3.39	17	0.52	189	9.98	264	7.06	17	3.42	44	3.55	<0.0001
Alcohol overuse or misuse	3,185	13.47	1,762	14.35	366	11.27	352	18.59	351	9.39	115	23.14	121	9.75	<0.0001
Overuse or misuse of other substances	299	1.26	162	1.32	43	1.32	17	0.90	40	1.07	15	3.02	18	1.45	0.0125
Behavioral addiction	763	3.23	394	3.21	204	6.28	19	1.00	66	1.77	12	2.41	49	3.95	<0.0001
Pediatric psychiatric symptoms	82	0.35	21	0.17	5	0.15	3	0.16	40	1.07	1	0.2	10	0.81	<0.0001
History of psychiatric diagnosis															<0.0001
Yes	7,392	31.26	3,321	27.05	651	20.04	519	27.42	1,874	50.12	318	63.98	434	34.97	
No	6,185	26.15	3,463	28.20	883	27.19	475	25.09	795	21.26	55	11.07	341	27.48	
Unknown	10,071	42.59	5,495	44.75	1,714	52.77	899	47.49	1,070	28.62	124	24.95	466	37.55	
Psychiatric diagnosis															
Schizophrenia	719	3.04	163	1.33	21	0.65	34	1.80	356	9.52	26	5.23	84	6.77	<0.0001
Bipolar disorder	401	1.70	160	1.3	30	0.92	15	0.79	133	3.56	24	4.83	28	2.26	0.0004
Depressive disorders	4,538	19.19	2,182	17.77	413	12.72	297	15.69	1,065	28.48	188	37.83	235	18.94	<0.0001
Anxiety disorders	660	2.79	305	2.48	60	1.85	27	1.43	177	4.73	35	7.04	29	2.34	0.0127
Adjustment disorder	60	0.25	28	0.23	6	0.18	0	0.00	15	0.4	2	0.4	5	0.4	0.2208
Somatic symptom disorder	34	0.14	15	0.12	3	0.09	3	0.16	10	0.27	2	0.4	1	0.08	0.9366
Sleep disorders	848	3.59	400	3.26	91	2.8	60	3.17	177	4.73	54	10.87	33	2.66	<0.0001
Neurocognitive disorders	518	2.19	210	1.71	5	0.15	105	5.55	143	3.82	8	1.61	29	2.34	<0.0001
Alcohol use disorders	733	3.10	351	2.86	64	1.97	66	3.49	137	3.66	43	8.65	34	2.74	<0.0001
Other substance-related disorders	12	0.05	8	0.07	0	0.00	0	0.00	2	0.05	0	0	0	0	0.7444

(Continued)

TABLE 2 | Continued

	Total people who died by suicide (n = 23,648)		Method of suicide												p
			Hanging (n = 12,279)		Gas poisoning (n = 3,248)		Pesticide poisoning (n = 1,893)		Jumping (n = 3,739)		Drug poisoning (n = 497)		Drowning (n = 1,241)		
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	
Behavioral addiction	14	0.06	3	0.02	6	0.18	0	0.00	4	0.11	0	0	1	0.08	0.0075
Pediatric psychiatric disorder	32	0.14	6	0.05	2	0.06	2	0.11	21	0.56	0	0	1	0.08	0.0001
Other	206	0.87	83	0.68	15	0.46	9	0.48	76	2.03	6	1.21	12	0.97	0.014
History of psychiatric treatment															<0.0001
Yes	7,333	31.01	3,279	26.7	644	19.83	496	26.2	1,886	50.44	312	62.78	440	35.46	
No	6,278	26.55	3,518	28.65	896	27.59	481	25.41	811	21.69	55	11.07	337	27.16	
Unknown	10,037	42.44	5,482	44.65	1,708	52.59	916	48.39	1,042	27.87	130	26.16	464	37.39	
Psychiatric treatment															
Outpatient clinic	5,931	25.08	2,617	21.31	493	15.18	377	19.92	1,613	43.14	257	51.71	349	28.12	0.3185
Admission	2,046	8.65	745	6.07	124	3.82	109	5.76	725	19.39	80	16.1	155	12.49	<0.0001
Treatment in other departments	295	1.25	140	1.14	15	0.46	22	1.16	82	2.19	19	3.82	7	0.56	0.0101
Counseling center	142	0.60	64	0.52	17	0.52	2	0.11	35	0.94	4	0.8	18	1.45	0.0016
Other	60	0.25	29	0.24	5	0.15	3	0.16	17	0.45	2	0.4	3	0.24	0.9991
Previous suicide attempt															<0.0001
Yes	3,986	16.86	1,952	15.90	610	18.78	211	11.15	713	19.07	137	27.57	207	16.68	
No	6,221	26.31	3,224	26.26	766	23.58	545	28.79	1,075	28.75	94	18.91	338	27.24	
Unknown	13,441	56.84	7,103	57.85	1,872	57.64	1,137	60.06	1,951	52.18	266	53.52	696	56.08	
Previous self-injury															<0.0001
Yes	903	3.82	451	3.67	99	3.05	17	0.9	192	5.14	30	6.04	55	4.43	
No	7,039	29.77	3,607	29.38	937	28.85	586	30.96	1,203	32.17	125	25.15	369	29.73	
Unknown	15,706	66.42	8,221	66.95	2,212	68.1	1,290	68.15	2,344	62.69	342	68.81	817	65.83	

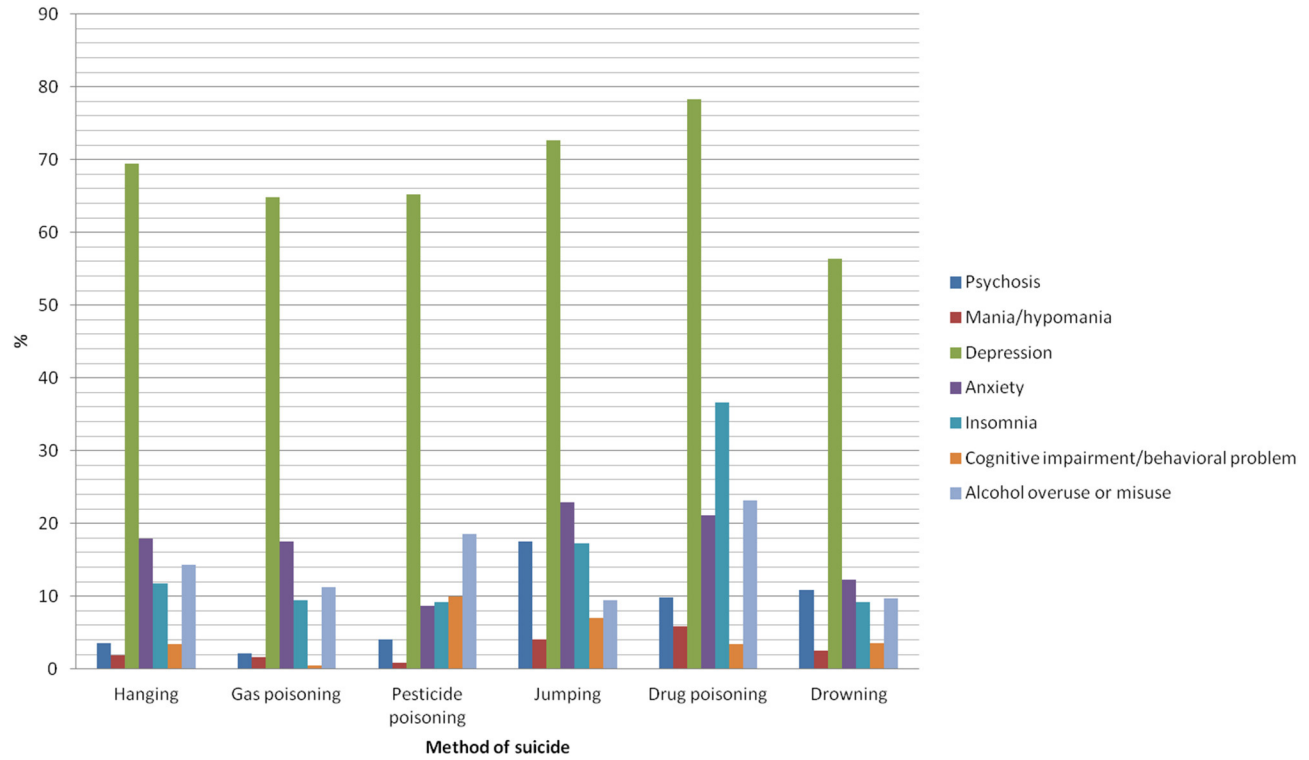

FIGURE 1 | Manifestation of psychiatric symptoms before death by suicide according to suicide method.

older, having alcohol use disorders, having schizophrenia, and being self-employed. In comparison to people who died by other methods of suicide, people who died by jumping were more likely to be 18 years of age or younger and to have been diagnosed with schizophrenia. People who died by drug poisoning were more likely to have a history of treatment in psychiatric outpatient clinics and have alcohol use disorders.

A previous study based on the Korean national data showed that 5.7% of people who attempted suicide used hanging as the method of suicide (22). In the current study's sample of people who died by suicide, hanging was the most common method of suicide. This difference in findings can be attributed to the high fatality of hanging. In our study, even though the associations between suicide risk factors and hanging were not very strong, a previous history of self-injury (one strong risk factor of suicide due to hanging) had clinical significance as an important risk factor, demanding assessments in clinical settings.

The second most common suicide method was jumping. Compared to other suicide methods, people who died by jumping were more likely to be younger and had been diagnosed with schizophrenia. Considering that about half of teenagers and subjects diagnosed with schizophrenia died by jumping, clinicians should be aware of the risk of jumping in these populations. Also, with the risk of suicide being high in this population, strategies to reduce accessibility to jumping may be necessary to prevent suicide.

Pesticide poisoning accounted for 8% of suicide deaths herein. The main finding is that pesticide poisoning cases were primarily concentrated in the elderly. Although the risk of pesticide poisoning increased for people as early as age 35, the risk increased abruptly in the group of people aged 65 years or older, with the risk in this group being about 23 times the risk in people aged 19–34 years. Moreover, having been diagnosed with schizophrenia and alcohol use disorders were strong risk factors for suicide by pesticide poisoning. Therefore, physicians should be aware of the risk of suicide by pesticide poisoning in people with these disorders and in the elderly and should evaluate at-risk people's access to pesticides (including uses for work).

Drug poisoning accounted for 2% of suicide deaths among the subjects herein. In a previous study of people who attempted suicide in South Korea, drug poisoning was the most common method, accounting for 53.7% of all suicide attempts (22). The low lethality of drug poisoning may explain such difference. In assessing the characteristics of the people who died by drug poisoning, females accounted for 48%, the highest proportion among all methods of suicide. Subjects who died by drug poisoning were more likely to have physical illnesses and psychiatric symptoms. Among comorbid psychiatric symptoms (while depression was the most common symptom), insomnia showed a large proportion in those who died by drug poisoning compared to other methods of suicide. Treatment in psychiatric outpatient clinics was a strong risk factor for suicide by drug poisoning. This result is consistent with the findings of previous

TABLE 3 | Adjusted odds ratios of potential risk factors for each method of suicide.

	Hanging (*n* = 12,279)	Gas poisoning (*n* = 3,248)	Pesticide poisoning (*n* = 1,893)	Jumping *n* = 3,739)	Drug poisoning (*n* = 497)	Drowning (*n* = 1,241)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female sex	0.91 (0.84–0.99)*	0.63 (0.54–0.73)***	1.50 (1.28–1.77)***	1.40 (1.26–1.56)***	1.74 (1.35–2.25)***	0.59 (0.49–0.72)***
Age (years)						
≤18	0.49 (0.33–0.71)***	0.32 (0.16–0.64)**	0.00 (<0.01–>999.99)	3.71 (2.63–5.22)***	0.00 (<0.01–>999.99)	0.94 (0.58–1.52)
19–34	Reference	Reference	Reference	Reference	Reference	Reference
35–49	1.43 (1.27–1.61)***	1.04 (0.89–1.21)	2.81 (1.55–5.11)***	0.62 (0.54–0.72)***	1.18 (0.84–1.68)	0.50 (0.40–0.63)***
50–64	1.60 (1.41–1.81)***	0.53 (0.44–0.63)***	10.43 (5.92–18.38)***	0.63 (0.53–0.73)***	0.91 (0.63–1.33)	0.42 (0.33–0.54)***
≥65	1.50 (1.31–1.72)***	0.19 (0.15–0.24)***	22.97 (12.97–40.67)***	0.75 (0.63–0.89)**	0.49 (0.31–0.77)**	0.32 (0.24–0.42)***
Employment status						
Employed	1.18 (1.06–1.31)**	1.03 (0.89–1.20)	0.89 (0.67–1.19)	0.82 (0.70–0.94)**	0.86 (0.61–1.22)	0.75 (0.60–0.93)*
Self-employed	1.26 (1.11–1.43)***	1.11 (0.92–1.33)	2.16 (1.76–2.66)***	0.46 (0.37–0.57)***	0.59 (0.35–0.97)*	0.38 (0.26–0.55)***
Student	0.71 (0.55–0.92)**	0.62 (0.43–0.90)*	0.49 (0.06–3.71)	1.47 (1.13–1.90)**	0.61 (0.24–1.56)	1.42 (1.01–2.01)*
Housewife	1.36 (1.15–1.60)***	0.51 (0.36–0.73)***	0.48 (0.32–0.72)***	1.14 (0.94–1.38)	0.51 (0.31–0.85)**	0.80 (0.52–1.23)
Unemployed	Reference	Reference	Reference	Reference	Reference	Reference
Other	0.91 (0.77–1.07)	1.34 (1.04–1.69)*	1.19 (0.84–1.70)	0.71 (0.56–0.89)**	1.79 (1.21–2.64)**	1.20 (0.87–1.64)
Physical illness	0.99 (0.90–1.09)	0.74 (0.63–0.87)***	1.28 (1.05–1.56)*	1.02 (0.89–1.16)	1.58 (1.16–2.16)**	0.92 (0.73–1.14)
Psychiatric diagnosis						
Schizophrenia	0.38 (0.30–0.47)***	0.25 (0.15–0.41)***	2.31 (1.49–3.57)***	2.39 (1.96–2.93)***	1.02 (0.63–1.65)	1.69 (1.21–2.36)**
Bipolar disorder	0.94 (0.75–1.18)	0.81 (0.53–1.22)	1.06 (0.61–1.86)	1.12 (0.88–1.42)	1.50 (0.94–2.38)	0.96 (0.63–1.47)
Depressive disorders	1.04 (0.91–1.19)	1.06 (0.82–1.36)	1.00 (0.78–1.29)	0.97 (0.84–1.13)	0.99 (0.71–1.37)	1.01 (0.78–1.32)
Anxiety disorders	0.98 (0.83–1.17)	0.85 (0.62–1.16)	0.74 (0.48–1.14)	1.17 (0.96–1.42)	1.14 (0.77–1.69)	0.76 (0.51–1.14)
Sleep disorders	0.87 (0.74–1.02)	1.31 (1.00–1.72)	0.99 (0.72–1.36)	0.98 (0.81–1.19)	1.59 (1.13–2.26)**	0.86 (0.58–1.28)
Neurocognitive disorders	0.71 (0.57–0.88)**	0.23 (0.07–0.72)*	1.67 (1.24–2.24)**	1.23 (0.96–1.58)	0.70 (0.33–1.50)	1.46 (0.90–2.39)
Alcohol use disorders	1.03 (0.86–1.24)	0.91 (0.66–1.26)	2.63 (1.86–3.71)***	0.73 (0.59–0.92)**	2.19 (1.49–3.24)***	0.71 (0.47–1.07)
Psychiatric treatment						
Outpatient clinic	0.77 (0.67–0.89)***	0.75 (0.58–0.97)*	0.76 (0.58–1.00)	1.79 (1.52–2.11)***	2.86 (1.92–4.26)***	0.99 (0.75–1.31)
Admission	0.70 (0.61–0.80)***	0.62 (0.48–0.80)***	0.63 (0.47–0.85)**	1.92 (1.66–2.22)***	0.83 (0.59–1.15)	1.20 (0.93–1.56)
Other	0.98 (0.79–1.22)	0.79 (0.52–1.21)	0.56 (0.34–0.90)*	1.32 (1.02–1.70)*	1.63 (0.97–2.73)	1.12 (0.71–1.74)
Previous suicide attempt	0.97 (0.85–1.11)	1.62 (1.33–1.98)***	0.71 (0.54–0.94)*	0.75 (0.63–0.89)**	1.43 (0.96–2.14)	0.93 (0.70–1.24)
Previous self–injury	1.24 (1.01–1.52)*	0.55 (0.39–0.77)**	0.65 (0.36–1.20)	0.96 (0.75–1.24)	0.90 (0.52–1.58)	0.92 (0.61–1.41)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

studies. A cross-sectional study conducted in Japan showed that poisoning by prescription drugs was used more frequently for suicide in people who saw a psychiatrist than in people who did not see a psychiatrist (23). These findings, however, should be interpreted with caution. Physicians and psychiatrists should not undertreat patients with psychiatric symptoms due to fear of patients dying by suicide using prescribed drugs. According to our results, 96% of the subjects with a history of treatment in psychiatric outpatient clinics died by suicide methods other than drug poisoning. Moreover, depression and insomnia are independent risk factors for suicide (24–28). Therefore, for psychiatric patients with a high risk of suicide, active intervention for symptoms, short intervals of prescription drug use, and regular evaluations of suicide risk stand to be more helpful for the prevention of suicide rather than limiting the prescription of drugs.

As mentioned above, there are significant differences in the proportions of methods for suicide and suicide attempt. Although suicide attempts and completed suicide are different phenomena, the history of a suicide attempt is one of the strongest predictors for completed suicide (29) and about 10–15% of those who attempt suicide eventually die by suicide (30). It is not well-known whether suicide attempters use the same methods when they subsequently die by suicide. However, a cohort study showed that although suicide attempters are likely to choose the same method, they will select a more lethal method when they change the method of suicide (31). Moreover, a psychological autopsy study reported that the majority of the suicide attempters switched to a different method for their final act that led to the death and this suggests that people who have attempted suicide are likely to change from previous methods with low lethality to those with high lethality (32). These imply that a person who survives after a suicide attempt by a method of low lethality should be considered at high risk for a subsequent fatal suicide attempt, and appropriate intervention should be taken to prevent suicide death.

TABLE 4 | Risk factors and protective factors for each method of suicide based on multivariate logistic regression[a].

	Hanging		Gas poisoning		Pesticide poisoning		Jumping		Drug poisoning		Drowning	
	Factor	**OR**	**Factor**	**OR**	**Factor**	**OR**	**Factor**	**OR**	**Factor**	**OR**	**Factor**	**OR**
Risk factors	Age 50–64 years	1.60	Previous suicide attempt	1.62	Age ≥ 65 years	22.97	Age ≤ 18 years	3.71	Psychiatric outpatient clinic	2.86	Schizophrenia	1.69
	Age ≥ 65 years	1.50			Age 50–64 years	10.43	Schizophrenia	2.39	Alcohol use disorders	2.19	Student	1.42
	Age 35–49 years	1.43			Age 35–49 years	2.81	Admission to psychiatry	1.92	Female sex	1.74		
	Housewife	1.36			Alcohol use disorders	2.63	Psychiatric outpatient clinic	1.79	Sleep disorders	1.59		
	Self-employed	1.26			Schizophrenia	2.31	Student	1.47	Physical illness	1.58		
	Previous self-injury	1.24			Self-employed	2.16	Female sex	1.40				
	Employed	1.18			Neurocognitive disorders	1.67						
					Female sex	1.50						
Protective factors	Schizophrenia	0.38	Age ≥ 65 years	0.19	Housewife	0.48	Self-employed	0.46	Age ≥ 65 years	0.49	Age ≥ 65 years	0.32
	Age ≤ 18 years	0.49	Neurocognitive disorders	0.23	Admission to psychiatry	0.63	Age 35–49 years	0.62	Housewife	0.51	Self-employed	0.38
	Admission to psychiatry	0.70	Schizophrenia	0.25	Previous suicide attempt	0.71	Age 50–64 years	0.63	Self-employed	0.59	Age 50–64 years	0.42
	Student	0.71	Age ≤ 18 years	0.32			Alcohol use disorders	0.73			Age 35–49 years	0.50
	Neurocognitive disorders	0.71	Housewife	0.51			Age ≥ 65 years	0.75			Female sex	0.59
	Psychiatric outpatient clinic	0.77	Age 50–64 years	0.53			Previous suicide attempt	0.75			Employed	0.75
	Female sex	0.91	Student	0.62			Employed	0.82				
			Admission to psychiatry	0.62								
			Female sex	0.63								
			Physical illness	0.74								
			Psychiatric outpatient clinic	0.75								
			Previous self-injury	0.55								

[a]*Factors have significance at $p > 0.05$; detailed statistical measures of each factor are listed in* ***Table 3****.*

In the results, about 70% of suicide victims were male, which is consistent with the results of previous psychological autopsy studies (32, 33). This difference in sex may be related to the tendency of men to choose more violent and fatal methods when attempting suicide (34). According to a previous study, about 62% of men died by suicide at their first attempt compared to 38% in women (33). It is not clear why men choose the methods with high lethality, but there has been a wide range of explanations, including the stronger intent to die (35), being less avoidant for disfiguring wounds (36) and biological factors such as lower brain serotonin level (37).

The strength of this study is the identification of demographic and clinical risk factors for methods of suicide using a large sample of examinations based on police reports conducted according to a validated and systematic protocol. Nevertheless, this study has several limitations. First, because this study is conducted using the populations of eight regions (out of a total of 17 regions) in South Korea, it is difficult to apply the results directly to other regions or countries or to generalize findings. Trends in suicide methods may change due to the accessibility to materials and sociocultural environments, which vary with regions and time. However, our results on risk factors for methods of suicide are generally consistent with the findings of previous studies conducted in various regions and countries. This suggests that specific characteristics are shared in the process of selecting a method of suicide, suicidal intent, acceptability of a suicide method, and psychosocial factors pertaining to access to certain materials and/or methods of suicide. Second, in this study, "methods of suicide" were recorded as the direct cause of death when a person used two or more methods for suicide. In addition, when two or more direct causes of death existed, the method with the higher fatality was recorded as the method of suicide. For example, when a person died by hanging after overdosing on drugs, per the KNIGHTS study protocol, the method of suicide was recorded as hanging. Therefore, it is possible that when two or more methods were used for suicide, methods with lower fatality were underestimated. Third, several important confounders that could affect the methods of suicide were not included in the analyses because data source does not include them or they were categorized into non-disclosure variables. For example, although several personal factors including level of education (18) and religious belief (38) are known to affect the selection of suicide method, we were not able to use them in the analyses. In addition, although the data of the KNIGHTS study included information on whether a suicide victim had attempted suicide before the suicide death, the information on the method of previous suicide attempts was not included.

The possibility of a switch to another suicide method should be considered in strategies for suicide prevention by predicting and intervening in the method of suicide. A controlled trial conducted in Hong Kong demonstrated that limiting retail access to charcoal has efficacy in preventing suicide by charcoal burning. Moreover, the overall suicide rate decreased with limited retail access to charcoal (27). This suggests that limiting access to materials used in specific suicide methods does not lead potential victims to immediately switch to alternative methods of suicide. When access channels to materials that can be used in suicide are clear and when intervention is possible—as in the case of charcoal—it is necessary to limit access to the purchasing of materials intended for suicide. For example, the removal of all charcoal packs from open shelves in major retail outlets, following the Hong Kong study, stands to be efficacious not only for a reduction in suicides using gas poisoning but also for the overall prevention of suicides by all methods.

In conclusion, there are differences in demographic and clinical risk factors according to methods of suicide. Strong risk factors for differing methods of suicide include being elderly for pesticide poisoning, being a teenager and having schizophrenia for jumping, and having treatment history in psychiatric clinics for drug poisoning. Predicting methods of suicide in people at high risk for suicide through evaluation in the accessibility related to individual socio-environmental factors and acceptability is may be an important and efficacious strategy for suicide prevention in clinical settings.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://data.psyauto.or.kr.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Samsung Medical Center. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HK contributed to the search for background literature, to writing the original draft of the manuscript, to reviewing, and to editing the subsequent manuscript revisions. GL and JC collected data. YK and M-HS contributed to formal analysis. HJ contributed to conceptualization, project administration, and supervision. All authors contributed to writing and editing the manuscript.

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Structured Professional Judgment to Assist the Evaluation and Safety Planning of Suicide Risk: The Risk of Suicide Protocol (RoSP)

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Background: The Risk of Suicide Protocol (RoSP) is a structured professional judgment (SPJ) scheme designed in line with NICE guidelines to improve clinicians' ability to evaluate and manage suicide risk.

Aims: This study aimed to evaluate the efficacy of RoSP in two settings: (1) unexpected deaths of people in the community who were known to mental health services; and (2) an inpatient hospital specializing in the assessment and treatment of patients with personality disorder.

Method: In Study 1, information from a database of unexpected deaths ($N = 68$) within an NHS health board was used to complete a RoSP assessment (blind to cause of death) and information from the Coroner's Court was used to assign people to suicide vs. natural causes/accidental death. In Study 2, patients ($N = 62$) were assessed on the RoSP upon admission to hospital and their self-injurious behaviors were recorded over the first 3 months of admission.

Results: (1) Evaluations using RoSP were highly reliable in both samples (ICCs 0.93–0.98); (2) professional judgment based on the RoSP was predictive of completed suicide in the community sample (AUC = 0.83) and; (3) was predictive of both suicide attempts (AUC = 0.81) and all self-injurious behaviors (AUC = 0.80) for the inpatient sample.

Conclusion: RoSP is a reliable and valid instrument for the structured clinical evaluation of suicide risk for use in inpatient psychiatric services and in community mental health services. RoSP's efficacy is comparable to well-established structured professional judgment instruments designed to predict other risk behavior (e.g., HCR-20 and the prediction of violence). The use of RoSP for the clinical evaluation of suicide risk and safety-planning provides a structure for meeting NICE guidelines for suicide prevention and is now evidence-based.

Keywords: suicide, self-injury, self-harm, structured professional judgement, risk management

INTRODUCTION

In the UK suicide is the leading cause of death in males aged 5–49 and in females age 5–34 (1). In the USA suicide is the 10th most common cause of death, the 2nd most common in 10–34 year olds (2), and leads to an estimated $51 billion in combined medical and work loss costs (3) with similar rankings in other developed regions worldwide (4, 5). Providing effective risk assessment, support and safety planning for those at risk of suicide is of paramount importance and poses a major challenge to professionals and health care services since suicidal ideation and suicide attempts are relatively common and death by suicide is relatively rare (6). Past research has challenged the predictive accuracy of unaided clinical judgements across a range of human risk behaviors (7) and previous studies have demonstrated that global clinical judgements of future self-injurious and suicide risk by psychiatric staff have low predictive value (8). A number of statistical or actuarial scales have arisen in an effort to help clinicians assess and manage suicide risk. However, these tools often fail to predict accurately future suicidal and self-injurious behaviors (9–11) and there is a concern that such measures place too much emphasis on labeling levels of risk and not enough emphasis on understanding and managing the risk. These problems have led to the National Institute for Health and Care (NICE) giving guidance against the sole use of actuarial "tick-box" risk assessment instruments. In particular, NICE guidelines (12) explicitly state: "do not use risk assessment tools and scales to predict future suicide or repetition of self-harm," (1.3.11 p.21) and "do not use risk assessment tools and scales to determine who should and should not be offered treatment or who should be discharged" (1.3.12 p.21).

In the domain of the assessment of violence to others in forensic psychiatric services, the debate between clinical opinion and actuarial instruments led to the development of the "Structured Professional Judgement" (SPJ) approach. SPJs are designed to systematically guide and assist a clinician in the production of a clinical formulation and a risk management plan (13) and are now regarded by many as the gold-standard method of violence risk assessment (14). Importantly, SPJs are not a form of actuarial instrument, where the focus is solely on obtaining a label of the level of risk of an individual, but are instead focused on structuring the clinician's assessment in a standardized and evidenced-based manner, and ensuring that all relevant areas of clinical risk are systematically assessed. There has been one previous attempt to develop an SPJ tool designed for the assessment of suicide risk (15). The Suicide Risk Assessment and Management Manual (S-RAMM) is a SPJ tool that has demonstrated good inter-rater reliability (16) and a good ability to prospectively predict self-injurious and suicidal behavior (17). However, despite the S-RAMM being developed in 2003, with validation studies being published in 2009 (17), it has not received wide acceptance in clinical practice (18). The current research reports the initial validation of the Risk of Suicide Protocol (RoSP). The RoSP is an SPJ scheme predicated upon the methodology and structure of the HCR-20 for violence risk assessment (19) and designed to facilitate detailed evaluation and safety planning of suicide risk with the development of an associated individualized risk management plan that meets NICE recommendations.

Whilst there is overlap between these two SPJ approaches to suicide evaluation, there are a few key differences between the two assessments. Firstly, the S-RAMM contains three subscales (Historical Factors, Current Clinical Factors, and Future Clinical Factors), whereas the RoSP comprises of four subscales (History, Current Clinical, Current Crisis, and Current Thinking). When considering the individual risk factors included in the two assessments, the RoSP places more emphasis on the individual's current social circumstances. Whilst the S-RAMM has one item (Psychosocial Stress) dedicated to evaluating the individual's current social circumstances, the RoSP has five items dedicated to considering an individual's physical health, romantic relationships, employment or financial situation, whether they are experiencing difficulties with the law, and whether they have experienced a recent loss in their life. These five risk factors were designed to structure a clinician's standardized assessment of current psychosocial difficulties and the interaction between these and their mental health. The added emphasis placed on social factors was designed to ensure that the RoSP adhered closely to the NICE guidelines that suggest the main components of an assessment of need following an episode of self-injury should include the individual's physical health issues, social circumstances and problems, personal relationships, financial problems and recent life difficulties (12). Moreover, whilst the S-RAMM contains items relating to demographic risk factors (e.g., age, gender, marital status), the RoSP deliberately excludes such items in an effort to focus more on dynamic risk factors that can be targeted and ameliorated through treatment and management. The RoSP aims to move away from a focus exclusively upon any variable with predictive validity (as would be contained in an actuarial risk instrument) to modifiable risk factors which clinicians can work upon to try to reduce and manage suicide risk moving forward. For example, although different age groups are associated with different rates of suicidal behavior (2), a clinician could not reasonably suggest altering one's age as a potential treatment or management plan. The same argument applies to gender.

An additional difference between the two measures is that the RoSP asks clinicians to consider an individual's history of violent behavior and their current feelings of anger. These items were included in the RoSP due to past research demonstrating that historical violence is associated with a 5-fold increase in risk of death from suicide (20) and that feelings of anger and hostility are linked to increased risk of suicide attempts (21, 22). Thus, it was felt important that an evaluation of a person's anger and risk behavior to others (in terms of past violence and aggression) was incorporated into the formulation about risk to self. Finally, the RoSP (20 items) contains fewer items than the S-RAMM (23 items). This is likely to be an important factor when considering the palatability of these assessments for clinical staff working in time-pressured clinical environments.

In summary, the Risk of Suicide Protocol (RoSP) is an SPJ scheme designed to facilitate detailed evaluation and safety planning of suicide risk with the development of an associated individualized risk management and treatment plan that meets

NICE recommendations. In this paper we evaluate the efficacy of the RoSP in two different populations: (1) a community setting for patients known to mental health services (a retrospective study); and (2) an in-patient setting for patients with a personality disorder (a prospective study).

METHOD

For study 1, the RoSP was evaluated by trained RoSP raters blind to the cause of death, from multi-disciplinary mental health records available at the last known contact with mental health services. These records were "cleaned" by another person who was not a rater to ensure that there was no mention of the cause of death contained therein. Data were entered into an anonymized database for research purposes. Ethical permission for the study was given by the National Health Service Research Ethics Committee (15/EM/0044).

For study 2, the RoSP was used as part of the standard assessment for patients as they were admitted to the hospital. Data on behavior, including all episodes of self-injury were recorded on a daily basis by nursing staff. Permission to use an anonymized version of this clinical database for research was granted by the National Health Service Research Ethics Committee (14/EM/1178).

Participants

For Study 1, information was gathered on service users who were known to mental health services in a UK NHS Health Board who had died unexpectedly between March 2009 and March 2013. Based on the verdict of an inquest in a Coroner's Court, two groups were defined: one where the Coroner judged the person to have completed suicide or had recorded an open verdict (suicide group), and one where the Coroner judged the person to have died from natural causes or from an accidental death (non-suicide group). People within the Older Adult Services were excluded from the study as it was decided that these people would be more likely than the other groups to have died from natural causes and this would have led to a systematic bias. Cases where the Coroner's verdict was unknown or uncertain were eliminated from the study. The suicide group consisted of 39 (57.9% male) cases and the non-suicide group consisted of 29 (58.6% male) cases. Mean ages were 50.1 and 45.1 years, respectively, which did not differ significantly [$t(65) = 1.78$, ns]. No other demographic details were recorded that were not otherwise coded within the RoSP (i.e., psychiatric diagnosis is included in the RoSP evaluation).

For study 2 participants were in-patients, resident in a low secure unit (Ty Catrin, Pastoral Healthcare, Cardiff) that specializes in the treatment and management of service users with a diagnosis of a personality disorder and who were admitted to the psychiatric hospital over the period of 2009–2014. The patients constitute a high-risk group as they were detained under the UK Mental Health Act (1983) due to the risk they posed to self and/or others. The hospital completed the RoSP as part of the initial clinical assessment of all service users. The assessments were completed within 1 week of admission by the service user's clinical psychologist (who was fully trained in RoSP) using both past clinical records and clinical interviews. This initial RoSP would be regularly updated according to new information (including new acts of self-injury) and treatment response in order to evaluate dynamic risk to self, as per recommended clinical practice. However, the present analysis uses only the first completion of the RoSP.

Of the 68 patients admitted to the hospital during the period of study, a RoSP was completed on 62 [36 women: mean age 30.0 ($SD = 8.9$, Range 18–56 years), 26 men: mean age 32.9 ($SD = 12.6$, Range 18–65 years)]. A RoSP was not completed on 6 patients because they were discharged from the hospital before a RoSP could be completed. Data for this study was taken from the first 3 months of the service user's stay at the hospital. All 62 patients stayed within the hospital for at least this period of time.

Measures

Risk of Suicide Protocol—RoSP (Snowden and Gray, 2020)

The RoSP (version 1.0) was written in 2007. Whilst a review of the scientific literature was our main source for deciding what risk factors would constitute the RoSP. We also carefully considered the clinical utility of each item from both the point of view of the ease of obtaining information for the assessing clinician and whether the risk factor was "dynamic" in that it could be targeted for treatment or management. We deliberately chose risk factors that had these properties.

During the first few years of development, RoSP underwent several updates and alterations based on feedback from clinicians and staff who were piloting the instrument in clinical practice. Items on the RoSP were rewritten or clarified, and some were dropped or morphed into the present version which we will refer to simply as RoSP. We mainly piloted the instrument in a low secure hospital for the assessment and treatment of people with personality disorder, as many of this group of service-users had complex clinical needs and posed many risks to both themselves and others. These complex clinical challenges afforded the developers of the RoSP a good opportunity to work through complex issues of assessment with the staff involved and also to have multiple outcome variables for analysis in what are relatively rare events in the general population (self-harm and attempted suicide). There were no completed suicides during the period of development of the RoSP, due mainly to the excellent and intensive clinical care that these patients were afforded by their clinical team.

The RoSP consists of 20 items that the clinician evaluates *before* formulating possible suicide risk of the individual and before making a judgement about the level and nature of safety planning and clinical intervention required for the service user, on the basis of suicide risk. Evaluation of each risk factor is not a simple "present" or "absent" as it would be for an actuarial instrument, but rather a detailed clinical formulation. The clinical formulation of each item attempts to provide details of the clinical presentation, or psychosocial problem, that is present for the person and to how the factor may be driving or maintaining suicide risk. Importantly, this includes not only clinical symptoms or presentation, but also psychosocial risk factors. An example of this would be for the item "Financial

TABLE 1 | Items and structure of RoSP.

History
1. Suicide attempts
2. Self-injury
3. Violent behavior
4. History of major mental disorder
5. Membership of high risk group
Current clinical
6. Personality disorder
7. Current depressive symptoms
8. Substance use problems
9. Other current symptoms of mental illness
10. Poor treatment/management outcomes
Current crisis
11. Recent loss of significant other
12. Severe health problems
13. Relationship problems
14. Employment or financial problems
15. Problems with the law
Current thinking
16. Lack of personal support
17. Feelings of hopelessness
18. Feelings of anger
19. Suicidal ideation
20. Preparatory activity

Problems." On the RoSP we would not simply rate this as "present" or "absent," but would provide detail of exactly how much debt, or financial difficulties, the person found themselves in and, crucially, their psychological or emotional reactions to this (e.g., feelings of failure, catastrophic thoughts about possible future outcomes, extreme anxiety about possible loss of home, loss of status, and loss off relationships, etc.). The preferred intervention would then be a psychosocial one—focusing on debt management—and perhaps on psychological intervention for the management of anxiety and catastrophic thoughts.

Thus, the process of completing the RoSP is designed to enhance safety planning for suicide and attempted suicide through the development of an individualized clinical formulation and risk management/treatment plan. We define suicide here as the deliberate attempt to take one's own life. We refer to acts of self-injury without the intention to die as "self-harm" and this is used synonymously with the term non-suicidal self-injury (NSSI), as used elsewhere in the literature (23). We acknowledge that this distinction between self-harm and attempted suicide is often difficult to ascertain (24) as it depends upon an evaluation of the person's intent at the material time, which is often unclear to the person themselves as well as to the clinical team providing care and management. We use the term "self-injury" to refer to any such act without regard for any intention to die or not.

The 20 items of the RoSP are separated into four domains (see **Table 1**). Detailed descriptions of the items, rationales for inclusion, and scoring guidelines are contained in the RoSP manual (obtainable on request from the first author). The first domain is termed "History" and evaluates historical factors, including previous suicide attempts and history of self-injury. The "Current[1] Clinical" domain evaluates the clinical factors that are, or were, recently active (e.g., symptoms of depression, substance use problems). The "Current Crisis" scale evaluates current psychosocial stressors (e.g., loss of others, financial problems, legal problems), and the "Current Thinking" domain evaluates thinking style, including indications of suicidal ideation and intent, and feelings or thoughts of hopelessness and helplessness. We note that inclusion of these factors are consistent with NICE guidelines (12) that suggest that the main components of an assessment of need after an episode of self-injury should include the person's social situation (including current living arrangements, employment, and debt), personal relationships (including any recent breakdown of a significant relationship), recent life events, psychiatric history, and a mental state examination (including any history of previous self-injury and alcohol or drug abuse). Assessment should also include any enduring psychological characteristics that are known to be associated with self-injury and motivation for the act. Each of these areas of need, or risk, as set out in the RoSP are designed to be consistent with NICE guidelines and to assist the clinician to be adherent to these best practice guidelines. Each area of need is completed as a "mini-formulation," presenting the details of each area of need for the person and how it has impacted on their mental state and ability to function, including the impact on the individual's suicidal ideation and intent. This process is then used to inform treatment and safety planning strategies specific to the individual.

The level of safety planning required for suicide risk was termed the structured professional judgment (SPJ) and could range from "*very low,*" to "*very high*" on a 5-point scale. For statistical purposes, each item was rated as present or absent by coding "Yes" if it was rated as being present or "No" if not present. If it was unclear as to whether an item was present or not, the item was rated as uncertain presence, or "?". For usual clinical practice the pattern of presence or absence of risk factors would underpin the developing risk formulation (defined as how the pattern of the individual's risk factors and strengths interact to lead to an understanding of the "why" of suicide risk, thus dictating in turn the most effective risk management, or safety, plan).

For study 1, the RoSP evaluators (AMc, SR, and NSG) received training on the RoSP from the authors of this instrument. All RoSP evaluations were made blind to outcome (suicide vs. natural causes/accidental death). Completion of the RoSP was based on material available within the person's mental health records. The evaluation of "current" clinical status (i.e., in the recent past) was based on information within the mental health

[1]The term "current" is meant to refer to the recent past and/or whether the effects of this risk factor, or area of clinical need, are still having an impact on the person. For example, the item "Recent Loss of Significant Other" could still be regarded as "present" if the person is still experiencing active psychological distress or grief from the loss, even if this significant other died several years ago.

records taken at the time of the last clinical contact with mental health services prior to the person's death.

For study 2, ratings were based on collateral information (e.g., medical and psychiatric records) and clinical interview(s) with the service user. Clinical formulations using the RoSP were completed by the patient's allocated clinical psychologist (with the aid of psychology assistants) within the hospital, all of whom were trained on the use of SPJs in general and were RoSP trained.

Aggression and Vulnerability Scale—AVS

The AVS (25) is a scheme for the evaluation and coding of problematic behaviors such as aggression to others and self-injury. Incidents were coded by clinical staff (nursing staff and psychology assistants trained in the use of the AVS) into one of 10 categories and a severity rating within this category was scored. The AVS has been shown to have good inter-rater reliability for both the categorical judgement and the severity judgment of behaviors (25).

Analysis

For both studies, we used the structured clinical judgment derived from RoSP as our main measure, but also used the "scores" from the RoSP to look at the overall performance of the RoSP, the four subscales and each of the individual items (which we term RoSP scores, as for data analysis purposes it was necessary to assign numbers to the risk evaluation of each area of need). Each item on the RoSP was scored on a three-point scale. Participants scored "0" if that risk factor was absent, "1" if it was partially present, and a "2" if it was present. The total RoSP and subscales scores were calculated by summing the relevant item scores. Missing items were prorated. For study 1, we used a signal detection analysis and calculated the area under the curve (AUC) for the Receiver Operating Characteristic (ROC) for group membership.

For study 2, the data were analyzed in two complimentary ways. The data were recoded to reflect "present" or "not-present" for: (1) any self-injurious behavior; and (2) any suicide attempt for a ROC analysis. However, we also calculated correlations between the frequency of challenging behaviors and RoSP scores. Frequencies of self-injurious behaviors were highly skewed and therefore Spearman's rho was used.

RESULTS

Study 1: Outpatients

Reliability

Ten cases (six men) were evaluated independently by two raters and the interclass correlation coefficients (ICCs) are shown in **Table 2**. All scales and subscales exhibited good to excellent reliability.

Validity

As illustrated in **Table 2**, the AUC for the discrimination of group membership showed large effect sizes for both the RoSP SPJ [AUC = 0.83, 95% CI [0.73, 0.93], $p < 0.001$] and RoSP scores [AUC = 0.80, 95% CI [0.69, 0.91], $p < 0.001$]. Three of the sub-scales (Current Clinical, Current Crisis, and Current Thinking) significantly discriminated between those who completed suicide and those who died from natural causes/accidental death with large effect sizes.

Data from the individual items of the RoSP are presented in **Table 3**. It is clear that not all items of the RoSP had predictive power in this sample. Indeed, some of the items appear to be "anti-predictive" (though not significantly so). For example, people who had completed suicide scored lower on the item "History of Mental Disorder."

TABLE 2 | Descriptive and inferential statistics for the RoSP in study 1.

	Mean (SD)	Range	ICC	AUC (SE) Completed suicide
SPJ	3.2 (1.2)	1–5	0.96**	0.83** (0.05)
Total score	16.9 (6.1)	5–31	0.98**	0.80** (0.06)
History	4.8 (2.3)	1–10	0.99**	0.63 (0.07)
Clinical	4.5 (2.2)	0–10	0.95**	0.74* (0.06)
Crisis	4.1 (1.8)	0–8	0.72*	0.70* (0.07)
Thinking	3.3 (2.2)	0–8	0.94**	0.78** (0.06)

*$p < 0.01$ **$p < 0.001$.

TABLE 3 | Mean RoSP scores and inferential statistics for the patients grouped into suicide vs. control for study 1.

	Control	Suicide	*t*	*p*	Hedges *G*
Suicide	0.63	1.29	3.42	< 0.001	0.83
Self-injury	0.57	0.66	0.45	0.33	0.11
Violence	0.60	0.72	0.61	0.28	0.15
Mental disorder	1.80	1.61	−1.33	0.30	−0.26
High risk group	0.63	1.11	2.21	0.02	0.53
Personality Dis	0.34	0.38	0.23	0.41	0.05
Symp. Depression	0.67	1.46	4.74	< 0.001	1.17
Substance misuse	0.63	1.41	3.69	< 0.001	0.89
Symp.of MD	0.77	0.84	0.33	0.37	0.08
Treatment compl.	1.03	1.43	2.03	0.03	0.50
Loss	0.46	0.72	1.21	0.12	0.30
Health	1.03	0.79	−1.28	0.27	−0.31
Relationships	0.87	1.54	4.28	< 0.001	1.04
Employment	0.80	1.11	1.60	0.06	0.39
Law	0.20	0.47	1.85	0.04	0.45
Support	0.90	1.03	0.80	0.22	0.19
Hopelessness	0.42	0.89	2.31	0.01	0.57
Anger	0.67	0.74	0.36	0.36	0.09
Ideation	0.11	1.08	6.59	< 0.001	1.65
Preparation	0.04	0.57	3.76	< 0.001	0.94

TABLE 4 | Descriptive and inferential statistics for the RoSP in study 2.

	Mean (SD)	Range	ICC	AUC Self-injury	AUC Suicide attempts	Rho Self-injury	Rho Suicide attempts
SPJ	3.4 (1.09)	2–5	0.93**	0.81**	0.80**	0.61**	0.56**
Total score	23.0 (4.8)	13–34	0.96**	0.73*	0.60	0.35*	0.19
History	7.2 (2.2)	3–14	0.96**	0.67*	0.60	0.23	0.15
Clinical	7.4 (1.7)	2–10	0.93**	0.57	0.44	0.02	−0.07
Crisis	3.1 (1.8)	0–7	0.79*	0.46	0.41	−0.06	−0.16
Thinking	5.1 (2.7)	0–10	0.86**	0.75**	0.71**	0.50**	0.39**

*$p < 0.01$, **$p < 0.001$.

Study 2: Inpatients

Reliability

Ten cases (five men) were evaluated independently by two raters and the ICCs are shown in **Table 4**. All scales and subscales exhibit good to excellent reliability.

Validity

Approximately two-thirds (68.3%) of the service users recorded at least one incident of self-injury in the 3-month time period following admission to hospital, with some harming themselves on many occasions (Mean = 18.7, Median = 5.0, Range 0–139). Considering only the instances that were judged to have suicidal intent, 47.5% of the service users had at least one incident (Mean = 3.42, Median = 0, Range 0–31).

Table 4 illustrates the results relating to the efficacy of RoSP. Evaluation of any self-injury produced large effect sizes for the RoSP SPJ [AUC = 0.81, 95% CI [0.69, 0.93], $p < 0.001$] and for the RoSP scores [AUC = 0.73, 95% CI [0.57, 0.87], $p < 0.01$]. When considering instances that were coded as suicide attempts, the RoSP SPJ was a strong predictor [AUC = 0.80, 95% CI [0.69, 0.91], $p < 0.01$] while the RoSP scores were not a significant predictor [AUC = 0.60, 95% CI [0.44, 0.73], ns]. There were no completed suicides during this period of study.

An examination of the subscales of the RoSP (**Table 4**) shows that the Current Thinking scale was highly associated (large effect sizes) with both outcome measures (incidents of self-injury and incidents of attempted suicide), whilst the History scale had some moderate associations with self-injury. However, the Current Clinical and Current Crisis scales had little ability to discriminate those service users that went on to engage in self-injury behaviors in this context. For completeness, we present data from the individual RoSP items in **Table 5**. Again, it should be noted that not all items are predictive of self-injury in this sample, with some items (e.g., Treatment Compliance) appearing to be somewhat anti-predictive of self-injury.

TABLE 5 | Mean RoSP scores and inferential statistics for the patients grouped as to whether they have an instance of deliberate self-injury during the study period.

	No Self-injury	Self-injury	*t*	*p*	Hedges *G*
Suicide	1.04	1.85	4.66	< 0.001	1.26
Self-injury	1.05	1.88	5.22	< 0.001	1.42
Violence[a]	1.83	1.89	0.43	0.34	0.16
Mental disorder	1.57	1.79	0.44	0.33	0.12
High risk group[b]	1.23	1.15	−0.38	0.71	−0.10
Personality Dis.	1.90	1.97	0.02	0.49	0.32
Symp. Depression	0.40	1.37	4.66	< 0.001	1.29
Substance misuse	1.17	1.47	1.00	0.33	0.36
Symp of MD[a]	1.24	1.36	0.99	0.16	0.09
Treatment compl.	1.86	1.58	−1.78	0.08	−0.48
Loss	0.43	0.68	1.24	0.11	0.33
Health	0.38	0.49	0.58	0.29	0.16
Relationships	0.71	0.56	−0.90	0.37	−0.24
Employment	0.33	0.48	0.71	0.24	0.19
Law	0.90	1.03	0.51	0.31	0.14
Support	1.05	1.23	0.96	0.17	0.26
Hopelessness	0.57	1.36	3.51	< 0.001	1.00
Anger	1.38	1.58	1.07	0.15	0.29
Ideation	0.38	1.25	4.00	< 0.001	1.08
Preparation	0.05	0.87	4.53	< 0.001	1.22

[a] *These items changed substantially when RoSP 2.0 was updated to RoSP 3.0. Only data from RoSP 3.0 is presented here.* [b] *This item underwent minor modifications when RoSP 2.0 was updated to RoSP 3.0. Data from both are combined in this analysis.*

DISCUSSION

Across two studies including very different mental health populations and different settings, we have shown that the RoSP can be reliably evaluated and is a valid indicator of serious self-injurious behavior, suicide attempts, and completed suicide.

There are already many instruments that could be used to make a prediction about the likelihood of future suicide attempts [e.g., (11, 26–28)], but analyses of these instruments have shown that they have limited clinical use, mainly due to the low prevalence rates of the behavior being predicted (9, 29). Instead, it is suggested that each individual being assessed for suicide risk needs a careful examination of their clinical needs and psychosocial vulnerabilities, across a range of different factors that have been found to be important to suicide risk. Therefore, the aim of RoSP was to produce a systematic guide to the evaluation of the needs of the individual across

four domains (History, Current Clinical, Current Crisis, and Current Thinking) that clinicians could use to structure their clinical evaluations and use across a range of clinical groups and different contexts. As such, the items were chosen with safety-planning, clinical intervention, and risk reduction and management as the over-arching aim. Hence, the items needed to have reasonable "availability" to clinicians and, ideally, should be amenable to change (i.e., capable of demonstrating potential "treatment responsiveness" or response to intervention). Our demonstration in the present paper that the RoSP's psychometric properties are in-line with similar SPJs used for the assessment of other adverse events, such as violence to others, demonstrates that the RoSP has reliability and validity. Importantly, our aim has not been to attempt to make comparisons with other instruments used for the evaluation of suicide risk (especially so-called actuarial instruments). This is because to attempt to do so would not be comparing like with like, given that the key aim of the RoSP is to develop a SPJ tool that is consistent with NICE guidelines, and which attempts to focus the mind of the evaluator on safety planning and intervention, rather than solely on accurate prediction. Indeed, with regards to the in-patient sample, the Structured Professional Judgment made after completing the RoSP, produced more accurate predictions of future suicidal behavior compared to the total RoSP score, as would be predicted. This finding places further emphasis on the point that the RoSP should not be used as a predictive or actuarial tool, but as a method of understanding risk and facilitating appropriate safety planning.

Looking across the two studies, some individual items of the RoSP were effective across both studies, such as a history of previous suicide attempts, current symptoms of depression, suicidal ideation, and preparatory activity. All of these factors are very well-established in the research literature on suicide completion (29) and our studies confirm their utility across these two very different service contexts. Other items or even subscales, for example Substance Use Problems, were related to self-injurious behavior in one context (community sample), but not in the other (in-patient sample). These differences may be due to the different contexts of the two samples. The in-patient sample had severely restricted access to alcohol and other substances of abuse within secure service provision, and therefore the power of this risk factor to bring about adverse outcome would have been severely restricted. Similarly, the item "Personality Disorder" was not predictive in sample two (in-patient sample). This is due to a lack of variance, where all patients within this sample had a diagnosis of personality disorder. We, therefore, argue that the evaluation of Personality Disorder in suicide risk on the RoSP should continue to be included, given that this item will most probably be of importance to clinical evaluation in samples with more mixed diagnostic characteristics. It is to be hoped that this research article will serve as a trigger to other researchers to evaluate the RoSP as an aid to clinical evaluation of suicide within other clinical settings and services, across different countries and cultures, and it will be expected that different combinations of risk factors and sub-scales will be more powerfully associated with adverse clinical outcomes in different cohorts of service-users.

Finally, some items did not appear to have any value in either setting (e.g., violence). One might be tempted to drop such an item to make a more streamlined assessment, or to replace it with another risk factor that is associated with completed suicide. Further, by giving stronger "weighting" to items that are more strongly associated with suicide one could improve on the ability of the RoSP to identify those at risk of completed suicide. However, we emphasize that predictive validity is not the major aim of the RoSP. Rather, intervention and enhanced safety-planning is the ultimate goal, ensuring that a comprehensive assessment is completed across all necessary clinical and psychosocial areas of potential importance to the individual clinical formulation. Thus, we chose items with a good evidence-base for association with suicide risk, that were likely to be easily available to a clinician, and which could be targeted for intervention. We maintain that across other contexts, (e.g., prison populations; young men from disadvantaged areas) these items will probably prove their worth and we do not want, at this juncture, to amend the RoSP prematurely.

Limitations and Strengths

There are a number of limitations to our current studies. The investigation of suicidal behavior poses significant ethical issues and we were only able to gather modest sample sizes. Fortunately, the effects sizes produced by the RoSP were very large and therefore even these modest samples were able to give highly significant results. However, the modest sample sizes have not allowed us to look at other important factors that might moderate the effectiveness of the RoSP, such as the effects of gender or the interval between assessment and outcome. Future studies are needed to investigate these factors, and to expand the evidence-base to other clinical settings such as emergency departments, child and adolescent mental health services, older adult services, prisons, and to other countries and cultures.

We also acknowledge that while our research has shown that the RoSP is predictive of suicidal behaviors, if it is used simply to categorize people in settings with low base-rates of suicide, its predictive value will remain low due to the low base rate of this behavior (29). Further, many people who die by suicide are not known to mental health services (30). Thus, our approach of increasing the quality of assessment and safety-planning of service users through RoSP, ensuring that this is adherent to NICE guidelines, and trying to focus on psychosocial needs as well as clinical presentation, has to also be accompanied by population-based strategies to suicide prevention.

A strength of RoSP is that it was developed and refined while being used in an actual service where assessment of suicide risk was one of the paramount issues in the management of these patients. The items and their scoring were therefore tested and altered by this "real-world" application of the instrument where issues, such as what information is available from clinical notes and interviews, place constraints on the usability of an instrument, even if it has a good research pedigree (31, 32).

Conclusion

In conclusion, we designed RoSP from factors known to be associated with suicide and attempted suicide. We have shown

that it can produce reliable and valid clinical judgments of suicide risk across two very different clinical settings: a community sample of people known to mental health services; and a sample of in-patients in low secure provision all of whom had a diagnosis of personality disorder. The structured professional judgement of suicide risk produced by the RoSP was related to suicidal behaviors in both clinical contexts with an efficacy equal or superior to other well-established structured professional judgment schemes for the prediction of violence to others. As such, we believe that these data provide the first step in the validation of the use of structured professional judgement methodology for suicide risk evaluation and safety-planning. We believe that the RoSP meets NICE (12) guidelines that:

> "All people who have self-harmed should be offered an assessment of needs, which should be comprehensive and include evaluation of the social, psychological, and motivational factors specific to the act of self-harm, current suicidal intent and hopelessness, as well as a full mental health and social needs assessment." (1.4.1.5 p.6).

RoSP can therefore provide a structure for meeting NICE guidelines for suicide prevention. Further studies are now needed to see if the scientific and clinical implementation of RoSP produces improved safety-planning and improved outcomes for service users across a range of clinical services and cross-culturally.

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 National Health Service Research Ethics Committee (15/EM/0044) and National Health Service Research Ethics Committee (14/EM/1178). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NG was a co-author of the RoSP scheme, helped design both experiments, led the data collection and project management, and participated in writing the manuscript. AJ advised on analysis of the data and commented on drafts of the manuscript. AM and SR completed the RoSP assessments in both study 1 and study 2 and commented on drafts of the manuscript. JK completed the RoSP assessments in study 2 and helped in writing the manuscript and with amendments to the RoSP scheme. RS was a co-author of the RoSP scheme, helped design both experiments, analyzed the data, and wrote the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Heart Rate Variability Duration: Expanding the Ability of Wearable Technology to Improve Outpatient Monitoring?

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Heart rate variability (HRV) evaluates beat-to-beat interval (BBI) differences and is a suggested marker of the autonomic nervous system with diagnostic/monitoring capabilities in mental health; especially parasympathetic measures. The standard duration for short-term HRV analysis ranges from 24 h down to 5-min. However, wearable technology, mainly wrist devices, have large amounts of motion at times resulting in need for shorter duration of monitoring. The objective of this study was to evaluate the correlation between 1 and 5 min segments of continuous HRV data collected simultaneously on the same patient. Subjects wore a patch electrocardiograph (Cardea Solo, Inc.) over a 1–7 day period. For every consecutive hour the patch was worn, we selected a 5-min, artifact-free electrocardiogram segment. HRV metric calculation was performed to the entire 5-min segment and the first 1-min from this same 5-min segment. There were 492 h of electrocardiogram data collected allowing calculation of 492 5 min and 1 min segments. 1 min segments of data showed good correlation to 5 min segments in both time and frequency domains: root mean square of successive difference (RMSSD) ($R = 0.92$), high frequency component (HF) ($R = 0.90$), low frequency component (LF) ($R = 0.71$), and standard deviation of NN intervals (SDNN) ($R = 0.63$). Mental health research focused on parasympathetic HRV metrics, HF and RMSSD, may be accomplished through smaller time windows of recording, making wearable technology possible for monitoring.

Keywords: heart rate variability, suicidality, wearable technology, anxiety, outpatient

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INTRODUCTION

Heart rate variability (HRV) evaluates the beat-to-beat time interval (BBI) differences during the cardiac cycle. HRV has been shown to correlate with several medical conditions (1, 2). One area of medicine with particular interest in HRV is mental health. One recent study found there were over 1.2 million annual emergency department visits by adolescents in the United States for suicidality. This has doubled from the most recent decade (3). Even worse, up to 20% of adolescents will have a repeat suicide attempt within 12 months from an initial attempt and almost half of patients will have a second emergency department visit after their first for mental health (4, 5).

The exponential increase in mental health crises over the past decade is overwhelming emergency departments. This has created a critical need for innovative approaches to early identification and intervention. HRV has been postulated in prior mental health research to reflect the balance of the autonomic nervous system. This has been proposed to be dysregulated in conditions such as suicidality; in particular a downregulation of the parasympathetic nervous system (6). Although HRV has been around for a long time, it has gained favor recently with the expansion of technology and mobile health applications specific to mental health (7). The ability to accurately measure HRV therefore has broad implication for mental healthcare.

HRV has traditionally been obtained from chest wall electrocardiography (ECG) and norms have been described previously (8). However, advancements in wearable technology like smartwatches can detect HRV through photoplethysmography (PPG). This obtains a plethysmogram optically by measuring microcirculatory changes in blood volume for BBI detection (9, 10). PPG introduces significant potential in a socially accepted platform: wrist-worn technology. This platform may have the potential for patients with mental health to monitor themselves at home. As the technology detects changes in the autonomic nervous system, patients can be notified to practice their coping mechanisms and therapies developed with their provider. HRV analysis utilizes small time changes to calculate specific time and frequency metrics over extended periods. One unique challenge to wrist-worn devices is motion artifact and its impact on being able to obtain long durations of accurate continuous BBI data. Studies show that HRV metrics can tolerate small shifts or loss of data caused by motion artifacts (11). Traditionally, the minimum recording for HRV metrics has been 5 min (12). This timeframe may be challenging for wrist technology to accurately measure HRV metrics aimed at mental health including parasympathetic measures of the high frequency component (HF) and root mean square difference (RMSSD) due to motion.

This study aims to determine if 1-min segments of gold standard ECG-derived HRV data correlate to 5-min segments. This data may establish a new standard for measurement in future HRV analysis studies, particularly to define procedures used on wearable technologies such as wrist-worn devices that are susceptible to occasional motion artifact.

MATERIALS AND METHODS

This was a prospective convenience sample of individuals of any age without a formal mental health or cardiac diagnosis wearing a patch ECG technology (Cardiac Insight, Cardea Solo). Subjects were recruited directly from the study team or healthy individuals if >13 years old, without daily medications or comorbid conditions including smoking, and not being evaluated in the emergency department for an acute complaint. This population was chosen to ensure there were not confounders related to mental health or cardiac disease affecting BBIs and allow for normal daily activities. This study underwent institutional review board approval at the study site (Oregon Health & Science University IRB study 16864). The patch ECG was placed over the left upper chest as described by the Cardiac Insight instructions. Subjects wore patches for 24–168 h with a goal of 96 h continuously during the day and night. BBIs were obtained directly from the patch ECG waveform data. Python 3 HRV-Analysis package (version 1.3) available from pypi.org then processed this data. The first steps in HRV-analysis are typically detection and removal of outliers and ectopic beats. Because this study is comparing two different lengths of HRV data where removal of data might affect the statistics, the data processing first searched for 5-min segments of artifact-free HRV data, where neither outliers nor ectopic beats were detected. Outliers were defined as those where the BBI was outside the range of 400–1,500 ms, which reflects a heart rate above 150 or below 40 BPM. Next, time domain features and frequency domain features were calculated for each 5-min, artifact-free segment. Many 5-min segments were available for each hour, but the study required only one segment per hour. To select the one segment for each hour, the study took the next segment that was acquired at least 60 min later than the most-recently selected 5-min segment.

From each 5-min segment, a 1-min segment was extracted from the first minute of this segment. HRV metrics calculated included high-frequency component (HF), root mean square of successive difference (RMSSD), low-frequency component (LF), and standard deviation of next normal interval (SDNN); the next normal interval is similar to the BBI. The LF and HF bands have frequencies from 0.04–0.15 Hz and 0.15–0.40 Hz, respectively. Prior literature has utilized these ranges for mental health research. For each category of HRV metrics, we calculated the correlation of the 1 and 5 min segments expressed as Pearson's Correlation Coefficients (R). The degree of correlation was categorized as excellent for an R of 0.9–1.0, good for an R of 0.7–0.89, moderate for 0.4–0.69, and low for <0.39 (13).

RESULTS

Continous patch ECG data was obtained for 492 h. This allowed for 492 5 min segments and 1 min segments for analysis. The patches were worn by 4 individuals, each at two unique time points. The average age was 34.5 years.

High Frequency

One minute segments of HF showed excellent correlation to 5 min segments of HF ($R = 0.90$) (**Figure 1**).

Root Mean Square of Successive Differences

One minute segments of RMSSD showed excellent correlation to 5 min segments of RMSSD ($R = 0.92$) (**Figure 2**).

Low Frequency

One minute segments of LF showed good correlation to 5 min segments of LF ($R = 0.71$) (**Figure 3**).

Standard Deviation of NN Intervals

One minute segments of SDNN showed moderate correlation to 5 min segments of HF ($R = 0.63$) (**Figure 4**).

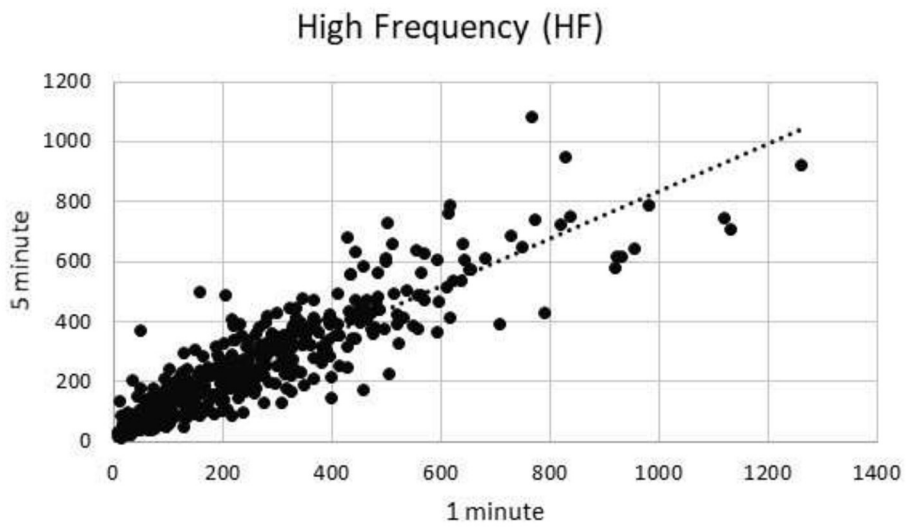

FIGURE 1 | High frequency component correlation.

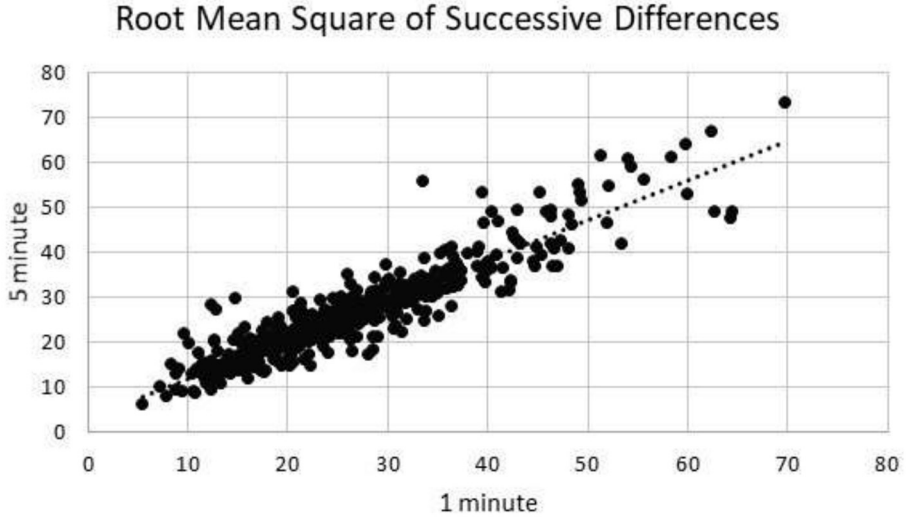

FIGURE 2 | Root mean square of successive differences correlation.

DISCUSSION

HRV monitoring is an old metric that has provided new insight into various medical conditions including mental health (14, 15). The growing technology and platforms to collect this data now include wrist devices in the outpatient setting, but motion artifact is an issue (11). This study evaluated the correlation between 1 and 5 min segments for the most common used HRV metrics in mental health. Our results found that HF and RMSSD showed excellent correlation, LF good correlation, and SDNN moderate correlation, which is promising for future wrist-worn technology data analysis.

HRV is a metric using the BBI which is different than the heart rate measured by many applications (16). Mental health is an area of medicine that has classically not utilized significant advances in technology clinically due to its complex multifactorial pathophysiology. Yet, HRV is particularly interesting in mental health care as a reflection of the autonomic nervous system. In particular it has the ability to evaluate the homeostasis of the sympathetic and parasympathetic nervous systems; namely a dysregulation of the parasympathetic nervous system in times of stress may be a marker of escalating mental health states (17). Prior studies have utilized HRV and shown a difference in the markers of the parasympathetic nervous system between patients with a history of suicidality and those without (14, 18).

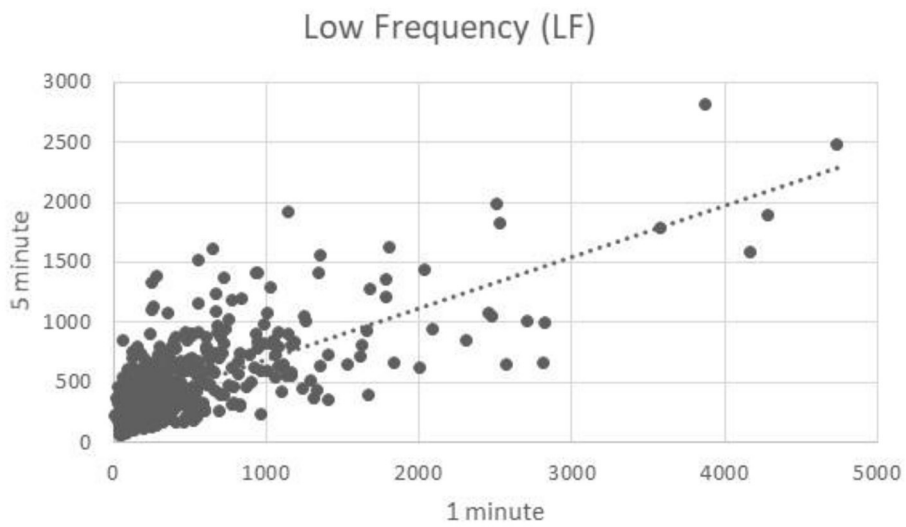

FIGURE 3 | Low frequency component correlation.

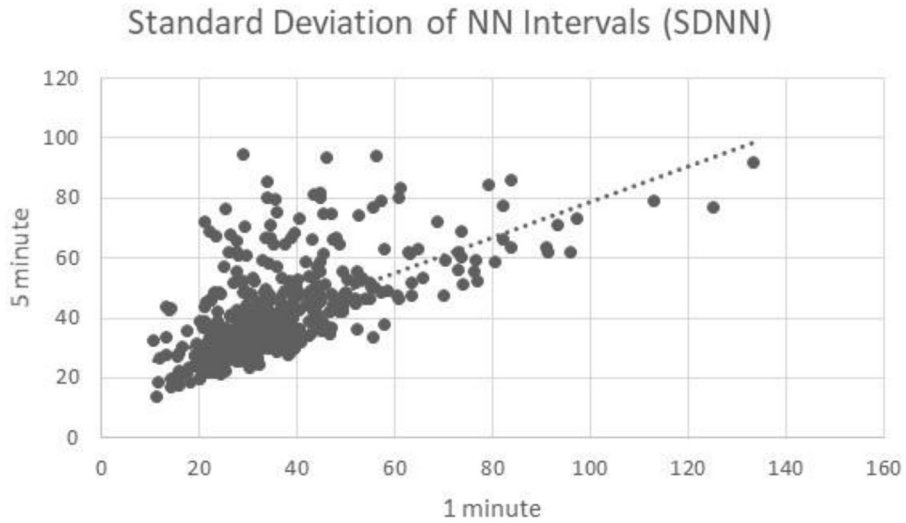

FIGURE 4 | Standard deviation of NN intervals correlation.

Recent studies have focused on the ability of the HF and RMSSD components to evaluate patients during various situations as a marker or stress and depression (17, 19, 20). These are encouraging as they have found a decrease in the parasympathetic measures in patients with a history of suicidality or depression compared to patients without when undergoing stressful tasks or baseline measurements. This creates the possibility that HRV may function as an important measure of stress that can be monitored in the patients. Many of these studies have utilized the laboratory setting and compared groups of patients with a history of suicidality and those without.

However, mental health and suicidality have been shown to be a dynamic process that changes throughout the day and most likely requires more consistent/continuous monitoring for symptom changes (21, 22). This introduces the possibility of wearable technology to significantly improve outpatient monitoring and care delivery from the current standard assessments that administer validated questionnaires (23). PPG utilizes an optical source for changes in blood volume that reflect the cardiac cycle and thus make heart rate and BBI calculations feasible with high accuracy (9). This technology is standard now in many smartwatches on the market creating a significant opportunity for outpatient medical care. One of the largest limitation to wrist device PPG compared to standard chest wall ECG is the motion artifact that impacts long durations of continuous data. However, prior studies have shown that even

having to remove small amounts of BBIs in a segment can result in no significant change in HRV metrics (11). Yet, expecting prolonged time courses of artifact-free data is unrealistic in individuals who are moving around freely. One prior study aimed to look at various durations of HRV data using machine learning and found durations <5 min to be quite accurate for detecting stress vs. non-stress in subjects (24). An addition study sought to compare the correlation between 24 h HRV segments and 5 min segments to evaluate how short of time courses are reasonable for future use (25). Similar to our results, this study evaluated the correlation between shorter and longer time frames of HRV. They found that the HF component had a strong correlation between the two sets of data ($R = 0.817$). Prior research has been published establishing norms and recommendations for monitoring durations with experimental designs in mental health studies (8, 26). These studies detail that comparing shorter to significantly longer durations or recording can confound the data. Therefore, the ability to collect short durations of HRV accurately across time settings can be very valuable as studies show it's utility. This is encouraging that separate studies had similar findings of shorter duration maintaining accuracy in the HF component, which may be the most important in future mental health studies.

The translation of this data has broad implications for medicine and mental health. The current standard of care for suicidality monitoring relies on subjective scoring tools requiring administration by a trained provider. In addition, this requires an individual in times of crisis to reach out to someone for help. Rather than this reactive approach, passive monitoring with technology can have an important role in proactive identification of crisis escalations to allow preventative treatments. Inherent confounders can be controlled for in this analysis including circadian rhythm as previously reported (27). Much research still needs to occur, but this data is encouraging for the possibility of outpatient HRV monitoring accomplished with shorter time frames to account for motion.

LIMITATIONS

There are several limitations to this study. The first is that the study was a small cohort of healthy individuals. This eliminates confounders of underlying cardiac disease or mental health that studies show have intrinsic differences in HRV. Therefore, the goal was to collect a large number of hours of continuous 1 and 5-min simultaneous data segments to compare. A second limitation is this was a foundational study to evaluate the shorter timeframes for HRV collection, but did not evaluate a specific medical condition. This was by design as HRV was not compared between subjects, but instead just the correlation between 1 and 5 min segments. Therefore, the patient population could be heterogeneous as the study compared the correlation within each patient's measurements. This data serves to inform future studies that can evaluate HRV changes over these short time frames in different populations of patients. The objective of this study evaluated the best-studied HRV metrics for mental health, HF and RMSSD, but the most frequently obtained metrics were calculated including LF and SDNN. Because the LF band's longest period includes 25 s, only 2.4 periods are included in a 1-min data segment making this inherently more challenging to monitor with shorter time frames. However, in this study across almost 500 h of data there was still good correlation. Finally, this study included gold standard chest electrodes. It may require confirmation with a wearable wrist technology using PPG for further validation as one would expect more motion artifact in that setting.

This study found that 1-min segments of HRV (HF and RMSSD) showed excellent correlation to 5-min segments. This is encouraging for future clinical studies on outpatient mental health monitoring with wearable technology but need to be confirmed or refuted in the future.

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 Oregon Health and Science University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DS, SB, and KD contributed to conception and design of the study. KD and RD organized the database. KD and DS performed the statistical analysis. DS wrote the first draft of the manuscript. KD, RD, and SB wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Completed Suicide With Violent and Non-violent Methods by the Elderly in Rural China: A Psychological Autopsy Study

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Background: Late-life suicide is a severe public health problem in rural China; however, knowledge regarding the specific characteristics and risk factors for completed suicide via violent and non-violent methods among elderly individuals in rural China is limited.

Methods: Subjects aged 60 years or older were selected from rural areas in Shandong, Hunan, and Guangxi provinces in China. This study was a 1:1 matched case-control design conducted by using the psychological autopsy method.

Results: According to the univariate analyses, the presence of mental disorder, higher degree of depression, loneliness, lack of social support, hopelessness, impulsivity, and increased quantity of life events were associated with suicide in both violent and non-violent methods. For violent suicide, another risk factor was the lack of pesticides at home. For non-violent suicide, other risk factors were not currently married, family suicide history, and alcohol use disorder ($P < 0.05$). Variables that remained in the logistic regression model were the severity of depressive symptoms for both violent and non-violent suicide. For non-violent suicide, the degree of hopelessness was another independent risk factor. In addition, violent suicides were more likely to lack pesticides at home, choose the spring season and have an increased quantity of life events than those who died by suicide via non-violent methods.

Conclusion: The major risk factor for both violent and non-violent suicide was the severity of depressive symptoms. Suicide prevention measures that focus on depression among this vulnerable population are urgently needed. Moreover, the characteristics of suicides via violent methods differed from those via non-violent methods among elderly individuals. Suicide prevention efforts should be tailored to the specific characteristics of the different suicide methods utilized by older adults in rural areas.

Keywords: suicide, violent method, non-violent method, rural, elderly

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INTRODUCTION

Suicide represents a severe public health problem in China and worldwide. According to data from the World Health Organization (WHO), the burden of suicide has shifted from Western to Eastern Europe over the past 50 years and currently appears to be the highest in Asia (1). The suicide rates among elderly individuals have been reported in several studies (2); older men and women (aged 65 or older) exhibit the highest suicide rates in almost all countries, reaching 34.5/100,000 in China (6.5 times more than the rate in the population younger than 65 years), and elderly people who live in rural areas are more likely to die by suicide than those who live in urban areas (incidence rate ratio = 1.83) (3).

Late-life suicide is a multidimensional behavior that has special characteristics and risk factors. Research has found that unemployment, not married, mental disorders, and depressive symptoms were independent risk factors related to suicide in older adults in rural China (4). Feeling left behind can elevate suicide risk due to increasing life stresses, mental disorders, and depressive symptoms and decreasing social support (4). Studies have shown that older adults with high suicide intent tend to choose highly lethal suicide methods and are well-prepared (5, 6). Investigating the specific characteristics of suicide methods among older adults is critical for suicide prevention.

Studies have found the remarkable differences of certain patterns of suicide methods in different countries. Jumping from high locations is a frequently used suicide method among older adults in New York (7), while more than half of elderly individuals who died by suicide used firearms in the USA (8). Hanging is the predominant method among older adults in Turkey (9). The choice of suicide method among elderly individuals is not random and depends on multiple factors, not only culture social-cultural acceptability, but also availability of suicide means. The ingestion of pesticides is the most common method among elderly individuals in rural China because of the high accessibility to pesticides (10). Furthermore, it was found that the method used at an unsuccessful suicide attempt may predict later completed suicide, suggesting study on suicide methods is of much significance in suicide prevention (11). A popular dichotomy of suicide methods is the characterization of methods as violent or non-violent (12): hanging, jumping from high locations, use of a firearm or shotgun, cutting and piercing with sharp objects, and getting run over by a train or other vehicle are classified as violent methods, whereas the ingestion of pesticides, overdose of drugs, poisoning by gases, and suffocation are classified as non-violent methods. Some sociodemographic and clinical characteristics are related to the choice of suicide method (13). A study of European populations found that males were more likely to choose violent and highly lethal methods than females (14), which is similar to the findings of studies on the Japanese population (15). Nevertheless, knowledge regarding the characteristics of violent and non-violent suicide methods in elderly individuals in rural China is limited.

In this study, we focused on investigating the differences between violent suicide methods and non-violent suicide methods among elderly individuals in rural China. Psychological autopsy was performed to compare the characteristics of individuals who utilized these two types of suicide methods, and the risk factors potentially related to violent suicide methods were examined.

METHODS

Sample and Sampling

A multistage stratified cluster sampling method was used to select research sites. All 31 provinces in mainland China were classified into three strata based on the GDP per capita; Shandong, Hunan, and Guangxi were selected from each stratum. The counties in the three provinces were also stratified into three strata based on average income. Twelve counties were randomly selected from the three provinces (one county in each stratum in Shandong and Hunan provinces and two counties in each stratum in Guangxi Province).

The study was a 1:1 matched case-control design. A consecutive sampling method was used to obtain the data, and 242 suicide cases aged 60 and above who died from suicide were entered into the study. One living control person was randomly chosen from the same or neighboring rural village for each suicide case, with the same gender and birth year ($\pm$ 3 years). All village doctors and local public health professionals involved in the death certification process were briefly trained and were required to report all suicides in older adults to the local Center for Disease Control and Prevention.

In this study, we divided all the suicide methods into a violent group (violent suicide cases and violent living controls included) and a non-violent group (non-violent suicide cases and non-violent living controls included). The violent suicide methods included hanging, drowning, jumping, and wrist cutting, whereas the non-violent suicide methods included the ingestion of pesticides or other poisons (16, 17).

Study Procedures

This study was conducted from June 2014 to September 2015. All the interviewers were intensively trained on the determination of manner of death, method of psychological autopsy, interview techniques, and instruments used.

When a suicide case was reported, interviews with informants of the suicide case were arranged 2–6 months later. The proxy data for suicide victims were provided by two informants: generally, the first informant was the next-of-kin who lived with the suicide victim, and the second informant was always a friend, a neighbor, or a remote relative. Each informant was interviewed separately by one trained interviewer. The average interview time was 90 min. In the interview process, to obtain the most accurate information on the target person and prevent the family members of the suicide victims from concealing the real situation, the second informant was interviewed at the same time as the first informant; the two informants were consistent in the survey time but were separated by survey location to avoid mutual interference. After the interview, the questionnaire was examined and completed by the interviewer, and then the questionnaire was submitted to the quality control person. The details of the interview procedures can be found in a previous study (4).

This study was approved by the Institutional Review Boards of Shandong University, Central South University, and Guangxi Medical University. Written informed consent was obtained from all who provided information about the individuals who died by suicide. Participants in the living control group and all the informants of living comparisons and suicide cases provided written informed consent to participate in this study.

Instruments and Recorded Measurements

Demographic Characteristics

The sociodemographic factors included age, gender, education level, marital status (currently married status: married and lived together, unmarried cohabitation, or remarried; unstable marital status: single, divorced, widowed, or married but separated), annual family income, and the storage of pesticides at home.

Suicidal Behavior

The characteristics of suicidal behavior included previous suicide attempts and the timing, and season of the suicide.

Suicide Intent Scale (SIS)

The SIS is composed of an objective section (items 1–8) and a subjective portion (items 9–15) and is used to evaluate the degree of suicidal intent. In this study, we used the first eight items of the SIS to estimate the level of suicidal intent. The possible score ranges from 0 to 16, and a high score indicates a strong suicidal intent. The Chinese version of the SIS has been shown to have satisfactory reliability and validity (18).

Life Events Scale for the Elderly (LESE)

Stressful life events over the final 12 months before death or investigation were measured by the LESE, which covers 46 life events and was developed specifically for older adults in China (19). Each event is assessed based on the following 5 aspects: occurrence time, event property (positive/negative life events), degree of psychological impact, duration, and frequency of occurrence. In this study, quantity of life events (the degree of psychological impact of life events × duration × frequency of occurrence) was used to reflect the impact of life events on an individual. High scores indicate an increased impact due to life events.

University of California Los Angeles Loneliness Scale-6 (ULS-6) Loneliness was measured by the Chinese version of the ULS-6, which is a 6-item instrument translated by Zhou et al. (20). Each item is rated on a 4-point scale ranging from 1 to 4. The total score ranges from 6 to 24, and high scores represent high levels of loneliness. In a previous psychological autopsy study, the Chinese version of the ULS-6 showed good reliability and validity among elderly individuals in rural China (21).

Beck Hopelessness Scale (BHS-4)

The Chinese version of the BHS-4 is an excellent instrument used to measure the degree of hopelessness. It is composed of 4 items relevant to success, a dark future, breaks (out of luck), and faith. Each item is rated on a 5-point scale. The total score ranges from 4 to 20, and a high score represents a great degree of hopelessness. The BHS-4 has been shown to perform as well as the original 20-item scale (BHS-20) (22–24).

Barratt Impulsiveness Scale (BIS-11)

The BIS-11 is a self-assessment tool used to measure impulsiveness. The current version includes 30 items, which cover the following three main dimensions of impulsive behavior: attentional impulsiveness, motor impulsiveness, and non-planned impulsiveness. Each item response ranges from 1 (never) to 4 (almost always), with a high score indicating high impulsivity. The BIS-11 has sound reliability and validity and can be used in the social and cultural context of China (25).

Duke Social Support Index (DSSI)

The 23-item DSSI is used to measure the level of social support. The total score ranges from 11 to 45, and a high score indicates a high level of social support. The DSSI has shown good reliability and validity in previous psychological autopsy studies in China (26).

Geriatric Depression Scale (GDS)

The severity of depressive symptoms was assessed by the GDS, which consists of 30 items. The possible total score ranges from 0 to 30, and a high score indicates severe depressive symptoms. The severity of depressive symptoms is categorized into the following three grades: no or mild depression (0–10), moderate depression (11–20), and severe depression (>20). The GDS has been validated among elderly individuals in rural China (27, 28).

Mental Disorders

The Chinese version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; SCID) (29, 30), was used in this study to generate current diagnoses of mental disorders. Diagnoses were made by psychiatrists in consensus meetings during which all information from both informants and previous medical records was presented. The following four categories of diagnoses were included: mood disorders, schizophrenia and other psychotic disorders, alcohol dependence, and anxiety disorders. Diagnoses of personality disorders or rare disorders (e.g., mental disorder with onset in childhood or adolescence, illicit drug abuse, eating disorders) were not included. Multiple diagnoses were made if appropriate.

Statistical Analysis

All statistical analyses were conducted with the Statistical Package for the Social Sciences (SPSS for Windows, version 20.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov Z-tests or T-tests were used to compare continuous variables such as age, quantity of life events, and the scores from the SIS, BHS, ULS, BIS, DSSI, and GDS. Chi-square tests were used to compare categorical variables such as sociodemographic factors (including gender, marital status, annual family income, education level), pesticides stored at home, family suicide history, mental disorders, previous suicide attempts, suicide timing, and suicide season. Binary logistic regression models were used to analyze factors related to the use of violent and non-violent suicide methods. Both backward stepwise and enter method inclusion of variables in the conditional logistic regression equation were tested to identify

TABLE 1 | Comparison of sociodemographic, psychological, social environment, and life event characteristics of suicide cases and living controls.

Variables	Violent			Non-violent			VCA vs. NCA
	Suicide cases (*n* = 109)	Living controls (*n* = 109)	χ2/t/z	Suicide cases (*n* = 133)	Living controls (*n* = 133)	χ2/t/z	χ2/t/z
Men, *n* (%)	62 (56.9)	62 (56.9)		73 (54.9)	73 (54.9)		0.10
Age, mean (SD), yrs	75.7 (8.16)	75.0 (8.23)	0.653	73.4 (8.17)	73.3 (8.05)	0.098	−2.15*
Marital status, *n* (%)			3.764			18.13***	1.10
Currently married	59 (54.1)	73 (67.0)		63 (47.4)	97(72.9)		
Non-currently married	50 (45.9)	36 (33.0)		70 (52.6)	36 (27.1)		
Annual family income, *n* (%)			1.18			2.19	2.59
0–3599	37 (33.9)	36 (33.0)		49 (36.8)	38 (28.6)		
3600–9999	38 (34.9)	32 (29.4)		34 (25.6)	36 (27.1)		
>10001	34 (31.2)	41 (37.6)		50 (37.6)	59 (44.4)		
Education, *n* (%)			0.906			2.35	3.44
Below primary school	46 (42.2)	41 (37.6)		65 (48.9)	55 (41.4)		
Primary school	47 (43.1)	54 (49.5)		58 (43.6)	62 (46.6)		
Above primary school	16 (14.7)	14 (12.8)		10 (7.5)	16 (12.0)		
Pesticides stored at home, *n* (%)	42 (38.5)	57 (52.3)	4.163*	85 (63.9)	75 (56.4)	1.57	15.47***
Family suicide history, *n* (%)	29 (26.6)	22 (20.2)	1.254	33 (24.8)	15 (11.3)	8.24**	0.10
Life events quantity, median (QL,QU)	54 (31, 76)	35 (12, 64)	−6.77***	40 (21, 64)	16 (4, 33.5)	−7.22***	−2.38*
BIS total score, mean (SD)	97.66 (16.80)	86.67 (16.46)	4.88***	99.71 (16.51)	87.11 (14.11)	6.70***	0.95
DSSI total score, mean (SD)	22.63 (5.47)	27.46 (6.82)	−5.76***	23.09 (6.39)	27.48 (6.84)	−5.41***	0.59
GDS total score, mean (SD)	21.92 (6.27)	9.35 (6.54)	14.49***	20.98 (5.66)	9.12 (6.35)	16.10***	−1.22
BHS total score, mean (SD)	14.39 (2.61)	9.75 (2.96)	12.26***	14.68 (2.49)	9.58 (2.52)	16.62***	0.91
ULS total score, mean (SD)	15.33 (5.17)	11.06 (4.19)	6.71***	15.72 (4.88)	10.94 (3.87)	8.86***	0.61
Any DSM-IV Axis I diagnosis, *n* (%)	49 (45.0)	5 (4.6)	47.66***	73 (54.9)	7 (5.3)	77.87***	2.36
Mood disorders, *n* (%)	40 (36.7)	3 (2.8)	39.66***	62 (46.6)	5 (3.8)	64.82***	2.42
Psychotic disorders, *n* (%)	9 (8.3)	1 (0.9)	6.71*	6 (4.5)	0 (0)	6.14*	1.45
Alcohol use disorder, *n* (%)	4 (3.7)	1 (0.9)	1.84	10 (7.5)	1 (0.8)	7.68**	1.63
Anxiety disorders, *n* (%)	4 (3.7)	1 (0.9)	1.84	3 (2.3)	1 (0.8)	1.02	0.43

SD, standard deviation; QL, lower quartile; QU, upper quartile; VCA, Violent Cases; NCA, Non-violent Cases; BIS, Barratt Impulsiveness Scale; DSSI, Duke Social Support Index; GDS, Geriatric Depression Scale; BHS, Beck Hopelessness Scale; ULS, University of California Los Angeles Loneliness Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

**A significant difference between groups, P < 0.05; **P < 0.01; ***P < 0.001.*

the most stable model. The level of significance was $P < 0.05$ in all the statistical analyses.

RESULTS

In this study, the most common method of suicide was pesticide ingestion, which accounted for 125 cases (51.7%). The second most common method was hanging (95, 39.3%), followed by drowning (9, 3.7%), ingesting poisons other than pesticides (8, 3.3%), jumping from high locations (3, 1.2%) and wrist cutting (2, 0.8%).

Demographic Characteristics

The demographic characteristics of suicide cases and living controls are summarized in **Table 1**. Those who died by suicide via violent methods were approximately 2 years older than those who died via non-violent methods ($P = 0.033$). No significant differences were observed in the sex distribution, marital status, education level, annual family income, and health conditions between the violent and non-violent suicide cases (all $P > 0.05$).

In addition, unstable marital status was associated with suicide via a non-violent method ($P < 0.001$) but not with a violent method ($P = 0.052$).

Psychological, Social Environment, and Life Event Characteristics

As shown in **Table 1**, there was no difference in the presence of a psychiatric diagnosis among suicide cases ($P = 0.124$). The most common mental disorder in both violent and non-violent suicide cases was mood disorder (36.7 vs. 46.6%).

The presence of a psychiatric diagnosis was overrepresented in the suicide group compared to the control group, and the proportion reached 45.0% of the suicide cases in the violent group ($P < 0.001$) and 54.9% of the suicide cases in the non-violent group ($P < 0.001$). The non-violent suicide cases were more likely to have alcohol use disorder than the living controls

TABLE 2 | Conditional logistic regressions of risk factors on violent and non-violent suicide methods.

Variables	VCA vs. VCO		NCA vs. NCO	
	p	OR (95% CI)	*p*	OR (95% CI)
BHS	0.118	1.08 (0.98–1.18)	<0.001	1.14 (1.06–1.22)
GDS	<0.001	1.10 (1.07–1.13)	<0.001	1.06 (1.03–1.10)

VCA, Violent Cases; NCA, Non-violent Cases; VCO, Violent Controls; NCO, Non-violent Controls; BHS, Beck Hopelessness Scale; GDS, Geriatric Depression Scale; OR, odds ratio; CI, confidence interval.
The backward stepwise method was used in this logistic regression model.

($P = 0.006$), but the difference was not significant in the violent group ($P = 0.175$).

Suicide cases were more likely to have a higher degree of impulsivity, loneliness, hopelessness, depression, and lack of social support than living controls in both the violent and non-violent groups (all P values < 0.001). However, there were no significant differences in the ULS, DSSI, BHS, BIS, and GDS scores between violent and non-violent suicide cases (all P values > 0.05).

Suicide cases in the violent group were associated with a higher quantity of life events than those in the non-violent group ($P = 0.018$). In addition, suicide cases were more likely to have a larger impact on life events than living controls in both the violent and non-violent groups (all P values < 0.001).

Those who died by suicide via non-violent methods were more likely to store pesticides at home than those who died by suicide via violent methods (38.5 vs. 63.9%; $P < 0.001$). The violent suicide cases were less likely to store pesticides at home compared to the living controls ($P = 0.041$), but the difference was not statistically significant in the non-violent group ($P = 0.210$).

A higher proportion of the non-violent suicide cases had a family suicide history compared to the living controls (24.8% vs. 11.3%; $P = 0.004$), but the difference was not statistically significant in the violent group ($P = 0.263$). No significant difference was found in family suicide history between violent and non-violent suicide cases.

Multivariate Conditional Logistic Regression Analysis

Table 2 shows the results of the multivariate analysis. The variable that remained in the model as a risk factor for both violent and non-violent suicide was the severity of depressive symptoms. For non-violent suicide, another risk factor was the degree of hopelessness.

Comparison of the Suicide Characteristics of Violent and Non-violent Suicide Cases

As shown in **Table 3**, there was a significant difference in the suicide season between the violent and non-violent suicide cases. Older individuals were more likely to choose violent suicide during spring. Furthermore, most of the 242 suicide cases occurred between 6:00 a.m. and 9:59 p.m. and at home. However, no significant differences were found in suicide time, suicide location, number of previous suicide attempts, or the SIS total score between the violent and non-violent suicide cases.

TABLE 3 | Comparison of suicide behaviors of suicide cases via violent and non-violent suicide methods.

Predictor	Violent (n = 109)	Non-violent (n = 133)	$\chi 2/t/z$	*p*
Previous suicide attempts, *n* (%)	24 (22.0)	21 (15.8)	1.54	0.215
SIS total score, mean (SD)	6.74 (2.98)	7.11 (2.68)	1.01	0.315
Suicide at home, *n* (%)	92 (84.4)	120 (90.2)	1.87	0.172
Suicide time, *n* (%)			0.40	0.821
10:00 p.m.-5:59 a.m.	17 (15.6)	24 (18.0)		
6:00 a.m.-1:59 p.m.	68 (62.4)	78 (58.6)		
2:00 p.m.-9:59 p.m.	24 (22.0)	31 (23.3)		
Suicide season, *n* (%)	70 (64.2)	64 (48.1)	17.61	0.001
Spring	50 (45.9)	29 (21.8)		
Autumn	23 (21.1)	31 (23.3)		
Summer	16 (14.7)	38 (28.6)		
Winter	20 (18.3)	35 (26.3)		

SD, standard deviation; SIS, Suicide Intent Scale.

Differences Between Suicide Cases in the Use of Violent and Non-violent Suicide Methods: A Logistic Regression

A binary logistic regression model was constructed to examine the differences between suicide cases in the use of violent and non-violent suicide methods. The independent variables included in the model were age (entered as a continuous variable), pesticide stored at home, suicide season and quantity of stimulating life events. After adjusting for age, the results showed that pesticides stored at home were negatively related to the use of violent methods, suggesting that people were more likely to die by suicide using violent methods if no pesticides were stored at home. Suicides via violent methods occurred more frequently in the spring and were associated with a higher quantity of life events than suicides via non-violent methods (see **Table 4**).

DISCUSSION

This study revealed the following major findings: (1) among elderly adults in rural China, the number of suicides via non-violent methods was higher than that via violent methods; (2) as a non-violent suicide method, pesticide ingestion was the leading method of suicide used by elderly individuals in rural China, and the most common violent suicide method was hanging; (3) among elderly individuals, those who died by suicide by means of violent methods tended to be older, be more likely to die by suicide during the spring, have a higher quantity of stimulating life events, and have no pesticides stored at home than those who died by suicide by means of non-violent methods; and (4) the major risk factor for both violent and non-violent suicide was the severity of depressive symptoms. For non-violent suicide, the degree of hopelessness was another major risk factor.

TABLE 4 | Factors related to violent suicide methods: a logistic regression model.

Variables	*p*	OR	95% CI
Age	0.196	1.02	0.99–1.06
Suicide season	0.001		
Spring		1	ref
Autumn	0.016	0.40	0.19–0.85
Summer	<0.001	0.24	0.11–0.53
Winter	0.002	0.31	0.15–0.66
Pesticides stored at home			
Yes	<0.001	0.34	0.19–0.60
No		1	Ref
Life events stimulating quantity	0.019	1.01	1.00–1.02
Constant	0.411	0.31	

OR, odds ratio; CI, confidence interval.
The Enter method was used in this logistic regression model.

Certain demographic factors were related to suicide via violent methods. Previous studies have indicated that those who attempted violent suicide were more likely to be older than those who attempted non-violent suicide (31), and elderly individuals who died by suicide were more likely to live without a spouse than younger individuals who died by suicide (32). In this study, we found that elderly individuals with unstable marital status were more likely to suicide via a non-violent method than via a violent method. Suicide prevention programs are needed to develop strategies specialized by suicide method to identify high-risk individuals in rural China.

Availability and acceptability were key factors influencing the choice of suicide method among adults aged 65 years and older (33). Pesticide ingestion is the most common suicide method, and it has a long history in rural China (10). In this study, pesticide ingestion (51.7%) was still the most favored suicide method among older adults in rural China. According to the logistic regression analyses of differences between suicide cases in the use of violent and non-violent suicide methods, individuals who had pesticides stored at home were less likely to die by suicide using violent methods. Although pesticide ingestion is a non-violent suicide method, it is still highly lethal. Pesticides are easily accessible in China, which is the largest producer and consumer of pesticides worldwide (34). Strong evidence suggests that limiting general access to highly hazardous pesticides (so-called means restriction) is an effective approach for suicide prevention (35). For example, in Sri Lanka, replacing highly toxic pesticides with less hazardous pesticides and integrated pest management has resulted in a 75% reduction in total suicides (36). In addition, restricting the availability of common and highly lethal suicide methods can reduce both method-specific and all-cause suicide rates (37).

Previous research found that seasonality was related to suicide via both violent and non-violent methods (38). Suicide exhibits pronounced seasonality in rural areas (39). In our study, older individuals who died by suicide were more likely to choose violent methods during spring than during other seasons. Individuals who died by suicide using pesticide ingestion accounted for 94.0% of all non-violent suicides in this study. Given that the use of pesticides increases according to agricultural work, which exhibits seasonality, the availability of pesticides may also display certain seasonality. In addition, previous studies have found that the duration of daily sunshine is significantly associated with seasonal variations in violent suicides and has a direct effect on violent suicides (40). During the spring, the sunshine hours per day are shorter in China. Sunshine may interact with brain serotonin systems and impact serotonin-related behaviors, such as depression, impulsiveness, and aggression, which are known to play key roles in suicidal behavior (41, 42). Therefore, different suicide prevention strategies should be designed according to different seasonal patterns in rural China.

Other suicide behavior features include suicide timing and location. In this study, we found that 60.3% of the suicides occurred between 6:00 a.m. and 1:59 p.m., and 87.6% of the suicides occurred at home, but there were no significant factors identified for violent suicide methods; this result highly differed from former research investigating younger individuals who died by suicide in rural China that showed that most suicides occurred at nighttime and that suicides via violent methods were more likely to occur outside than inside (43).

Previous studies have shown that individuals who died by suicide in later life tended to exhibit high suicide intent (6, 44). A previous suicide attempt is an important indicator of suicide (13, 44). Furthermore, previous research found that committing violence was associated with a high suicide intent in individuals with previous suicide attempts (45). In the present study, we did not find statistically significant differences in suicide intent and a prior history of suicide attempts between the violent and non-violent groups among elderly individuals, which is inconsistent with a study that reported that a relatively high suicide intent score was associated with the use of violent methods in rural China (16). Our data indicated that suicide intent and previous suicide attempts might not determine the use of violent or non-violent suicide methods among elderly individuals in rural China.

The influence of life events on suicide was measured by the quantity of stimulating life events in this study. We found most of the elderly individuals who died by suicide (93.3%) had experienced multiple life events during the year before death. According to the logistic regression analyses of differences between suicide cases in the use of violent and non-violent suicide methods, quantity of life events was positively associated with violent suicide methods. Thus, suicide cases with a high quantity of life events were more likely to choose violent suicide methods than those with a low quantity. In this case, intervention work should be targeted to prevent violent suicides with high lethality and offer financial and medical help to rural residents who are experiencing despair or overwhelming life changes.

In the present study, the severity of depressive symptoms provided a more powerful predictor of suicide. Previous studies found that mental disorders were also a risk factor for suicide in elderly individuals and were associated with violent suicide methods (43, 45). Our results showed that the elderly suicide cases were more likely to have mental illness compared to the living controls in both the violent and non-violent groups.

However, the presence of categorical diagnoses did not remain in the final regression model either for violent or for non-violent suicide methods. In addition, there were no significant differences in the distribution of mental disorders and GDS scores between the violent and non-violent suicide cases; this result differs from that found in younger individuals with mental disorders who tend to use violent suicide methods (43).

Previous studies indicated that substance abuse was associated with suicide (46), but our study did not find that. In this study, we observed that the elderly suicide cases were more likely to have alcohol use disorder compared to the living controls in the non-violent groups. However, alcohol use disorder did not remain in the final regression model for non-violent suicide methods. In addition, there were no significant differences in the distribution of alcohol use disorder between the violent and non-violent suicide cases. Our finding is inconsistent with a study in US that in older adulthood, individuals were more likely to drink alcohol when they used poisoning (compared with firearm or hanging) (47). A previous study also indicated that acute use of alcohol may influence the selection of a suicide method based on its lethality (48).

Previous studies (4, 16, 32, 49) found that loneliness, hopelessness, impulsiveness and low social support were risk factors for suicide in elderly individuals. In the present study, suicide cases were more likely to have a higher degree of impulsivity, loneliness, hopelessness, and lack of social support than living controls in both violent and non-violent groups. However, only hopelessness remained in the final regression model for non-violent suicide methods, not for violent suicide methods. This result is inconsistent with a study that 15–34 age suicides with a high degree of hopelessness were more likely to suicide with violent methods in rural China. A previous study in rural Shandong also indicated that degree of hopelessness was the most common risk factor for violent and non-violent suicides. These differences may be due to age; therefore, different suicide prevention strategies should be adopted for different age groups.

CONCLUSION

Our findings may have important implications for suicide prevention in elderly individuals in rural areas in China. However, this study focused specifically on violent and non-violent methods among elderly individuals in rural China and found some specific characteristics in older individuals who died by suicide that differed from those in younger individuals who died by suicide in rural China. More importantly, depression was the major risk factor for suicide in both violent and non-violent elderly suicides. Suicide prevention measures that focus on depression among this vulnerable population are urgently needed. Furthermore, we found that pesticide ingestion, which is a non-violent suicide method, remained the most frequently used suicide means among elderly individuals in rural China, and factors related to violent suicide methods were a lack of pesticides stored at home, spring season, and a high quantity of stimulating life events. Clearly, further efforts should be made to inform suicide prevention strategies according to the risk factors for the suicide methods and the characteristics of the elderly individuals who have died by suicide in rural China.

LIMITATIONS

This study has several limitations. The key limitation was that the psychological autopsy method has methodological shortcomings. It is not noted that the tools used to obtain information from informants were not validated in informants but rather in individuals (who, in this study, died by suicide). Informant answers may be influenced by their personal mental state, relationship to the deceased, etc. Information errors and bias due to informants' subjective observations and recall mistakes might exist.

In this study, we did not focus on the role of media, which is sometimes an important factor impacting suicidal behavior and methods (50). It was difficult to collect information on whether elderly suicide cases watched programs, read the newspaper or used the internet related to suicide due to the inherent methodological limitation of using proxy-based information.

To minimize this limitation, much of the information in this study was based either on prior documented data or *post hoc* independent psychiatric evaluation. The validity of this procedure with regard to the type of variables used in the current study has been well-demonstrated in previous study (51).

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

This study was approved by the Institutional Review Boards of Shandong University, Central South University, and Guangxi Medical University. Written informed consent was obtained from all who provided information (including the next-of-kin who lived with the suicide victim, and a friend, a neighbor, or a remote relative) about the individuals who died by suicide.

AUTHOR CONTRIBUTIONS

LZ, Z-YM, and C-XJ did the study design, coordinated the study, and recruited participants. R-TZ analyzed the study data and drafted the manuscript. LZ edited the manuscript. All authors contributed to the article and approved the submitted version.

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Incidence Trends and Risk Prediction Nomogram for Suicidal Attempts in Patients With Major Depressive Disorder

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Background: Major depressive disorder (MDD) is often associated with suicidal attempt (SA). Therefore, predicting the risk factors of SA would improve clinical interventions, research, and treatment for MDD patients. This study aimed to create a nomogram model which predicted correlates of SA in patients with MDD within the Chinese population.

Method: A cross-sectional survey among 474 patients was analyzed. All subjects met the diagnostic criteria of MDD according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Multi-factor logistic regression analysis was used to explore demographic information and clinical characteristics associated with SA. A nomogram was further used to predict the risk of SA. Bootstrap re-sampling was used to internally validate the final model. Integrated Discrimination Improvement (IDI) and Akaike Information Criteria (AIC) were used to evaluate the capability of discrimination and calibration, respectively. Decision Curve Analysis (DCA) and the Receiver Operating Characteristic (ROC) curve was also used to evaluate the accuracy of the prediction model.

Result: Multivariable logistic regression analysis showed that being married (OR = 0.473, 95% CI: 0.240 and 0.930) and a higher level of education (OR = 0.603, 95% CI: 0.464 and 0.784) decreased the risk of the SA. The higher number of episodes of depression (OR = 1.854, 95% CI: 1.040 and 3.303) increased the risk of SA in the model. The C-index of the nomogram was 0.715, with the internal (bootstrap) validation sets was 0.703. The Hosmer–Lemeshow test yielded a *P*-value of 0.33, suggesting a good fit of the prediction nomogram in the validation set.

Conclusion: Our findings indicate that the demographic information and clinical characteristics of SA can be used in a nomogram to predict the risk of SA in Chinese MDD patients.

Keywords: prediction model, suicidal attempt, major depressive disorder, Chinese population, nomogram

INTRODUCTION

Suicide is widely prevalent and constitutes a clinical and public health concern. Close to eight hundred thousand people die annually by suicide every year. Furthermore, suicide is the second leading cause of death among people aged 15–29 globally. Suicide accounted for 1.4% of all deaths worldwide, making it the 18th leading cause of death in 2016. Suicide occurs all over the world, however, 79% of global suicides occur in low- and middle-income countries (1). According to Silverman et al's. research, suicidal behavior includes suicidal thoughts, suicide plans, and suicide attempts (SA) (2). Suicide and SA are widely prevalent on a global scale among psychiatric patients (3). A prior history of SA is a significant predictor of eventual death by suicide (4). In addition, a previous SA is the strongest risk factor for subsequent SA and suicide death (5, 6). MDD is the most common psychiatric disorder among people who die by suicide (7) and a well-established risk factor for SA (8). Globally, the lifetime risk of SA in people with MDD is estimated between 16 and 40% (9), showing a wide range that requires further exploration to better understand the actual risk percentage.

Worldwide, SA in people with MDD is constituted as an increasing clinical and public health concern (10, 11), with less investigation of the rate of suicide and its related risk predictors in China (12). In China the percentage of MDD with SA is reported to be between 14.3 and 25% (13). Previous studies explored the prediction of suicide by machine learning (14–16), and the risk factors of suicidal thought in adults based on decision tree analysis (17). However, these studies do not provide sufficient information on clinical implications to be implemented. In a previous study on suicidality in MDD patients, when compared with the full remission period the SA rate was 21-fold during the acute phase of remission and 4-fold during the partial remission period (18). Identifying the risk factors associated with SA in people with MDD during the acute phase of remission is vital for early identification to reduce death by suicide. Despite the substantial literature on risk and protective factors for SA, there does not exist studies that explore the prediction model of SA using socio-demographic information and clinical characteristics.

This study aimed to provide a prediction model to identify the correlates with SA and diagnosed MDD. The researchers' hypothesized that demographic information and clinical characteristics would interact to predict SA in MDD patients. The hypothesis tested the association of demographic information and clinical characteristics, both interactively and individually, with the risk of SA among MDD patients using survey data.

MATERIALS AND METHODS

Participants

This study was cross-sectional and retrospectively analyzed using a clinical database from Beijing Anding Hospital (a tertiary hospital for psychiatric disorders in Beijing, China). All participants were recruited from December 2013 to November 2016 from the Department of Major Depressive Disorder, Beijing Anding Hospital. All participants met the diagnostic criteria of MDD according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and were diagnosed by an experienced psychiatrist. The data of participants was then collected into the electronic medical record system by two experienced psychiatrists. The personal information of subjects was removed to provide a layer of anonymity to the patients. All patients had previously been informed of and agreed that the information in their medical record could be shared anonymously for the purpose of research. The study protocol was approved by the Ethics Committee of Beijing Anding Hospital.

Initially, 545 participants' data was retrieved, and 71 were excluded. The excluded participants were due to various reasons, including, incomplete sociodemographic information and/or clinical variables. The researchers reviewed the complete medical history from patients and patients with other psychiatric illnesses including schizophrenia, schizoaffective disorder, bipolar disorder, personality disorder, and intellectual disability were excluded. Also, those who had a history of a psychiatric illness that presented with a comorbidity of alcohol or drug abuse were excluded. Finally, 474 patients with complete records were included in the study. Anti-depressant medications, including anti-depressants and atypical anti-psychotics, for the enrolled patients did not affect the participants' data from being included in the study.

Materials

The socio-demographic information and clinical variables included age, duration, number of episodes, age of onset, number of hospitalizations, the features of anxiety and psychiatric symptom, marital status, income, level of education, and employment status.

The assessment of suicide was completed by a psychiatrist and was part of the medical record. Within the medical record, lifetime suicidal thoughts, and suicide plans were defined as a "yes" response to the questions: "Have you ever thought about suicide?" and "Have you ever had a plan for how to kill yourself?". SA was defined as a "yes" response, in the record, to the question: "Have you ever tried to kill yourself?". Based on the responses, the MDD patient records were then classified into two groups: patients with SA (MDD-S) and patients without SA (MDD-N). Patients who had suicidal thoughts or suicide plans were enrolled in the MDD-N group, as they had not acted on the thoughts or plans. It is important to note that suicidal ideation, suicide plan, and suicide preparation were not the criteria for enrollment in the group MDD-S. The definition of SA can only be satisfied if the patient has engaged in specific suicidal attempts (such as drug overdose, etc.) at any time in the past. These definitions are commonly used by previous researches studying suicide (19–21).

Statistical Analyses

In this study, continuous and categorical variables were, respectively, described using mean (standard deviation) and count (percent). The Chi-Squared Test, *t*-test, and the Wilcoxon Rank-Sum Test were used to assess the differences between the two groups and were based on demographic information and

clinical characteristics at baseline. Logistic Regression Analyses was then used to identify suicide risk factors associated with the demographic information and clinical characteristics before and after adjusting for sex and age. Effect-size estimates are expressed as Odds Ratio (OR) and at a 95% confidence interval (CI). Meanwhile, the nomogram was created based on the independent prognostic factors determined by applying both forward and backward stepwise selection methods in the logistic regression model.

The statistical analyses of this study follows the statistical methods of previous studies (22, 23). A prediction nomogram was created using significant risk factors by assigning a graphic preliminary score to each of the predictors with a point ranging from 0 to 100. The preliminary scores were then summed to generate a total score. The prediction nomogram was lastly converted to the logit and then to an individual probability (from 0 to 100%) of the patients with SA. The performance of the nomogram was evaluated by Harrell's concordance index (C-index) and the calibration plot (24). Generally, C-index >0.7 reflects a well-fitted feature of the predictive model. Independent significant variables were used to develop the nomogram. The internal validation was performed using the bootstrap method. The Hosmer–Lemeshow test was used to assess goodness of fit of the nomograms. A Hosmer–Lemeshow test $p > 0.05$ meant that the nomograms showed good fit. A function based on the variance inflation factor was used to check for the collinearity of variables that were included in the regression equation. A variance inflation factor higher than 10 implies multi-collinearity (25).

In order to explore the accuracy of the prediction model, the researchers created the basic model using four factors: age, time of onset, employment status, and sex. The prediction accuracy gained by adding significant risk factors was assessed using both calibration and discrimination viewpoints. Integrated Discrimination Improvement (IDI) (26, 27) was used to evaluate the discrimination capability of significant risk factors. Calibration capability was calculated using the −2log likelihood ratio test. The researchers used Akaike Information Criteria (AIC) to evaluate the predicted probability of adding a significant risk factors to the actual risk and the global fit of the modified risk model (28). Furthermore, Decision Curve Analysis (DCA) was enrolled to inspect the net benefit of this addition (29). In this curve, the X-axis denotes threshold probability, and the Y-axis denotes net benefits. Moreover, the Receiver Operating Characteristic (ROC) curve was also calculated in this study.

The estimation of study power was performed using the PS-Power Simple Size software (version 3.1.2). The generated nomogram, DCA, and ROC curve were generated by R-language (version 3.5.2). Statistical analyses of this study were conducted using the STATA software special Release 14.0 (Stata Corp, TX). Results were considered statistical significance at $p < 0.05$.

RESULTS

Demographic Characteristics

Four hundred and seventy-four hospitalized MDD patients were involved in the present analysis (mean age: 45.2 years old, SD = 13.6), including 290 females and 184 males. The mean duration of hospitalization for MDD patients was 7.8 years (MDD-N: 7.1 years and MDD-S: 9.8 years), and the mean age of onset of MDD was 37.5 years old for all patients (MDD-N: 38.3 years old and MDD-S: 35.1 years old). The duration of illness, number of episodes, age of onset, employment status, and level of education had significant differences between the MMD-N group and the MDD-S group. Meanwhile, there were no differences in age, sex, marital status, and income level between the MMD-N and MDD-S groups (**Table 1**).

TABLE 1 | Demographic information and clinical characteristics.

	MDD-N ($n = 347$)	MDD-S ($n = 127$)	*P*-value
Age (years)*	45.3 (13.3)	44.9 (14.5)	0.932
Sex (*n*, %)			0.361
Female	208 (59.9)	82 (64.6)	
Male	139 (40.1)	45 (35.4)	
Duration (year)*	7.1 (8.4)	9.8 (9.7)	0.006
Number of episodes*	2.6 (2.2)	2.7 (1.5)	0.011
Age of onset*	38.3 (12.9)	35.1 (12.7)	0.024
Number of hospitalization*	1.3 (1.1)	1.4 (0.8)	
Anxiety features (*n*, %)	165 (47.6)	50 (39.4)	
Psychotic symptom (*n*, %)	62 (17.9)	24 (18.9)	
Marital status (*n*, %)	285 (82.1)	100 (78.7)	0.068
Employment Status (n, %)	297 (85.6)	95 (74.8)	0.006
Income (*n*, %)			0.626
0–1,000 Yuan	30 (25.7)	12 (9.4)	
1,000–3,000 Yuan	118 (34.0)	47 (37.0)	
3,000–5,000 Yuan	91 (26.2)	34 (26.8)	
5,000–Yuan	72 (20.7)	25 (19.7)	
UN	36 (10.4)	9 (7.1)	
Level of education (*n*, %)			<0.001
Primary school	20 (5.7)	8 (6.3)	
Junior high school	70 (20.2)	48 (38.8)	
High school	119 (34.3)	44 (34.6)	
College school	138 (39.8)	27 (21.3)	

Mean (SD).

Identification of Risk Factors

The effect-size estimates of the examined factors in correlation with demographic information and the risk factors of SA (after adjusting for sex and age) are shown in **Figure 1**. In this study, the risk prediction of duration of illness, age of onset, and level of education was significantly associated with SA ($p < 0.01$) after adjusting for age and sex. The risk prediction of the number of episodes, marital status, and employment status was also significantly associated with SA ($p < 0.05$). Furthermore, after multi-variable logistic regression analysis, marital status (OR = 0.473, 95% CI: 0.240 and 0.930) and level of education (OR = 0.603, 95% CI: 0.464 and 0.784) decreased the risk of the SA. However, number of episodes (OR = 1.854, 95% CI: 1.040 and 3.303) increased the risk of SA in this study.

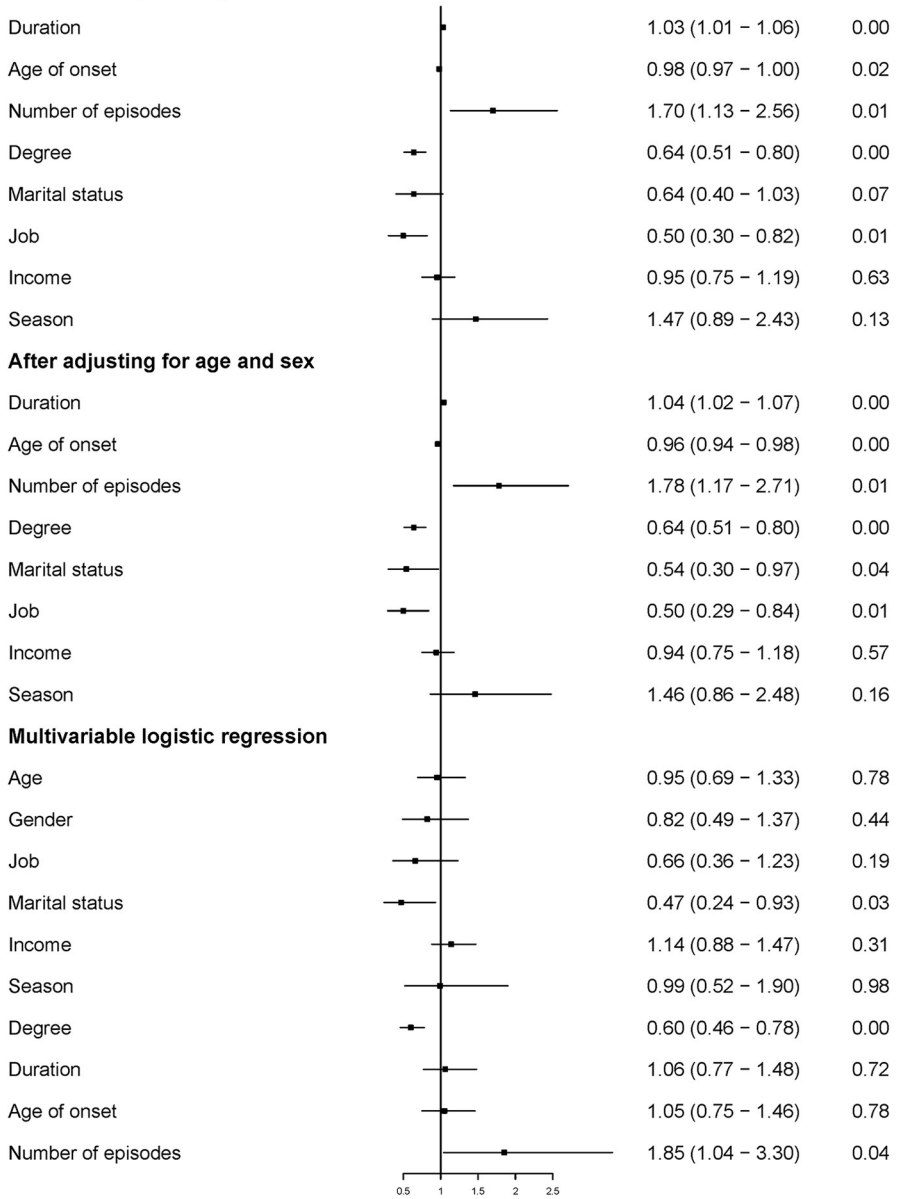

FIGURE 1 | Risk prediction of demographic information and clinical characteristics for the risk of SA.

Prediction Model

As in **Figure 2**, a nomogram model was developed to predict the risk of the SA based on the above significant factors in the logistic regression analyses, including: age, duration, age of onset, level of education, marital status, number of episodes, and employment status. In the prediction model, participants with a level of education up to 12 years were defined as 3, 2 if educated for 9–12 years, 6–9 years was defined as 1, and <6 years was defined as 0. If the subjects were married it was defined as 1, otherwise, it was 0. If number of episodes were greater than one, this was set at 1 in the nomogram. Patients who had a stable job were defined as 1, otherwise they were defined as 0. For example, in the nomogram, a MDD patient aged 50 years old would receive 50 points if they had a duration of 5 years (10 points), with an age of onset of 45 years old (43 points), a level of education up to junior high school (28 point), unmarried (18 points), number of episodes ≥1 (14 points), and who had a job (0 points) would have a total score of 163 point. The probability of SA would then approximately be estimated as 50%. The calibration curve of the nomogram demonstrated good agreement between predicted

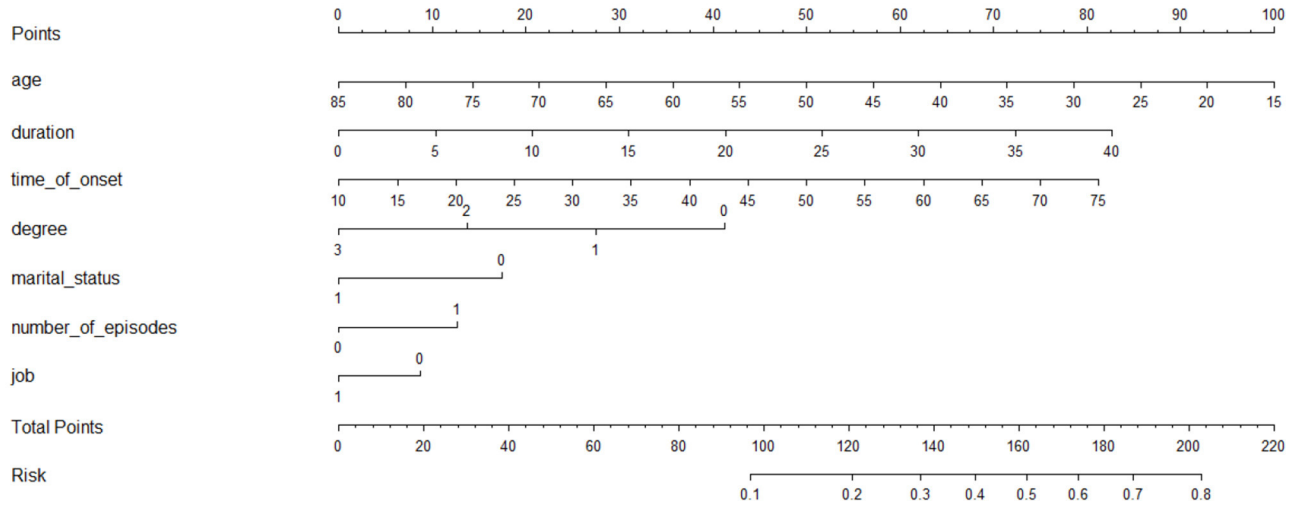

FIGURE 2 | The prediction nomograms of risk factors for SA in MDD patients.

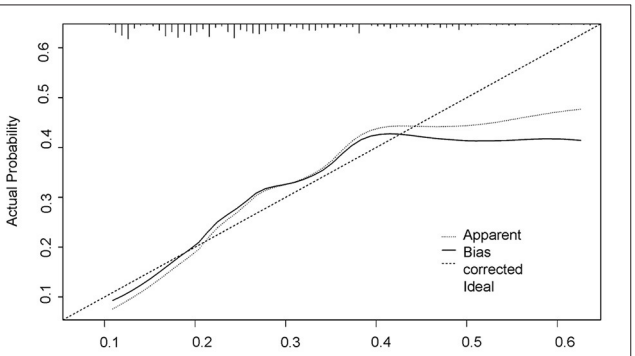

FIGURE 3 | The logistic calibration curve of the prediction nomograms of risk factors for SA in MDD patients.

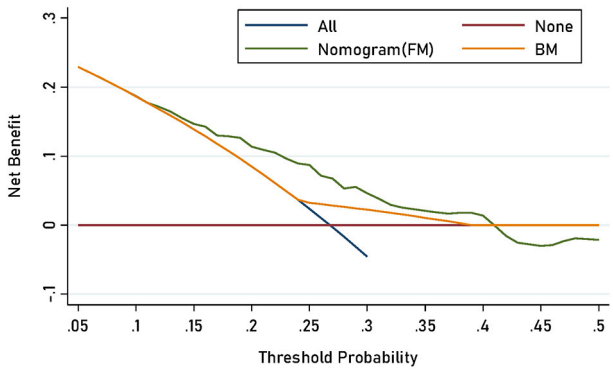

FIGURE 4 | DCA for the prediction nomograms of risk factors for SA in MDD patients.

and observed risk of SA. The C-index of the nomogram was 0.715, and turned into 0.703 in the internal (bootstrap) validation sets (**Figure 3**). A c-index value of 0.70 or higher indicates that the nomogram had a good consistency. The Hosmer–Lemeshow test yielded the $P = 0.33$, suggesting a good fit of the prediction nomogram in the validation set. Multi-collinearity was tested using variance inflation factors (VIF), with VIF higher than 10 indicating multicollinearity (25). The variance inflation factors of the nine potential predictors ranged from 1.69 to 8.57, indicating no multi-collinearity.

Prediction Accuracy Assessment

The power to detect the incidence trends for SA was estimated to be marital status (74%), degree (17.8%), duration (4.9%), time of onset (5.0%), and number of episodes (78.8%), respectively. **Table 2** shows the prediction accuracy gained by separately adding aforementioned risk factors to the basic model. Reduction in AIC statistics was >10 after adding risk factors to the basic model. A difference value >10 indicates that the model has a good calibration capability (20). Additionally, likelihood ratio tests revealed statistical significance ($p < 0.001$). From discrimination aspects, IDI indicated that the addition of risk factors to the basic model significantly improved the power of discrimination ($P < 0.001$), which was further confirmed by DCA and ROC (**Figures 4**, **5**).

DISCUSSION

This is the first study to explore the interaction between demographic information and clinical characteristics to predict SA in MDD inpatients. The nomogram model was created to predict the risk of SA. The full model had good prediction accuracy.

In the nomogram model, the younger age of MDD patients played a key role in predicting risk factors of SA. Borentain et al.'s findings indicated a higher proportion of suicidal ideation among

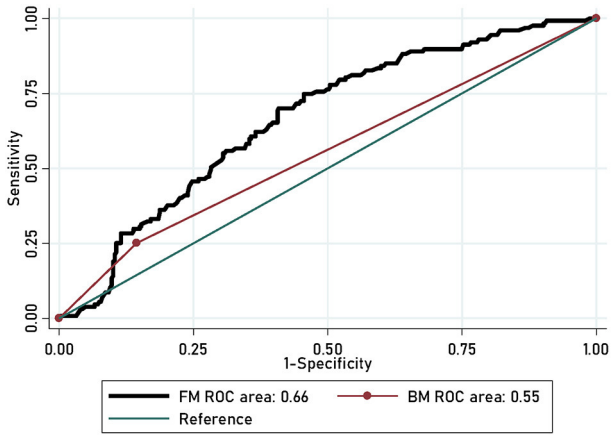

FIGURE 5 | ROC plots of risk factor for SA in MDD patients.

TABLE 2 | Prediction accuracy gained by adding risk factors to basic model for the risk of SA.

Statistics	Basic model	Full model
Calibration		
AIC	543.9	533.8
BIC	564.8	571.3
LR	Ref.	20.33
LR (*P*)	Ref.	<0.001
Discrimination		
IDI	Ref.	<0.001
ROC curve	Ref.	13.01
ROC curve (*P*)	Ref.	<0.001

AIC, Akaike information criterion; BIC, Bayesian information criterion; LR, likelihood ratio; IDI, integrated discrimination improvement; ROC, Relative operating characteristic curve; Ref., reference group.
Basic model included age, time of onset, job; Full model included age, time of onset, job, duration, level of education, marriage times of episode.

young MDD patients, with almost 50% under 35 years of age (30). Similar findings were also reported in earlier research (31, 32) confirming that the younger the MDD patient, the higher the risk of SA. Our prediction model supported the findings in these above studies.

In this nomogram model the duration of having MDD is an important risk factor to predict the risk of SA. A previous study also showed that duration was a critical risk factor for suicidal behavior in MDD inpatients (33). Rice and colleagues reported that MDD patients may be exposed to a higher risk of suicidal behavior if they do not receive effective treatment at an early stage (34). The result suggested that early diagnosis and treatment for MDD patients may contribute to reducing the risk of SA.

This study showed that a late-onset of MDD was associated with an increased risk of SA when compared to early-onset MDD. A similar result was also mentioned in a previous study of 3,284 adults, which found that the factors of SA were evaluated with longer exposure time (years at risk) (10). It concluded that older patients with MDD who were exposed to related risk factors for longer periods of time had a higher risk of SA. However, other findings showed that if onset of MDD occurred before adulthood there may be a higher risk of suicidal behavior, which was inconsistent with the findings of this study (10, 35, 36). This is likely a result of cultural differences, decades of studies have found that there are cultural protective factors and risk factors that are associated with suicidal behavior (37, 38). Previous studies have also supported that the risk factors of SA vary among people in different countries and cultures (39, 40). Meanwhile, many patients are hospitalized before suicidal ideation progresses to SA. The selection of such a sample would cause the result to deviate from real world data (41).

As expected, having a status of single, having a low-level education, and having a higher number of episodes of depression, impacted on the risk of SA. Inconsistent with previous studies (42, 43), the current study also found that status of single was a significant risk factor for SA. In the nomogram model for this study, as predicted, unmarried MDD patients exhibited an increased risk of possessing SA when compared to married patients. Compared to married patients, unmarried patients may be more vulnerable to SA due to a lack of protective factors, such as social and family support, an outlet for relieving stress, etc. (44). Looking at the impact of level of education on the risk of SA, this study's finding was corroborated in line with several previous studies, suggesting that a lower level of education was associated with increased risk of SA (45, 46). Previous research demonstrated that a lower education level was predictive of SA, independent of clinical factors (47). This could be due to those with lower education having increased odds of divorce, unemployment, and falling into poverty (48), which are risk factors for SA. Meanwhile, less successful social functioning, as mentioned above, was related to a greater risk of SA (49–51). In our study, the researchers also found that the number of episodes was a predictive factor of SA in this study. A similar result was also been found in a representative study that showed that recurrent MDD appeared to confer a higher risk for suicidal behavior (52). Meanwhile, Chaudhury et al. also emphasized the importance of the higher number of episodes of depression in SAs (50). The researchers speculate that the effect of the higher number of episodes on the risk of SA could be explained by the repetition of depression during the depressive episodes, or the extended presence of deep despair.

Psychotic symptom, anxiety features, and sex showed no significant differences between the MDD and S-MDD groups. The results indicate that symptoms and sex may not be risk factors when predicting SA in MDD patients. This finding is in contrast to previous studies (53, 54). Previous research at general hospitals in China found significant risk factors for MDD in outpatients, included being female and having a comorbidity with an anxiety disorder (12). The researcher team considered the possibility that they did not find the correlation in symptoms and sex might have been impeded by enrolled patients who were hospitalized. Therefore, further research should clarify the differences between in and outpatients in a nomogram model to predict the risk of SA between outpatients and hospitalized MDD patients.

This study had some limitations. First, in terms of living situations, the study did not take into account circumstances other than being married and single (unmarried), which ignores patients who were divorced or separated. Future research should explore the living situation instead of marital status to be more inclusive. Second, because the study was retrospective there was no control over the variables collected. Future research should explore a more exhaustive set of socio-demographic variables. The retrospective study precludes further comments on the cause-effect relationship between physical examination, laboratory tests (homocysteine, serum total cholesterol, triglycerides, free thyroxine) (55, 56), and SA. All participants were hospitalized and may not reflect the general population, requiring further external validation in future studies. Finally, an insufficient sample size might have influenced the validity of the nomogram model. It was deduced that the poor corresponding power of risk factors was also related to the small sample size. Referring to previous studies, more than 1,000 subjects are the recommended sample size of a nomogram [(22), 57]. Considering the small sample size, the researchers did not divide our data into three sub-groups (train, validation, and test). However, the researchers did use bootstrap re-sampling to verify the results, appropriately.

In conclusion, our findings indicated that age, duration, age of onset, level of education, marital status, numbers of episode, and employment status may serve as early-stage predictive factors for SA. The prediction model could enhance earlier identification, effective prevention, and improve the prognosis and treatment for SA in MDD patients. The prediction model created shows good prediction accuracy when administered to Chinese patients with MDD.

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.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SL and JZ: writing-original draft and writing-review and editing. QZ: conceptualization. AW and JH: formal analysis and writing-review and editing. YL: formal analysis, methodology, and writing-review and editing. XS and SS: formal analysis. YW and LZ: data curation and writing-review and editing. All authors contributed to the article and approved the submitted version.

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Factors Related to the Level of Depression and Suicidal Behavior Among Men With Diagnosed Depression, Physically Ill Men, and Healthy Men

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Depression is the most common psychiatric disorder in people who die by suicide. Awareness of risk factors for suicide in depression is important for clinicians. The study was aimed at establishing models of factors related to the level of depression and suicidal behavior among men from three different groups—in men with depressive disorder, in comparison to men with physical disorder and healthy men. A total of 598 men were included in the study. The following questionnaires were used in research model: test with sociodemographic variables, AUDIT Test, Fagerström Test, Generalized Self-Efficacy Scale (GSES), Inventory for Measuring Coping with Stress (Mini-COPE), Resilience Evaluation Questionnaire (KOP-26), Suicide Behaviors Questionnaire—Revised (SBQ-R) by Osman, and Gotland Male Depression Scale. In men with depression, the positive factors strongly related to the intensity of depression and suicidal behavior were as follows: vocational education, active coping, turning toward religion, social competence for resilience, and bachelor status. The factors negatively related to the intensity of depression and suicidal behavior in this group were as follows: unemployed status, student status, low satisfaction with the financial situation, having children, history of mental disorders in family, alcohol addiction, and seeking instrumental support. In the group of men with physical disorders, the following protection factors were identified: the medium or small city as a place of living, active coping, venting, and personal competence. The following risk factors were identified in this group: psychiatric treatment in the past. In the group of healthy men, the following protective factors were identified: the medium city as a place of living, positive reappraisal, planning abilities, and personal and social competence for resilience. In this group, the following risk factors were identified: vocational and higher education, student status, satisfaction with the financial situation, having more than one children, the occurrence of mental disorders in the family, the occurrence of alcohol abuse in the family, and use of psychoactive

substances as a strategy of dealing with stress. The risk factors identified in this study should be included in the clinical assessment of depression and suicidal behavior risk in male patients. There are some protective factors identified, including productive coping and personal and social competencies, which can be developed and should be especially considered and strengthened in mental health promotion programs aimed at men.

Keywords: depressive disorders, physically ill, suicidal behavior, risk factors, protective factors

INTRODUCTION

Mental well-being and mental disorders result from a complex combination of events and conditions that take place in biological, individual–psychological, social–psychological, and structural domains. The interplay between the individual and the environment is crucial. The population health model encompasses the full range of risk and protective factors that determine health (at the individual; family, friend, peer; organization, community; sector/system, and society levels) (1).

Depression in men may often manifest by unspecific symptoms, which makes it difficult to establish a proper diagnosis and to estimate a real number of patients (2). Studies by Rice et al. (3) indicate six characteristic symptoms of male depression, i.e., suppression of emotions, alcohol or drug use, anger and aggression manifestation, somatic symptoms, and risky behaviors. The number of suicides in Poland (despite the noteworthy decline between 2015 and 2018) is very high, exceeding 5,000 people annually (even exceeding the number of car accident victims). Men commit suicide much more often than women (6:1) (4). Depressive disorders are connected with suicidal tendencies; in the majority of countries, suicide is one of the most frequent causes of death among depressive patients (5). More specifically, estimates indicate that ∼60% of suicide victims suffered from major depressive disorder and other mood disorders (6). Masculine norms may be deleterious to the mental health of young males, placing them at greater risk of suicidal ideation (7).

The National Institute of Mental Health (8) noted that the main depressive risk factors are as follows: personal or family history of depression, major life changes, trauma, stress, certain physical illnesses, and medications. According to the World Health Organization (9), risk factors for suicide include, for instance, previous suicide attempt(s), mental health problems and disorders, problematic substance use, job loss or financial loss, trauma or abuse, and chronic pain or illness, including cancer, diabetes, and HIV/AIDS. There are also some factors that can have a protective dimension. Particularly noteworthy are individual factors related to personality (e.g., self-efficacy), environmental factors (e.g., lifestyle practice of positive coping strategies, social support in the place of residence, financial security, strong personal relationships, social competencies), and individual factors related to beliefs (e.g., religious or spiritual beliefs).

This study was aimed to determine factors strongly positively and negatively related to the intensity of depression and suicidal tendencies in the group of men diagnosed with depressive disorder, as compared to physically ill men and healthy men. In this study, we analyzed two types of predictors connected with depression and suicidal behavior—negative (risk factors) and positive (protective factors). It is the first study on depression and suicidal behavior comparing three different groups of men. Awareness of risk and protective factors for suicide in depression is especially important for clinicians (10).

MATERIALS AND METHODS

Material

The studies were conducted in three groups: Group I (clinical group), group II (first control group—CG1), and group III (second control group—CG2). The study inclusion criteria for the clinical group (group I) were as follows: (1) age at least 18 years, (2) male gender, (3) diagnosis of depressive disorders (F31—in the depressive phase, F32, and F33), (4) undergoing pharmacological and psychotherapeutic treatment in the 2nd Clinic Psychiatric Institute of Psychiatry and Neurology in Warsaw or Mazowieckie Specialist Health Center prof. Jan Mazurkiewicz, and (5) informed consent to participate in the study.

The study inclusion criteria for the first control group (CG1) were as follows: (1) age at least 18 years, (2) male gender, (3) no current pharmacological and psychotherapeutic treatment at any psychiatric hospital, (4) informed consent to participate in study, and (5) currently undergoing treatment of any physical illness in four randomly selected hospitals in Warsaw at randomly selected departments. Patients from randomly selected hospitals in Warsaw were selected for the first control group to collect responses from men with no history of depressive disorder. The randomness of hospitals and departments was used to reduce the error resulting from the health condition of the male respondents from the control group. Patients qualified for the first control group stayed in the following hospitals:

1. Samodzielny Publiczny Centralny Szpital Kliniczny (Independent Public Central Clinical Hospital), Department of Internal Diseases, Pneumonology and Allergology, ($N = 45$).
2. Wojskowy Instytut Medyczny Centralny Szpital Kliniczny MON (Military Institute of Medicine Central Clinical Hospital of the Ministry of National Defense), Department of Internal Medicine, Nephrology and Dialysis, ($N = 40$).
3. Miedzyleski Szpital Specjalistyczny (Miedzyleski Specialist Hospital), Department of Adult Dermatology, ($N = 48$).

4. Mazowiecki Szpital Bródnowski (Mazowiecki Bródnowski Hospital), Traumatic and Orthopedic Surgery and Rehabilitation Department Complex, ($N = 50$).

The study inclusion criteria for the second control group (CG2) were as follows: (1) age at least 18 years, (2) male gender, (3) no current pharmacological and psychotherapeutic treatment at any psychiatric hospital, (4) informed consent to participate in study, and (5) feeling physically and mentally healthy. The snowball method was used to include the participants in this group.

A total of 598 questionnaires were collected: 197 from the clinical group (CG, group I), 198 from CG1, and 203 from CG2. For CG1, Gotland Male Depression Scale revealed that 1 person showed depression syndromes and 14 men met the criteria of possible depression (for CG2: 1 person with depression and 5 with possible depression). Therefore, those 15 persons (7.6%) were excluded from CG1 (6 persons, 3.0% from CG2) and further analysis included only men with no signals of depression in control groups ($n = 183$ for CG1 and $n = 197$ for CG2).

Sociodemographic characteristics of study groups are presented in **Table 1**. Men in CG1 were significantly older (47.97 ± 17.40 years) than in CG (44.14 ± 14.27 years) and CG2 (42.99 ± 14.48 years) with weak effect size, $\eta^2 = .02$; $p = 0.005$. Education, place of living, professional activity, and marital status were also significantly different between groups with weak scale effect (V from 0.21 to 0.30; $p < 0.001$ for each characteristic). Patients from villages and small cities were found more frequent in CG than in other groups (in total 36 vs. 15% in CG1 and 5% in CG2). Primary and secondary education was more frequently noted in CG, while vocational and higher education was noted in control groups. Responders from control groups were more often professionally active than CG patients (52% in CG vs. 64% in CG1 and 80% in CG2) and were more frequently married (34% in CG vs. 59% in CG1 and 56% in CG2). Patients from the clinical group (CG) were more often unemployed or bachelors than in control groups. The number of children was significantly different among groups with small scale effect (52% in CG vs. 68% in CG1 and 60% in CG2; $V = 0.13$; $p = 0.009$).

Instruments

The survey included standardized screening questionnaires and socio-demographic variables with few additional questions (Have you ever had thoughts of suicide? Have you ever tried to take your own life? Have you had/are there any mental disorders in your family? Have you ever been treated psychiatrically? The last question was detailed with the number of treatment episodes, a diagnosis that has been identified in the course of treatment, and the extent of treatment support received from a family ranging from very high, high, moderate, low to none).

The following standardized questionnaires were used in this study:

1. AUDIT test—the Alcohol Use Disorders Identification Test

A test commissioned by the World Health Organization, consisting of 10 questions arranged in three parts: the first part evaluates risky drinking (frequency of drinking, the average amount of alcohol drunk, frequency of excessive drinking), the second part evaluates symptoms of addiction (loss of control over drinking, drinking as an increasingly important issue in life, the need to drink in the morning), and the third part contains questions on harmful drinking (feeling guilty after alcohol drinking, memory lapses caused by drinking, physical injuries caused by alcohol drinking, the concern of others about your drinking) (11). The Polish version of AUDIT was used (Cronbach's $\alpha = 0.78$ in the original study and 0.903 in our study) (12).

2. Fagerström Test

The Fagerström Nicotine Addiction Test consists of six questions, which can be scored from 0 to 10. A score from 0 to 2 means a very low level of addiction; score 3–4, low; score 5, moderate; score, 6–7, high; score 8–10, very high level of addiction (13). The Polish version of the Fagerstrom Test was used—Cronbach's $\alpha = 0.76$ in the original study and 0.65 in our study (14).

3. GSES—Generalized Self-Efficacy Scale

The scale by Schwarzer, Jerusalem, and Juczyński in the Polish adaptation by Juczyński (15). The scale consists of 10 statements, which determined the level of self-efficacy of the examined person—Cronbach's $\alpha = 0.85$ in the original study and 0.908 in our study.

4. MINI-COPE Questionnaire (Brief COPE Inventory)

Coping strategies were measured by the MINI-COPE Questionnaire (Brief COPE Inventory) (16) in the Polish adaptation by Juczyński and Ogińska-Bulik (15). There are 28 statements integrated into 14 coping strategies (i.e., two statements per strategy): active coping, planning, positive reframing, acceptance, sense of humor, religious solace, use of emotional support, use of instrumental support, self-distraction, denial, venting, substance abuse, behavioral disengagement, and self-blame. The respondent selected one out of four possible answers ranging in scores from "I have almost never been doing this" (0 points) to "I have almost always been doing this" (3 points). Each of the coping strategies was assessed separately, and the higher the score, the more often a particular strategy was adopted. Depending on subscale, Cronbach's $\alpha = 0.45$–0.82 in the original study and 0.484–0.912 in our study.

5. Resilience Evaluation Questionnaire (KOP-26)

This questionnaire was created by Gasior, Chodkiewicz, and Cechowski (17). The questionnaire consists of 26 items. The assessment of the extent to which the respondent agrees with a given statement is made on a five-point Likert scale [from 1 (I completely disagree) to 5 (I completely agree)]. Four variables are assessed based on the questionnaire: personal competencies, family competencies, social competencies, and general resilience (assumed by all three types of competencies). The Polish version

TABLE 1 | Sociodemographic characteristic of study groups.

Characteristic	Clinical group	Control group 1 (somatic disease—CG1)	Control group 2 (healthy—CG2)	Effect size	*p*
N	197	183	197		
Age, years	44.14 ± 14.27	47.97 ± 17.40	42.99 ± 14.48	0.02	0.005
Place of living					
Large city (>200k habitants)	84 (42.6)	110 (60.1)	155 (78.7)	0.26	<0.001
Medium city (50k–200k habitants)	41 (20.8)	45 (24.6)	33 (16.8)		
Small city (<50k habitants)	41 (20.8)	13 (7.1)	6 (3.0)		
Village	31 (15.7)	15 (8.2)	3 (1.5)		
Education					
Primary	20 (10.2)	3 (1.6)	12 (6.1)	0.23	<0.001
Secondary	87 (44.2)	41 (22.4)	39 (19.8)		
Vocational	38 (19.3)	65 (35.5)	44 (22.3)		
Higher	52 (26.4)	74 (40.4)	102 (51.8)		
Work status					
Student	8 (4.1)	7 (3.8)	17 (8.6)	0.30	<0.001
Unemployed	34 (17.3)	2 (1.1)	1 (0.5)		
Working	101 (51.5)	117 (63.9)	157 (79.7)		
Retired/pensioner	43 (21.9)	56 (30.6)	21 (10.7)		
Dependence on another family member	10 (5.1)	1 (0.5)	1 (0.5)		
Marital status					
Married	66 (33.5)	107 (58.5)	110 (55.8)	0.21	<0.001
Separated/divorced	33 (16.8)	11 (6.0)	17 (8.6)		
Widower	8 (4.1)	10 (5.5)	6 (3.0)		
Bachelor	66 (33.5)	29 (1.8)	29 (14.7)		
Informal relationship	23 (11.7)	26 (14.2)	35 (17.8)		
Having kids	102 (52.0)	123 (67.6)	119 (60.4)	0.13	0.009
Number of kids	2.00 (1.00;2.00)	2.00 (1.25;2.00)	1.00 (1.00;1.00)	0.004	0.320

of KOP-26 was used. Cronbach's $\alpha = 0.90$ for total scale, 0.78–0.90 for subscales in the original study and 0.943 for total scale, 0.847–0.925 for subscales in our study.

6. Suicide Behaviors Questionnaire-Revised (SBQ-R) by Osman

The scale created by Osman et al. (18) in the Polish adaptation by Chodkiewicz and Gruszczyńska (19). The questionnaire is a self-descriptive measure of suicidal tendencies (suicidal behaviors, including ideation and attempts) composed of four questions. Cronbach's $\alpha = 0.83$ in the Polish adaptation study and 0.866 in our study.

7. Gotland Male Depression Scale

The scale was created by Rutz (20) in the Polish adaptation by Chodkiewicz (21). A scale consists of 13 statements describing the depressive symptoms of the people examined a month before. Each of the statements is scored on the four-point Likert scale: from 0 ("completely untrue") to 3 ("completely true"). The overall result is in the range from 0 to 39 points. The authors adopted the following interpretation of the results on the full scale: 0–12 points, no signs of depression; 13–26, possible depression, appropriate treatment should be considered; 27–39, depression, most likely treatment is necessary (including pharmacological). Cronbach's $\alpha = 0.85$ in the Polish adaptation study and 0.948 in our study).

Procedure

The study was carried out in 2018–2020 using the paper-pencil method. The researchers obtained approval from the management of all hospitals to conduct the study on its premises. The researcher, after making an appointment with the head of a ward participating in the study, was introduced to the ward staff and later was introduced to patients selected by the head of the ward, staying in the ward (the patients' state of health had to allow obtaining informed consent to participate in the study). The researcher introduced himself and discussed the study participation procedure. Before providing the patient with a questionnaire to complete, informed consent to participate in the study was obtained from each patient. It took the patients about 20–25 min to complete the questionnaire. The survey was voluntary and anonymous.

The collected and digitized data was stored by the researcher under the guidelines in force at the Medical University of Warsaw.

Ethical Declarations

The study was approved by the Bioethics Committee of Warsaw Medical University No. KE-0254/335/2015.

Statistical Analysis

For ease of reading, study groups were described as CG (clinical group), CG1 (somatic disease, mentally healthy), and CG2 (physically and mentally healthy).

Multivariate regression was used for each of the groups (TG, CG1, CG2) separately to identify factors impacting the level of depression. At first, we performed univariate regression models with all predictor variables and with GMDS and SBQ-R as outcome variables. Separate models were created to model the level of depression (based on GMDS score) and risk level of suicidal behaviors (based on SBQ-R score). Based on univariate models, into the final multivariate models, only these predictor variables were included, which were statistically significant in univariate regression models. A stepwise approach was used. Additionally, we verified the level of multicollinearity between predictor variables using variance inflation factors (VIFs) and values above 10 indicating high multicollinearity (22). Finally, R-squared was calculated to assess the explanatory power of each model.

Apart from the multivariate model in each group, additional models using logistic regression analysis were created for depression level to identify the group of factors predicting the presence of depression. One model included predictor variable understood as 1 = clinical group patients with depression/potential depression; 0 = control group 1 patients (somatic disease patients without depression). The second model included predictor variable understood as 1 = clinical group patients with depression/potential depression; 0 = control group 2 patients (healthy patients without depression). At first, we performed univariate logistic regression models with all predictor variables, based on which we included into the final multivariate models only these predictor variables that expressed $p < 0.25$ in univariate regression models, as per Hosmer and Leweshow recommendations (23). A stepwise approach with AIC criterion was used. As logistic regression was used, model coefficients were presented as log-odds (i.e., when the predictor increases by one unit, the outcome increases by log-odds). For ease of interpretation, log odds were exponentiated into odds ratios (OR) such that when the predictor increases one unit, the expected change in the outcome is described in terms of % odds. Models' evaluation was based on the R2 Nagelkerky coefficient and Hosmer and Lemeshow goodness of fit (GOF) test.

All tests were two-tailed, and results were regarded as statistically significant at the level of $p < .05$. Analysis was conducted in statistical software R (version 3.5.1).

RESULTS

Multivariate regression analysis confirmed that in the clinical group, the following variables were significant predictors of depression (GMDS level): education vocational vs. primary, β = −3.01; CI_{95} (−5.15 to −0.86]; $p = 0.006$, unemployed vs. working work status, β = 2.51; CI_{95} (1.02–3.99); $p = 0.001$, student vs. working work status, β = 3.42; CI_{95} (0.62–6.23); $p = 0.017$, satisfaction from financial situation, β = 0.60; CI_{95} (0.09–1.10); $p = 0.020$, having kids, β = 1.64; CI_{95} (0.40–2.88); $p = 0.010$, presence of mental disorders in family, β = 2.49; CI_{95} (1.30–3.68); $p < 0.001$, alcohol addiction AUDIT, β = 0.14; CI_{95} (0.08–0.20); $p < 0.001$, active coping strategy of dealing with stress, β = −1.31; CI_{95} (−2.22 to −0.40); $p = 0.005$, turning to religion strategy of dealing with stress, β = −0.94; CI_{95} (−1.52 to −0.37); $p = 0.001$, seeking instrumental support strategy of dealing with stress, β = 1.18; CI_{95} (0.37–2.00); $p = 0.005$, and social competence for resilience, β = −0.36; CI_{95} (−0.49 to −0.22); $p < 0.001$. The model explained 47% of variation in depression variable.

Similar model for CG1 group resulted in the following range of variables predicting significant depression level: medium vs. large city place of living, β = −0.58; CI_{95} (−1.14 to −0.01); $p = 0.047$, small city vs. large city place of living, β = −0.95; CI_{95} (−1.87 to −0.03); $p = 0.043$, psychiatric treatment in the past, β = 3.51; CI_{95} (1.27–5.76); $p = 0.002$, and active coping strategy of dealing with stress, β = −0.74; CI_{95} (−1.27 to −0.20); $p = 0.007$. The model explained only 13% of variation in depression variable.

Depression level in CG2 group was significantly modeled by the following: medium vs. large city place of living, β = −0.83; CI_{95} (−1.40 to −0.25); $p = 0.005$, education: vocational vs. primary, β = 1.67; CI_{95} (0.69–2.64); $p = 0.001$, education: higher vs. primary, β = 1.38; CI_{95} (0.40–2.35); $p = .006$, professional activity: student vs. professionally active was concerned, β = 2.00; CI_{95} (0.90–3.10); $p < 0.001$, satisfaction with financial situation, β = 0.79; CI_{95} (0.46–1.12); $p < 0.001$, number of children, β = 0.23; CI_{95} (0.01–0.45); $p = 0.042$, occurrence of mental disorders in family, β = 1.39; CI_{95} (0.68–2.10); $p < 0.001$, occurrence of alcohol abuse in family, β = 0.84; CI_{95} (0.33–1.35); $p = 0.001$, positive reappraisal strategy of dealing with stress, β = −0.86; CI_{95} (−1.29 to −0.44); $p = 0.001$, and use of psychoactive substances as a strategy of dealing with stress, β = 0.69; CI_{95} (0.25–1.04); $p < 0.001$. The model explained 43% of variation in depression variable (**Table 2**).

Multivariate regression analysis confirmed that in the clinical group (CG) the following variables were identified as significant predictors of suicidal behaviors: professionally status: unemployed vs. professionally active, β = 3.15; CI_{95} (1.73–4.58); $p < 0.001$, working status student vs. professionally active, β = 3.14; CI_{95} (0.24–6.05); $p = 0.034$, marital status: bachelor vs. married, β = −1.80; CI_{95} (−3.22 to −0.38); $p = 0.013$, occurrence of mental disorders in family, β = 2.03; CI_{95} (0.79–3.27); $p = 0.001$, active coping strategy of dealing with stress, β = −1.09; CI_{95} (−2.02 to −0.17); $p = 0.021$, turning toward religion as a strategy of dealing with stress, β = −0.79; CI_{95} (−1.39 to −0.20); $p = 0.009$, seeking instrumental support strategy of dealing with stress, β = 0.97; CI_{95} (0.17–1.78]; $p = 0.018$, and social competence for resilience, β = −0.34; CI_{95} (−0.49 to −0.20); $p < 0.001$. The model explained 48% of variation in suicidal behaviors variable.

In the CG1 group, a similar model resulted in the following range of variables predicting significant suicidal behaviors risk level: place of living: medium vs. large city, β = −0.60; CI_{95}

TABLE 2 | Multivariate regression analysis for depression severity at men.

Multivariate regression model for depression severity	Clinical group				Control group 1 (somatic disease)				Control group 2 (healthy)			
	β	95% CI for β	B	*P*	β	95% CI for β	B	*p*	β	95% CI for β	B	*p*
Place of living, Large cities = baseline medium city					−0.58	−1.14 to −0.01	−0.35	0.047	−0.83	−1.40 to −0.25	−0.47	0.005
Small city					−0.95	−1.87 to −0.03	−0.57	0.043				
Education, Primary = baseline vocational	−3.01	−5.15 to −0.86	−0.66	0.006					1.67	0.69–2.64	0.85	0.001
Higher									1.38	0.40–2.35	0.78	0.006
Work status, Working (professionally active) = baseline	2.51	1.02–3.99	0.55	0.001								
Unemployed												
Student	3.42	0.62–6.23	0.76	0.017					2.00	0.90–3.10	0.94	<0.001
Financial situation satisfaction	0.60	0.09–1.10	0.16	0.020					0.79	0.46–1.12	0.41	<0.001
Having children	1.64	0.40–2.88	0.18	0.010								
Number of children									0.23	0.01–0.45	0.14	0.042
Psychiatric treatment in the past					3.51	1.27–5.76	0.23	0.002				
Mental disorders in family (1 = yes)	2.49	1.30–3.68	0.26	<0.001					1.39	0.68–2.10	0.25	<0.001
Alcohol abuse in family (1 = yes)									0.84	0.33–1.35	0.20	0.001
Alcohol addiction (by AUDIT)	0.14	0.08–0.20	0.29	<0.001								
Mini-COPE Active coping	−1.31	−2.22 to −0.40	−0.19	0.005	−0.74	−1.27 to −0.20	−0.20	0.007				
Positive reappraisal									−0.86	−1.29 to −0.44	−0.32	0.001
Turning to religion	−0.94	−1.52 to −0.37	−0.21	0.001								
Seeking instrumental support	1.18	0.37–2.00	0.20	0.005								
Use of psychoactive substances									0.69	0.25–1.04	0.27	<0.001
Social competence	−0.36	−0.49 to −0.22	−0.42	<0.001								
Constant	8.54	4.53–12.56	0.21	<0.001	6.02	4.80–7.24	0.14	<0.001	−4.93	−8.19 to −1.67	−0.66	0.011
R2		0.47				0.13				0.43		
R2 adj.		0.42				0.11				0.36		
VIF range		From 1.23 to 1.90				From 1.02 to 1.03				From 1.11 to 4.65		

β, beta coefficient (non-standardized); 95% CI for β, 95% confidence interval for beta coefficient; B, beta coefficient (standardized); VIF, variance inflation factors.

(−1.17 to −0.03); $p = 0.038$, psychiatric treatment in the past, β = 4.05; CI_{95} (1.81–6.29); $p = 0.001$, active coping strategy of dealing with stress, β = −0.75; CI_{95} (−1.32 to −0.19); $p = 0.009$, venting of emotions as a strategy of dealing with stress, β = −0.62; CI_{95} (−1.12 to −0.12); $p = 0.015$, and personal competence of resilience, β = −0.09; CI_{95} (−0.18 to −0.01); $p = 0.038$. The model explained 23% of variation in suicidal behavior variable.

In the CG2 group, the suicidal behavior risk level was significantly modeled by the following: place of living: medium vs. large city, β = −0.97; CI_{95} (−1.52 to −0.41); $p = 0.001$, satisfaction with financial situation, β = 0.68; CI_{95} (0.38–0.97); $p < 0.001$, occurrence of alcohol abuse in family, β = 0.82; CI_{95} (0.30–1.33); $p = 0.002$, planning strategy of dealing with stress, β = −0.66; CI_{95} (−1.21 to −0.12); $p = 0.017$, use of psychoactive substances as a strategy of dealing with stress, β = 0.67; CI_{95} (0.31–1.02); $p < 0.001$, total resilience, β = 0.11; CI_{95} (0.07–0.16); $p < 0.001$, personal competence of resilience, β = −0.22; CI_{95} (−0.33 to −0.12); $p < 0.001$, and social competence of resilience, β = −0.12; CI_{95} (−0.18 to −0.05); $p = 0.001$. The model explained 38% of variation in suicidal behaviors variable (**Table 3**).

Additional logistic regression models were created for depression evaluation. Factors significantly increasing the risk of depression in the clinical group (CG) vs. healthy patients were as follows: living in a small city vs. large city, or living in a village vs. large city, the occurrence of mental disorders or alcohol abuse in the family, nicotine addiction as evaluated by Fagerström questionnaire, alcohol addiction as evaluated by

TABLE 3 | Multivariate regression analysis for suicidal behaviors at men.

Multivariate regression model for SBQ-R	Clinical group				Control group 1 (somatic disease)				Control group 2 (healthy)			
	β	95% CI for β	B	*p*	β	95% CI for β	B	*p*	β	95% CI for β	B	*p*
Place of living, Large cities = baseline Medium city					−0.60	−1.17 to −0.03	−0.36	0.038	−0.97	−1.52 to −0.41	−0.55	0.001
Work status, Working (professionally active) = baseline	3.15	1.73–4.58	0.70	<0.001								
Unemployed												
Student	3.14	0.24–6.05	0.70	0.034								
Financial situation satisfaction									0.68	0.38–0.97	0.35	<0.001
Marital status, Married = baseline Bachelor	−1.80	−3.22 to −0.38	−0.40	0.013								
Psychiatric treatment in the past					4.05	1.81–6.29	0.26	0.001				
Mental disorders in family (1 = yes)	2.03	0.79–3.27	0.45	0.001								
Alcohol abuse in family (1 = yes)									0.82	0.30–1.33	0.47	0.002
Mini-COPE Active coping	−1.09	−2.02 to −0.17	−0.16	0.021	−0.75	−1.32 to −0.19	−0.21	0.009				
Planning									−0.66	−1.21 to −0.12	−0.17	0.017
Religion	−0.79	−1.39 to −0.20	−0.17	0.009								
Use of instrumental support	0.97	0.17–1.78	0.16	0.018								
Venting					−0.62	−1.12 to −0.12	−0.21	0.015				
Substance use									0.67	0.31–1.02	0.26	<0.001
Resilience (KOP-26) Personal competence					−0.09	−0.18 to −0.01	−0.18	0.038	−0.22	−0.33 to −0.12	−0.58	<0.001
Social competence	−0.34	−0.49 to −0.20	−0.40	<0.001					−0.12	−0.18 to −0.05	−0.29	0.001
Constant	9.44	5.51–13.38		<0.001	8.23	5.22–11.23	0.13	<0.001	−0.09	−3.14–2.97	0.004	0.955
R2		0.48				0.23				0.38		
R2 adj.		0.40				0.17				0.34		
VIF range		From 1.30 to 2.12				From 1.10 to 1.51				From 1.11 to 7.67		

β, beta coefficient (non-standardized); 95% CI for β, 95% confidence interval for beta coefficient; B, beta coefficient (standardized); VIF, variance inflation factors.

AUDIT questionnaire, and turning toward religion as a strategy of dealing with stress. At the same time, working vs. non-working and GSES significantly decreased the risk of depression in the same group. Another model predicting the risk of depression in the clinical group (CG) vs. mentally healthy or men with somatic illness resulted in the following significant predictors of depression: occurrence of alcohol abuse in the family, nicotine addiction (by Fagerström questionnaire), alcohol addiction (by AUDIT), and self-blame strategy of dealing with stress (all of them increased the risk of depression), as well as GSES, the strategy of positive reappraisal strategy of dealing with stress, use of psychoactive substances strategy of dealing with stress, and social competence decreased the risk of depression (**Table 4**). Both logistic regression models had a good fit to the data (GOF test for model 1 with $p = 0.087$ and model 2 with $p = 0.389$). Nagelkerke R2 level also confirms a good quality of both models (R2 for model 1 was 0.75, while for model 2 R2 = 0.78).

DISCUSSION

In-house study shows that there are some common depression risk factors for the group of men: student status, low satisfaction with the financial situation, having children/more children, and the occurrence of mental disorders in the family. There are some risk factors of depression that are characteristic only for men with this type of mental disorder: unemployment, alcohol abuse/addiction, and seeking instrumental support in coping with stress. Some of these risk factors coincide with risk factors for suicidal behavior for men with diagnosed depression, which include unemployment, student status, the occurrence of mental disorders in the family, and seeking instrumental support.

TABLE 4 | Multivariate logistic regression analysis for depression severity at men.

Characteristic	Model 1 (CG vs. CG2)			Model 2 (CG vs. CG1)		
	OR	95% *CI* for *OR*	*p*	*OR*	95% *CI* for *OR*	*p*
Small city	11.47	2.34–67.68	0.004			
Village	34.36	6.53–220.66	<0.001			
Work status, Not-working = baseline Working	0.27	0.11–0.64	0.004			
Mental disorders in family (1 = yes)	6.32	2.35–17.73	0.003			
Alcohol abuse in family (1 = yes)	3.28	1.34–8.27	0.010	6.44	2.43–18.50	<0.001
Nicotine addiction (Fagerström)	1.41	1.21–1.67	<0.001	1.61	1.37–1.94	<0.001
Alcohol addiction (AUDIT)	1.10	1.04–1.17	0.001	1.29	1.17–1.45	<0.001
Self-efficacy (GSES)	0.81	0.74–0.87	<0.001	0.81	0.70–0.92	0.001
Mini-COPE						
Positive reappraisal				0.16	0.06–0.40	<0.001
Turning to religion	2.50	1.64–3.92	<0.001			
Use of psychoactive substances				0.42	0.23–0.75	0.005
Self-blame				3.22	1.65–6.65	0.001
Social competence				0.87	0.77–0.98	0.027
Constant	40.01	3.09–619.76	0.06	4,957	113–372,284	<0.001

OR, odds ratio; 95% CI for OR, 95% confidence interval for odds ratio.

The present study noted the key role of socioeconomic factors in the development of depression. This is consistent with the results of other studies. Socioeconomic status has been found to play an important role in depression (24). A meta-analysis of population-based surveys confirmed the association of increasing intensity of depression symptoms with decreasing social position (especially for income level) (25). According to a study conducted among male truck drivers by Da Silva-Júnior et al. (26) wage-earning (OR = 2.84; $P = 0.01$) is one of the main risk factors of depression. In our study, men were assessing their satisfaction with the financial situation, which can reflect their material aspects of socioeconomic status—low satisfaction with the financial situation turned out to be a risk factor of depression among men with diagnosed depression and in the healthy group. It should be noted that the increased risk of depression in men with low income may be directly related to the workload and working conditions. Other studies emphasize that working conditions are a strong determinant of depressive disorders in men. For example, work overload under unfavorable conditions can translate into job satisfaction as well as financial satisfaction (27).

Unemployment is another socioeconomic variable that is associated with the subjective assessment of financial satisfaction. Our study shows that unemployment is one of the risk factors related to the level of depressions and suicidal behavior for men with diagnosed depressive disorder. Suzuki et al. (28) proofed that the risk of depressive tendencies is significantly higher in men who were not working (OR, 3.57; 95% CI, 1.31–9.72). Evidence suggests that the risk of depression increases steadily for 6 months after the individual becomes unemployed, then reaches a plateau and is reversed almost immediately on finding work (29). Unemployment is associated also with greater depressive symptoms, and this relationship is only observed in men and not in women (30). During unemployment, there is a critical time between 3 months and a year during which people may be the most at risk of mental disorder. This time is thought to coincide with the growing sense of hopelessness that may accompany the perceived transition from short- to long-term unemployment. The long-term unemployed have a greater risk of suicide and attempted suicide compared to those unemployed for the short term (31). Male suicide mortality increased linearly with the length of unemployment. Men may have been more likely to derive social status and prestige from their work. The male role as the primary breadwinner, either perceived or real, appears to have given unemployment a greater negative effect on men than on women (32). Individuals in poor health are at increased risk of unemployment and also suicide. The higher relative risk of suicide among the unemployed seems to be, in part, a consequence of the exclusion of less healthy individuals from the labor market (33).

The present study also shows the important role of the level of education. Other researchers emphasized that level of education is another component of socioeconomic status (34). Our results show that student status increases the level of depression and suicidal behavior among healthy men and men who have depression disorders. Scientific reports indicate a frequent occurrence of depression in students. According to a systematic review of studies of depression prevalence in university students, there is wide variation in the proportion of students identified as depressed, from relatively low rates around 10% to high rates of between 40 and 84% with a weighted mean prevalence of 30.6%. It was also estimated that the prevalence of depression among male students is about 24.9% (35). A study by Akhtar-Danesh and Landeen (36) showed that the lowest rates of depression based on the level of education were seen among individuals with less than secondary school. Moreover, according to this study, the odds of living with lifetime depression among individuals with any kind of post-secondary education is 1.54

times compared to individuals with lower than post-secondary education. Oquendo et al. (37) noted that being more educated and at the earlier age of onset of depression increased the risk for future depression in men. On the other hand, a study by Da Silva-Júnior et al. (26) is in opposition to these results—they noted that low educational level is one of the depression risk factors among men (OR = 3.03; $P = 0.01$). Also, dos Santos et al. (38) showed that the risk of depression decreases as the schooling years increase. This correlation is not unambiguous and requires further analysis. Individuals with higher educational achievement may be more prone to suicide risk when facing failures, public shame, and high premorbid functioning (39). Vijayakumar et al. (40) found an association between high education levels and high male suicide rates pointing to the fact that those with relatively high socioeconomic standing had the highest suicide rates.

A strong correlation is noticed between alcohol abuse and depressive disorders in men (2). They often use alcohol to cope with their mental pain. Our study confirms this dependency—one of the risk factors related to the level of depression among men with diagnosed depression is alcohol abuse/addiction. These factors do not occur in the control groups, so it is specific for men with depression. A study by Bazargan-Hejazi et al. (41) showed that alcohol overuse is one of the predictive characteristics of depression in men. Moreover, men who overused alcohol were 2.5 times more likely to report greater depression (95% CI = 1.37–4.45). Data from the National Comorbidity Survey estimated the lifetime prevalence of major depression to be nearly one quarter (24.3%) among alcohol-dependent men exceeding the prevalence rates among individuals without alcohol use disorder. In clinical samples, the lifetime rates of co-occurrence are greater still, ranging from 50 to 70% (42).

According to Richards and Sanabria (43) and Hamano et al. (44), risk factors associated with depression included the history of family depression and alcohol overuse. A review and meta-analysis of the genetic epidemiology in major depression have indicated that major depression is considered a familial disorder, which mostly or entirely results from genetic influences (45). Moreover, the risk for major depressive disorder was highest among grandchildren with two previous generations affected by the disorder, suggesting the potential significance of a family history of depression beyond two generations (46). A study of Angelini et al. (47) noted that individuals who were exposed during childhood to a parent with mental health problems suffered from depressive symptoms more often in late adulthood than those who were not (OR, 1.76; 95% CI, 1.43–2.17). Our study is noting that the occurrence of mental disorders in the family is one of the risk factors related to the level of depression in healthy men and men with depressive disorders. Suicidal behavior remains a risk factor in men with diagnosed depression. Family history of suicidal acts tripled the risk of future suicidal acts. Suicidal behaviors cluster in families, independently of the transmission of psychiatric conditions (34). A large epidemiologic study (48) showed that a family history of psychiatric disorders increased the risk of suicide completion. In a meta-analysis of Carrasco-Barrios et al. (49), significant OR for family history of mental disorder when considering all types of suicidality and suicidal ideation was obtained. A systematic review of Hawton et al. (10) noted that male gender (OR, 1.76; 95% CI, 1.08–2.86) and family history of psychiatric disorder (OR, 1.41; 95% CI, 1.00–1.97) are factors significantly associated with suicide.

Parenthood is associated with physical and mental health. Wang et al. (50) found that the number of children was not associated with a decreased prevalence of depression in men. Some studies showed that under certain conditions (i.e., unemployment), married fathers living with minor children report more distress than mothers (51). The study of fathers at age 18–40 revealed major depression symptoms more frequently in those men that became a father during adolescence (52). In our study, having children turned to be a risk factor related to the level of depression among depressive men. We found a correlation between the number of children and the risk of depression in patients from the control group of healthy men. Results of Mirowsky and Ross (53) showed that the later in life men become fathers, the more they seem to benefit emotionally from being a parent—they are less depressed the longer they delayed parenthood.

Mood disorders like recurrent depressive disorder or depressive episode may be an important factor contributing to the negative assessment of ability to cope with difficult situations and a greater tendency to perceive stressful events as overwhelming. Patients with depression more often use ineffective and avoidance strategies to cope with stress compared to healthy controls (54). A study by Walker et al. (55) showed that depressive symptoms were directly related to the use of less adaptive coping methods and directive instrumental social support. According to Nadler et al. (56), men sought help more often for instrumental-informational reasons. Shell and Eisenberg (57) demonstrated that instrumental (or direct) support did not result in feelings of threat, low perceived control, or high dependency in boys. In our study, seeking instrumental support in coping with stress remains depression and suicidal behavior risk factor characteristic for men with diagnosed depression. Kelly et al. (58) and Matud et al. (59) also noted that men use more problem-focused or instrumental methods of handling stressful experiences. Those results differ from other studies on this topic published recently. In the study of Liang et al. (60), instrumental support [Adj' OR = 0.90, 95% CI (0.84–0.97)] was significantly less likely to be used by the group of patient with attempted suicide, but it has to be kept in mind that about 68% of the studied group consisted of women. Moreover, according to Ambrus et al. (61), only avoidant coping may be associated with increased suicide risk in psychiatric patients independently of a history of attempted suicide. The topic of male coping strategies should be investigated in the future.

A group of depression and suicidal behavior risk factors, including student status, low satisfaction with the financial situation, having children/more than one children, the occurrence of mental disorders in the family, unemployment, alcohol abuse, and seeking instrumental support should be analyzed by the therapists, doctors, and other professional staff engaged in the therapy of men who can suffer from depression.

Our study shows that active coping strategy and living in a middle-size city are two common protective factors against depression for men. There are some positive factors related to the level of depression that are characteristic only for men with depressive disorder: vocational education, the use of religious practices to deal with stress, and presenting social competencies. Some of these factors coincide with protective factors against suicidal behavior, which are common for all men: active coping, living in a middle-size city, and personal and social competencies. We also selected a group of protective factors against suicidal behavior characteristics for men with depression: bachelor status and using religion to cope with stress.

There are numerous studies on protective factors against depression and suicide. A study by Breton et al. (62) showed that productive coping is one of the protective factors against depression and suicidal behaviors. Our results confirm this association in males—active coping with stress is a very important protective factor against both depression and suicidal behavior. It should be noted that active coping with stress (engagement coping) involves active dealing with stressors or related emotions, whereas disengagement coping involves escaping stressors or subsequent emotions. Engagement coping is associated with improved well-being, and disengagement coping is associated with negative mental health outcomes (63). Active coping with stress is a factor of protection against a negative mental state, and thus against depression.

The living environment seems to have neurobiological effects that contribute to different course and outcome of psychiatric disorders (64). Research has also found that urbanity/rurality shapes intra-regional differences in suicide (65). According to a recent study by Barry et al. (66), men living in rural areas are more likely to effectively commit suicide. There are many possible explanations for increased suicide risk in rural areas. Despite popular clichés about anonymous city-dwelling, rural living can lead to social isolation, resulting in less intimate face-to-face contact with family and friends, which, in turn, increases the risk for suicidal behavior (64). Rural dwellers have easier access to lethal means, which increases their suicide risk (67). Country living is often related to a lower socioeconomic status as well as stigmatized attitudes toward visiting mental healthcare facilities [e.g., general practitioner (GP) and psychiatrists], and long travel distances diminish the accessibility to specialized healthcare providers (68). Several empirical studies emphasized an elevated vulnerability in rural areas, whereas others drew an opposite conclusion (66). In our study, living in middle-size and small cities is significantly more protective against depression among men than living in large cities. According to male suicidal behavior, living in middle-size cities has a protective dimension. Poor social networks such as residence in a rural location and having few contacts with friends were the identified risk factors of depression in late life (69). Another study emphasized that rural areas upheld traditional gender roles. Consequently, men who cannot fulfill their roles may experience increased stress. Men showed susceptibility to a wider range of stressors (e.g., financial stress) as compared with women (70).

Results of Omary research (71) suggested that higher education levels might play a protective role against suicidal ideation among men with depression. Our results show an opposite correlation—vocational education is a statistically significant positive factor related with the level of depression in men with diagnosed depression. What is interesting, the same factor turned to be a depression risk factor in a group of healthy men. To explain this discrepancy, one should thoroughly analyze the degree of satisfaction with a patient's work. The research results show that men are more sensitive than women to work stress, work problems, and financial problems. These factors may be more important than the level of education itself. Additionally, there is still a belief among the society that a man should be responsible for the maintenance of his family. This stereotype may increase stress related to the performed work and negatively affect the male mental state, including increasing the risk of depression (70). Therefore, a simple conclusion of the results of the correlation between education and depression should be taken with caution.

An extensive review of Koenig et al. (72) showed that religion and active participation in religious practices have the power to neutralize life stress and might help both to prevent the onset of depression, and if depression develops, they shorten the time it takes to resolve. A recent study by Arjan et al. (73) showed that religiosity tended to be more protective in persons with psychiatric symptoms than in people with physical illnesses. A study of McFarland (74) presented that organizational religiosity decreases symptoms of depression and increases levels of optimism and self-esteem over time for men. Religion provides men a unique context in which they were able to reap more benefits from religious activities. Organizational religious activity (i.e., involvement in religious services, bible groups, and prayer groups) appears to have a more pronounced impact on mental health for men. Religious attendance was protective for men (75). Our study shows that applying religion to cope with stress has a protective dimension in a group of men with depression disorders. These results stay in contradiction to the findings of Orr et al. (76)—they found that higher initial religious engagement is associated with higher initial depressive symptoms, especially among men. A systematic review that examined the correlation of religion and suicide conducted by Koenig et al. (77) found that most of the studies (84%) indicated fewer suicides or more negative attitudes toward suicide among the more religious people. Recent research suggests that religion prevents suicide primarily through religious doctrines that prohibit suicide (78). A systematic review of Lawrence et al. (79) seeking to identify the specific dimensions of religion (participation, affiliation, doctrine) that are associated with specific aspects of suicide (ideation, attempt, completion) found that religious affiliation does not necessarily protect from suicidal ideation but does protect from suicide attempts. It further found that religious service attendance is not protective against suicidal ideation but does protect from suicide attempts and may also have a protective effect against effective suicide. The protective effect of religion was noted by Kralovec et al. (80) especially against the capability aspect of suicide among men. Further research is warranted in the area of religion, depression, and suicidality to better understand the relationship between religiosity and gender. Also, the influence of religion on the

various groups within the dominant religions remains under-investigated (81).

Results of our study indicate that social competencies are positive factors related to the level of depression and suicidal behavior among depressive males, while personal competencies have a protective dimension of male suicidal behavior. It is believed that the post-aggregation of one's social competencies may depend on the mood of a depressed person. It has been noted that people with depression tend to negatively assess their own competencies in comparison to people without depression. Moreover, people with depression also rate their partners as less competent than people without depression (82). Other researchers also emphasize the negative style of social functioning of patients with depression—these patients have impaired social communication (impaired emotion recognition, diminished cooperativeness) and impaired social perception (reduced empathy, theory-of-mind deficits) and their impact on social networks (83). Bearing these results in mind, we can explain the obtained results of our research. Similar observations were noted as personal competencies are concerned, which are directly related to social competencies because they affect the quantity and quality of relationships created with others. They enable engaging in effective social interactions and are associated with resilience and positive adaptation to the environment in which the individual lives. Therefore, it is a protective factor against the development of depression and suicidal thoughts (84).

Most of the scientific reports emphasize that marriage appeared protective against suicide especially in men (85). Suicide data by the year 2019 published by Polish National Police show that about 37% of men who committed suicide were bachelor and 43% were married. The lowest number of suicides was among widowers (8%) and divorced/separated men (11%) (4). Similar statistics presented by Park et al. (86) show that the highest relative suicide risks occur in never-married men aged 55–64 years. Also, the study by Augustine et al. (87) noted that couples in separation were exposed to suicide risk that was nearly 52% greater than that of the married. In the study of Griffiths et al. (88) for single and divorced men aged 25 and over, suicide rates were around three times higher than for married men throughout 1983–2004. Results of Omary (71) suggested that marriage might play a protective role for suicidal ideation among men with depression. Our results present a completely different dimension—bachelor status is a characteristic protective factor for suicidal behavior among men with diagnosed depression. Discrepancies that were noted should be interpreted with caution as they do not take into account the full characteristics of the study subject. e.g., social situation and social competencies are not known. Our study also emphasizes the need for a broader look at the risk factors of depression in men, including protective factors. This is because they are not isolated factors, but often interact.

Factors positively related to the intensity of depression should be checked in future studies to see if they constitute a factor in the development of depressive disorders throughout life. The role of factors, the negative relationship of which with the level of depression has been shown in the study as potential protective factors, also needs to be checked.

LIMITATIONS

Our study is not without limits. First of all, researchers used self-report methods, so questionnaires were self-filled. However, study participants completed questionnaires at the hospital. The second important limitation of the study is voluntary participation in the study. This means that only some of the patients agreed to participate in the study. This could have influenced the results obtained. Another limitation is that there is no information about the co-occurring somatic and psychiatric disorders among the groups and also specific somatic disorders among CG1. Men from CG2 self-evaluate their physical and mental health. It could also have influenced the obtained results.

CONCLUSION

The risk factors identified in this study should be included in the clinical assessment of depression and suicidal behavior risk among male patients. Further large-scale studies are required to clarify the role of some factors. They may improve prognostic accuracy in major depression and suicidal behavior among men. There are some protective factors, including productive coping and personal and social competencies, which can be developed and should be especially considered and strengthened in mental health promotion programmes aimed at men.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee of Warsaw Medical University No. KE-0254/335/2015. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Profiling Suicide Exposure Risk Factors for Psychological Distress: An Empirical Test of the Proposed Continuum of Survivorship Model

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The Continuum of Survivorship proposes a way in which individuals may experience the suicide death of someone known to them along a continuum from being exposed to the death through to long-term bereavement. The present study provides a first empirical testing of the proposed model in an Australian community sample exposed to suicide. Using a Latent Profile Analysis, we tested the suicide exposure risk factors (time since death, frequency of pre-death contact, reported closeness, and perceived impact) to map to the Continuum of Survivorship model. Results revealed identification of five profiles, with four ranging from suicide exposed to suicide bereaved long-term broadly aligning with the proposed model, with one further profile being identified that represented a discordant profile of low closeness and high impact of suicide exposure. Our findings demonstrate that while the proposed model is useful to better understand the psychological distress related to exposure to suicide, it cannot be used as "shorthand" for identifying those who will be most distressed, nor those who may most likely need additional support following a suicide death. Implications and future research directions are discussed.

Keywords: continuum of survivorship, latent profile analysis, suicide exposure, closeness, impact, time since death, frequency of contact, psychological distress

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INTRODUCTION

With over 3,300 suicide deaths occurring in Australia in 2019 (1) and nearly one million suicide deaths worldwide, suicide is generally recognized as a major public health issue (2). Globally, suicide accounts for 1.4% of all deaths; it the 15th leading cause of death among all age groups and the second leading cause of death among youth (2, 3). Until recently, accurate data examining exposure to suicide among the general population has been lacking (4). Emerging research indicates the prevalence of suicide exposure is far greater than the estimate of six previously offered (5), with up to 135 people affected by each death (6). A recent meta-analysis based on population-based research indicated that past-year exposure to suicide was 4.31% and life-time prevalence of exposure to suicide was 21.83% (7). Additionally, findings from the 2016 General Social Survey in the United States found that 51% of the respondents in this representative sample reported knowing at least one person who died by suicide in their lifetime (8), with ∼35% of all respondents were identified as "bereaved," defined as the respondent indicating that the death was to some extent or very distressing.

Continued methodological (9) and ethical (10) issues in designing prospective studies on impact following exposure to suicide (given it is still a rare and unpredictable event) exist. This is compounded by an ongoing interest in whether bereavement following suicide is similar or different to other forms of unexpected or traumatic death. Over the decades, researchers continue to find that exposure to suicide death is quantitatively similar, yet qualitatively different (11). Nevertheless, deleterious effects from exposure to suicide are numerous and well-reported and include poor mental health outcomes, such as depression and anxiety (12), and suicide risk in both kin (13) and non-kin (4).

To better appreciate who is exposed and affected by suicide death, Cerel et al. (14) proposed a Continuum of Survivorship[1] theoretical model illustrating the possibility of varying levels of impact to suicide death in the general population. The Continuum model suggests that there is a large number of people who are exposed to every suicide death. Defined as "anyone who knows or identifies with someone who dies by suicide," the Suicide Exposed group in the Continuum model is hypothesized to be the largest group and may include first responders, community members, acquaintances, colleagues, or fans of celebrities and high-profile public figures, for example (p. 594). Cerel et al. suggest that the effects of suicide exposure for the Suicide Exposed group are likely of low intensity and short duration. Many of those exposed to the suicide will go on to be affected, meaning that their life is at least temporarily disrupted by the death. This category—called Suicide Affected—includes people who experience significant distress but may not be considered bereaved, such as people who witness a suicide or are predisposed to an intense reaction due to pre-existing circumstances (e.g., their own mental health issues).

Further, a smaller number will go on to be Suicide Bereaved (short-term), experiencing a major or devastating life disruption as a result of the death though for a short period of time, or Suicide Bereaved (long-term), meaning that the life disruption continues for a considerable amount of time after the death. It is proposed that those most affected (i.e., bereaved in the short- and/or long-term) will be in close relationship with the person now deceased, including family, extended kin, and friends.

Where such links between a suicide death and the impact on others has been the focus of research, the aim has primarily been bereavement focused, as evidenced in the Continuum model. Rightly, this model demonstrates that suicide impacts many more people than those who are bereaved, yet simultaneously proposes that those impacted most by the exposure to suicide are bereaved. Bereavement, within the traditional understanding of the concept, requires the loss of a significant relationship, typically defined as parents, partners, siblings, children, and friends, and the grief associated with the loss of a loved one is the focus of the bereavement (15). Yet, when examining the breadth of exposure to suicide, many people are exposed, and significantly impacted from that exposure, beyond those grieving a loss. A clear example of this is those who are occupationally exposed to suicide, including health care professionals (16) and first responders such as firefighters (17), ambulance staff (18), and law enforcement officers (19). Additionally, community members who find the deceased when a suicide occurs in public, referred to as zero responders, may not ever have known the person prior to their death, yet still experience impact resulting from the exposure (20). Seemingly, the important suicide exposure risk factors for psychological distress are the self-perceived impact of the death and reported closeness of the relationship. Further, the closer proximity to the death is likely to be a period of heightened distress, as is the frequency of pre-death contact (21, 22).

To date, no empirical research has examined a profile-based approach to map empirical data testing the Continuum of Survivorship model, and how the proposed survivorship profiles are associated with psychological distress. Identification of such typologies of survivorship can provide new insights into how different risk factors combine or co-exist within an individual and how each of these survivorship profiles are related to psychological distress. Traditional variable-centered statistical approaches examine the relationships between variables and results are at the variable-level, thus limiting our ability to form inferences about individuals (23, 24). The point in case is a standard regression variable-based approach that explores the main effects in addition to any interactions, but it does not guarantee that the implied "groups" (with high scores on one variable and low on another) obtained in a regression-based moderation analysis are always meaningful. On the other hand, person-centered approaches, such as a *latent profile analysis* (LPA) groups individuals into homogenous probability-based groupings and examines the relationships between individuals and their different patterns of responses (25).

LPA specifically helps identify specific combinations of variable scores that occur naturally within a sample and classify respondents with similar scores across a set of variables. LPA provides a novel approach to examine the prevalence of different patterns of responses on a range of individual difference variables in a sample (24, 26, 27). Accordingly, we adopted this approach to empirically test the Continuum of Survivorship model by answering the following research question: What survivorship typologies exist and how are these related to psychological distress?

MATERIALS AND METHODS

Participants and Procedure

An online survey was distributed through existing networks by a national peak suicide prevention organization, Suicide Prevention Australia from April through August 2016. Due to this recruitment procedure, we do not know the reach of the survey nor the response rate. Ethics approval was obtained through the University of New England [Approval number HE16-030].

A total of 3,220 unique participants (as per Internet IP address) responded to the survey, 874 cases were excluded for not meeting the inclusion criteria (152 participants reporting no exposure to suicide; 58 cases provided no further information about the nature or impact of the death exposure, 657 cases with extensive missing data, and 7 cases were under 18 years of age).

[1]Survivors of suicide is commonly used in North America to refer to those who have been bereaved by suicide.

This resulted in a final sample of 2,346 participants who reported exposure to suicide death and provided full data on key study variables included in the LPA analysis. Full details are reported elsewhere (22).

The mean age of participants in the final sample was 44.58 years (age range = 18–86, *SD* = 11.98). Our sample comprised 78.9% of women, 20.2% men; 0.7% other, and 0.2% preferred not to report their gender. It is common across suicide research to have higher female than male respondents (9). Just over half of the respondents (53%) lived in a metropolitan area, 29.5% in regional, 14.2% in rural, 3.2% in remote areas, with 0.2% not reporting their location. Majority of the sample (92.2%) reported not of Aboriginal and Torres Islander (ATSI) descent with 7.6% ATSI participants and 0.2% did not provide data.

Measures

To examine the variables likely to contribute to an individual being psychologically distressed by exposure to suicide into latent profile groupings, we utilized the following measures from the survey: Time since the person's death, frequency of pre-death contact, closeness to the person, perceived impact of the person's death and psychological distress. Where multiple exposures to suicide attempt and death were reported, participants were asked to answer in relation to the death they regarded as the most impactful to them. Cronbach's α is only reported for measures comprising 2 or more items.

Time Since the Person's Death

Participants were asked to report how long since the person died by suicide (in weeks, months, or years). For the analysis, time since death was converted into one single unit as in years.

Frequency of Contact

Participants reported the frequency of their contact with the person who died by suicide in the 6 months prior to the death. Contact frequency was assessed on a 6-point scale ranging from 1 = daily to 6 = infrequently. This item was reverse scored so that higher score indicates more frequent contact.

Closeness With the Person Who Died

Using 1-item closeness scale (28), participants reported their closeness to the person whose suicide death was most impactful. Closeness was assessed on a 5-point Likert scale ranging from 1 = not close to 5 = very close.

Perceived Impact of the Suicide Death

We used 1-item to assess perceived impact for the most impactful death exposure (28). Impact was assessed on a 5-point Likert scale ranging from 1 = had little effect on my life to 5 = had significant/devastating effect on me that I still feel.

Psychological Distress

A 10-item measure Kessler-10 (29) was used to assess psychological distress in suicide exposed and bereaved participants. K10 asks participants to identify how often they experienced the problem (i.e., tiredness, nervousness, and hopelessness) in the last 30 days. Items are assessed on 5-point Likert scale ranging from 1 = none of the time to 5 = all of the time) and are summed with higher scores indicating greater levels of distress. Scores on the K10 range from 10 to 50. The Australian Bureau of Statistics (30) categories provide a population level comparison group, being 10–15 = low levels of distress; 16–21 = moderate levels of distress; 22–29 = high levels of distress; and 30–50 = very high levels of distress. Cronbach's α in the present study was 0.94, indicating an excellent internal reliability.

Statistical Analyses

A LPA using Mplus8.3 (31) was conducted to classify respondents based on shared pattern of their responses on a range of risk factors for suicide. LPA is considered a sophisticated analytical tool used to assess how unique combinations of continuous latent variables and underlying categorical latent variables cluster within homogeneous groupings within a sample. Several model fit indices were assessed to determine the optimal profile model, including the Bayesian Information Criteria (BIC), which assesses improvement in fit after adjusting for the number of parameters in a model, sample size adjusted BIC (32, 33), Vuong-Lo-Mendel-Rubin (VLMR) Adjusted test, and the Bootstrapped Likelihood Ratio test (BLRT). The VLMR and BLRT assess difference in goodness-of-fit between model k and model $k-1$, where k refers to the number of retained profiles. The preferred model is indicated by a combination of smallest BIC and adjusted BIC values with highest number of profiles, and significant p-values for LMR and BLRT indicate best fit, i.e., model $k-1$ should be rejected in favor of model k (31). Entropy was also used as an index of model assessment, with values close to one considered ideal (34). In addition to statistical adequacy, we also considered theoretical conformity and meaningfulness and interpretability of the preferred profile-solution to guide our decision regarding retaining the number of profiles (35–37).

To facilitate interpretation of profiles, we standardized the four profiling variables to a mean of 0 with a standard deviation of 1. A multivariate analysis of variance (MANOVA) was conducted to determine significant profile differences in the risk factors (used as profiling variables) and psychological distress (DV). Finally focused chi-squared contingency tests were conducted to examine the proportion distribution of kin/non-kin and gender across the profile membership.

RESULTS

Descriptive Statistics

Table 1 shows intercorrelations, means, and standard deviations of key study variables within the LPA sample. More time passed since death was significantly associated with high frequency of contact, and less perceived impact for the most impactful death exposure and psychological distress. However, time since death was not significantly associated with reported closeness to the person who suicide death was most impactful. As expected, high frequency of contact with the person was significantly associated with reported closeness, perceived impact, and psychological distress. Reported closeness with the person was also significantly associated with greater impact and

TABLE 1 | Intercorrelations among key study variables.

Variables	1.	2.	3.	4.	5.
1. Time since death	–	0.05*	0.01	−0.08***	−0.10***
2. Contact frequency		–	0.63***	0.50***	0.14***
3. Closeness			–	0.72***	0.14***
4. Impact				–	0.23***
5. Psychological distress					–
Mean	9.10	3.25	3.39	3.67	20.78
SD	9.63	1.94	1.46	1.26	8.78

*N = 2346. *p < 0.05, ***p < 0.001.*

TABLE 2 | Model fit indices for 1- through 7-profile solutions.

Profiles	BIC	*Adj* BIC	VLMR	BLRT	Entropy
1.	26,685.27	26,659.85	–	–	–
2.	23,633.38	23,592.07	<0.001	<0.001	0.87
3.	22,830.64	22,773.45	<0.001	<0.001	0.89
4.	22,259.46	22,186.38	<0.001	<0.001	0.88
5.	**21,911.17**	**21,822.21**	**0.004**	**<0.001**	**0.91**
6.	21,752.29	21,647.45	0.006	<0.001	0.90
7.	21,477.81	21,357.08	0.999	1.00	0.90

N = 2,346. A combination of lowest BIC and adjusted BIC with highest number of profiles and significant p-values for VLMR and BLRT indicate best fit. Entropy values close to 1 indicate best fit. Best fitting profile solution shown in bold.

psychological distress, and more impactful the suicide death was, greater the psychological distress.

On average, participants reported 9 years since the suicide death occurred. The mean scores for frequency of contact (assessed on a 6-point scale) and reported closeness with the person who died (assessed on a 5-point scale) was just below the mid-point. On the other hand, the mean score for perceived impact of the suicide death was just above the mid-point on a 5-point scale. Overall, the study sample reported moderate levels of psychological distress.

Latent Profile Analysis

To empirically test the Continuum of Survivorship model, we conducted a LPA to identify profiles based on combinations of the four suicide exposure risk factors: time since the person's death, frequency of contact, reported closeness and perceived impact of the person's death. **Table 2** provides a summary of various model fit indices for 1- through 7-profile solutions.

Results revealed that the 5-profile solution met the criteria for all the relevant fit indices. In addition to the statistical adequacy, our preferred profile solution also demonstrated practical meaningfulness of the profiles mapping onto the Continuum of Survivorship model. Therefore, we interpreted the 5-profile solution in the present study. **Figure 1** shows the standardized mean scores of the profiling variables (time since the person's death, frequency of contact, reported closeness and perceived impact of the person's death). Profile 1 (n = 603, 25.7% of the sample), labeled as "Suicide exposed" comprised individuals who reported being suicide exposed but reported no impact. Profile 2 (n = 352, 15%), labeled as "Discordant group," comprised individuals who reported discordant patterns of low levels of reported closeness with person but very high levels of perceptions of impact of the suicide death. Respondents in Profile 3 (n = 318, 13.6%), labeled as "Suicide affected," reported above average time since death and frequent contact with the person but low levels of closeness and impact of death. Profile 4 (n = 380, 16.2%), labeled as "Suicide bereaved short-term," comprised individuals reporting frequent contact and high levels of closeness and impact but time since death was more recent. Finally, Profile 5 (n = 693, 29.5%), labeled as "Suicide bereaved long-term," was the largest group in the study comprising individuals who reported the most frequent contact with the person, closeness and severe impact of the person's death and with average time since death.

Examining Profile Differences in the Risk Factors and Psychological Distress

We conducted one-way MANOVA to examine profile differences in the suicide exposure risk factors (profiling variables) and psychological distress (DV). Results found a significant profile differences in the four risk factors, $F_{(20,9,360)} = 331.32$, $p < 0.001$; Pillai's Trace = 1.66; partial $\eta^2 = 0.42$, a large effect size. *Post-hoc* comparisons, summarized in **Table 3**, revealed that individuals in Profile 2 reported significantly less time since death than that of Profile 3 who reported the most time elapsed since their person's death. There were no other significant profile differences on this risk factor. In contrast, there were significant profile differences in frequency of contact and reported closeness with the person. Specifically, Profile 1 reported least contact, followed by Profiles 2, 4, 3, and 5, respectively. In terms of reported closeness to the person whose suicide death was most impactful, Profile 1 reported the least closeness followed by increasing closeness as indicated by Profiles 3, 2, 4, and 5, respectively. Respondents in Profile 1 also reported the least impact of the person's death and was significantly different from other profiles, with Profile 5 reporting greatest impact. However, there was no significant difference between Profiles 2 (Discordant group) and 4 (Suicide bereaved short-term). Results based on adjusted standardized residuals from the contingency table analyses suggested significantly greater number of kin relationships in "Suicide bereaved long-term" profile (Profile 5), and significantly greater number of non-kin relationships in "Suicide exposed" profile (Profile 1). There were significantly more females in the "Suicide bereaved-long term" profiling group (Profile 5) and more males in the "Suicide exposed" profile (Profile 1).

Finally, profile membership was significantly associated with psychological distress (DV). In particular, Profile 1 reported significantly lower levels of psychological distress than that of Profiles 2, 4, and 5, respectively. However, there was no significant difference in distress levels between Profiles 1 (Suicide exposed) and 3 (Suicide affected). Profile 5 reported significantly highest levels of distress compared with Profiles 1, 3, and 4, respectively. However, there were no statistically significant differences in distress levels between Profiles 2 (Discordant

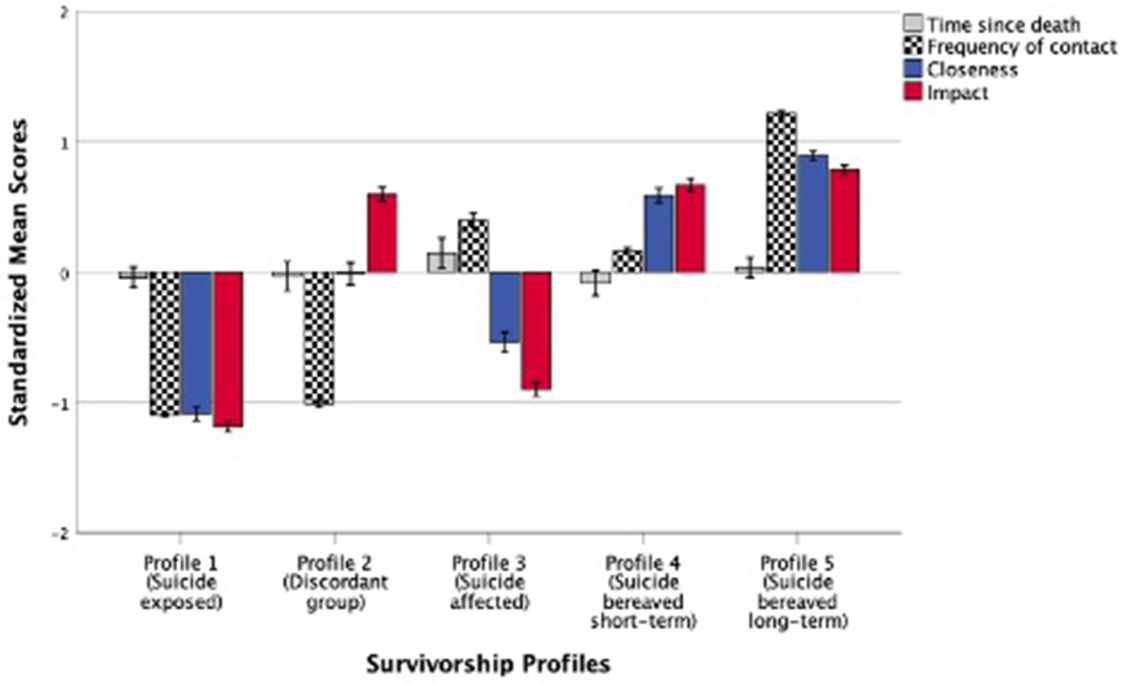

FIGURE 1 | Standardized mean scores ($M = 0$, $SD = 1$) of suicide exposure risk factors across five survivorship profiles. Error bars represent standard errors (SE) ±1.

group) and 5 (Suicide bereaved long-term), and between Profiles 3 (Suicide affected) and 4 (Suicide bereaved short-term), respectively. **Table 4** provides a summary of matching between the Continuum of Survivorship model and profile typologies identified in the present study.

DISCUSSION

The current study aimed to empirically test the proposed Continuum of Survivorship model (14). This was achieved by conducting a Latent Profile Analysis as a means of establishing combinations of suicide exposure risk factors in a community sample of suicide exposed and bereaved people to determine how these survivorship profiles might be related to psychological distress and whether this fits within the groups proposed in the Continuum model. The present study presents a novel approach within the suicide bereavement literature and highlights the utility of looking beyond variable-level analysis. The main findings and implications are discussed below.

Profile Segmentation

LPA revealed five distinct survivorship profile typologies: Profile 1 comprised suicide exposed individuals, Profile 2 comprised a discordant group of respondents who reported less closeness but high impact related to the person's death. Profile 3 included suicide affected people, who were experiencing high psychological distress, but for whom the death was more recent. Finally, Profiles 4 and 5 comprised suicide bereaved individuals. When comparing these profiles with the Continuum of Survivorship model there is both confirmation of the model, and deviation from it. The following discussion follows the progression through the model as proposed by Cerel et al. (14) and presented in **Table 4**. Profile 1 overlaps with the definition of "Suicide exposed" —and was numerically the second largest profile grouping as expected by the Continuum model. These individuals were neither close to the person who died, nor did they report heightened psychological distress. Profile 3 relates to the Continuum group of "Suicide affected," whereby these individuals report distress in the absence of a close relationship. Conversely, Profile 3 includes higher pre-death contact suggesting a relationship with the person was present, but there was no statistically significant difference in psychological distress to those in Profile 1. Profile 4 is similar to those in the Continuum who are "Suicide bereaved short-term" as the death was more recent. Those in this profile grouping may or may not go on to experience long-term bereavement, yet for whom this occurs is not able to be predicted by the Continuum nor by the current empirical testing using LPA. Suicide bereaved long-term matches our Profile 5 group, however, length of time from death was not statistically significant from the other Continuum groups suggesting that time may not be the important feature for those who are most affected by suicide death exposure. Finally, our results identified a discordant group who are not proposed as a distinct group in the Continuum. This discordant profile grouping identifies those for whom there was high impact from the suicide death exposure with low reported closeness, less time since death and moderate distress levels similar to Profiles 3, 4, and 5. This group requires further investigation to better understand those for whom there is high impact of a death while seemingly not as

TABLE 3 | Means, standard errors (SE), and mean differences or distributions across five survivorship profiles.

	Profile 1 Suicide exposed	Profile 2 Discordant group	Profile 3 Suicide affected	Profile 4 Suicide bereaved short-term	Profile 5 Suicide bereaved long-term	Univariate	
	(*n* = 603)	(*n* = 352)	(*n* = 318)	(*n* = 380)	(*n* = 693)		
Profiling variables			M(SE)			$F_{(4, 2,341)}$	Partial η^2
Time since death	8.69^{abc} (0.39)	8.78^{abc} (0.51)	10.50^{b} (0.54)	8.27^{c} (0.49)	9.43^{abc} (0.37)	2.97*	0.01
Contact	1.11^{a} (0.02)	1.28^{b} (0.03)	4.01^{c} (0.03)	3.55^{d} (0.03)	5.61^{e} (0.02)	7,135.98***	0.92
Closeness	1.79^{a} (0.04)	3.36^{b} (0.05)	2.59^{c} (0.05)	4.24^{d} (0.05)	4.69^{e} (0.03)	1,026.04***	0.64
Impact	2.17^{a} (0.02)	4.42^{b} (0.03)	2.53^{c} (0.03)	4.51^{b} (0.03)	4.66^{d} (0.02)	2,113.53***	0.78
Outcome variable							
Psychological distress	18.68^{a} (0.35)	21.50^{bce} (0.46)	19.47^{ac} (0.48)	20.73^{c} (0.44)	22.87^{e} (0.33)	21.50***	0.04
ABS (2012) categories	Moderate	Moderate-high	Moderate	Moderate	High		
Demographics							
Relationship with the person^{+}			*n*				
Non-kin						$\chi^2_{(4)} = 539.38$***	
	474	160	282	148	193		
$Z_{Residual}$	14.4	−3.2	13.5	−6.2	−16.3		
Kin							
	126	189	35	230	499		
$Z_{Residual}$	−14.4	3.2	−13.5	6.2	16.3		
Gender^{++}							
Female						$\chi^2_{(4)} = 20.27$***	
	457	290	232	292	579		
$Z_{Residual}$	−2.1	1.6	−2.6	−0.9	3.4		
Male							
	139	60	81	83	110		
$Z_{Residual}$	2.1	−1.6	2.6	0.9	−3.4		

*Means in rows with different superscripts are significantly different using Bonferroni adjustment for multiple comparisons. Time since the person's death measured in years. Frequency of contact assessed on a 6-point scale whereas closeness and impact of the person's death assessed on a 5-point scale. *p < 0.05, ***p < 0.001.*

$^{+}$Data available from 2,336 participants. $^{++}$Data available from 2,323 participants (Other = 13, Prefer not to say = 5).

$Z_{Residual}$ = Adjusted standardized residual, where $Z_{Residual} = 2$ is significant at $p < 0.05$.

a result of the loss of an attachment given the low closeness of the relationship.

The present study is the first empirical testing of the theorized Continuum of Survivorship model. Previous research has applied the model to samples of suicide exposed groups by simply overlaying impact of the death to the categories which are relationship based along the continuum. For example, Cerel et al. (14) suggest that an impact scale, such as the one used in this study, could potentially be used as "short-hand to identify people in each of the proposed categories" (p. 598). The results of this study suggest this does not accurately reflect the experiences of all individuals exposed to, and impacted by, suicide. People occupationally exposed to suicide, particularly first responders, are an important example for consideration. Emerging research on the personal and professional impact of exposure to suicide among ambulance personnel suggests that staff experience considerable impact due to the complex challenges associated with experiencing multiple suicide exposures and compassionately responding to people on scene without adequate training to do so, though this distress may be not acknowledged or supressed due to lack of appropriate work-based supports, reluctance to access available support related to concern about confidentiality and competence of support staff, and a culture of stigma associated with asking for help (18). While the Continuum model proposes first responders as individuals who may fit in the categories of suicide exposed or suicide affected given their lack of closeness to the person who died, our results suggest another conceptualization of this experience, where closeness to the decedent is minimal yet the impact of the exposure is significant and life disrupting. We note that our findings align with emerging qualitative research with these groups (16), where the absence of closeness with simultaneous impact suggests that an attachment theory-based model does not adequately explain all responses to exposure to suicide death.

The Continuum of Survivorship model is based on attachment theory, and presumed closeness is evident in the types of

TABLE 4 | Matching the Continuum of Survivorship with profile typologies.

Continuum model	Profile typologies	Similarities	Differences
Suicide exposed. *Neither close to the person nor experience distress*	**Profile 1: Suicide exposed.** *Report exposure to suicide but no impact nor closeness and least psychological distress. 25.7% of the sample.*	Close alignment between continuum and profile typology	–
Suicide affected. *Experience distress, but not grieving loss of attachment*	**Profile 3: Suicide affected.** *Closer to time of death and higher pre-death contact; low closeness and impact. 13.6% of the sample.*	Experience moderate levels of distress	No statistically significant difference in psychological distress compared with "Suicide exposed" profile rather the proximity to the death and contact with the person pre-death.
Suicide bereaved short-term. *Grieving the loss of an attached person, including intimate relationships, but do not progress to long term bereavement*	**Profile 4: Suicide bereaved short-term.** *Frequent pre-death contact, high closeness and impact of death, death more recent, increased psychological distress. 16.2% of the sample.*	Experience statistically significant greater levels of distress than "Suicide affected" profile	Unknown at time of data collection whether the greater levels of distress in close proximity to the death will result in progressing to long-term bereavement or not.
Suicide bereaved long-term. *Those who struggle for protracted periods of time, aligned with prior "suicide survivors" definitions*	**Profile 5: Suicide bereaved long-term.** *Most frequent pre-death contact, highest closeness and severe impact. Average time since death. Highest levels of psychological distress. 29.5% of the sample.*	Experience statistically significant highest levels distress than any other profile	This is the largest profile group due to sampling procedure. Time since death was not statistically different from other profiles, and was an average time (9 years) rather than the proposed continuum "protracted" time.
No continuum category	**Profile 2: Discordant.** *Low/High group—low closeness and high impact. 15% of the sample.*	–	Discordant group where low closeness but high impact was reported. Less time since death, moderate levels of distress similar to Profiles 3, 4, and 5.

individuals proposed to be within each category on the Continuum (14). However, without fully appreciating the complexity of impact and relational closeness within kinship relationships and beyond appears to conflate perceived impact with bereavement based on an assumption of attachment as most significant for the experience of impact. The highest levels of impact are presumed to be indicative of bereavement, though closeness or attachment to the person who died has never before been a consideration in the mapping process. For example, in the General Social Survey (GSS) Feigelman and colleagues (8) included questions to assess exposure to suicide among a representative sample of American adults. The GSS also included a measure of bereavement: "Was that person's death emotionally distressing to you?" For the purpose of analysis, respondents who answered 1) Yes, greatly or 2) Yes, to some extent were coded as "bereaved by suicide," resulting in 35% of respondents deemed bereaved by suicide due to the reported emotional distress caused by the death. However, a distressing death and resultant bereavement are not the same and our results raise important questions about the presumed equivalence of bereavement and emotional distress, as in the Feigelman et al. (8) study, or impact as in the Continuum model (14). While there are some individuals for whom impact does equate to bereavement, further work is required to unpack the conflation of impact and bereavement commonly reflected in the suicide exposure literature.

Individuals within the discordant profile grouping are not bereaved in the traditional sense of the term, as they are not grieving the death of a close relation, yet they report high levels of impact reflective of significant disruptions to life for either a short- or long-period of time. Many of these individuals may require support to mitigate against potential harms resulting from exposure, yet it is likely that traditional postvention services, such as support groups and bereavement counseling, would not be appropriate given their focus on those bereaved are often family and close friends. For example, individuals in the discordant group with workplace exposure to suicide may experience both personal and professional impacts, such as Vicarious Trauma and Post-traumatic Stress Disorder (38). Trauma-specific interventions, such as Eye Movement Desensitization and Reprocessing (EMDR), have been suggested to mitigate effects of workplace exposure to trauma (39), and may be a more suitable alternative to traditional bereavement counseling interventions which focus on grieving the loss of an attached person. Research is needed to better appreciate the heterogeneous nature of impact and resulting needs among individuals in the discordant group.

The results of the LPA contribute significantly to the ongoing theoretical evolution to assist in understanding why some people are more vulnerable to psychological distress following exposure to suicide regardless of the relationship to the deceased. Our analysis adds empirical testing to the proposed Continuum of Survivorship model. The proposed model usefully explains that for those who lose an attached relationship through suicide are most likely to experience significant distress. However, time since death may not be

a useful indicator for those who will continue to experience this significant loss. Utilizing this novel, person-centric analytic approach has also uncovered nuance within those self-identifying as exposed to suicide indicating that there are more complex relationships and impact from exposure to suicide than the continuum currently explains. Importantly, these are individuals who are deserving of our attention, given they are less likely to be in contact with services as they are not the "traditionally bereaved," and may be reluctant to utilize available resources (20, 40). As we expand our understanding of the discordant group, targeted resources and outreach to individuals based on the nature of impact and their needs may result in greater service utilization.

Limitations and Future Research Directions

The present study is novel and not without its limitations, therefore, findings should be interpreted with caution. First, the use of a cross-sectional survey design limits any causal inferences about the obtained effects, and the present study used self-report measures, which are susceptible to social desirability. We also acknowledge that the profiles identified in the present study might not reflect existing subgroupings within the actual population (35). The current study design is focused on a point in time profile groupings, future research could employ longitudinal extensions of LPA to track trajectories of survivorship profile membership over time to develop targeted postvention (20). Second, our study comprised a self-selected predominantly white, Australian community sample responding to a request to participate in a survey about exposure to suicide death. Therefore, this may have been more appealing to those who may represent the profile membership in different ways to those for whom exposure to suicide was not a significant event in their life, nor those who are highly distressed. Future research might also replicate the present findings with different age and population groups (including those from First Nations and culturally and linguistically diverse backgrounds), especially the use of a clinical sample is recommended. Third, the ways in which individuals experience multiple suicide exposures remains an area for future investigation as the present study survey asked participants only to focus on the death that was most distressing to them. For whom and in what circumstances result in the discordant profile is a priority for future research. Fourth, the K10 is a measure of global distress and not specific to suicide exposure, and thus future research should examine more nuanced tools, especially assessing suicide exposure distress. Finally, our LPA results identified a discordant profile that did not match with the Continuum of Survivorship model. Further exploration of the experiences of individuals in the discordant profile grouping is necessary to explicate the dimensions of this category and propose revisions to the Continuum model accordingly. In particular, future research could explore the meaning associated with the exposure to suicide and its impact, as others have found the meaning made following exposure to suicide impactful to future vulnerability to suicide (41, 42).

CONCLUSION

Overall, our findings contribute a novel approach to the suicidology literature, specifically in relation to better understanding how survivorship profiles correlate with psychological distress. Our study provided the first empirical testing of the Continuum of Survivorship model. We support the use of a profile approach in this area of research, and encourage further research which operationalizes this perspective to move beyond a variable-level approach, so as to capture the multi-dimensionality of an individual's trait combinations and its impact on behavior. Further, terminology that better captures the breadth of experience following exposure to suicide is required beyond survivorship based on assumptions of loss of attachment.

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 Human Research Ethics Committee, University of New England. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM: original project design. NB and MM: conceptualization and methodology. NB, MM, and RS: analysis and final draft. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: MM was a member elected Director on the Board of Suicide Prevention Australia at the time this study survey was disseminated.

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SYSTEMATIC REVIEW
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Nonsuicidal Self-Injury and Perfectionism: A Systematic Review

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Background: Nonsuicidal self-injury (NSSI) and perfectionism mean a huge concern related to mental health and psychopathology. Recently, there has been a growing interest in research on the exploration of the association of perfectionism and NSSI, but till today there is no systematic review has been prepared in this topic.

Aims: Therefore, we performed a systematic literature review of published studies that investigated the association between NSSI and perfectionism.

Methods: The systematic search was made on PubMed, OVID Medline, PsychInfo, Scopus, and Web of Science. The search terms were ("nonsuicidal self-injury" OR "nonsuicidal self-injury" OR NSSI OR "self-injury" OR "self-injurious behavior" OR SIB OR "self-harm" OR "deliberate self-harm" OR DSH) AND (perfectionism). The inclusion criteria were as follows: written in English; reported empirical data; used validated self-report measures; investigated the association of nonsuicidal self-injury and perfectionism. There were no restrictions on participants regarding age, gender, race or ethnicity. Exclusion criteria: not written in English; was a review/meta-analysis; measured suicide behavior; measured self-injury irrespective of motivation or suicidal intent; was not about the association between nonsuicidal self-injury and perfectionism.

Results: After the screening process, 15 studies were included in our systematic review. The majority of studies (12) were published in the last 10 years. Nine (60%) recruited participants from community samples, four (26.7%) from clinical populations, and two (13.3%) both from community and clinical participants. Fourteen (93.3%) of the studies were cross-sectional studies, and one study contained a longitudinal investigation. The majority of studies included only or mainly female participants (62.3–87.2%) and two studies contained a balanced male-female ratio population. Fourteen (93.3%) studies from the 15 studies found a significant positive association between NSSI and perfectionism.

Limitations: The heterogeneity of used instruments makes it difficult to compare the results of involved studies. Only two studies investigated populations with balanced gender ratios. Only two studies examined both clinical and community populations. Clinical investigations enrolled mainly eating-disordered (ED) patients.

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Conclusions: The results of the current systematic review highlight the role of perfectionism in NSSI engagement. This systematic review may help the development of effective prevention initiatives and treatment strategies.

Keywords: NSSI, nonsuicidal self-injury, perfectionism, review, clinical sample, community sample

INTRODUCTION

Nonsuicidal self-injury (NSSI) is a growing clinical and mental health problem, especially for youth and young adults (1–3). It is characterized by intentional self-inflicted damage to body tissue without suicidal intent (such as cutting, burning, scraping skin, hitting, and biting oneself), which is not culturally sanctioned behavior (4, 5). Nonsuicidal self-injury disorder (NSSI-D) was introduced in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), under section III, "Conditions for Further Study (5)." According to the diagnostic criteria, self-injurious acts should be completed on five or more separate days in the past year. Expectations of people who engage in NSSI actions is that self-injury behavior provides (a) relief of a negative affective/cognitive state after the NSSI, or (b) resolution of interpersonal difficulties or (c) cause positive feelings (5).

NSSI engagement generally occurs in early adolescent years; the typical age of onset is 12–14 years (6). NSSI prevalence increases in early adolescence; the peak is around 15–17 years, so it is a serious mental health problem among youths (6, 7). In late adolescence, NSSI prevalence decreases (1). Prevalence in community adolescents was found to be 17–46.5% (2, 8–10) and in clinical samples of adolescents was 60–80% (11, 12). Among adult community samples, NSSI prevalence was 4–23% (2, 13, 14). A meta-analysis concluded that NSSI incidence is more common among women compared to men (15).

The most common forms of NSSI behavior include cutting, scratching, burning, head banging, self-hitting and biting (2, 4, 16). The majority of individuals who engaged in NSSI use more than one methods (17). NSSI behavior serves multiple psychological functions: affect regulation, self-punishment, interpersonal influence, anti-dissociation, anti-suicide, sensation seeking, interpersonal boundaries (4), and affect regulation and self-punishment are the most common functions (18). Previous study concluded that the majority of individuals use multiple functions (12, 19).

In the literature there is great heterogeneity of definitions of self-injurious behaviors (1, 20), and there have been described different terms regardless of their suicidal intent (1, 20). In contrast, the NSSI definition contains behaviors without suicidal intent (5).

Perfectionism is commonly defined as "the setting of excessively high standards of performance [21, p. 450]," which is accompanied by overly self-critical evaluations (21). The literature emphasizes the multidimensional nature of this construct with personal and social dimensions (21, 22). Multidimensional measurements have been developed.

One of the two widely used measures of perfectionism was developed by Frost et al. (21). The Frost Multidimensional Perfectionism Scale (FMPS) proposed six facets of perfectionism: concern over mistakes (CM, reacting negatively in case of mistakes, interpret mistakes as failure), doubts about actions (DA, doubting related to the ability of one's performance), parental criticism (PC, perceiving parents as being extremely critical), parental expectations (PE, perceiving that one's parents set high goals and expectations on one's performance), personal standards (PS, striving for high standards and goals which important for self-evaluation) and organization (O, importance of order and neatness) (21). These six subscales demonstrate positive and negative dimensions of this construct. Hewitt and Flett (22) subsequently created the Hewitt Multidimensional Perfectionism Scale (MPS) (22). It consists of three subscales: self-oriented perfectionism (SOP, unrealistic high expectations for oneself), other-oriented perfectionism (OOP, unrealistic high expectations for others) and socially-prescribed perfectionism (SPP, the belief that others have high expectations related to oneself to be perfect). Factor analysis was used to analyse these two perfectionism scales, and consistently two main factors of perfectionism were differentiated by researchers: maladaptive evaluation concerns (EC, negative aspects of perfectionism, concerning on failure and mistakes and other's evaluation) and positive achievement striving (PS, adaptive aspects of perfectionism, high expectations, experience of successful performance) (23) (**Table 1**). Others mentioned the same two main dimensions as personal standards perfectionism (PSP, similar to PS it means the setting of high standards, expectation for oneself) and evaluative concerns perfectionism (ECP, similar to EC it means extremely high critical evaluation for oneself and concerns related to others criticism) (25), or simply adaptive (positive striving) and maladaptive (evaluative concerns) perfectionism (24).

TABLE 1 | Two main factors of perfectionism (23, 24).

Measures of Perfectionism	Maladaptive Evaluation Concerns (Maladaptive Perfectionism)	Positive Achievement Striving (Adaptive Perfectionism)
Frost Multidimensional Perfectionism Scale (FMPS)	Concern over mistakes (CM)	Personal standards (PS)
Frost Multidimensional Perfectionism Scale (FMPS)	Parental criticism (PC)	Organization (O)
Frost Multidimensional Perfectionism Scale (FMPS)	Parental expectations (PE)	
Frost Multidimensional Perfectionism Scale (FMPS)	Doubts about actions (DA)	
Hewitt Multidimensional Perfectionism Scale (MPS)	Socially-prescribed perfectionism (SPP)	Self-oriented perfectionism (SOP)
Hewitt Multidimensional Perfectionism Scale (MPS)		Other-oriented perfectionism (OOP)

Perfectionistic concern is associated more strongly with negative outcomes, and perfectionistic striving is characterized by more positive affect, conscientiousness, life satisfaction and achievement (23, 26). However, according to meta-analyses both positive and negative perfectionism can result in psychological distress (27) and psychopathology (28). The effect of positive perfectionism is not perfectly clear, because perfectionistic strivings can have both adaptive and maladaptive consequences (27). Moreover, positive and negative perfectionism do not occur separately; there is an interaction between them, and they can reinforce one another (28–30). Different combinations between the interaction of positive and negative perfectionism have a variety of influences on psychopathology (31, 32).

Problematic perfectionism is highly prevalent among children and young people (23–41%) (33–36). As perfectionistic people want to seem perfect, they tend not to seek help when it is required and they hide their intrapersonal sensitivity, vulnerability and their true pain (37).

Previous literatures emphasizes the importance of childhood and adolescence years in the development of perfectionism (38–43) and NSSI (3, 44–47). Both NSSI and perfectionism are associated with cognitive-affective deficits (1, 27, 48, 49). A large body of evidence suggests that several internalizing and externalizing mental disorders are associated both with NSSI (6, 50–53) and perfectionism (24, 28, 31, 54–63). Furthermore, NSSI is a huge risk factor for suicidal ideation and behavior (28, 51, 64–68), and perfectionism has also a relationship with suicide (28, 67, 68). Both phenomena mean huge concerns related to mental health and psychopathology (1, 28).

Perfectionistic people have a tendency of overconcern for mistakes, doubting related to the ability of appropriate performance and tend to react with strong negative emotions (e.g., shame, guilt) in case of failure in their results (21, 69). Perceived failure can maintain their negative self-evaluation (21), and self-destructive feelings can increase the likelihood of NSSI (4). Self-criticism has a strong relationship with NSSI (70), and emotion regulating function and self-punishment are the most common functions of NSSI behavior (18). Previous studies emphasize that shame may have a key role in NSSI engagement (71, 72), and shame regulation has strong relationship with affect regulation and self-punishment function of NSSI (71, 72). Claes et al. (73) also found that maladaptive perfectionism (evaluative concerns perfectionism) associated with self-punishment, self-torture, and cry-for-help functions of NSSI.

Separately related to NSSI and perfectionism there are available many previous research studies, but only a few investigated the relationship between the two phenomena. More studies suggest that there is an association between NSSI and perfectionism (73–75), but some contain inconsistent findings related to this relationship (73, 76). In recent years the number of research works that have reported results related to the association of perfectionism and NSSI has grown, but till now to the best of our knowledge, no systematic review has been done on this topic. Therefore, we performed a systematic literature review, and the main aim of the study was to include every published study that explored the association between NSSI and perfectionism with both cross-sectional and longitudinal design, without any restrictions on participants age, gender, race or ethnicity in order to explore relationship between two phenomena and clarify the nature of this relationship to improve effective prevention initiatives and treatment strategies. To best of our knowledge, this is the first systematic review to explore relationship between two phenomena. Because of the great conceptual heterogeneity of self-injury definitions (20), not only "NSSI" as a search word was used in our study, but also other search words for self-injurious behavior. We primarily focused on direct, deliberate self-harm without suicidal intent; therefore, we included only those studies in which the meaning of self-injurious behavior definition was similar to the NSSI definition.

The aim of this study is to identify: (a) terminology and definitions of self-injurious behavior, (b) methods for measuring NSSI and perfectionism and (c) the association between NSSI and perfectionism.

METHODS

The methodology of this systematic descriptive review follows the PRISMA guidelines (77). We performed a systematic review of the literature on 31 January 2021 using the following scientific electronic databases: OVID Medline, OVID PsychInfo, PubMed, Scopus, and Web of Science. As search terms we used: ("nonsuicidal self-injury" OR "nonsuicidal self-injury" OR NSSI OR "self-injury" OR "self-injurious behavior" OR SIB OR "self-harm" OR "deliberate self-harm" OR DSH) AND (perfectionism). The full electronic search strategy and search terms were discussed by both authors, and an electronic search was conducted by the first author. The EndNote 20 software program was used to manage the systematization of the papers. For inclusion, studies had to: (a) be written in English, (b) reported empirical data, (c) used validated self-report measures to assess self-injurious behavior and perfectionism and (d) investigate the association of nonsuicidal self-injury and perfectionism. There were no restrictions on participants regarding age, gender, race or ethnicity. Exclusion criteria were studies that (a) that were not written in English, (b) were reviews or meta-analyses, (c) measured suicidal behavior, (d) measured self-injury irrespective of motivation or suicidal intent and (e) were not about the association between nonsuicidal self-injury and perfectionism. Duplicates were searched both automatically by EndNote software and also manually by reading authors and titles again. Articles were first screened by title and abstract by the first author. Of the remaining studies, the full text of articles was read and inspected by the first author. The second author reviewed and supervised the whole screening process. The final selection of relevant studies was verified by both authors according to inclusion and exclusion criteria. Disagreements were resolved by discussion between the authors, and the inclusion or exclusion of the paper was decided by consensus. The final decision related to relevant studies was made by the two authors. A PRISMA flowchart of the selection process is summarized in **Figure 1**. Two authors assessed independently the methodological quality assessments

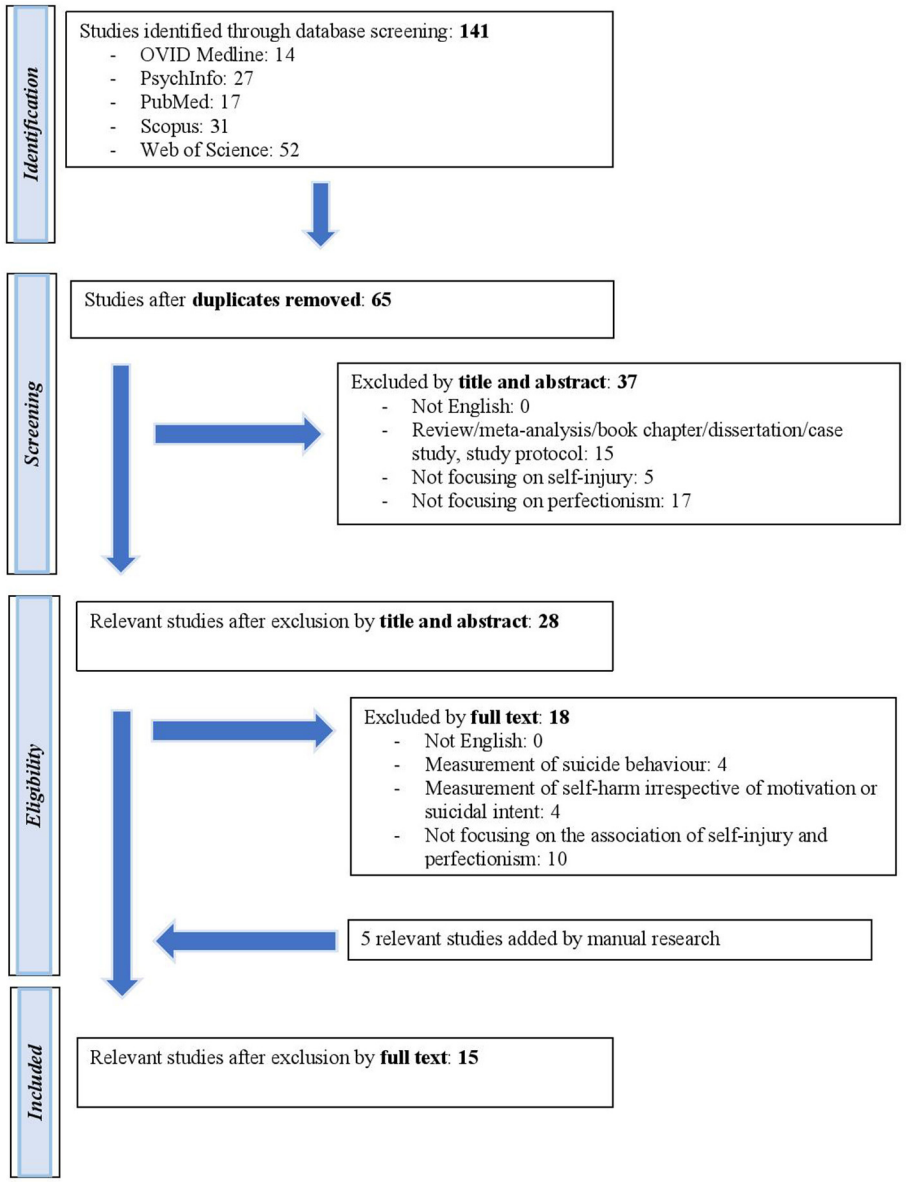

FIGURE 1 | PRISMA flowchart of inclusion-exclusion process.

of included studies (**Table 3**) according to Newcastle-Ottawa Scale (78). Disagreements between the authors were resolved by discussion.

RESULTS

We found 14 papers in OVID Medline, 27 papers in OVID PsychInfo, 17 papers in PubMed, 31 papers in Scopus and 52 papers in Web of Science, making a total of 141 studies, including duplicates. Furthermore, five papers were added by manual search. After excluding duplicate articles, and after the remaining articles has been checked by inclusion and exclusion criteria, a total of 15 papers were included in our systematic descriptive review (**Figure 1**, **Table 2**). **Table 3** contains the quality assessment of the included papers.

Description of the Studies Selected

Table 2 provides a summary of the data obtained from each study. All 15 studies were published in the last 16 years-−12 of them were brought out in the last 10 years, and 7 of the 15 studies were written in the last 5 years (76, 83–88).

Regarding to geographical distribution, eight of the 15 studies (53.3%) reported data from the United States (47, 79, 80, 82, 83, 86–88), while one was Canadian (84) and four were (26.7%) European, containing data form Belgium (two papers) (73, 75), Spain (one paper) (83) and Portugal (one paper) (76). There was

TABLE 2 | Included relevant articles ($N = 15$) examining association between nonsuicidal self-injury and perfectionism.

References	Country	Design	Age Group	No. of Participants	Terminology for Self-Injurious Behavior	Measurement of Self-Injurious Behavior	Measurement of Perfectionism	Main Results
Nock and Prinstein (79)	USA	Cross-sectional, clinical sample, psychiatric inpatient	Age range: 12–17 years, $M = 14.7$ ($SD = 1.4$)	$N = 89$ (23 boys, 66 girls 74.15%) psychiatric inpatients, adolescent	Self-mutilative behavior (SMB)	Functional Assessment of Self-Mutilation (FASM)	Child and Adolescent Perfectionism Scale (CAPS)	Socially prescribed perfectionism was related to the social negative and social positive reinforcement functions of SMB. Self-oriented perfectionism had no relationships with SMB functions.
Yates et al. (47)	USA	Cross-sectional and longitudinal, community sample	n.a.	Cross-sectional sample of 9–12th graders ($N = 1$, 036, 51.9% girls, 538 girls, 498 boys), longitudinal sample from the 6th through 12th graders: ($N = 245$, 53.1% girls, 130 girls, 115 boys).	NSSI	Functional Assessment of Self-Mutilation (FASM)	Parental criticism scale from the Frost Multidimensional Perfectionism Scale (FMPS)	Parental criticism predicts NSSI in both cross-sectional and the longitudinal samples. Youth alienation toward parents emerged as a relevant process underlying this pathway.
Hoff and Muehlenkamp (80)	USA	Cross-sectional, community sample	$M = 19.82$ years ($SD = 2.86$)	$N = 165$ undergraduate students (24.7% male, 75.3% female) (56 with a history of NSSI and $N = 109$ control subjects with no history of NSSI)	NSSI	Deliberate Self-Harm Inventory (DSHI)	Frost Multidimensional Perfectionism Scale (FMPS)	Participants with NSSI significantly differ from no-NSSI participants on three perfectionism subscales. Individuals with NSSI reported significantly higher score on concern over mistakes and parental criticism and significantly lower on organization subscales of FMPS.
Claes et al. (73)	Belgium	Cross-sectional, clinical sample, ED patient	Age range: 14–42 years, $M = 21.5$ years ($SD = 6.23$)	$N = 95$ ED patients (women)	NSSI	Self-Injury Questionnaire (SIQ)	Frost Multidimensional Perfectionism Scale (FMPS)	ED patients with NSSI reported significantly higher levels of parental criticism and evaluative concerns perfectionism (ECP) compared with ED patients without NSSI. ECP was positively related to the self-punishment, self-torturing and cry-for-help functions of NSSI. PC was negatively related to cry-for-help function of NSSI. ECP was found to mediate the association between parental criticism and NSSI symptoms. There was no relationship between PSP and NSSI.

(Continued)

TABLE 2 | Continued

References	Country	Design	Age Group	No. of Participants	Terminology for Self-Injurious Behavior	Measurement of Self-Injurious Behavior	Measurement of Perfectionism	Main Results
Fujimori et al. (74)	Japan	Cross-sectional, both clinical and community sample	ED + SIB sample: *M* = 24.3 years (*SD* = 5.6), ED + no SIB sample: *M* = 26.9 years (*SD* = 7.9), healthy control group: *M* = 19.5 years (*SD* = 1.2)	Clinical sample: *N* = 80 female ED patients (ED + SIB: *n* = 25, ED+ no SIB: *n* = 55), healthy control sample: *N* = 120 female university students	Self-injurious behavior (SIB)	SIB were established through own developed questions.	Perfectionism subscale from the Eating Disorder Inventory	Perfectionism score was significantly higher for the ED + SIB group compared to the ED/no SIB and control groups.
Flett et al. (81)	Canada	Cross-sectional, community sample	*M* = 18.89 years (*SD* = 2.30)	*N* = 319 university students (112 men, 207 women 64.9%)	Deliberate self-harm (DSH)	Deliberate Self-Harm Inventory (DSHI), Self-Harm Inventory (SHI)	Multidimensional Perfectionism Scale (MPS), The Frost Multidimensional Perfectionism Scale (FMPS)	Increased self-harm in men had negative relationship with other-oriented perfectionism. Increased self-harm in women was related to increased parental criticism and SPP.
Miskey et al. (82)	USA	Cross-sectional, community sample	*M* = 19.10 years (*SD* = 2.05)	*N* = 292 undergraduate students (62.3% women)	NSSI cutting	Deliberate Self-Harm Inventory (DSHI)	Perfectionism Inventory (PI)	NSSI cutting duration was associated positively with perfectionistic rumination. NSSI cutting onset age was positively correlated with concern over mistakes, and need for approval scales of PI. Frequency of NSSI cutting was predicted by perfectionistic rumination, organization, and low concern over mistakes (accounting for 31% of the variance).
Luyckx et al. (75)	Belgium	Cross-sectional, both clinical and community sample	Community sample: *M* = 15.95 years (*SD* = 1.30), psychiatric sample: *M* = 28.09 years (*SD* = 9.84)	Community sample: *N* = 348 female high school students, psychiatric sample: *N* = 131 female psychiatric patients (80 ED, 51 BPD)	NSSI	Self-Injurious Questionnaire-Treatment Related (SIQ-TR)	Perfectionism subscale from the Eating Disorder Inventory-2	According to hierarchical logistic regression analysis, perfectionism was associated with a significantly greater likelihood of engaging in NSSI in female adolescent sample.
Eichen et. al. (83)	USA	Cross-sectional, community sample	Age range 18–25 years, *M* = 20.61 years (*SD* = 1.97)	Community sample, women (*N* = 508)	NSSI	Functional Assessment of Self-Mutilation (FASM)	Perfectionism subscale from the Eating Disorder Inventory-2	There was no significant difference between the score of perfectionism across four groups: no NSSI/Suicidal Ideation, NSSI-only, Suicidal Ideation-only, and NSSI/Suicidal Ideation.

(Continued)

TABLE 2 | Continued

References	Country	Design	Age Group	No. of Participants	Terminology for Self-Injurious Behavior	Measurement of Self-Injurious Behavior	Measurement of Perfectionism	Main Results
Varela-Besteiro et al. (84)	Spain	Cross-sectional, clinical sample	Age range 12–17 years, *M* = 14.74 years (*SD* = 1.53)	Adolescents with ED, *N* = 109; 87.2% female (*n* = 95), 12.8% (*n* = 14) male.	NSSI	Based on clinical interview	Child and Adolescent Perfectionism Scale (CAPS)	NSSI group of ED patients had significantly higher scores as compared to the non-NSSI ED group (without self-injurious behavior) on all EDI-2 perfectionism scales and on the CAPS total score.
Kaur and Martin (85)	Australia	Cross-sectional, community sample	Age range: 19–36 years, *M* = 23.1 years (*SD* = n.a)	Postgraduate medical students, *N* = 260 (139 males and 121 females, 46.5%)	NSSI	Deliberate Self-Injury Questionnaire	Frost Multidimensional Perfectionism Scale (FMPS)	Participants with NSSI compared to those without NSSI reported higher scores on perfectionism total score, on parental expectations, on concern over mistakes, on doubts about action. The largest effect has concern over mistakes. Maladaptive perfectionism was also significantly higher in NSSI group.
Vieira et al. (76)	Portugal	Cross-sectional, clinical sample	Age range: 14–49 years, *M* = 22.12 years (*SD* = 6.31)	ED female outpatients, *N* = 245	NSSI	Oxford Risk Factor Interview for Eating Disorder	Oxford Risk Factor Interview for Eating Disorder: subject's mental health domain—perfectionism subdomain.	There is no relationship between perfectionism and NSSI among ED patients.
Lucas et al. (86)	USA	Cross-sectional, community sample	Age range: 18-46 years, *M* = 19.6 years (*SD* = 3.12)	*N* = 386 college students (267 females 69, 2%, 116 males 30, 8%)	NSSI	The Self-Harm Inventory (SHI)	Frost Multidimensional Perfectionism Scale (FMPS)	FMPS dimensions (concern over mistakes, parental expectation, parental criticism, doubts about action) were positively associated with NSSI. According to results of hierarchical regression analysis, perfectionism (concern over mistakes dimension) is a significant predictor of NSSI.
Chang et al. (87)	USA	Cross-sectional, community sample	Age range: 18–25 years, *M* = 20.2 years (*SD* = 1.61)	*N* = 287 women college students	NSSI	The Self-Harm Inventory (SHI)	Frost Multidimensional Perfectionism Scale (FMPS)	Perfectionism was found to predict additional unique variance in NSSI, even after accounting for sexual assault history. Evaluative concerns dimension is the most consistent unique predictor of NSSI.
Newman et al. (88)	USA	Cross-sectional, community sample	Age range: 18–27 years, *M* = 18.9 (*SD* = 1.19)	*N* = 410 undergraduate psychology students (77.1% female)	Self-harm	One item from the Nonsuicidal Self-Injury Assessment Tool (NSSI-AT)	Perfectionism Inventory (PI), Perfectionistic Cognitions Inventory (PCI)	With principal components analysis four different profiles of perfectionism were defined: obsessive, constructive, non-perfectionist, motivated. Profiles of perfectionism were significantly associated with differences in self-harm.

TABLE 3 | Quality assessment of the included studies.

References	Selection	Comparability	Exposure
Nock and Prinstein (79)	**		*
Yates et al. (47)	**		*
Hoff and Muehlenkamp (80)	****	**	**
Claes et al. (73)	***	**	*
Fujimori et al. (74)	****	**	**
Flett et al. (81)	**		*
Miskey et al. (82)	**		*
Luyckx et al. (75)	****	**	**
Eichen et al. (83)	****	**	**
Varela-Besteiro et al. (84)	***	**	**
Kaur and Martin (85)	****	**	**
Vieira et al. (76)	***	**	**
Lucas et al. (86)	**		*
Chang et al. (87)	**		*
Newman et al. (88)	**		*

also one study form Japan (74), and one form Australia (85) were involved in our systematic review.

Altogether, nine of the 15 studies (60%) recruited participants from community samples (47, 80–83, 85–88), four (26.7%) enrolled clinical populations (73, 76, 79, 84), and two studies (13.3%) represent data from both community and clinical participants (74, 75). Yates et al. (47) investigated two different community samples. One was recruited from the local community and schools for a cross-sectional investigation; the other sample was a New England Study of Suburban Youth (NESSY) cohort for a longitudinal investigation.

Six studies (40%) enrolled college, undergraduate students, whose mean ages were between 18.89 and 20.61 years (74, 80–83, 87). Four (26.7%) studies recruited adolescents with a mean age range of 14.7–15.95 years (47, 75, 79, 80). A further six studies recruited a wider age range, form 14-49 years, including adolescent and adult participants (73, 75, 76, 85, 86, 88). Yates et al. (47) enrolled adolescents from 9 to12th graders for their cross-sectional studies, and for a longitudinal sample children were recruited from the 6th grade and were followed annually through the 12th grade. Other than school grade information, the mean ages of included children and adolescents are not reported in the paper.

Regarding gender distribution, six (40%) papers included only female participants (73–76, 83, 87), and the other nine involved studies (60%) investigated both female and male populations (47, 79–82, 84–86, 88). Of these nine studies, seven investigated mainly female participants (62.3–87.2% in the examined population), and only two studies contained an approximately balanced male-female ratio population (47, 85).

Considering the study design, 14 (93.3%) were cross-sectional studies, while one consisted of a cross-sectional and longitudinal investigation (47).

Terminology and Definitions of Self-Injurious Behavior Related to Relevant Included Studies

Because of the great conceptual heterogeneity of self-injury definitions, we have summarized how the definition of self-injurious behaviors was used in the included studies.

Altogether, five different terms of self-injurious behavior were mentioned in the 15 investigated papers. All 15 defined and measured self-injurious behavior as a nonsuicidal act (47, 73–76, 79–88).

Of the 15 studies selected, 10 (66.7%) represented studies on NSSI (47, 73, 75, 76, 80, 82, 83, 85–87). The term "NSSI" was the one most commonly used, and this term was used similarly to the official definition (5). NSSI is a physical self-injurious behavior, although Varela-Besteiro et al. (84) used the term of self-inflicted physical harm, including also a drug overdose without suicidal intent. According to this term, they use NSSI as an expression related to self-injurious behavior.

Newman et al. (88) use "self-harm," but they did not give a definition. However, in the chapter on measurement can be found the question "Have you ever hurt your body on purpose but without wanting to end your life?," which shows how they explored self-injurious behavior.

Flett et al. (81) define "deliberate self-harm" (DSH) as intentional self-injury without suicidal intent. Beyond direct physical self-harm, they consider self-harm behavior to include substance abuse or putting oneself in a dangerous situation.

Fujimori et al. (74) use the term of "self-injurious behavior" (SIB) in a nonsuicidal meaning, similar to the official NSSI definition, as direct and deliberate physical damage of one's body surface.

Nock and Prinstein (79) use "self-mutilative behavior" (SMB). It is also used in a nonsuicidal meaning as direct physical damage of one's body.

All the included papers in this study apply the term of self-injurious behavior with nonsuicidal meaning of these acts.

Measurement of Self-Injurious Behaviors in the Included Studies

Among the 15 papers involved, both diagnostic interviews and self-reported questionnaires were used to measure self-injurious behaviors. Altogether, eight different instruments were used.

Self-report questionnaires were applied for measuring self-injurious behaviors in 12 studies (47, 73, 75, 79–83, 85–88). The Functional Assessment of Self-Mutilation (FASM) (89) was used in three studies (47, 79, 83). Over the previous 12 months it enables us to assess the frequency of different methods of SMB, the degree of physical pain, the use of alcohol or drugs during SMB, the amount of time about the incident before engaging and the awareness of this behavior by friends. The Deliberate Self-Harm Inventory (DSHI) (17) appears in three studies (80–82). It assesses with 17-items the different types of DSH. This instrument enables us to evaluate also the frequency, severity and duration of self-harm acts. With it, Miskey et al. (82) focused only on NSSI cutting. The Self-Injury Questionnaire (90) was applied in the study of Claes et al. (73)

to measure self-injury in the previous 12 months by means of hair pulling, scratching, bruising, cutting and burning. It also enables us to assess the age of onset, the frequency, the function of self-injurious behavior, pain, emotional experiences during engagement and the injured body part. Luyckx et al. (75) used the Self-Injurious Questionnaire-Treatment Related (SIQ- TR) (91). It measures the type, frequency, duration, age of onset, emotional experiences before and after of engagement, injured body part and functions of self-injury. The Self-Harm Inventory (SHI) (92) was mentioned in three studies (81, 86, 87). It was used to assess with 22 items the history of self-harm, ranging from eating disorder-specific actions (exercised an injury on purpose) to those related to medical concerns (e.g., not allowing a wound to heal). Flett et al. (81) measured self-harm with 22 items, using questions drawn from the DSHI (17) and SHI (92). Newman et al. (88) used one item ("Have you ever hurt your body on purpose but without wanting to end your life?") from the Nonsuicidal Self-Injury Assessment Tool (NSSI-AT) (93). The Deliberate Self-Injury Questionnaire (94) was mentioned in the study of Kaur and Martin (85). They measured the frequency, purpose, types and cessation of self-injurious behavior.

Vieira et al. (76) applied the Oxford Risk Factor Interview (RFI) (95). This semi-structured interview assesses the putative risk factors of eating disorders patient and focuses on the period before the onset of eating pathology. They used three questions in connection with occurrence, type and frequency.

Varela-Besteiro et al. (84) measured self-injurious behavior during clinical interviews.

Fujimori et al. (74) used their own developed questions related to occurrence, injured body-part and degree of felt pain during acts.

Measurement of Perfectionism in the Included Studies

The majority of papers (14 studies from the 15 ones) used self-reported questionnaires in order to assess perfectionism, while one study used interviews. Six different instruments were used in the included studies.

The most frequently used questionnaire was the FMPS (21). It was mentioned in seven studies (47, 73, 80, 81, 85–87). It measures with 35 items the adaptive and maladaptive dimensions of perfectionism with six different subscales. Hoff and Muehlenkamp (80) and Lucas et al. (86) measured multiple aspects of perfectionism with all 35 items of the FMPS (six subscales). Yates et al. (47) used only the PC subscale form the FMPS with four items. Claes et al. (73) and Chang et al. (87) measured two factors: maladaptive perfectionism or ECP (containing the CM, DA subscales) and adaptive perfectionism or PSP (containing the PS subscale) (25). In addition, Claes et al. (73) also used the PC scale. After conducting factor analyses, Kaur and Martin (85) used the FMPS-29 (96) with five subscales (CM, DA, PE/PC, O, PS).

Flett et al. (81) used those versions of the FMPS that did not include the O factor (97). In addition, they also measured the level of SOP, OOP and SPP with MPS (22).

The Child and Adolescent Perfectionism Scale (CAPS) (98) was applied in two studies (79, 84). It measures multiple dimensions of perfectionism with two subscales (self-oriented, socially prescribed perfectionism) with 22-items.

In three studies (74, 75, 83), perfectionism was assessed with the perfectionism subscale of the Eating Disorders Inventory (EDI) (99). It measures perfectionism only unidimensionally without differentiation of negative and positive aspects.

The Perfectionism Inventory (PI) (100) was applied in two studies (82, 88). It enables us to measure perfectionism with eight scales: organization, striving for excellence, planfulness, high standards for others, concern over mistakes, need for approval, rumination, and perceived parental pressure.

Newman et al. (88) used the Perfectionistic Cognitions Inventory (PCI) (101), which assesses with 25 items the automatic thoughts related to the need to be perfect.

Vieira et al. (76) used the RFI (95) to measure self-injury as well as perfectionism. To assess perfectionism, participants were asked, "If you go back to your adolescence and childhood, did you have very high goals and demands at work/school and in other areas, more than other people your age? Would you be angry if you did not meet these goals and demands?"

Association Between NSSI and Perfectionism

In this section we summarize results related to the association between NSSI and perfectionism separately in clinical and community samples. We also summarize the comparison between clinical and control groups.

Association in Clinical Samples

Nock and Prinstein (79) measured the features and functions of SMB among 89 adolescent psychiatric inpatients (74.1% girls, 12–17 years, $M = 14.7$, $SD = 1.4$). Four SMB functions were measured: automatic negative reinforcement, automatic positive reinforcement, social positive reinforcement and social negative reinforcement in connection with socially prescribed and self-oriented perfectionism. According to their results, socially prescribed perfectionism was associated with SMB social negative reinforcement functions ($\beta = 0.23$, $p < 0.001$) and with SMB social positive reinforcement functions ($\beta = 0.30$, $p < 0.01$). Self-oriented perfectionism had no relationships with the measured SMB functions.

Claes et al. (73) examined the difference between female ED patients ($N = 95$, age range: 14–42 years, $M = 21.5$ years, $SD = 6.23$, 38.9% with NSSI) with and without NSSI related to PSP and ECP. ED patients with NSSI have significantly higher scores on ECP [$F_{(3, 83)} = 5.58$, $p < 0.05$] and PC [$F_{(3, 83)} = 5.62$, $p < 0.05$] compared to ED patients without NSSI. Linear regression analyses showed a significant positive association between the self-punishment ($\beta = 0.30$, $p < 0.05$) and self-torturing ($\beta = 0.30$, $p < 0.05$) and cry-for-help ($\beta = 0.36$, $p < 0.01$) functions of NSSI and ECP. In addition, the cry-for-help function of NSSI has a negative relation with PC ($\beta = -0.29$, $p < 0.01$). According to regression analysis, the effect of PC on NSSI was significant ($\beta = 0.28$, $p < 0.01$). However, this initial association between PC and NSSI turned to non-significant after taking into account ECP, and

the relationship between PC and NSSI was only indirect through a mediation effect of ECP (PC-ECP association: $\beta = 0.34$, $p < 0.001$; ECP-NSSI association: $\beta = 0.22$, $p < 0.05$). According to results, there was no relationship between PSP and NSSI.

Varela-Besteiro et al. (84) explored in adolescents ED patients ($N = 109$, 87.2% female, 12.8% male, $M = 14.74$ years, $SD = 1.53$) the association between self-injurious behavior and suicidal thoughts, and symptoms of depression, anxiety, motivation for change and perfectionism. According to the presence of self-injurious behavior, they defined two groups: an NSSI group ($n = 34$), and a non-NSSI group ($n = 75$). The NSSI group of ED patients had significantly higher scores compared to the non-NSSI ED group on EDI-2 perfectionism scales (NSSI group: $M = 6.91$, $SD = 3.69$; non-NSSI group: $M = 4.51$, $SD = 4.24$; Mann-Whitney U-test = 779.50, $p = 0.001$), and on the CAPS total score (NSSI group: $M = 70.29$, $SD = 11.89$; non-NSSI group: $M = 63.55$, $SD = 15.86$; Mann-Whitney U-test = 945.50, $p < 0.05$).

Vieira et al. (76) explored the potential risk factors for NSSI among female ED patients ($N = 245$, $M = 22.12$, $SD = 6.31$). There was no significant difference between the non-NSSI group ($n = 156$, 67%) and the NSSI group ($n = 77$, 33%) related to perfectionism. Because there was not an initial significant association between perfectionism and the non-NSSI or NSSI group, the perfectionism variable was not involved in further regression analysis.

Association in Community Samples

Yates et al. (47) explored the pathways between the perceived PC perfectionism dimension and NSSI among 9–12th graders in a cross-sectional sample ($N = 1{,}036$, 51.9% girls, 538 girls, 498 boys) and in a longitudinal sample ($N = 245$, 53.1% girls, 130 girls, 115 boys) followed from the 6th through 12th grades. According to mediation analysis in the cross-sectional sample among girls, perceived PC had a direct relationship with an increased probability of engaging in NSSI ($B = 0.11$, SEB = 0.02, $p < 0.05$, 95% CI = 0.07, 0.16) but had no association with the frequency of NSSI ($B = 0.02$, SEB = 0.01, $p > 0.05$). When parental alienation was added to the mediation analysis, the direct association between PC and NSSI was no longer significant ($B = 0.02$, SEB = 0.03, $p > 0.05$, 95% CI = −0.03, 0.07), and only an indirect path through parental alienation was significant (PC-parental alienation: $B = 0.69$, SEB = 0.04, $p < 0.001$; parental alienation-probability of NSSI: $B = 0.15$, SEB = 0.02, $p < 0.001$). Among boys in cross-sectional samples, perceived PC had a direct relationship with both probability of NSSI ($B = 0.08$, SEB = 0.03, $p < 0.05$ 95% CI = 0.02, 0.13) and with the frequency of NSSI ($B = 0.07$, SEB = 0.02, $p < 0.01$ 95% CI = 0.04, 0.11). Similarly, to girls, when parental alienation was involved in the mediation analysis there was only an indirect relationship between PC and the probability of NSSI (PC-parental alienation: $B = 0.61$, SEB = 0.05, $p < 0.001$; parental alienation—probability of NSSI: $B = 0.12$, SEB = 0.03, $p < 0.001$) and between PC and the frequency of NSSI ($B = 0.61$, SEB = 0.05, $p < 0.001$; $B = 0.07$, SEB = 0.03, $p < 0.05$) through parental alienation. Similar to the results of the cross-sectional sample, in the case of the longitudinal sample among girls, perceived PC in grades 6 to 8 has a direct significant relationship with the probability of NSSI in grade 12 ($B = 0.13$, SEB = 0.07, $p < 0.05$ 95% CI = 0.01, 0.26). When parental alienation was added to mediation analysis, this direct pathway turned to non-significant ($B = 0.08$, SEB = 0.08, $p > 0.05$ 95% CI = −0.08, 0.25). In addition, there was also no indirect relationship between PC and the probability of NSSI through parental alienation (PC-parental alienation: $B = 0.49$, SEB = 0.09, $p < 0.001$; parental alienation—probability of NSSI: $B = 0.10$, SEB = 0.08, $p > 0.05$). In the case of boys, the initial direct effect between PC and the probability of NSSI was not significant ($B = 0.14$, SEB = 0.08, $p < 0.10$), so a mediated model was not examined. In the longitudinal sample the relationship between PC and the frequency of NSSI was not significant in both genders.

Hoff and Muehlenkamp (80) examined the association between NSSI and perfectionism, cognitive rumination, depression and anxiety in 165 college students (56 with NSSI, 109 control, $M = 19.82$ years, $SD = 2.86$). The NSSI group (individuals with a history of NSSI) compared to the controls (individuals without NSSI) reported a significantly higher score on two subscales of the FMPS: CM $F_{(1, 153)} = 9.58$, $p < 0.01$, and PC, $F_{(1, 153)} = 8.94$, $p < 0.01$, and a significantly lower score on the O subscale: F $F_{(1, 153)} = 18.34$, $p < 0.01$. According to the results of a binary logistic regression analysis, the O subscale of the FMPS was negatively significant with NSSI ($B = -1.94$, $SE = 0.049$, Wald Statistic = 15.68, $p < 0.01$).

Flett et al. (81) measured the self-punitiveness model (including perfectionism, overgeneralisation, self-criticism, and shame) as it related to DSH among 319 university students (64.9% female, $M = 18.89$ years $SD = 2.30$). According to the results, in men increased self-harm had a negative relationship with OOP ($r = -0.40$ $p < 0.01$). Increased self-harm in women was associated with increased PC ($r = 0.20$ $p < 0.01$) and with increased SPP ($r = 0.16$ $p < 0.05$).

Miskey et al. (82) explored the role of the Big Five personality dimension and perfectionism in predicting nonsuicidal cutting among 292 undergraduate students (62.3% women, $M = 19.10$, $SD = 2.05$). NSSI cutting duration was associated positively with the rumination scale of PI ($r = 0.29$ $p < 0.05$). The onset age of NSSI cutting was positively correlated with the PI scales of concern over mistakes ($r = 0.25$ $p < 0.05$) and need for approval ($r = 0.24$ $p < 0.05$). According to multiple regression analyses, perfectionism variables rumination ($\beta = 0.809$, $p < 0.05$), concern over mistakes [negatively weighted, $\beta = -0.784$, $p < 0.01$) and organization ($\beta = 0.452$, $p < 0.05$)] predict statistically significant the NSSI cutting frequency ($F = 2.324$, $p = 0.037$), and accounting for 31% of the variance.

Eichen et al. (83) examined the association between depression, anxiety, and stress and eating disorder-specific psychopathology among college-aged women ($N = 508$, $M = 20.61$ years, $SD = 1.97$) with and without NSSI and with or without suicidal ideation. They divided all participants into four groups: no NSSI/suicidal ideation ($n = 400$, 78.7%), NSSI-only ($n = 70$, 13.8%) suicidal ideation-only ($n = 25$, 4.9%) and NSSI + suicidal ideation ($n = 13$, 2.6%). The perfectionism score did not differ significantly across groups: no NSSI/suicidal ideation ($M = 4.09$, $SD = 1.15$), NSSI-only ($M = 4.24$, $SD = 1.10$), suicidal ideation-only ($M = 4.21$, $SD = 1.19$) and NSSI + suicidal

ideation ($M = 4.22$, $SD = 1.23$); $F_{(3, 503)} = 0.43$; $p = 0.74$, partial $\eta^2 = 0.003$.

Kaur and Martin (85) examined nonsuicidal self-injury among medical students ($N = 260$, 139 males (53.4%), 121 females, $M = 23.1$ years, $SD =$ n.a.) and its relationship with level of perfectionism. Participants with NSSI compared to those without NSSI reported higher scores on the perfectionism total score: $F_{(1, 258)} = 9.21$, $p < 0.01$; on PE: $F_{(1, 258)} = 3.92$, $p < 0.01$; on CM: $F_{(1, 258)} = 9.16$, $p < 0.01$; on DA: $F_{(1, 258)} = 4.96$, $p < 0.05$. The largest effect was concern over mistakes. Maladaptive perfectionism was also significantly higher in the NSSI group: $F_{(1, 258)} = 12.85$, $p < 0.001$.

Lucas et al. (86) examined the association between perfectionism, social problem solving, and NSSI among college students ($N = 386$, 69.2% female, $M = 19.6$ years, $SD = 3.12$). Four FMPS dimensions were associated positively with NSSI: CM ($r = 0.24$ $p < 0.001$), PE ($r = 0.12$ $p < 0.05$), PC ($r = 0.18$ $p < 0.001$) and DA ($r = 0.18$ $p < 0.001$). According to results of a hierarchical regression analysis before controlling for suicide risk, perfectionism accounted for 9% of the variance in NSSI [$F_{(6, 321)} = 5.56$, $p < 0.001$], and after controlling for suicide risk, perfectionism accounted smaller 3% of variance in NSSI [$F_{(6, 320)} = 2.33$, $p < 0.05$]. Within perfectionism, only the CM dimension was a significant predictor for NSSI before ($\beta = 0.31$, $p < 0.001$) and also after ($\beta = 0.22$, $p < 0.01$) controlling for suicide risk. It should be mentioned that when social problem solving was entered in the model of regression analysis before perfectionism, the effect of perfectionism before [$F_{(6, 316)} = 1.83$, $p > 0.05$] and also after controlling for suicide risk [$F_{(6, 315)} = 1.05$, $p > 0.05$] and CM dimension turned to non-significant ($\beta = 0.14$, $p > 0.05$), and it did not predict NSSI significantly.

Chang et al. (87) examined the relationship between sexual assault history and perfectionism (positive strivings, evaluation concerns dimensions) with NSSI and suicidal behaviors in women college students ($N = 287$, ages ranged from 18 to 25 years, $M = 20.2$ years, $SD = 1.61$). According to results, positive strivings have a positive relationship with evaluative concerns ($r = 0.36$, $p < 0.001$). The PS subscale correlated significantly with DA ($r = 0.19$ $p < 0.001$) and CM ($r = 0.40$, $p < 0.001$) subscales. Results of a hierarchical regression analysis show that perfectionism was found to account for 4% of variance in NSSI behavior [$F_{(2, 281)} = 6.22$, $p < 0.01$). Within perfectionism, evaluative concerns predicted NSSI significantly ($\beta = 0.21$, $p < 0.001$). The interaction term of personal strivings x evaluative concerns had no significant effect on the variance of NSSI $F_{(1, 280)} = 0.08$, $p > 0.05$). After controlling the overlap between NSSI and suicidal behaviors, perfectionism was found to account for a marginally significant 1% of variance in NSSI behaviors $F_{(2, 280)} = 2.67$, $p < 0.10$). Only the evaluative concerns dimension was a significant predictor for NSSI behavior ($\beta = 0.13$, $p < 0.05$). In this case the interaction term of personal strivings x evaluative concerns also had no significant effect on the variance of NSSI $F_{(1, 279)} = 0.41$, $p > 0.05$).

Newman et al. (88) examined emotions, cognitions and behaviors related to healthy and unhealthy expressions of perfectionism among undergraduate students ($N = 410$, $M = 18.9$ years, $SD = 1.19$). Based on six factors of perfectionism which were identified (rumination, planfulness, drive, academic management, compulsion and emotional suppression) by submitting measures of behavioral, emotional, and cognitive correlates with principal components analysis, they set four different profiles of perfectionism: obsessive ($n = 84$), constructive ($n = 87$), non-perfectionist ($n = 122$) and motivated ($n = 117$). Profiles of perfectionism were significantly associated with differences in self-harm [$F_{(3, 402)} = 2.85$, $p = 0.037$]. Mean scores related to self-harm for profiles: obsessive ($M = 0.33$), constructive ($M = 0.11$), non-perfectionist ($M = 0.28$), motivated ($M = 0.25$). Obsessive perfectionists have the worst mental health, with high rumination, planfulness and compulsion tendency.

Comparison of the Association Between Clinical and Community Samples

Fujimori et al. (74) evaluated the relationship among parental bonding, ED and SIB among 80 female ED patients ($M = 24.3$ years, $SD = 5.6$) and 120 healthy female university control students ($M = 19.5$ years, $SD = 1.2$). According to their results, the ED + SIB group ($n = 25$) reported a significantly higher score on perfectionism ($M = 9.7$, $SD = 4.1$) than ED/no SIB ($n = 55$) ($M = 7.0$, $SD = 4.6$) and control groups ($n = 120$) ($M = 4.3$, $SD = 4.1$) [$F_{(2, 197)} = 20.6$, $p < 0.001$, *post-hoc* test: ED+SIB > ED/no SIB > control].

Luyckx et al. (75) examined whether identity process predicted NSSI above and beyond anxiety, depression, Big Five personality traits, perfectionism and effortful control. They involved 348 female adolescents ($M = 15.95$ years, $SD = 1.30$) and 131 female psychiatric patients (80 ED and 51 BPD) ($M = 28.09$ years, $SD = 9.84$). Spearman Rho's correlation coefficient shows that engaging in NSSI was positively related to perfectionism in both samples ($r = 0.25$, $p < 0.01$). Hierarchical logistic regression analyses demonstrated in the female high school adolescents sample that perfectionism was related to a significantly greater likelihood of engaging in NSSI ($B = 0.85$, SE = 0.21, Wald statistic = 16.47, $p < 0.001$). In psychiatric patients, there was no significant association between NSSI and perfectionism ($B = 0.19$, SE = 0.27, Wald statistic = 0.50, $p > 0.05$).

DISCUSSION

This paper provides an up-to-date overview of the existing literature related to the association between NSSI and perfectionism. To our knowledge, this is the first systematic review on this topic. To perform this systematic review, we involved 15 studies. Our aim was to summarize and clarify the nature of the relationship between two phenomena. Summarizing the results of the included studies, there is a clear relationship between NSSI and perfectionism.

Regarding descriptive findings, the majority of studies (60%) reported data from North America, while 26.7% were from Europe. More than half (60%) of included studies investigated community samples (47, 80–83, 85–88), while about a fourth (26.7%) were enrolled from clinical populations (73, 76, 79, 84); only two of the 15 studies (13.3%) (74, 75) compared both

community and clinical samples in connection with self-injury and perfectionism. Although a large body of previous literature emphasizes that several mental disorders, both internalizing and externalizing disorders, are associated with both NSSI (6, 50–53) and perfectionism (24, 28, 31, 54–63), the majority of the clinical samples investigated ED populations (73–76, 84). Almost all the studies had a cross-sectional design and only one study contained both a cross-sectional and longitudinal investigation (47). This draws the attention of researchers to the need of longitudinal studies on this topic that will be able to examine the possible causal relationship between NSSI and perfectionism.

The first NSSI engagement generally occurs in early adolescent years; the typical age of onset is 12–14 years (6), and the peak of NSSI prevalence is around 15–17 years (6, 7). Furthermore, it was found that in late adolescence, NSSI prevalence decreases with age (1). According to previous evidence, the prevalence of NSSI in community adolescents was found to be 17–46.5% (2, 8–10); in clinical samples of adolescent it was 60–80% (11, 12), and among adult community samples it was found to be around 4–23% (2, 13, 14). The importance of childhood and adolescence years related to the development of perfectionism (38–43) and NSSI (3, 44–47) has also been proved. Despite previous evidence in our systematic review, only four studies, or about one quarter of the studies (26.7%), (47, 75, 79, 84) investigated the association between the two phenomena, especially in the adolescent sample. Three of these four studies measured this relationship in a clinical adolescent sample (75, 79, 84) and two of them in ED population (75, 84). Only Nock and Prinstein (79) enrolled adolescent psychiatric inpatients irrespective of psychiatric diagnosis. Altogether, 40% (six of 15) of the studies explored undergraduate students with a mean age between 18.89 and 20.61 years (74, 80–83, 87); another 40 % (again 6 from 15) of the studies involved a population with a wider age range of 14–49 years (73, 75, 76, 85, 86, 88), so the differentiation of results between adolescent and adult participant is not possible.

NSSI behavior is more common among women than in men (15). In our systematic review, the studies examined mainly female participants. Altogether, 40% (six of 15) of papers involved only women participants (73–76, 83, 87), and although in the other 60% (9 from 15) studies the populations were derived both from female and male participants, in seven of the nine studies the proportion of females was much higher than men, between 62.3 and 87.2% (79–82, 84, 86, 88). In spite of the fact that NSSI is more common among women, further studies should have more focus on NSSI behavior in men as well for understanding the reasons.

Related to the terminology of self-injury, five terms were mentioned in the 15 investigated papers. All the papers apply the term of self-injurious behavior with nonsuicidal meaning. Among these terms, NSSI was the most common—it was used in two-thirds (66.7%) of the studies, according to the definition suggested by DSM-5 (5). Although this definition emphasizes that this is a deliberate, direct, nonsuicidal, self-inflicted destruction of body tissue without social acceptance, and does not contain drug overdose (5), Varela-Besteiro et al. (84) used the expression of NSSI related to self-injurious behavior including also drug overdose. The terms of SIB and SMB were used similarly to the NSSI definition, focusing on nonsuicidal physical damage of body surface (74, 79). Flett et al. (81) applied DSH also in a nonsuicidal meaning, but this term contains as well substance abuse and putting self to dangerous situation. Only Newman et al. (88) used the expression of self-harm without determination of definition.

Among the majority of the studies included in our systematic review, self-reported questionnaires and diagnostic interviews were used to assess the phenomenon of self-injury. The most frequently used self-reported instruments were the FASM (47, 82, 87), DSHI (80–82) and SHI (81, 86, 87). Newman et al. (88) used only one item form the NSSI-AT, and Fujimori et al. (74) applied their own developed questions. Altogether, eight different instruments were used in the 15 investigated papers, and this heterogeneity of instruments used made it difficult to compare the results of involved studies.

Related to the measurement of perfectionism, the vast majority of studies used self-reported questionnaires; only one study applied interviews (76). Although only two studies from the 15 (80, 86) measured multidimensional aspects of perfectionism with all six subscales of the FMPS, it was the most widely used questionnaire (in 7 of the 15 studies) (47, 73, 80, 81, 85–87). Other studies also measured multidimensional aspects of the FMPS but with fewer scales (73, 81, 85, 87). One-fifth [3 of the 15) of the studies measured perfectionism from self-oriented, socially prescribed, and other-oriented aspects (79, 81, 84), and a fifth (again 3 out of 15) of the studies explored only unidimensional the perfectionism (74, 75, 83). Altogether, six different instruments were used to measure this phenomenon in the 15 studies, so it made it difficult to integrate results related to this phenomenon.

Till now, relatively few studies have empirically explored the association between perfectionism and NSSI. In the 15 studies involved, we gained results both from clinical and community samples, but most studies relied on community samples, while the majority of clinical samples was enrolled from ED patients. Nock and Prinstein (79) found that among those psychiatric adolescent patients who think that other persons have high expectations of them to be perfect (SPP dimension of perfectionism), they used SMB in order to get attention, and support from others, or to avoid inconvenient situations and remove others' high expectations. Claes et al. (73) reported that women ED patients who engaged in NSSI tend to be more concerned about making mistakes, suffer from high self-criticism (ECP perfectionism, maladaptive dimension) and reported higher perceived parental criticism. Besides this, Claes et al. (73) wanted to explore the effect of adaptive perfectionism, but PSP (positive characteristics of perfectionism: setting high standards and goals) was unrelated to NSSI occurrence in women ED patients in their study. From the 15 selected relevant studies, only Nock and Prinstein (79) and Claes et al. (73) explored the function of NSSI engagement, and Claes et al. (73) show that patients with a highly self-critical and negative self-evaluation orientation (maladaptive perfectionism) tend to use NSSI as a means of self-punishment and self-torture. Regarding the association of the social function of self-injury behavior and perfectionism, Claes et al. (73) found evidence that was

both consistent and inconsistent with Nock and Prinstein (79). Consistent with Nock and Prinstein (79), they found that ED patients with high maladaptive perfectionism used NSSI in order to get attention and support from other people (the cry-for-help function of NSSI). But they also found that ED patients with higher parental criticism do not use the cry-for-help function of self-injury. In this critical environment they may tend to avoid their social environment when they feel distress (73). It is inconsistent with the results of Nock and Prinstein (79), because they reported that adolescent psychiatric patients who feel that others have high expectations of them used self-injury in order to get social support and attention. Results may be influenced by the different ages of the examined study populations and by different psychiatric disorders. Nock and Prinstein (79) involved psychiatric adolescent patients with different mental disorders and with a mean age of 14.7 years, while Claes et al. (73) focused only on women ED patients with a wider age range (14–42) and with a mean age of 21.5 years. Maybe adolescent psychiatric patients are more dependent on their social environment than adult ED patients.

According to previously mentioned results, people with high maladaptive perfectionism may strive to control the situation and their environment due to the continual feelings of concern over mistakes and doubt about action (73). This attitude can be associated with the NSSI control function (interpersonal influence) (18), and perfectionistic people may use self-injury in order to get control and predictability in their environment (73). Previous results emphasize the role of social environment, parental expectation and parental perfectionism in the development of maladaptive perfectionism (39, 41, 42, 60). Claes et al. (73) also support this theory, because they reported that maladaptive perfectionism has a mediating effect between parental criticism and NSSI in female ED patients. It means that parental criticism plays an important role in the development of self-critical and negative self-evaluative orientations (maladaptive perfectionism), which can lead to NSSI engagement.

Varela-Besteiro et al. (84), Fujimori et al. (74), and Luyckx et al. (75) explored only the unidimensional aspect of perfectionism. Three research papers' results were consistent regarding maladaptive perfectionism and self-injury. Varela-Besteiro et al. (84) used adolescent ED sample, Fujimori et al. (74) adult female ED patients, and they found the same results as Claes et al. (73), who explored women ED patients. They all concluded that higher maladaptive perfectionism is significant risk factor for self-injury.

In our systematic review, only two studies (74, 75) compared how clinical and community samples relate to the association between NSSI and perfectionism. Fujimori et al. (74) and Luyckx et al. (75) used mainly ED patients in their clinical samples. Fujimori et al. (74) showed that ED patients with self-injury behavior are more perfectionistic than ED patients without self-injury and control university students. While Luyckx et al. (75) found that in both female ED and BPD patients and in female adolescent samples, there is a positive relationship between engaging in NSSI and perfectionism, but regression analysis showed a significant similar effect only in the female adolescents sample. In this study, the number of female high school students was much higher ($N = 348$) than psychiatric patients ($ED = 80$, $BPD = 51$), so the lower number of psychiatric patients in the sample might affect the power and significance of the results.

Interestingly, findings of Vieira et al. (76) do not support the relationship between perfectionism and NSSI among female ED patients. They did not find a difference between the non-NSSI group and the NSSI group related to perfectionism. Contrary to previous evidence, in which perfectionism and NSSI were assessed by self-reported questionnaires, Vieira et al. (76) measured putative risk factors for ED patients with semi-structured interviews (RFI), using questions related to self-injury and perfectionism focused on the period before the onset of eating pathology.

In community samples, the findings of Yates et al. (47) and Hoff and Muehlenkamp (80) are consistent with the results of Claes et al. (73) in women ED patients, and emphasize that maladaptive perfectionism (particularly concern over mistakes) is a potential risk factor for NSSI engagement. Moreover, critical parenting behavior may contribute to avoiding social environments (because of negative representations of others), when adolescents feel distress and this parenting behavior can increase the likelihood of NSSI (47). The study of Yates et al. (47) is the only one study in our review which measured the two phenomena both in cross-sectional and longitudinal samples. In cross-sectional sample among both girls and boys, parental critical behavior can lead to alienation toward parents, which can predict self-injurious behavior. In longitudinal sample, only among girls is it found that perceived PC in grades 6 to 8 can predict NSSI in grade 12. So, parental criticism reported by youths predicts increased self-injury over time. Interestingly, in longitudinal sample the mediation effect of parental alienation between PC and NSSI was not significant, but the longitudinal sample size was much lower than in cross-sectional sample, which can influence the power and significance of results. Hoff and Muehlenkamp (80) show that for self-injurious participants among college students are presented with difficulties in organizing and controlling over their daily lives and situations (80). Consistent with previous findings (47, 73, 79, 80), Flett et al. (81) also found higher NSSI occurrence among those female university students who perceived higher PC and felt that others have high expectations (SPP dimension of perfectionism) for them. In addition, they found among male university students that self-injury has a negative relationship with other-oriented perfectionism. Because of the different results, the authors emphasize that it would be profitable if future studies analyse and differentiate the association of self-injurious behavior in men vs. women (81). Results of Kaur and Martin (85) among medical students, Lucas et al. (86) among female college students and Chang et al. (87) among women college students also support previous evidence, which emphasizes the role of a high level of maladaptive perfectionism (especially concern over mistakes) (47, 73, 80) and high parental expectations in greater NSSI engagement (85). Chang et al. (87), similar to Claes et al. (73), found that PSP (adaptive dimension of perfectionism) has no relationship with NSSI occurrence. So, PSP plays no adaptive or protective factor in the context of NSSI behavior according

to these studies. From all 15 studies, only Chang et al. (87) measured the interaction of adaptive (PSP) and maladaptive (ECP) perfectionism related to self-injurious behavior. Although the positive strivings perfectionism dimension has a positive relationship with evaluative concerns, and the PS subscale (adaptive dimension of perfectionism) was associated positively with the DA and CM subscales (maladaptive dimension of perfectionism) in their study, the interaction of PSP and ECP has no significant effect on NSSI behavior. Related to this interaction analyse authors used a 2 x 2 model of perfectionism (30) which is based on low positive striving and high evaluative concerns, so this model based on the maladaptive aspects of perfectionism, and the positive aspects of positive strivings, but previous evidence shows that the effect of positive (adaptive) perfectionism is not squarely clear, because perfectionistic strivings can have both adaptive and maladaptive consequences (27). Future research needs to analyse this interaction in more complex way accounting for NSSI behaviors, because in Chang et al. (87) study positive strivings has positive relationship with evaluative concern, and PS subscale was associated positively with DA and CM subscales, which means that people who have high standard, set higher goals, expect higher performance simultaneously feel doubt related their everyday things, and have concern over performance mistakes.

Miskey et al. (82) focused on only the cutting form of NSSI; they found that those undergraduate students who tend to ruminate (rumination scale of RI) have a longer NSSI cutting duration period. Inconsistent with previous results (73, 80), Miskey et al. (82) found that those orderly persons, who have ruminative tendencies and low concern over mistakes, have a higher NSSI cutting frequency. In this study, the rumination was the strongest predictor for NSSI frequency. Regarding these curious results, the authors suggested a deep evaluation of the content of ruminative thought as it relates to self-injurious behavior (82). In their study, maladaptive perfectionism and the need for approval of others predict significantly the age of onset of NSSI cutting. It means that the older those people are who start to engage in NSSI, the more they are concerned about mistakes and the need the approval of others (82).

Eichen et al. (83) measured only unidimensional aspects of perfectionism among college-aged women. According to their results, there is no difference regarding to perfectionism among participants with NSSI only, with NSSI/suicidal ideation, no NSSI/suicidal ideation and with suicidal ideation-only. The authors suggested that these results could be because they used the perfectionism subscale of EDI-2 (99), which does not enable a complex measurement of the dimension of perfectionism, which might show differences between investigated groups (83). Newman et al. (88) examined things from other aspects of perfectionism. According to their results, obsessive perfectionistic people have the worst mental health, with a high rate of self-injury behavior, high rumination, planfulness and compulsion tendency.

Nonsuicidal self-injury (NSSI) is a growing clinical and mental health problem, especially for youth and young adults (1–3), and both NSSI and perfectionism is a serious risk factor for suicidal ideation and behavior (28, 51, 64–68). Previous systematic and meta-analytic reviews found similar evidence related to the association between perfectionism and suicidality (suicide ideation or behavior) to what we found in our systematic review related to the relationship between NSSI and perfectionism. Maladaptive perfectionism dimensions, especially SPP, CM, DA, PC, PE are risk factors for both suicide ideation and attempts (68, 102), and meta-analytic review found that perfectionistic striving (SOP, PS) also predicts suicide ideation (102). Because there is a huge comorbidity between NSSI and suicidal behavior (28, 51, 64–68), and negative perfectionism is associated with self-injury and increased risk for suicidal behavior, our review may raise attention to appropriate treatment of perfectionistic people in order to prevent suicidal behavior when self-injurious behavior without suicidal intent has already appeared. Maladaptive perfectionism should be the focus of prevention and intervention.

Based on our systematic review we have the following suggestions for future studies in connection with the association between perfectionism and NSSI: (a) using large clinical samples with different mental disorders, (b) identifying the role of comorbidities, (c) identifying potential gender differences, (d) examining other functions of NSSI related to perfectionism, (e) monitoring the interaction between adaptive and maladaptive perfectionism dimensions, (f) using longitudinal study designs in order to assess the nature of this relationship, and (g) examining the additional plausible mechanisms behind the perfectionism-NSSI relationship.

To wrap up our main findings, our results highlight the important role of an elevated level of maladaptive perfectionism in NSSI engagement. According to studies examined, concern over mistakes and parental criticism perfectionism dimensions have the strongest effect on nonsuicidal self-injurious behavior. Our systematic review highlight that some aspects of perfectionism may influence vulnerability to NSSI.

LIMITATION

Our systematic review needs to be interpreted with several limitations. From the 15 studies, only one used a longitudinal examination, while the other 14 studies had cross-sectional study designs. Therefore, no causal relationship was revealed among investigated factors. The majority of the studies included only samples of women. Only two studies investigated balanced gender ratios, so the findings may not be generalisable to both genders. Although a large body of evidence suggests that several mental disorders, both internalizing and externalizing are associated with both NSSI (6, 50–53) and also with perfectionism (24, 28, 31, 54–63), most of the 15 studies with clinical investigation enrolled ED patients; therefore, the results cannot be generalisable for all other mental disorders. Our review attempted to understand the main causes and function of NSSI engagement in connection with perfectionism through studies on clinical and non-clinical populations, but many aspects remain unclear, especially regarding the effect of the interaction of adaptive and maladaptive perfectionism related to NSSI

engagement. Moreover, the heterogeneity of used instruments makes it difficult to compare the results of involved studies.

Further methodological limitation is that we involved only those papers that were written in English. Another limitation is that our systematic review is a narrative synthesis of the included relevant studies, quantitative analysis was not the objective of this study. Meta-analytic review, or meta-analysis was not performed due to the considerable heterogeneity between studies related to assessed outcomes and used measurements.

CONCLUSION

To the best of our knowledge, this is the first systematic review to explore the relationship between two phenomena and clarify perfectionism as a particularly high risk factor for NSSI engagement. NSSI is a common phenomenon and is associated with elevated maladaptive perfectionism among adolescents and adults in both community and clinical samples. Furthermore, given the increased rates of NSSI and perfectionism, both are significant predictors for suicidal behavior. These phenomena are important public health issues, resulting in a growing need for a coordinated response. Perfectionistic people tend to hide behind their flawlessness mask, which makes it difficult to detect their need for help. There is an urgent need to identify effective prevention initiatives and treatment strategies aimed at these people.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

DG: Performed the article selection process, participated in the data analyzing, presentation of the results, and discussion, drafted the manuscript. JB: Supervised the steps of the data analyzing and the selection process, drafted the manuscript. All authors read and contributed to the article and approved the final version of manuscript.

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A Local Review on the Use of a Bio-Psycho-Social Model in School-Based Mental Health Promotion

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Background: Schools are a key setting for student well-being promotion. Various school-based mental health programs have been implemented worldwide, with greater emphasis placed on psychological and social aspects. The bio-psycho-social model provides a holistic and integrated view of mental health based on theory and research evidence. Given the importance of considering all three dimensions in mental health promotion, this study explored reasons for the relative neglect of this approach by studying the early phase of school well-being program development and implementation.

Method: In total, 77 Hong Kong government-funded student well-being programs implemented in 2000–2009 were reviewed for the use of biological, psychological, and social interventions. Questionnaires and interviews were conducted to explore program leaders' usage and views regarding theoretical frameworks and evidence-based practice and program evaluation. Challenges encountered in the initial stage of school well-being program development and implementation were identified and analyzed.

Results: Of the 77 programs reviewed, only 5 addressed all three bio-psycho-social factors of mental health. A significantly greater number of programs addressed psychological ($n = 63$) and social ($n = 40$) factors compared to those that covered biological factors of mental health ($n = 13$). Of 24 program implementers who responded to the online survey, 75% claimed to have studied or applied a theoretical framework yet only 41.7% considered evidence-based practices to be important. The majority of interviewed participants valued their own practical experience over theory and research evidence. Many programs lacked rigorous evaluation of clear objectives and measurable outcomes, thus the mechanisms of change and program effectiveness were uncertain. Perceived barriers to program adoption and continuation were identified.

Conclusion: This study highlighted a neglect of the biological contribution to mental health in school well-being promotion initiatives, possibly due to lack of theoretical knowledge and evidence-based practice among program leaders and implementers in the early phase of school mental health promotion. The bio-psycho-social model should therefore be recommended for student well-being programs as a holistic and integrated

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theory of mental health underpinning program objectives, mechanisms of change, and measurable outcomes. To develop effective practices in student well-being promotion, more thorough documentation, a rigorous evaluation framework, and support for frontline educators to evaluate their practices were recommended.

Keywords: bio-psycho-social, mental health, well-being, school health, universal intervention, program evaluation

INTRODUCTION

Suicide is a leading cause of death among youths globally, claiming close to 800,000 lives annually (1). In Hong Kong, a recent survey has shown that youths (aged 24 and below) experienced significantly more symptoms of PTSD and depression than older age groups when affected by population stressors such as COVID-19 and social unrest (2). As the age of onset of many mental health problems occurs early in adolescence, there is great need for early universal mental health intervention (3).

Schools are a key setting for mental health promotion and suicide prevention among children and youth. Universal interventions in the school context refer to those delivered to the whole student population (4). School settings have the benefits of accessibility, cost-effectiveness, flexibility in delivering interventions and established relationships, and regular contact between youths and teachers (5). The school itself is also an important social and environmental factor in adolescent development, hence a health-promoting environment that values student well-being is key for facilitating their mental health (6, 7). To date, there is significant research interest in the design and implementation of the best approach to universal school mental health interventions.

The bio-psycho-social (BPS) model is a holistic and integrated framework of mental health. Although this is important for mental health promotion and has immense potential for school application, reviews of existing school programs worldwide show that it has yet to be well-integrated into school interventions.

This study is a historical review of the initiation of school-based well-being programs in Hong Kong. Alarmed by a sharp rise of suicide rate in Hong Kong from 1997 to 2003 in the general population and, in children aged 15 or below, a rise from 0.5 to 1 per 100,000 in 1997–2000 (8), children and youth's mental health and suicide risks have since received significantly greater attention from the government. Between 2000 and 2009, the Quality Education Fund established by the Hong Kong government welcomed applications from service providers to develop programs for students, with one of the aims being to cultivate positive values and well-being (9). Through this review, we aimed to evaluate implementers' consideration and use of bio-psycho-social components throughout the initiation process, from conception and dissemination (where the funder's aim of promoting student mental health through school-based programs was conceived and spread), adoption (the school or organization committed to developing a program), to implementation and maintenance of the program as part of the school culture and curriculum (10, 11).

The bio-psycho-social model is a holistic approach that considers the interaction of biological, psychological and social factors in contributing to health and well-being. It was conceptualised in response to the biomedical model of illness, under which the significant influence of psychosocial factors in physical health would often be overlooked (12). In the case of mental health, it is crucial to not only consider psychological factors but its interdependent interaction with biological and social factors.

According to the model, each of the three factors do not operate in isolation, but both affect and are affected by each other. In one of the largest meta-analyses of suicide risk factors, Franklin et al. found that the evidence for singular risk factors considered individually (e.g., social isolation, hopelessness) was relatively weak, and instead, they must be considered in complex additive and interactive relationships with other multi-domain factors to explain suicide risk (e.g., life events, physical health) (13). Psychological vulnerability and protective factors span interacting biological, social, and psychological domains (14). Studies show that protective mental health measures such as self-esteem, self-compassion and hope are both influenced by and can influence social and biological factors (15). Research on suicide among those with physical health issues describes the negative impact of the condition and hospitalisation on social isolation and the capacity to participate in valued activities, which increased their psychological helplessness and undermined their sense of meaning (16). The gap from suicidal ideation to action can also be explained by bio-psycho-social factors. Impulse control and desire to act significantly distinguish ideation from action, and these can be influenced by bio-psycho-social interactions beyond simply mental disorders, such as personality disposition, substance use and its physical effects, negative life events and pain (17). Therefore, in mental health promotion and suicide prevention, the three domains should not be approached in isolation, but together. Likewise, effective reduction of risk factors such as life stress, substance use, bullying or maladaptive coping patterns would entail spanning across the three domains of BPS and addressing their interactions. For example, reducing depressive symptoms may require addressing problems of negative cognitive patterns (psychological), unsupportive peer culture (social), as well as physical wellness impacting mood (biological). Without an integrated approach, the original goal of addressing the mental health vulnerability may be greatly impeded.

Therefore, an effective BPS approach to universal whole-school mental health promotion would consider how biological, psychological, and social factors interact and contribute to student mental health and well-being. With a deeper

understanding of students' bio-psycho-social needs, risk and protective factors within the school setting, and the underlying mechanisms that link them to mental health, schools can then design more effective and relevant programs and activities to promote students' well-being.

Schools and education authorities around the world have designed and implemented various mental health promotion programs. A review of existing research literature as well as national guidelines on whole school mental health programs reveal a wide range of theoretical underpinnings (5). Worldwide, there has been a trend towards psycho-social interventions, such as Social and Emotional Learning (SEL), positive psychology, and interventions based on elements of Cognitive Behavioural Therapy (CBT). In particular, SEL appears to be the most widely used and studied, with the largest evidence base (18). However, these approaches tend to target social and/or psychological factors of student mental health to the relative neglect of biological factors.

Other approaches may focus more on biological factors alone. For instance, the WHO's Health Promoting Schools program has been shown to benefit student health behaviours (e.g., diet, physical activity, and tobacco use) worldwide. However, while mental health is mentioned in the model, in practice, the appearance of psychosocial interventions is limited (19). Other programs may incorporate a selection of topics or elements across the BPS domains, such as bullying, health behaviour, mental health or substance abuse (20). However, it is unclear if these choices necessarily come from a guiding theoretical approach. In fact, one finding from a systematic review evaluating universal school-based mental health programs is that clear theoretical underpinnings were missing from some program designs (5). This is a concern, as a guiding theoretical approach in intervention design has the function of considering and directly addressing the key causal mechanisms behind the problem, and its absence may therefore result in a less effective intervention (21).

Government-published guidelines such as Personal, Social, Health, and Economic education (PSHE) in the UK and the Whole School, Whole Community, Whole Child Model (WSCC) from the US have indeed incorporated all three bio-psycho-social elements into their frameworks. However, beyond general guidelines, there is variability in the program practice and implementation quality. In PSHE, the factors of BPS are clearly outlined, though these categories are more separate and distinct and it is unclear whether there is emphasis on discussing the interaction of the three components. In the case of WSCC and its holistic BPS consideration, there is not much documentation or empirical research literature to date on its implementation practices and evaluation (22). Before new evidence surfaces to demonstrate otherwise, bio-psycho-social factors still appear to be compartmentalised rather than well-integrated in school mental health promotion, often emphasising one or two factors in isolation to the neglect of another.

Other challenges in BPS school program implementation include evaluation practices and research quality. Reviews of school program evaluation literature have cited the need for higher research quality in conducting rigorous evaluation, including the use of control groups and clearer documentation of program protocol and implementation (20). Recommendations include clear measurement of target outcomes to empirically evaluate intervention effectiveness and follow-up measurements to understand its longer-term impact (18, 23). As BPS factors are theoretically known to contribute to mental health, school programs would ideally go one step further to verify the mechanisms of change in more detail, e.g., how the interplay of factors influences mental health outcomes across different student age groups, characteristics, and sociocultural and economic contexts. Without rigorous evaluation, it is difficult to compare the effectiveness of different theoretical approaches and program designs and to identify correctly, with reliable evidence, the very mechanisms and practice that are effective for youth mental health promotion and suicide prevention. The lack of high-quality evaluation is therefore hindering advancement of the BPS model as applied to school programs.

Informed by theory and empirical evidence, we propose that a bio-psycho-social model of student mental health would consider all three components and their interdependence, systematically addressing the multi-modal and intertwined needs of the child in an integrated, evidence-based manner. Applying this theoretical model of mental health in schools and gathering empirical evidence on its effectiveness across different settings would be key to building a strong universal level of suicide intervention among children and youth.

Given international research has suggested that school interventions have tended to approach mental health promotion in a compartmentalised topic-based manner (20) with a bias towards addressing the psychosocial dimension (5), this is the first study to test the hypothesis that historically, well-being programs in Hong Kong schools have also lacked the holistic and integrated approach that is key to understanding and addressing mental health. In addition, Hong Kong school communities are primarily pre-occupied by academic success and the cultural significance of morality and virtues remains influential on their conceptualisation of growth and development among children and youth. These sociocultural influences may indeed lead to a lack of emphasis on the interplay of BPS factors in student mental health. Therefore, we aimed to conduct a thorough review of government-funded school programs which, were initiated and implemented between 2000 and 2009 that promoted student well-being, to evaluate the patterns of application of the BPS components, explore underlying reasons for these patterns in the local context, and to identify universal challenges and recommendations for improving future BPS application and mental health promotion in schools.

METHODS

This study reviewed 77 school-based programs on student well-being that were funded by the government under the theme "developing students' positive attitudes and values" and implemented between 2000 and 2009. Under the funding scheme, schools were expected to implement a 1-year program on life, moral, value, and/or sex education. This was the

first territory-wide initiative for enriching student learning (9). Although mental health was not stated as an explicit goal, it was nevertheless the government's largest funding scheme for schools promoting student well-being at the time.

The review of the 77 programs began in 2014. Upon completion, a resource handbook and a report documenting the findings were produced (24, 25). Since then, a territory-wide project on school mental health promotion has been initiated and funded by the Education Bureau of the Hong Kong government. The project currently engages around 30 schools in the secondary, primary, and pre-school sectors to implement a well-being curriculum as well as other well-being-promoting activities in school. Building on review findings, school programs covering BPS components in an integrated manner are currently being developed and implemented.

The present study examines multiple sources of evidence generated from the review exercise to examine the initiation stage in detail.

Three research methods, namely, document analysis, survey, and in-depth interview, were adopted to examine the application of the bio-psycho-social (BPS) theoretical model, to identify challenges and obstacles, and to evaluate the quality of the programs. Lessons learnt from a successful case in implementing the BPS framework in school well-being promotion in Hong Kong were discussed.

Collection and Analysis of Program Documents

The main review of the 77 programs was performed by assessing their corresponding proposals, final reports and deliverables including program manuals, pamphlets, and booklets. Program information and data extracted included objectives, target population, contents, evaluation, challenges, and outcomes.

One key objective of this study was to investigate the application of the BPS framework in school-based well-being programs in Hong Kong, and how each component of the BPS model related to such programs. By examining the program materials and coding them for their use of biological, psychological, and social interventions in the school-based programs, we aimed to illustrate historically the focus of programs with respect to the BPS model.

A set of criteria for assessing program quality was developed by the research team (24) to indicate whether or not (1) a program was designed based on any theoretical framework, (2) program activities met the objectives, (3) multidisciplinary collaboration was involved, (4) program evaluation was conducted and if yes, which method(s) used (qualitative, quantitative, self-rated, observed-rated, and/or follow-up assessment), (5) a rigorous evaluation methodology was adopted and, (6) a program had measurable outcomes.

Questionnaire Survey

An online questionnaire survey was designed to collect general views and opinions from program leaders/implementers involved in the 77 programs. Most of the program implementers were school teachers while others were social workers. Qualitative data was collected from open-ended questions about the implementers' views on (1) the meaning of developing students' positive attitudes and values, (2) how they evaluated the effectiveness of programs, and (3) difficulties encountered. Analysis of qualitative data was performed by documenting all responses to each question and identifying key categories or themes. A multiple-choice question was included to identify if the program design was based on a theoretical framework, evidence-based practice, teacher or social worker's experience, and/or expert opinion. Participants were also asked to indicate if their program would continue. Due to turnover of personnel over the years, only implementers of 24 programs responded to the online survey.

In-Depth Interview

Program implementers were interviewed to further explore the details of program design, implementation, and impacts on students. Most of the program implementers were school teachers while others were social workers. Guidelines for the interview were designed to investigate for each program the theoretical origin and objectives, its implementation process, the evaluation methods employed, the program outcomes, the obstacles and challenges encountered as well as the intention to continue vs. discontinue the program. Examples of interview questions include "What does a theoretical framework mean to you?", "Did you design the programs based on any theoretical framework, and if yes, what framework is it?", "What does evidence-based practice mean to you?", "Why and how did you choose your target population?", and "How did you evaluate the effectiveness of the program?". When selecting programs for the in-depth interview, a good representation was sought, reaching out to the full range of grantee sectors including pre-primary, primary, secondary, and special schools, tertiary institutes and non-government organizations (NGOs). Due to high personnel turnover, only implementers from 19 programs agreed to participate in the interview. Each interview lasted for about one hour and was audio taped and transcribed.

RESULTS

Overview of Target Student Populations

The distribution of programs across target student populations was calculated to give an overview of the targeted groups. Of the 77 well-being programs, 33 (42.8%) were developed and delivered to secondary school students only and 22 programs (28.6%) targeted primary school students only. An additional 9 programs (11.7%) served both primary and secondary schools. Pre-primary sector only accounted for 11 (14.3%) programs and the least number of programs served special school students, with only 2 (2.6%) programs available for review.

Distribution of Bio/Psycho/Social Components Among School-Based Well-Being Programs

Adoption of Single-, Dual-, or Multi-Component Approach

The use of BPS interventions was coded for each well-being program and the composition of programs by their adoption

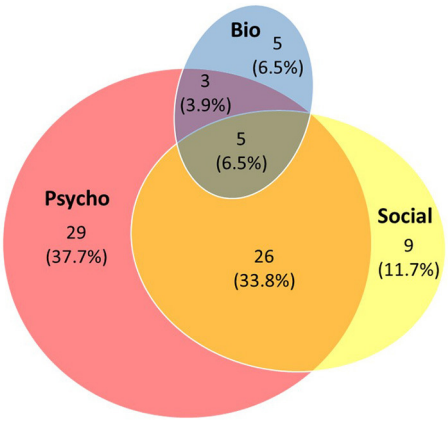

FIGURE 1 | Composition of the 77 school-based well-being programs in Hong Kong with respect to biological, psychological, and social components.

of a single-, dual-, or multi-component approach was analyzed (**Figure 1**). Out of the 77 programs, 43 (55.8%) adopted only one single component of the BPS framework, 29 (37.7%) covered two of the three components, and only 5 (6.5%) adopted a multiple approach comprising all three components of the BPS model.

Among the 43 programs adopting a single-component approach, the ones with a sole focus on psychological components ($n = 29$; 37.7%) outnumbered those focusing on social ($n = 9$; 11.7%) or biological factors ($n = 5$; 6.5%). Among the 29 programs adopting a dual-component approach, the majority ($n = 26$; 33.8%) focused on psychological and social aspects of student well-being, whereas only a handful adopted the combination of psychological and biological elements ($n = 3$; 3.9%). No program selected the pairing of social and biological components, but they did appear together in the five (6.5%) programs that covered all three components.

Coverage of the BPS Components

The coverage of BPS components in all well-being programs was further analyzed (**Table 1**). As mentioned above, psychological aspects of student well-being were by far the most addressed. Four out of five programs ($n = 63$, 81.8%) had objectives set to facilitate the psychological development of children and adolescents (**Figure 1**, pink circle). Examples included activities aimed to enhance participants' self-esteem, resilience, and emotion regulation skills.

Social development was the second-most focused facet in the school well-being programs. Over half of the programs ($n = 40$, 51.9%) aimed to strengthen students' communication skills and social relations (**Figure 1**, yellow ellipse). The biological component, on the other hand, was least targeted. Only 13 programs (16.9%) comprised elements for biological development of students such as healthy living and eating habits (**Figure 1**, blue ellipse). Of these, more than half ($n = 8$; 61.5%) were implemented in pre-primary and primary sectors, targeting the youngest students.

Similar patterns of disproportionate coverage of BPS components in well-being programs were seen across all target student populations, except for those who had special needs; merely two programs were dedicated to serve special school students that the extremely low number appeared insufficient to reflect the phenomenon.

TABLE 1 | Programs covering biological, psychological, and social components by target student population.

Target student population	No. of programs covering components of BPS model (% within each target student population[§])		
	Biological	Psychological	Social
Pre-primary ($n = 11$)	4 (36.4%)	8 (72.7%)	6 (54.5%)
Primary ($n = 22$)	4 (18.2%)	20 (90.9%)	12 (54.5%)
Primary and secondary ($n = 9$)	2 (22.2%)	8 (88.9%)	3 (33.3%)
Secondary ($n = 33$)	2 (6.1%)	27 (81.8%)	18 (54.5%)
Special ($n = 2$)	1 (50.0%)	0 (0%)	1 (50.0%)
Total no. (%*) of programs covering bio/psycho/social component	13 (16.9%*)	63 (81.8%*)	40 (51.9%*)

[§]*Percentage of programs out of the total number (n) of programs targeting each student population, which covered biological, psychological, and social components.*
[*]*Percentage of programs out of the 77 programs under review, which covered biological, psychological, and social components.*

Quality of Well-Being Programs

Based on the criteria (24) we developed to assess program quality in the areas of theory, evaluation, and outcome, it was found that most of the programs succeeded in meeting the objectives, and some form of evaluation was conducted to assess their effects and outcomes. Nonetheless, some programs were found to have no theoretical framework in program design, nor adopted a rigorous evaluation methodology. Follow-up assessment of program effectiveness was rare.

Interviewing the implementers revealed that a questionnaire was the most used method of evaluation (for example, assessing participants' satisfaction about program activities), followed by observation of students' performance and learning progress. Some programs simply conducted post-program interviews with participants without pre-program assessment or interview to compare them with. Remarkably, only very few programs adopted rigorous research designs such as controlled experiments and quasi-experimental approach, leaving the majority without any systematic methodology to evaluate program effectiveness. Key performance indicators and measurable outcomes were often lacking and at most, participants' satisfaction levels of programs were acquired instead.

Rationale and Reality Behind Well-Being Program Designs

From the results of coding for the use of biological, psychological, and social interventions in the school-based programs, it appeared that a holistic and integrated approach of the BPS theoretical framework for promoting well-being was overlooked, whereas much emphasis was placed on the psychological and social dimensions alone. An online questionnaire survey was

then conducted to explore how the conceptualisation of the program first came about. In-depth interviews of program implementers were conducted to further explore the rationale for designing the mental health programs and any other issues of design and implementation. Due to turnover of personnel over the years, implementers of only 24 programs responded to the online survey, giving a response rate of 31.2%. For the interview, implementers from a range of organizations that developed and delivered the programs participated. These included staff members of one special school, two primary schools, three secondary schools, six tertiary institutions, and seven NGOs.

Origins of the Well-Being Program Designs

Qualitative responses were collected from the online survey using open-ended questions; feedback from the 24 program implementers provided insight into how frontline educators in Hong Kong perceived the objectives of implementing school-based well-being programs. In their opinion, helping school children develop positive attitudes and values, i.e., the major theme of the government-funded scheme, was to teach them to be responsible, motivated, proactive, optimistic, resilient, and hopeful. To this end, it was meant to equip students with skills and knowledge such that psychologically, they become capable of coping with challenges in life and managing negative emotions while socially, they learn to care for and respect one another. Their pre-existing concept of nurturing students' positive attitudes and values may explain why almost all well-being programs disproportionately addressed the psychological and social development of students while some placed much emphasis on building moral characters. Incidentally, implementers went on to elaborate that in the process of program design, schools were often prompted by specific current social and societal issues such as juvenile violence incidents in the community or perceived deficiency in children's moral character building. Current issues thus played a role in the conceptualisation stage, shaping the program objectives, as described by interviewees:

"Unlike researchers, their start point was to cater for the needs of the target population such as students and teachers after assessing what they really needed and reviewing what was and was not effective based on literature reviews."

Quantitative data from the online survey summarized the rationale behind designing the well-being programs. From the 24 program implementers who responded, 75% claimed to have designed their programs based on a theoretical framework; similarly, 75% of implementers relied on past experiences of teachers or social workers when designing program contents and activities. More than half of them (58.3%) consulted other professionals or organizations on program design. However, only 41.7% took into consideration evidence-based practice in their program design.

Meanings of Theory and Evidence-Based Practice

Contrary to the quantitative data collected from the online survey, interview data revealed that most of the 19 implementers did not design their programs based on any theoretical framework. Some interviewees claimed that they made reference to theories relevant to development of positive attitudes and values in children and young people but they did not completely put the theories into practice. Some interviewees developed their own framework based on past experience. These interviewees, who were either social workers or teachers, explained that as frontline professionals, they were accustomed to drawing on relevant experience from the past when designing activities and programs for students. Specifically, the experience of interacting with students was adopted by social workers, teachers, and school principals as the key reference, a finding in line with the online survey responses**.** Most interviewees claimed that, for school-based well-being programs, "*practical knowledge is more important than theory*." Some interviewees considered observation as a type of evaluation as well. They observed the students' performance in class, tracked the students' learning process and communicated with them to understand their needs and evaluate their progress. Some teachers required the participants to write a brief reflection after each activity. They had designed corresponding worksheets with questions asking about the students' feelings. They also considered the briefing and debriefing sessions before and after their project activities.

For most interviewees who worked in schools and NGOs, evidence-based practice meant "practical knowledge" which is built through conducting pilot trials, class observations, having conversations with the target population, and refining the execution plan before launching the programs. Based on such practical knowledge, some interviewees developed their own frameworks for designing well-being programs. In contrast to programs initiated by tertiary institutions, which in general demonstrated evidence-based practice supported by comprehensible theoretical frameworks and rigorous methodology, many interviewees either did not fully understand what theoretical framework and evidence-based practices are or did not have their programs clearly documented, resulting in limited information available for developing evidence-based practice.

Challenges in Promoting Student Well-Being in School Settings

Among the 24 schools that responded to the online survey, just over half (54.2%) continued the well-being programs after the funding period. Both the online survey and interviews revealed that shortage of manpower and time constraint were top challenges to most implementers in executing the well-being programs. While regular curricula had already been scheduled and lessons were tightly packed, well-being program activities often led to extra working hours and additional tasks for teaching staff including administrative works, program planning and design, teacher training, as well as documentation and evaluation. Another challenge cited by program implementers was related to human resources:

"For projects that were carried out by school teachers, the main obstacles were to find external professionals to help with

the projects. The frequent transfer of personnel, which caused inconsistency of the projects, was another problem."

For programs initiated by NGOs, school recruitment and student dropout were the main obstacles. The reluctance of schools joining their programs was due to the very same reasons of tight teaching schedules and limited human resources available for cooperating with the NGO even when the latter was the service provider. In one program that incorporated the biological components, physical health-related activities were restricted because of the lack of space and sports facilities in school and the community.

It is worth noting that recruitment of students to a school-based well-being promotion program was also challenging due to two main reasons. The first was found to be a fear of being stigmatised by association with any mental health issue, and the second was low motivation to engage in such activities. The latter could be due to the high demands put on students to demonstrate academic achievement first and foremost in Hong Kong. For schools that were determined to prioritize student well-being, perceived difficulty in applying for government funding posed another major obstacle to initiating and sustaining school-based well-being-promoting programs. The administrative cost of following the complicated funding application procedures was cited by implementers as a significant deterrent.

Case Study–A Program Successfully Applying BPS Principles to School Well-Being Program

Among the five programs that addressed all three dimensions of the BPS model in school well-being programs, the one initiated by the Boys' and Girls' Clubs Association of Hong Kong (BGCAHK) provided a good demonstration of consideration of a theoretical framework and application of the BPS principles in an integrative manner. The Comprehensive Health Program for Young Children Development targeting pre-school children was implemented by the BGCAHK in 2006 for 1 year. With reference to the longstanding concept of health as defined by the World Health Organization, that is "*health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*" (26), BGCAHK designed the program with the aim to help children achieve a healthy state on all the biological, psychological, and social levels.

On top of a nutrition and healthy eating curriculum, getting children interested in exercise and to build a fitness habit formed part of their program objectives that addressed the biological component. A joint-school parent-child sports event and mini Olympic Games were organized with the focus on exercising for fun, team spirit, and engaging children and their parents together, thereby integrating the biological with the social components in a natural context. Besides physical health, the cognitive development of young children was also recognized to be an important biological factor in mental health. Supported by developmental theories on the crucial role of play in young children's cognitive development, the program also included a range of game activities, quiet and interactive, for children to acquire and exercise problem solving skills on their own or together with others.

To strengthen protective factors of mental health in the psychological and social domains, the program taught pre-schoolers to recognize, manage, and express their emotions appropriately through interaction with fellow students and family members. From the program, children learned to listen to and understand others' feelings and were guided to put them into practice in the classroom setting; the concept of gratitude was introduced to pre-schoolers by creating a culture of appreciation at home and at school. Empathy, a complementary character of gratitude, was also taught experientially, for example, by accompanying children on a visit to an elderly centre to learn about other people's lives. Through experiential learning, children developed virtues of love and care in the contexts of classroom, family, and community.

It is worth noting the program did not only target and benefit pre-school children but also their parents and teachers. Several workshops for parents were delivered by physiotherapists, psychologists, and social workers, and these aimed at increasing their knowledge around bio/psycho/social topics of children's physical and mental wellness. Parent workshops also included the sharing of well-designed exercise and game ideas for parents and children and training in parenting and communication skills. Teachers gained understanding in the concept of holistic health and hands-on experience in developing and running well-being programs suitable to their kindergarten. Evaluation in the form of pre- and post-program questionnaire surveys were administered to teachers, which recorded improvements (higher mean scores) of children's physical health, self-managing ability, emotion control, problem solving, social skills, and empathy, according to teachers' observation.

To summarize, this program is a representation of a good and effective school-based program for promoting well-being at a young age. The program drew on developmental and educational theories for its content and activity design; its activities covered all three components of the BPS model while integrating them at times as well. The objective of supporting children to achieve healthy states biologically, psychologically, and socially were clearly defined and achievement was demonstrated by the documentation of changes in the students before and after the program. A whole-school approach that increased teachers' and parents' mental health literacy and involvement also served to increase the school's overall awareness and capacity of promoting holistic health and well-being among young children as an important school priority.

DISCUSSION

The Importance of Theoretical Understanding of Student Mental Well-Being and Adopting a Holistic Approach using the BPS Model in Mental Health Interventions

This study revealed that, similar to global trends, the majority of the reviewed school-based well-being programs from the period

between 2000 and 2009 in Hong Kong did not follow the holistic approach of the BPS model. Three further observations are highlighted here. Firstly, the psychological domain was without a doubt perceived as the single most important area of well-being, according to their appearances in programs. Secondly, the psychosocial dual-component programs were also popular, suggesting a tendency among program developers to see them as closely-related domains and highly relevant to student well-being. Thirdly, whether on its own or in combination with another component of the BPS model, biological interventions were by far the least selected component across the 77 programs. The absence of programs that combined it with the social component also suggests that the pair were possibly perceived as least related. These findings point to the general lack of regard for the interrelationship between all three components and their function in student mental health.

Considering these findings in the local context, we identified some explanations for the imbalanced coverage of BPS. At the knowledge level, insufficient understanding of the BPS theoretical underpinnings and knowledge about its evidence-based practice was apparent, despite many implementers claiming to have adopted a theoretical framework. Implementers also frequently drew on personal experience, practical knowledge, and their understanding of current social issues to develop programs, while few considered evidence-based theoretical frameworks to be essential. This may be related to the general lack of mental health training received by school teachers and social workers working with school children and youth. Without a good understanding of how the bio-, psycho-, and social components of mental health are interrelated, it was not surprising to find that most programs employed a single or dual, instead of multiple, integrated approach to promoting student well-being. The lack of rigorous evaluation also meant that there was little objective evidence to highlight the importance of a multi-faceted, integrated approach. As a result, frontline implementers would either turn to personal experience first, consider practical concerns as more important, or follow popular local and global trends, focusing on psychosocial factors to the neglect of the biological domain.

Sociocultural factors also came into play. In Hong Kong, the positive attitudes and values promotion programs were government-funded with an aim to promote student well-being, initially focusing on four major areas, namely, life, moral, value, and/or sex education. On the one hand, traditional Asian education philosophy emphasises morality and virtues when conceptualising whole-person development, which may have resulted in fewer attempts by program developers to integrate the biological domain into their design of well-being programs. On the other hand, the imbalance of BPS components may equally reflect a bias or lack of consideration on the part of policymakers when they defined the remit of this territory-wide funding scheme. Finally, the lack of common discourse about mental health in the education sector could be a limiting factor on the program's content development. This was reflected in students' fear of being stigmatised by participating in a program on mental health.

The Need for Defined Objectives, Measurable Outcomes, and Rigorous Evaluation for Establishing Evidence-Based Practices in School-Based Mental Health Interventions

Although there was extensive effort made to assess the quality of the programs, the assessment was constrained, evidenced by the limited information available in the program final reports. A full picture of program details was rarely captured by program implementers with the aim to produce reliable evidence. Our findings revealed at least two major factors that accounted for the overall lack in documenting and evaluating effective practices.

Firstly, knowledge and understanding played an important part. Much of the focus of evaluation was on participants' satisfaction with the program activities *per se* rather than clearly defined and measurable outcomes, the indicators of whether or not the program was effective in promoting student well-being. These findings suggest that implementers lacked true understanding of the purpose of evaluation, perhaps with the tendency to see it as a demonstration of program accountability more than a key method to verify and document intervention effectiveness for continued application.

Secondly, findings suggest that even if implementers did understand what was required in evaluation to measure program effectiveness, they perceived the costs to be too high. Conducting a comprehensive and rigorous evaluation would require a high level of resource, effort, and expert knowledge, and in turn the corresponding incentive needed for the school and program implementers to invest themselves would also be high. Overall, implementers may have faced obstacles of having sufficient theoretical knowledge, skills or incentive to conduct rigorous documentation and evaluation of their practices.

Practical Challenges of Delivering Well-Being Programs in School

This study also sheds light on several other barriers that prevented successful program adoption and implementation. At the practical level, insufficient training and support for the delivery of well-being programs in schools were highlighted. The shortage of manpower and time constraint appeared to have contributed to a high dropout rate. As one of the most common reasons for the discontinuation of school-based mental health programs around the world, it is worth investigating the underlying factors in each local context. For example, in our study, teachers cited their tight subject teaching schedule as a barrier to implementing the well-being program. Students also showed low incentives to participate. Subsequently, we consider the lack of time and motivation for well-being programs to be related to a lower priority given to teaching and learning about mental health topics compared to academic subjects. At a deeper level, it may also reflect a system not yet prepared to put student well-being at the centre of their school vision. Therefore, an education system that prioritises student well-being and shows determination to help schools overcome practical challenges is fundamental to the success of any suicide prevention attempts to bring in change and sustain it for long-term impact.

Well-Being of Students and School Mental Health Promotion in the Past Decade

In the past decade, after the initial stage of mental health programs was introduced, some critical events at large have influenced the development of well-being initiatives in schools. Firstly, following a surge in suicides among school-aged children and youth in 2016, Hong Kong educators have become very sensitive to news of students suffering from mental health issues. The widespread assumption that academic pressure is one of the most prominent risk factors contributing to suicide among the Hong Kong student population has made school leaders wary and actively looking for solutions.

Secondly, the social unrest that took place in Hong Kong during 2014-20 was unprecedented in its recent history. Coinciding with the escalated social conflicts was the start of Covid-19, which together have critically impacted the well-being of school-aged children and youth as well as schools' effort to promote it. A research study on the effects that perpetual traumatic experiences from these critical events can have on the population's mental health showed that depression and PTSD symptoms were significantly greater among young people (aged 24 and under) compared to older groups (2). This study alerted us to give urgent attention to the risks posed by critical events in the larger environment to students' mental health.

Reacting to the surge of suicides in 2016, educational organizations and schools have since become more proactive in learning about mental health and what they can do to enhance its promotion. For example, school leaders, management, and frontline staff regularly attend seminars and talks on mental health and have placed greater value on evidence-based programs demonstrated to be effective in improving student well-being. In recent years, the Education Bureau and charities have initiated and funded larger-scale school projects, many inviting tertiary institutions to be their collaborators, to aid the development of well-being programs in schools.

Schools should be a source of protective factors for student mental health. One of its core functions is to provide a protective and health-promoting environment in which students learn and develop in adaptive ways. Unfortunately, schools in Hong Kong have experienced much disruption due to school closures since 2019. Further, because of the widespread pressure to perform academically despite school closure and disruption, most schools have chosen an academically intensive approach aiming at boosting students' knowledge on tested contents. Consequently, curricular and extracurricular activities such as sports and arts, which enrich students' development and strengthen their resilience in challenging circumstances, are pushed aside. The implementation of the well-being curriculum has also been affected as teachers struggled to engage students through online teaching and learning.

In summary, there has been a heightened awareness and proactiveness among schools to promote student mental health due to higher levels of mental health literacy and sensitivity about suicide risk. Schools are now in a greater state of readiness to adopt and develop programs that are theory-driven and evidence-based for improving student mental health. Our recommendation for the next stage is for schools to critically examine whether their education aims and approach to boost student learning and development are beneficial or detrimental to student well-being. In particular, the BPS model would help school leaders and management to re-consider how the school, through their well-being-driven priorities and practices, can facilitate, rather than undermine, bio-psycho-social factors that strengthen student well-being. For example, more, not less, exercise ought to be encouraged when students have been shut in for long periods of time. Risk factors that have led to the rise of sleep problems and gaming addiction must also be understood and addressed properly through school education and interventions. Considering the BPS factors behind these problems in an integrated way would help generate solutions more effectively.

Recommendations for Improved BPS Application in School Mental Health Promotion and an Example Program Outline

Based on the review findings, which are in accordance with existing research worldwide, we would argue that school programs aimed to improve student well-being will be more effective when supported by a good theoretical understanding of mental health among young people (5, 21), clearly defined objectives and measurable outcomes founded on scientific studies (18, 23), and the documentation of evidence on effective practices identified through rigorous intervention implementation and evaluation (20).

BPS offers a holistic and integrated model for understanding and improving mental health. To this end, we suggest that program implementers recognize all three domains of factors as essential and interactive components influencing young people's mental health (see **Tables 2**, **3** for an example of program outline and session rundown). We also recommend future research to investigate this interplay of the three domains, their relationship with socioculturally-shaped constructs such as virtues in Asian cultures, and the mechanisms of change that lead to better mental health in the youth population. These theoretical advancements will enhance our solutions to student mental health and suicide prevention, making school-based programs more efficacious and cost-effective.

At the same time, having clearly defined objectives and measurable outcomes are essential for keeping a program's direction consistent throughout and demonstrating its effectiveness in reaching its goals. We recommend program funders and implementers to clearly articulate their program goals, objectives, theories of change, and evaluate how intervention activities would lead to the intended measurable outcomes (27).

Finally, considering mental health interventions in their everyday settings, practical concerns and barriers expressed by implementers must be properly understood through in-depth investigation of on-the-ground operations and experience. The documentation of the implementation process and participants'

TABLE 2 | Example of program outline of a primary school bio-psycho-social mental health promotion.

Session and theme	Content
1. Understanding emotions	• Identifying emotions, mental and bodily awareness, learning skills to express emotions
2. Managing emotions and problem-solving skills	• Managing emotional responses appropriately in different situations, learning problem-solving skills and frameworks, apply to existing problem
3. Physical health and emotional well-being	• Healthy Nutrition, Exercise, and Sleep and their impact on biological and psychological well-being • Interactive and physical activities
4. Empathy, compassion, and social skills	• Thinking from others' perspective and caring • Positive communication skills
5. Gratitude	• Importance of gratitude, how it can benefit mental health, and how to practice them

TABLE 3 | Example of basic rundown for session 1 "understanding emotions" with bio-psycho-social components.

Time (Mins)	Activity	Bio-psycho-social components
5	Warmup: mindful breathing and muscle relaxation exercise	Psychological and physical relaxation; Becoming aware of own mental and bodily sensations
10	What are emotions? a. Students identify different emotions e.g., Emotion card games (sort cards into positive/negative) b. Reflection activity—describe the feeling, a time when you felt like this	Psychological and biological knowledge and awareness about emotions—the sensations, causes, triggers, and purpose of emotions
20	How can we express emotions? a. Roleplay activities b. Group discussion c. Teacher shares an experience of how they handled negative emotions	Emotion management skills, capacity for listening and empathizing with others' emotions, and sense of connection built through social activity
5	Check-out: Use Movement/Drawing to express current emotional state a. Share product and feelings with a partner	Capacity to reflect on physical and psychological states, express emotions and communicate to others about them, experience social connectedness

experiences would help implementers identify the program's strengths and weaknesses and where resources are needed for subsequent improvements to be made.

Strengths and Limitations

A strength of this study is the large scope of the review, consisting of 77 participating programs funded by the Hong Kong government spanning almost a decade (2000–2009). It contributed to a more comprehensive understanding of the initiation stage of local mental health promotion programs in a range of sectors including pre-primary, primary, secondary, and special schools, tertiary institutes, and NGOs. In terms of methodology, a range of quantitative and qualitative methods were used to achieve a thorough and in-depth evaluation of programs to review their coverage of the bio-psycho-social components, and of designers' and implementers' views in order to understand their design rationale and challenges in practice when initiating well-being programs in school.

One limitation is that the programs were designed and implemented over a decade ago. While this historical review captures the process and challenges of initiating school mental health programs, as mentioned there have been changes in mental health awareness and trends that have grown beyond the initiation stage. Furthermore, societal events that have influenced mental health promotion programs have taken place since, highlighting the need to review the effectiveness and refine the ongoing territory-wide school mental health initiative on a regular basis so as to adapt to the ever-changing conditions of students.

CONCLUSION

Mental health education and promotion in schools is one of the most important initiatives of suicide prevention among children and youth. By systematically reviewing programs developed as part of Hong Kong's first territory-wide mental health initiative, common experiences, challenges, and recommendations were identified. Firstly, the review has reflected a need to increase program providers' theoretical understanding of the bio-psycho-social model and the importance of addressing all three in an integrated manner as a key part of improving school mental health interventions for suicide prevention.

Secondly, having examined intervention gaps and challenges in the local context, the review highlighted program evaluation as a key issue to resolve in order to strengthen school mental health programs. Evaluation is key to advancing the theoretical understanding of a holistic, integrated BPS approach to mental health, thereby constituting a fundamental step forward in suicide prevention among children and youth. The evidence generated from rigorous evaluation will also provide valuable directions for improving intervention and implementation effectiveness and demonstrate the program's worthiness for continued support and investment.

Following the review, the local government and educators have been advised on specific components that contribute to optimum school-based mental health interventions. As such, the review has facilitated their strategic selection of areas to focus on in terms of promoting mental health in schools. Although the context of this review was specific to Hong Kong, we believe that it has demonstrated universal experiences and struggles echoed by program developers and implementers in other parts

of the world and therefore contributed knowledge to the larger landscape of mental health and suicide prevention initiatives.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data analyzed in this study was obtained from the Quality Education Fund (QEF) and access to data requires permission from the QEF. Requests to access the datasets should be directed to Prof. Paul Yip, sfpyip@hku.hk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee, The University of Hong Kong. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PY conceptualised and designed the study. AS and EL organized the database and performed the analysis. AW, IC, and CT wrote the draft of the manuscript. PY and AC critically reviewed the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Adversity Over the Life Course: A Comparison Between Women and Men Who Died by Suicide

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Purpose: This study sets out to compare the presence of life events across different domains throughout the life course which may contribute to the burden of adversity experienced differently among men and women who died by suicide.

Method: In a sample of 303 individuals (213 men and 90 women), data was derived from extensive clinical interviews conducted with informants. Models allowed the identification of patterns of life trajectories.

Results: Overall, the burden of adversity was similar across the life course except for the 5–9, 25–29, and 30–34 age ranges, where a significant difference appeared between genders [t-test = 2.13 ($p < 0.05$), 2.16 ($p < 0.05$) and 3.08 ($p < 0.005$), respectively] that seems to disadvantage women. The early adversities of violence and neglect, between 0 and 19 years old, are important for both groups. During the life course, women were more exposed to interpersonal adverse events such as being victims of negligence and violence, relational difficulties or abuse from their spouse, as well as tension with their own children. Men encountered more academic difficulties, legal entanglements and financial difficulties, and were more than three times more likely to develop an alcohol/drug abuse problem than women.

Conclusions: The data suggests some gender differences in exposure to longstanding and severe life problems contributing to suicide vulnerability. For women, the continuing burden emerges from chronic interpersonal adversities, whereas, for men, the adverse events are to a larger degree socially exposed, compounded with alcohol misuse. The adversities, especially those of a public or social nature, may be witnessed by others, which should favor the detection of vulnerability over the life course, and psychosocial or mental health services should be offered and provided earlier during the life course. Yet more men die by suicide than women. Resiliency and protective factors may benefit women to a greater degree. Future research should tackle the challenge of investigating these important elements. Meanwhile, from a public health perspective, access to psychosocial and mental health services and social acceptability of seeking services should be part of an ongoing effort in all institutional structures as a way of decreasing downstream mental health problems and vulnerability to suicide.

Keywords: suicide, men and women comparaison, adversity over the life course, stressful events, risk factors

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INTRODUCTION

The existing literature observes significant differences in age-standardized suicide rates between genders across the life span (1–3), with lower suicide rates among females and higher suicide rates in men increasing in later life (4–6). The most important risk factors for suicide, have reached a growing scientific consensus, but have mostly been documented among males.

More recently, developmental approaches suggest that differential risk factors and adverse events could alter life courses toward suicide in different ways. Exposure to adverse childhood experiences can be either an acute event, which may be limited in duration (e.g., parental abuse or neglect), a chronic situation, which may increase the risk of other cumulative events (e.g., sexual abuse), or a long-term threat to mental health (7, 8). For example, the impact of early childhood adversity such as physical and/or sexual violence was found to be an important adverse variable, contributing to suicide vulnerability (9–12). They specifically promote the emergence of mediating variables such as aggressiveness, impulsivity, less efficient coping styles, mental disorders and, consequently, suicidal behaviors (13, 14). Differences in the types of childhood abuse have shown that women are more at risk from sexual abuse and men from physical abuse (10, 15, 16).

Developmental risk factors are associated with the complex transition that emerging adulthood (17) and midlife (18, 19) represent. Related stressful events increase the interplay between multiple roles, interrupt the achievement of major goals and may expand the feelings of distress. Therefore, gender roles may be affected differently whereas, change in status over the life course may have an impact on the access to the labor force, and leads to more women being financially independent, which has made it easier to end unsatisfying intimate relationships (20–22). Marital breakup leaves vulnerable males more exposed to solitude and to a higher suicide risk (23, 24). The increased use of social support by women (20, 25, 26), having family responsibilities (27) and being a mother (28), being pregnant (29), and raising young children (30), has been reported as protective factors for women. Other developmental risk factors, more often observed among men, include aggression, risk taking and impulsivity, which tend to peak during the period from early to mid-adulthood (31–34).

Other studies examining proximal or precipitating risk factors suggest that many stressful events are consistent with socialized gender roles, such as events that threaten one's social status or have an impact on self-esteem, identity, or well-being (35–38). Several specific events have been identified as triggers for suicidal behaviors among males, such as the end of a relationship (39), difficulties at work or the loss of a job (37), and suicide attempts (40). One of the most robustly identified proximal variables is the availability of more violent and lethal means of suicide resulting in more fatalities among men (41, 42).

Impact of Cumulative Stressful Events Over the Life Course

The differential suicide rate among women and men is mostly explained by isolated risk or protective factors (20, 25, 26) which are rarely specific to suicide outcomes. However, integrative understandings suggest that the complex process that contributes to suicidal behavior may differ between genders (43), suggesting that men progress through the suicidal process faster than women. Explanations from social theories of role construction (28, 44) suggest that difficult transitions over the life course by experiencing loss of social status, social failures or defeat, relationship breakdowns, not achieving a conventional socially structured life or violation of expectations in regards to the timeline in which normative events should happen, tend to shape response patterns to stress. This may in turn increase suicide vulnerability (22) by threatening an individual's sense of competence.

Research methodology should take into account the impact of cumulative stress that influences risk trajectories over the life course (45). In an individual-environment interaction perspective, one must consider that exposure to stressful events may not occur at random and/or have the same impact whatever the circumstances. It is worth noting that risks or protective factors are often identified among subgroups and may not have the same benefit or harm universally (43, 46). As well, personality factors may also be the hidden causes of stressor exposure, as individuals may be more exposed to conflicts or breakdowns in relationships emerging from instability, fear of abandonment or impulsive behaviors (47, 48). Stressful events themselves may trigger a cascading effect, setting in motion other events resulting in more vulnerability to suicide (49–51). Constantly changing social and environmental factors may impact functioning and shape health disparities along gender lines (52).

The concept of allostatic load stems from biological research to explain the consequences of chronic or repeated adverse experiences by postulating the wear and tear of stress-regulatory mechanisms (45). Allostatic load may lead to illness (53) and compromises health, not only because of the stress experiences themselves, but also because of damaging behaviors and maladaptive coping strategies that frequently accompany chronic stress states (53). Research on the association between stressful life events and health (7) showed empirical substantiation for the role of stressors in disease risk and ultimately on suicide vulnerability.

By considering the consequences of cumulative adverse events under the notion of burden of adversity, this paper aims to identify the differences in life courses toward suicide between men and women.

METHODS

Participant Recruitment

Through an ongoing partnership with the Quebec coroner's office, our research group is constantly recruiting family members of individuals who recently died by suicide in the province of Quebec (Canada). We report on 303 suicide cases: 213 men and 90 women. Data was retrieved from participants recruited in the provinces of Québec and New Brunswick, Canada, across four different research projects conducted between 2003 and 2012. In each project, the protocol was established as follows: after the family received an introductory letter from the coroner's office, a research assistant followed up

with a telephone call (∼70% of the close relatives referred by the coroner's office agreed to participate in the study), and, if participants agreed to participate, an appointment was made for the interview. This successful partnership has enabled our research group to pursue recruitment of suicide cases for all these studies.

Procedure for Data Collection

The interviews occurred between 6 and 18 months after the death, when written informed consent was signed. Skilled investigators conducted two in-depth interviews with each informant which lasted 2 to 3 h on average and comprised three sections: exploration of socio-demographic characteristics; psychopathological investigation with the administration of the SCID I (54) and SCID II (55); and inventory of adverse life events [life trajectory calendar method (56)]. Personal written documents belonging to the deceased and the informants, such as photos, agendas and diaries, were also used if available as memory triggers during the interview. After the interview process, medical and psychosocial files of the deceased were also examined to corroborate the information on the presence of adversity and mental health diagnoses during specific periods of life. These medical and psychosocial reports were obtained upon signed agreement of family members. Afterwards, a case vignette containing a summary of all clinical information was drafted and submitted to a panel of experts. This panel established a consensus rating every 5 years throughout the life course in regards to a summary variable identified as "burden of adversity" ranging in a six-point scale from severe to low adversity.

The protocol received approval from the ethics review boards of the Douglas Mental Health University Institute and the University of Québec in Outaouais (Nos. 2,362; 2,533; 2,608; 2,856). All informants signed a consent form.

Measurements

Interview to Determine Post-mortem Diagnosis

The post-mortem diagnoses were assessed using a validated follow-back method (57, 58), using a semi-structured questionnaire, the Structured Clinical Interview for DSM-IV, for both Axis I and Axis II disorders (SCID I and II) (54, 55), with an informant who had known the deceased well. This procedure has been described in other papers (59, 60). A series of studies over the past decade have established the concordance of DSM diagnoses generated by informant report with chart diagnoses and the psychological autopsy method have been proven with good reliability (58, 61, 62). Categorical inter-rater reliability revealed moderate to excellent inter-rater agreement of the Axis I disorder, while most categorically and dimensionally measured personality disorders showed excellent inter-rater agreement (63).

Interview to Retrace the Life Trajectory

To collect all the possible life events that the participants had encountered, we carried out semi-structured conversational explorations inspired from life calendar narrative methods (64–66). The interviews explored events occurring during the life course and type of events occurring in different qualitative spheres of life. During the interviews, a "life calendar" explored nine clearly described conceptual spheres: parent-child relationship and early adversities; affective life sphere; procreation and family life; relationship with siblings and extended family; academic difficulties; professional difficulties; social life and relational difficulties; living conditions; and losses/personal adversity such as legal and financial difficulties. For each sphere events possibly occurring were investigated. For example, in the sphere of parent-child relationship and early adversities, events such as maltreatment, physical, and sexual abuse, negligence, tension in parent child relation were investigated. In the affective life sphere, relational difficulties with spouse such as violence, multiple breakups, etc., were investigated.

The method explores major events which may occur at a specific age for each sphere and assesses the severity and duration of each event chronologically. The integration of a visual calendar helps with the recall of events (the horizontal axis represents the passing of time and the vertical axis, the specific spheres in which events occurred). Participants were also encouraged to access other visual aids to help them recall events during the interview process.

The full list of events was inspired from widely accepted comprehensive interview guides, such as the Life History Calendar (67) or the or the Childhood Experience of Care and Abuse (CECA) (68), which we completed from a scoping review of the main self-administered life adversity questionnaires. Based on our extensive practice of narrative explorations, the resulting adversity statements were refined to minimize overlaps between items while ensuring the broadest coverage of possible significant stressful experiences.

After the interviews, clinical case histories (case vignettes) were drafted. The vignettes took into account information from the socio-demographic questionnaire, the SCID I and II, the information from hospital files and information gathered with the life trajectory questionnaire. While narrative methodology is largely used qualitatively, it can also be used in quantitative and mixed methods studies (69) with data transformation.

Data Transformation Into a Score of Burden of Adversity

Qualitative data collected from the narrative interviews was transformed into a summary variable identified as "burden of adversity." This summary variable was built to reflect the "contextual threat" weighting on the individual, which is based on the morbidity burden or low disease burden approach (70, 71) used to identify the overall morbidity that affects health. It is also related to the concept of allostatic load, which links psychosocial stress (with the neurobiological and genetic dimensions) and its impact on mental disorders and suicide (45, 69).

To estimate the level of burden of adversity, a panel of clinicians and researchers analyzed the life trajectory vignettes and evaluated the relative adversity weight within the respondent's developmental circumstances. Based on this evaluation, experts gave, for each 5-year interval, an overall burden of adversity rating ranging from low (rating of 1 or 2)

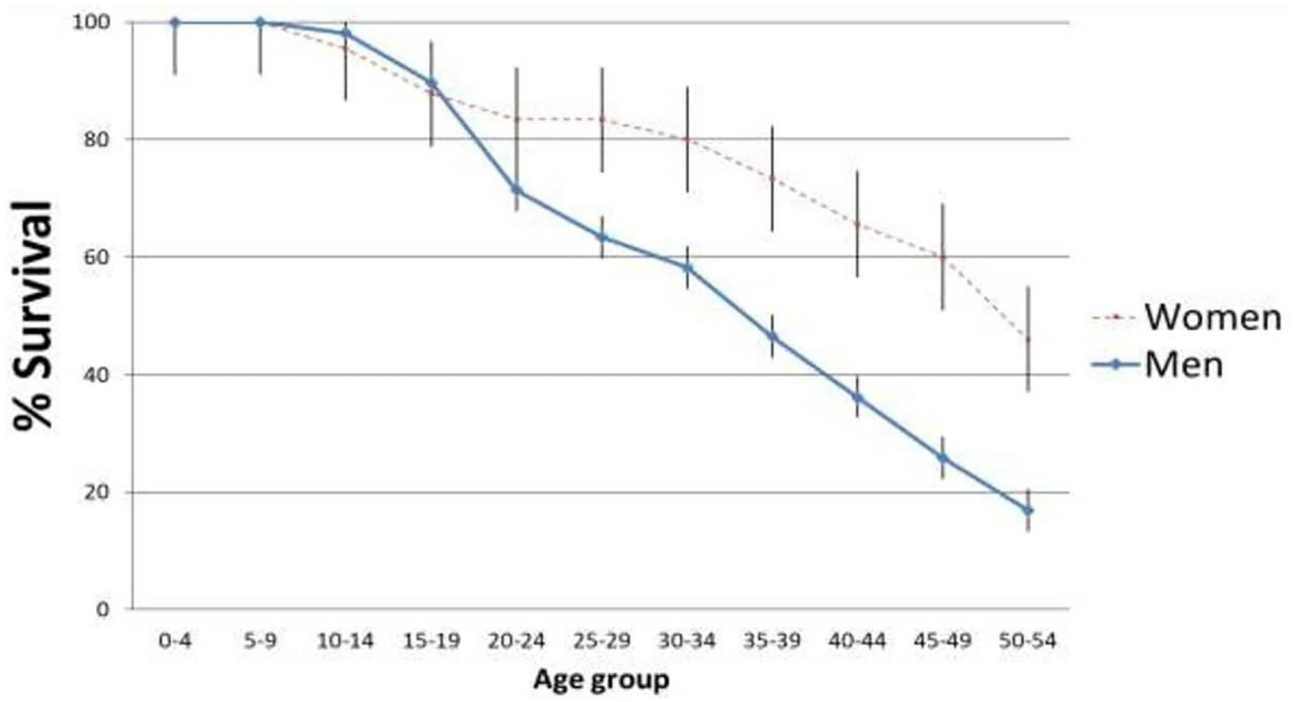

FIGURE 1 | Survival analysis of groups in regards to the occurrence of death. Vertical bars corresponds to standard errors.

to moderate (3 or 4) to severe (5 or 6). For example, a severe rating (5 or 6) would entail sustaining major adversity, such as being a victim of physical and sexual violence persistently and having other constant adversities in other spheres of life during the same 5-year period. A low rating (1 or 2) would be characterized as having occurrences of adversities confined to one or two spheres of life, while sustaining protective factors in other spheres. Case reference logs were written and used to maintain the same level of evaluation across all cases. In each case, the evaluators independently coded each 5-year period before reaching a consensus through discussion. In studies from our group, the intra-pair agreement for each 5-year segment ranged from 97 to 76%, where the lowest intra-group agreement was in the 0 to 4-year age group (56). This methodology has previously been presented in other papers in great detail (59).

Analytical Strategy

To examine the characteristics obtained from the life trajectory questionnaire that distinguish gender along gender lines, we grouped questionnaire items into themes, such as being a victim of early violence, negligence, intimate relationship difficulties, academic difficulties, social difficulties, etc., which were themselves representative of the different spheres. These thematic characteristics were simply scored as present or absent (dichotomous variables). A series of contingency table analyses were conducted to determine the association of each individual theme separately in relation to the gender. Effect size was given as odd ratios (OR).

Burden of adversity trajectory data were examined *via* latent growth curve analysis (LGCA) in MPLUS based on the structural equation modeling framework with gender as the group variable. In testing growth models with discrete time survival analysis (DTSA) (joint model, taking into account the time-dependent risk of dying) or without DTSA, quality of the different models was estimated by the following information criteria: Akaike (AIC) and Bayesian (BIC). Lower AIC and BIC values indicate a better-fit model. A binary covariate (deceased/living) appeared in the joint model only, for every time point in the DTSA part. There was no covariate in the growth model without DTSA. The latent growth parameters intercept, linear and quadratic terms of women and men were compared by Z-score of differences. Specific age-period data points were compared by a *t*-test. Socio-demographic data was analyzed by *t*-test or contingency tables where appropriate and Chi square values given. Survival Analysis was determined by Kaplan-Meier curves and confidence intervals at each age period. Furthermore, a Chi square logrank calculation was applied to compare gender survival curves.

RESULTS

Socio-Demographic and Survival Data

Among the 303 suicide cases, 70% were men, with a mean age at the time of death for women was 45.5 (SD = 17.3), and that of men was 38.4 (SD = 15.4). Survival analysis (**Figure 1**) clearly indicates an earlier occurrence of death in men and a lower median survival time (30–39 vs. 40–49). Kaplan-Meier curves and confidence intervals of each time point are represented in

Figure 1. A logrank analysis revealed a significant Chi-square value of 10.17 ($p < 0.005$), indicating a sharp difference in pattern for gender. All points beyond the 15–19 age period was significantly different for men and women and there was some form of parallelism in the curve shapes after 24 years of age.

Based on the socio-demographic information (**Table 1**), at the time of death, men and women had a similar profile with respect to marital status and paid work habits. Differences appeared in other areas of comparison. Although, approximately half of the subjects (both genders) had no children, a higher percentage of women had two or more children compared to men (42.2 vs. 28.2%; $\chi^2 = 5.71$, $p < 0.05$). A greater proportion of men were self-supported (45.5 vs. 28.8%; $\chi^2 = 7.26$, $p < 0.05$), while a greater proportion of women were State-supported (25.6 vs. 8.9%; $\chi^2 = 14.66$, $p < 0.001$) and had obtained a University-level degree (22.2 vs. 10.8%; $\chi^2 = 6.78$, $p < 0.01$).

Mental Health Data

Table 2 compares life and active psychiatric diagnoses between men and women. Although, the proportion of individuals with anxiety, affective and psychotic disorders was similar between genders, alcohol-related disorders were more prominent in males (life: 52.1 vs. 30.0%, $\chi^2 = 12.47$, $p < 0.001$; active: 45.1 vs. 18.9%, $\chi^2 = 18.54$, $p < 0.001$). Men were also more likely to have two or more Axis I disorder (54.5 vs. 26.7%, $\chi^2 = 19.66$, $p < 0.001$), a conduct disorder (12.7 vs. 2.2%, $\chi^2 = 7.99$, $p < 0.01$) and two or more Axis II disorders (23.5 vs. 10.0%, $\chi^2 = 7.32$, $p < 0.01$) than women.

Life Events and Burden of Adversity Data

When considering life events, men and women differed on certain aspects of specific life spheres (**Table 3**). Results indicate that both groups suffered important adversity between the age of 0 and 19 years old, such as sexual/physical or psychological violence. Ranging between 19 and 37% for women, increasing from ages 5 to 14, then decreasing slightly. For men, the sexual/physical or psychological violence ranged between 22.5 and 27% over the course of different age periods from 0 to 19 years old. Another important adversity is the presence of discipline/neglect tension in the relationship with parents, ranging from 50 to 76% for women and from 47 to 69% for men. Although, there was a decrease in neglect and violence in adult years, women were more prone to be victims of neglect in the 25–29 age group (ORs significantly lower than 1). During youth, men encountered more academic difficulties than women (ages 10–14, 32.4 vs. 17.8%), and were more prone to legal entanglements (ages 15–19, 16.5 vs. 5.8%). Women are approximately three times more likely to encounter relational difficulties with their spouse until 44 years of age.

At ages 25–29, women incur more discipline, neglect and tension with their own children, in parent-child relationships, than men (34.7 vs. 16.4%). As adults, men continue to have greater legal difficulties until 35 years of age. During the period between 40 and 44 years old, one third of men experience financial difficulties.

In testing growth models with or without discrete time survival analyses in MPLUS, the model without discrete time survival analysis showed lower values of AIC (5130.280 vs. 5629.895) and BIC (5204.555 vs. 5719.025), so the model without was adopted. On examining the burden of adversity trajectories, both genders exhibited significant gradual increases over age periods (**Figure 2**, **Table 4**). Overall, the burden of adversity was similar except for the 5–9, 25–29 and 30–34 age periods, where a significant difference appeared between genders [t-test = 2.13 ($p < 0.05$), 2.16 ($p < 0.05$), and 3.08 ($p < 0.005$), respectively]. Growth model parameter analysis (**Table 2**) results indicate that a significant intercept, linear, and quadratic terms exist in both genders' trajectory, revealing a V-shape deviation in the burden of adversity values in mid age periods. On comparing the different term values of genders, no significant z-values appeared ($Z = 1.56$, -0.30, and 0.16 for intercept, linear, and quadratic terms, respectively).

TABLE 1 | Socio demographic characteristics.

	Women $n = 90$	Men $n = 213$	Ch^2	*P*-value
Marital status				
Married	28 (31.1%)	63 (29.6%)	0.07	NS
Dating	35 (38.9%)	99 (46.5%)	1.48	NS
Separated/divorced/ widow(er)	27 (30.0%)	49 (23.0%)	2.65	NS
Unknown	0 (0%)	2 (0.9%)		
Number of children				
0	39 (43.3%)	111 (52.1%)	1.95	NS
1	13 (14.5%)	39 (18.3%)	0.66	NS
2+	38 (42.2%)	60 (28.2%)	5.71	<0.05
Unknown	—	3 (1.4%)		NS
Education				
High School not completed	2 (2.2%)	17 (8.0%)	3.57	NS
High School	52 (57.8%)	140 (65.7%)	1.72	NS
Collegey	16 (17.8%)	33 (15.5%)	0.24	NS
University	20 (22.2%)	23 (10.8%)	6.78	<0.01
Income				
Self-supported	26 (28.8%)	97 (45.5%)	7.26	<0.01
From family member	18 (20.0%)	51 (23.9%)	0.56	NS
From State	23 (25.6%)	19 (8.9%)	14.66	<0.01
Unknown/missing	23 (25.6%)	46 (21.6%)		
Living arrangements				
Lives alone	37 (41.1%)	65 (30.5%)	3.18	NS
Lives with a family member	29 (32.2%)	89 (41.8%)	2.43	NS
Shares with room-mate/transition home	5 (5.6%)	17 (8.0%)	0.55	NS
Other	19 (21.1%)	42 (19.7%)		
Paid work				
Yes	48 (53.3%)	119 (55.9%)	0.16	NS
No	31 (34.4%)	76 (35.7%)	0.04	NS
Unknown	11 (12.2%)	18 (8.5%)	1.04	NS

TABLE 2 | Presence of psychiatric diagnoses current and life course.

Disorder	Men (213)		Women (90)		Chi^2	*P*-value
	N	%	*N*	%		
Anxiety (life)	31	14.6	14	15.6	0.05	NS
Anxiety (active)	23	10.8	8	8.9	0.25	NS
Affective (life)	87	40.8	38	42.2	0.05	NS
Affective (active)	137	64.3	55	61.1	0.28	NS
Psychotic (Life)	15	7	6	6.7	0.01	NS
Psychotic (active)	16	7.5	6	6.7	0.07	NS
Alcohol (life)	111	52.1	27	30	12.47	<0.001
Alcohol (active)	96	45.1	17	18.9	18.54	<0.001
Conduct disorder (before 18 years of age)	27	12.7	2	2.2	7.99	<0.01
0 Axis I diagnosis	23	10.8	13	14.4	0.8	NS
1 Axis I diagnosis	64	30	45	50	10.94	NS
2+ Axis I diagnoses	116	54.5	24	26.7	19.66	<0.001
Unknown	10	4.7	8	8.9	1.99	NS
Personality disorder	87	40.8	27	30	3.17	NS
0 Axis II diagnosis	83	39	26	28.9	2.79	NS
1 Axis II diagnosis	53	24.9	28	31.1	1.25	NS
2+ Axis II diagnoses	50	23.5	9	10	7.32	<0.01
Unknown	27	12.7	27	30		

DISCUSSION

Socio-Economic Disparities

Survival analysis shows that men have a lower life expectancy than women. Compared to men, more women report living alone, having lower income and being financially supported by State income, even if more women attain a higher level of education. Results of our study indicate that almost half of the women (43%) and more than half of the men (52%) did not have children, while 42% of those mothers and 28% of fathers had two children or more. Research at the population level indicates that parenthood among 25 to 44-year-olds is associated with a lower suicide risk in both men and women, but to a larger extent among women, and particularly in parents with two or more children (72). However, for vulnerable individuals, having children may not always be protective, and other cumulative events may impact on their feeling of being a burden to their families.

The importance of socio-demographic factors in suicide research, except for age and gender, is often overlooked. In the present study, women seem to be at a disadvantage regarding some socio-demographic variables (such as work, income, living alone, parental responsibilities). Socio-demographic variables such as education, access to well-paying jobs and access to daycare for children are important determinants of health (73). Conversely, research indicates that early socioeconomic adversity contributes to poor mental health trajectories, disrupt successful transition into adulthood, and endangers social, academic, and occupational attainment (74). Several studies do make the case for socio-demographic disparities between genders (75) which contribute to the overall burden of adversity by increasing the probability of cumulative risk factors. In this study, while women have more risk factors in regards to socio-demographic variables, this fact doesn't translate into mental health disparities, when compared to what is observed among men.

Mental Disorder Differences

Our results didn't show inter-gender differences in depressive disorders. However, men display overall more frequent mental disorders than women and are three times more likely to have alcohol/drug abuse problems. In early life, they also exhibited more frequent conduct disorders, which may signal differential psychopathological pathways toward suicide between men and women with more internalizing of problems in girls and externalizing of problems in boys (33). However, it is important to note the ongoing debate as to the prevalence, and lack of appropriate gender criteria for conduct behavior may lead to underreporting conduct disorders in females.

Results also indicate that men are more prone to alcohol misuse during the life course and in the months prior to death. Researchers found alcohol abuse and drug use to be the most common factor among suicide cases (76). Alcohol abuse may generate a succession of events including professional and romantic failures, difficulties in social relationships, distress and mental health problems; trigger adverse life events; and progressively lead to an earlier exhaustion of adaptative mechanisms. Compounded with early mental health difficulties (such as conduct disorders), men display, during their adult life, more comorbid psychiatric disorders than women. The presence of early externalized conduct (32), and an ongoing abuse of drugs/alcohol, is seen as a distal and proximal risk factor

TABLE 3 | Life events: comparison between man and women.

Life events ***N* = 303**	**Men (*n* = 213)**		**Women (*n* = 90)**		**OR**	**$CI_{95\%}$**	***p***
	n	**%**	***n***	**%**			
Age 0–4	101	47.4	45	50.0	1.05	0.686–1.620	NS
Discipline/neglect/ tension in parent-child relationship							
Sexual abuse/physical- psychological violence of S	48	22.5	17	18.9	0.84	0.457–1.536	NS
Age 5–9	(*n* = 213)		(*n* = 90)				
Discipline/neglect/ tension in parent-child relationship	117	54.9	58	64.4	1.17	0.787–1.750	NS
Sexual abuse/physical- psychological violence of S	57	26.8	28	31.1	1.16	0.694–1.950	NS
Academic difficulties	46	21.6	14	15.60	0.72	0.377–1.376	NS
Relational difficulties	0	0	0	0	–	–	NS
Age 10–14	(*n* = 213)		(*n* = 90)				
Discipline/neglect/ tension in parent-child relationship	129	60.6	68	75.6	1.25	0.850–1.830	NS
Sexual abuse/physical- psychological violence of S	52	24.4	33	36.7	1.5	0.910–2.479	NS
Mental health problems	46	21.6	18	20.0	0.93	0.505–1.684	NS
Academic difficulties	69	32.4	16	17.8	0.55	0.302–0.997	<0.05
Relational difficulties	7	3.3	4	4.4	1.35	0.386–4.734	NS
Legal difficulties	12	5.6	2	2.2	0.39	0.087–1.798	NS
Age 15–19	(*n* = 212)		(*n* = 86)				
Discipline/neglect/ tension in parent-child relationship	125	59.0	60	69.8	1.18	0.796–1.760	NS
Sexual abuse/physical- psychological violence of S	49	23.1	29	33.7	1.46	0.865–2.462	NS
Mental health problems	72	34.0	20	23.3	0.68	0.393–1.193	NS
Academic difficulties	58	27.4	15	17.4	0.64	0.343–1.186	NS
Professionnal difficulties	15	7.1	3	3.5	0.49	0.139–1.746	NS
Relational difficulties	44	20.8	25	29.1	1.4	0.807–2.430	NS
Financial difficulties	23	10.8	3	3.5	0.32	0.094–1.100	NS
Legal difficulties	35	16.5	5	5.8	0.35	0.133–0.929	<0.05
Age 20–24	(*n* = 191)		(*n* = 79)				
Discipline/neglect/ tension in parent-child relationship	64	33.5	30	38.0	1.13	0.683–1.881	NS
Mental health problems	121	63.4	48	60.8	0.96	0.627–1.467	NS
Professionnal difficulties	21	11.0	7	8.9	0.81	0.329–1.972	NS
Relational difficulties	62	32.5	25	31.6	0.97	0.572–1.662	NS
Relational difficulties with spouse	22	11.5	25	31.6	2.75	1.463–5.159	<0.005
Financial difficulties	33	17.3	8	10.1	0.59	0.259–1.325	NS
Legal difficulties	35	18.3	53	3.8	0.21	0.062–0.693	<0.01
Age 25–29	(*n* = 152)		(*n* = 75)				
Discipline/neglect/ tension in parent-child relationship	25	16.4	26	34.7	2.11	1.140–3.900	<0.05
Mental health problems	87	56.2	45	60.0	1.05	0.666–1.650	NS
Professionnal difficulties	17	11.2	12	16.0	1.43	0.650–3.150	NS
Relational difficulties	35	23.0	18	24.0	1.04	0.554–1.961	NS
Relational difficulties with spouse	24	15.8	24	32.0	2.03	1.080–3.804	<0.05
Financial difficulties	24	15.8	9	12.0	0.76	0.336–1.716	NS
Legal difficulties	30	19.7	9	4.0	0.2	0.060–0.686	<0.02
Age 30–34	(*n* = 135)		(*n* = 72)				
Mental health problems	78	57.8	45	60.5	1.08	0.679–1.723	NS
Professionnal difficulties	19	14.1	8	11.1	0.79	0.329–1.892	MS
Relational difficulties	23	17.0	14	19.4	1.14	0.354–2.352	NS
Relational difficulties with spouse	22	16.3	27	37.5	2.3	1.223–4.327	<0.01
Financial difficulties	29	21.5	12	16.7	0.78	0.374–1.612	NS
Legal difficulties	19	14.1	2	2.8	0.2	0.045–0.871	<0.05
Age 35–39	(*n* = 124)		(*n* = 67)				
Mental health problems	79	63.7	45	67.2	1.05	0.658–1.690	NS
Professionnal difficulties	17	13.7	11	16.4	1.2	0.530–2.704	NS

(Continued)

TABLE 3 | Continued

Life events $N = 303$	Men ($n = 213$)		Women ($n = 90$)		OR	$CI_{95\%}$	p
	n	%	*n*	%			
Relational difficulties	29	23.4	14	20.9	0.89	0.442–1.810	NS
Relational difficulties with spouse	25	20.2	30	44.8	2.22	1.209–4.080	<0.01
Financial difficulties	32	25.8	14	20.9	0.81	0.404–1.622	NS
Legal difficulties	22	17.7	8	11.9	0.67	0.284–1.594	NS
Age 40–44	($n = 99$)		($n = 62$)				
Mental health problems	64	64.6	42	71.2	1.1	0.664–1.825	NS
Professionnal difficulties	16	16.2	10	16.9	1.05	0.447–2.462	NS
Relational difficulties	22	22.2	16	27.1	1.22	0.594–2.510	NS
Relational difficulties with spouse	18	18.2	24	40.7	2.24	1.121–4.465	<0.05
Financial difficulties	35	35.4	8	13.6	0.38	0.167–0.882	<0.05
Legal difficulties	14	14.1	4	6.8	0.48	0.151–1.525	NS
Age 45–49	($n = 77$)		($n = 54$)				
Mental health problems	60	77.9	42	77.8	1	0.590–1.689	NS
Professionnal difficulties	13	16.9	7	13.0	0.77	0.287–2.051	NS
Relational difficulties	16	20.8	15	27.8	1.34	0.609–2.932	NS
Relational difficulties with spouse	16	20.8	16	29.6	1.43	0.657–3.096	NS
Financial difficulties	25	32.5	11	20.4	0.63	0.285–1.382	NS
Legal difficulties	11	14.3	4	7.4	0.52	0.157–1.715	NS
Age 50–54	($n = 55$)		($n = 42$)				
Mental health problems	41	74.5	35	83.3	1.12	0.611–2.045	NS
Professionnal difficulties	12	21.8	4	9.5	0.44	0.131–1.450	NS
Relational difficulties	8	14.5	5	11.9	0.82	0.250–2.683	NS
Relational difficulties with spouse	13	23.6	10	23.8	1.01	0.403–2.520	NS
Financial difficulties	18	32.7	9	21.4	0.65	0.267–1.603	NS
Legal difficulties	10	18.2	6	14.3	0.79	0.264–2.334	NS

Parent-child relationship and early adversities we regrouped specific events into two categorie.
(i) problems with discipline/neglect/tension in the parent child relationship including incoherent rules, lack of discipline, role reversal, affective distance, parental mental health difficulties, witnessing parental violence.
(ii) sexual abuse/physical and psychological violence.
Mental health problems included variables such as Axis I diagnosis, personality disorder, alcohol and drug abuse, number of suicide attempts, other problems of mental health, and psychiatric hospitalization.
Relational difficulties with spouse include psychological, physical and sexual violence, breakups, infidelity, jealousy, control over one partner, entrapment, etc.
Relational difficulties included variables such as conflict with peers, social isolation, bad influence from peers, separation or loss of a friend, etc.
Academic difficulties included events such as: underachievement, failure in school, behavioral problems in school, being a bully, etc.
Legal problems included all types of behaviors resulting in negative events with the justice system.
Financial losses included bankruptcy, financial hardships etc.

for suicide (46). Resulting interpersonal difficulties and social isolation further fuel the spiral of adversity.

A prior history of suicide attempts is considered one of the most robust predictors of completed suicide. The presence of one or more suicide attempts is an important factor for subsequent death (77). In a Swedish study, researchers found a mean of 3.5 suicide attempts before the eventual suicide (78). Coherent with these observations, our data indicates that 45% of the men and 28% of the women had attempted suicide at least once in their life course.

Stressful Events and Burden of Adversity

The data indicates that both groups suffered important early adversity between the ages of 0 and 19 years old. Although, both genders were exposed to longstanding and severe life problems, likely to have contributed to suicide vulnerability, the nature of this adversity differed between men and women. For women, the parent/child relationship adversities evolved in some way into interpersonal adversities with their marital partner/spouse and, later on, into difficulties in relationships with children. As for men, the adverse events are to a larger degree socially exposed events such as academic difficulties (10–14 years old), downstream legal difficulties (between 15 and 34 years old) and financial difficulties (between 40 and 44 years old) compounded with alcohol misuse. From a social perspective, women who are victims of violence experience myriad devastating consequences in regards to health, well-being, quality of life, and impact on their participation and engagement in society at large (79).

Results indicate that life trajectories between men and women differ by the number and nature of adverse events, that burden of adversity over the life course is slightly higher for women at almost all periods of life, except for a merging period around

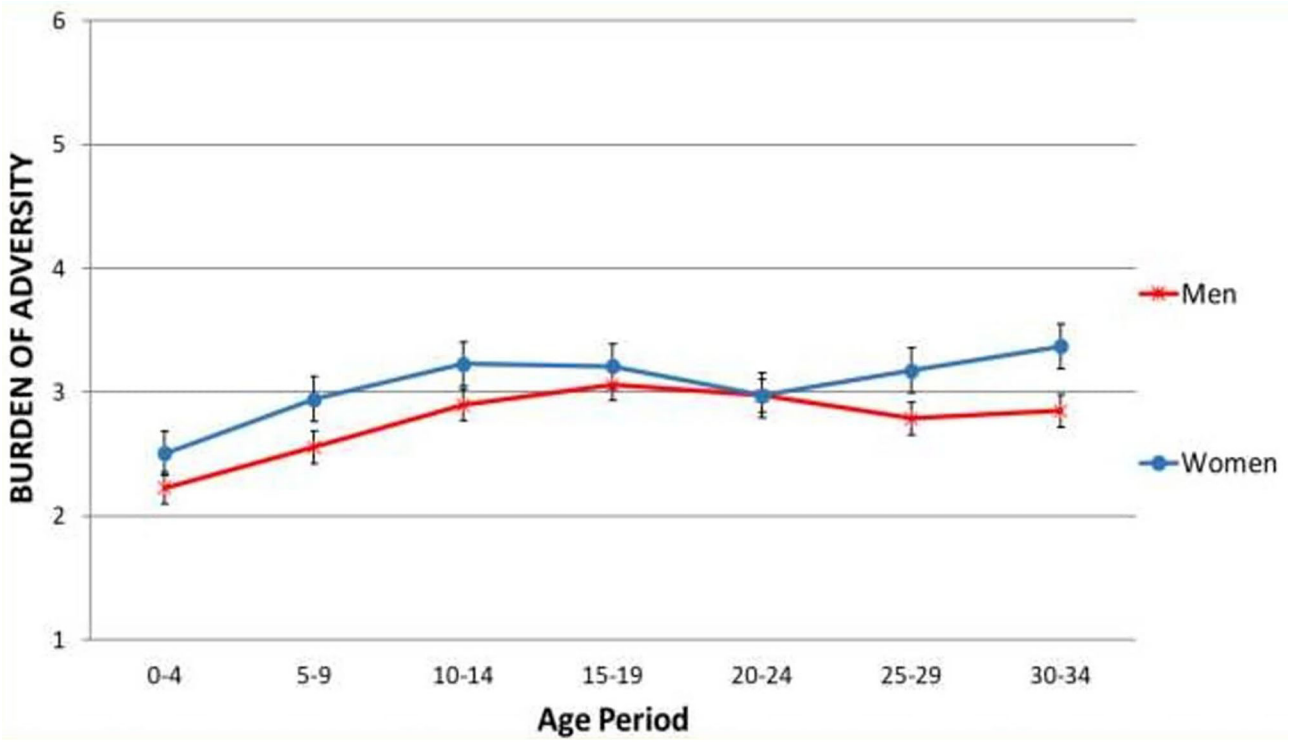

FIGURE 2 | Growth model analysis representing the burden of adversity trajectories. Vertical bars corresponds to standard errors.

the early twenties. The burden of adversity remains low to moderate (score of 2 to 3) throughout the life course. A number of participants did experience severe adversity, having lived through extreme and traumatic events at some period of their lives. When aggregating all scores of "total burden of adversity" in order to obtain a comparison between groups, we lose the intra-group differences.

Suicide vulnerability is explained through complex mechanisms and interactions and a number of developmental risk factors lead to the presence of mental disorders and adverse life events as proximal factors leading to the suicidal outcome. However, the complexities of theses mechanisms (impulsivity traits, attachment, internalization vs. externalization, emotional regulation, etc.), may be difficult to observe or confirm, especially from retrospective research with informants. In the present research, those developmental mechanisms were not evaluated, but we may suspect the presence of an internalization or externalization mechanism which could be accounted by the specific types of adverse events occurring among men and women. We found men to have more alcohol, conduct, and personality disorder compared to women and men were more prone to negative academic, legal, financial problems compared to women. Other published data indicate that externalizing spectrum disorders (ESDs), are known to be associated to academic underachievement, underemployment, criminal behavior, incarceration, and other adverse outcomes (80). In comparison, the presence of interpersonal difficulties observed among women, may indicate the presence of internalization behaviors from an early age. A longitudinal study in a community sample of mistreated adolescents found that internalizing symptoms were predictive of dating aggression (81). The link between symptoms of distress and internalizing symptoms among females may be a gender specific consequence of an inability to effectively cope with affective distress (82). Data from other research (83), have shown that child abuse is associated with either internalizing or externalizing behaviors for both males and females. The impact of these early adversities may put into motion complex developmental mechanisms, along the lines of internalization or externalization behaviors which may have a gendered specific component and may generate different types of negative events across the life cycle.

These findings suggest that gender is an important variable to explore, since the lives of women and men are characterized by different trajectories of adversities (74) and a higher rate of suicide mortality among men. Future research should tackle the challenge of collecting and analyzing a broad range of measures from biological to psychosocial dimension at multiple time points in order to better understand the mechanisms by which certain individuals may be more resistant to stressful live adversity (75).

Limitations and Methodological Considerations

Firstly, this sample may not be representative of all suicide cases due to a selection bias. However, to our knowledge, it's the largest

TABLE 4 | Burden of Adversity trajectories curve parameters.

Parameters (SE)	Men	Women
Intercept	2.224 (0.089)[a]	2.586 (0.169)[a]
Linear change	0.347 (0.042)[a]	0.275 (0.075)[a]
Quadratic change	−0.026 (0.007)[a]	−0.019 (0.011)

[a]$p < 0.001$.

sample of suicide for which in-depth collection of adverse life events has been carried out so far.

Secondly, in this paper, we proposed to examine an aggregated pathway for women and men in order to compare the main difference between the groups, which may have masked intra-group differences. Eventually, research should concentrate on divergent pathways and accompanying growth models, which would capture more diversified developmental stages.

Thirdly, using a follow-back and life calendar method to assess the presence of mental health symptoms and life events by third parties entails recall biases or imprecise information and underreporting (84). Recall biases when collecting data through proxy-based, retrospective explorations of suicide trajectories have been frequently discussed in the literature (85). Informants may remember more easily mental health symptoms or events that are observable, e.g., externalized behaviors vs. internalized behaviors. Even good informants may not have been aware of a number of mental health symptoms or personal adverse events. By definition, life description will mostly be based on publicly known events. As well, the events reported by informants are usually marked or moderate in intensity, which is why they are able to remember specific events. Another possible bias may have been introduced by not concealing decedent gender form panel. The severity of some events may have been perceived differently in regards to gender, but the overall adversity score for each 5 years period were based on a coding book based on the presence of types of adversity their numbers and duration over the 5-year period.

While keeping these limitations in mind, numerous authors suggest that narrative-rating instruments provide large gains in reliability and validity in the measurement of major stressful events (50, 65). Lin et al. (86) indicate that the recall error usually reflected underreporting rather than overreporting. In previous publications, we provided detailed descriptions of the measure we took to minimize these biases (59, 87). In brief, we used semi-structured and conversational-style interviews, searched for pre-specified adverse life events, used memory anchors, stimulated recall efforts with calendars and photos and cross-checked collected data from various sources. However, the possibility of remaining reporting filters and omissions cannot be completely discounted.

CONCLUSION

Results indicate the importance of recognizing differential adverse events in the lives of women and men which develops onto longstanding and severe problems creating difficulties in relating to close relationships and society in large. From a public health perspective, it is important to better identify the severe adverse events occurring during key developmental periods, from childhood (being a victim of violence and neglect), to adolescence (academic difficulties, social isolation), to adulthood (misuse of alcohol/drugs, mental health problems, violence, interpersonal difficulties), and implement specific targeted preventive strategies. Results from this study suggest that the nature of the events during adolescence and adulthood should favor the detection of vulnerability, especially when the adversities are of public nature. These adversities, especially if they are repetitive, may be witnessed by others over the life course, and psychosocial or mental health services should be offered and provided. From a public health perspective, access to psychosocial and mental health services and, more specifically, addressing the social acceptability of seeking these services should be part of an ongoing effort in all institutional structures (schools, work places, households) and should be "tucked in" every health strategy, as a way of decreasing downstream mental health problems and vulnerability to suicide.

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 Douglas Mental Health University Institute and the University of Québec in Outaouais (Nos. 2362; 2533; 2608; and 2856). All informants signed a consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS conceived the original idea, conducted the literature review, set the conceptual basis of the model, collected the data, and lead the writing of the manuscript. GB did the statistical analyses and helped with the writing of the manuscript. C-ÉN reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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The Role of Perceived Social Support in the Association Between Stressful Life Events and Suicidal Behavior

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Background: Suicide is a serious public health concern for which there have been well-established protective and risk factors reported in literature. There is a lack of evidence on the indirect effects of other variables on these factors. Specifically, the association between stressful life events and suicidal behavior may be affected by perceived social support, but its role in this association is largely uninvestigated.

Objectives: Thus, this paper aims to explore the role of perceived social support in the association between stressful life events and suicidal behavior. Perceived social support will be explored as a mediator and as a moderator in this association.

Methods: Data were obtained from the Determinants of Suicidal Behavior Conventional and Emergent Risk (DISCOVER), a study conducted to identify risk factors of suicidal behavior. The study participants are individuals with suicide attempts admitted to hospital. Participants ($n = 343$) were recruited from hospital setting. Suicidal behavior was measured using two outcomes (1) the occurrence of a suicide attempt (2) level of suicide intent as measured by the Pierce Suicide Intent Scale. Perceived social support was measured using the Sarason Social Support Questionnaire.

Results: Stressful life events were significantly associated with suicide attempts (OR 1.440, 95% CI 1.440, 1.682, $p < 0.001$) and perceived social support (B −0.785, 95% CI −1.501, −0.068, $p = 0.032$). There was no significant mediation effect by perceived social support in the association between stressful life events and suicide attempts (Sobel's test statistic 1.64, $p = 0.100$). Perceived social support did not moderate the relationship between stressful life events and suicide attempts [(OR 1.007, 95% CI 0.987, 1.027, $p = 0.514$] or the relationship between stressful life events and level of suicidal intent (B −0.043, 95% CI −0.132, 0.046, $p = 0.343$).

Conclusion: Stressful life events are associated with increased risk of suicide attempts. The study also identified an inverse relationship between stressful life events and perceived social support. These associations were independent of perceived social

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support. This study highlights the effects of stressful life events on suicide risk is not affected by perceived social support, requiring further investigation into measures to reduce the impact of social stressors on people with risk of suicide.

Keywords: suicide, mediation, moderation, stressful life events, social support

BACKGROUND

Suicide and suicidal behavior are serious social and health concerns. Every year, about 800,000 people worldwide die by suicide, and it is one of the leading causes of death for 15–29 years old (1). Researchers have identified a multitude of risk and protective factors for suicide in recent years. Factors such as depression (2–6), family history of suicide (7–9), and stressful life events (10–14) have been found to have direct relationships with suicidal behavior. It is important to elaborate on these well-established direct effects to uncover and clarify causal links through which these effects may occur, and to ultimately inform suicide prevention and intervention efforts with specific, defined pathways rather than broad associations. As such, a growing area of research interest is the examination of the indirect effects of such factors on suicidal behavior, and interactions between different risk or protective factors (15, 16). Recently, studies have attempted to clarify indirect effects of well-established risk factors for suicide; for example, studies looking at depression and suicide that suggest the inclusion of variables such as life satisfaction and psychiatric status to induce the causal pathway between depression and suicide (17, 18). The recent evidence for the influence of different factors on the well-established association between depression and suicide presents reason to clarify the links between other known associations relating to suicidal behavior. One such established association is between stressful life events and suicidal behavior, for which a direct pathway has been consistently reported (10–14).

Stressful life events are defined as unexpected and undesired life events that often have the capacity to influence health and well-being (19). The association between stressful life events and suicidal behavior has been extensively studied, but there is limited evidence on indirect factors that moderate or mediate the relationship between the two variables. Perceived social support is defined as the individual's subjective understanding of the level of social support that can be provided by members of their social network (20). Current literature has shown moderating effects of perceived social support in the association between stressful life events and depression (21, 22), stressful life events and hopelessness (23, 24), and stressful life events and subjective well-being (25). There is also evidence for perceived social support as a moderator in the association between stressful life events (i.e., traumatic events, discrimination, medical diagnosis) and suicidal behavior in specific populations such as South African adolescents and transgender samples (26–28). There is limited evidence for perceived social support as a mediator (29) in the association between stressful life events and suicidal behavior but there is reason to suggest that perceived social support and stressful life events are correlated. Specifically, there are studies that show there is deterioration of perceived social support after the occurrence of a stressful life event (30, 31), and there has been a recent study in adolescents that established perceived social support as a mediator in the association between stressful life events and suicidal ideation and suicide attempts (32). Furthermore, a study looking at relationship between stress and health suggests that the stress-health connection is influenced by perceived social support, and can only be appropriately understood after the consideration of moderating and mediating factors (19). Thus, although there is limited evidence of perceived social support as either a moderator or mediator in the association between stressful life events and suicide, there are indications in literature that perceived social support is involved in the association between stressful life events and suicidal behavior. Furthermore, stressful life events are risk factors that are difficult to address with suicide prevention strategies as they can be unpredictable events (33, 34). In contrast, social support is a modifiable factor that is likely able to be influenced by suicide related prevention and intervention strategies, and as such, more investigation is needed to determine how perceived social support fits into the association between stressful life events and suicidal behavior.

This study will expand on current literature by investigating the role of perceived social support in the association between stressful life events and suicidal behavior in patients with suicide attempts admitted to psychiatric hospital. The limited evidence on the role of perceived social support in the association, combined with the established direct associations between stressful life events and suicidal behavior (10–14), perceived social support and suicidal behavior (35–37), and adequate evidence for stressful life events and perceived social support (30–32) provide further reason to clarify the associations between these three variables. Thus, this study will explore the role of perceived social support in the association between stressful life events and suicidal behavior by assessing its role as a mediator or moderator. The findings from this study will add to current literature that is defining the indirect effects of variables on well-established relationships between protective and risk factors for suicide and suicidal behavior. The goal of this research is to identify an actionable modifiable factor such as social support to reduce the risk of suicide.

OBJECTIVES

The objectives of this study are to explore the role of perceived social support in the association between stressful life events and suicidal behavior by investigating if:

1 the association between stressful life events, reported within the last year, and the occurrence of suicide attempts is mediated by the self-reported level of perceived social support,

2 the association between stressful life events, reported within the last year, and the occurrence of suicide attempts is moderated by the self-reported level of perceived social support,
3 the association between stressful life events, reported within the last year, and level of suicide intent is mediated by the self-reported level of perceived social support,
4 the association between stressful life events, reported within the last year, and level of suicide intent is moderated by the self-reported level of perceived social support.

METHODS

Reporting

The study is reporting according to the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies (38).

Setting and Study Design

The data from this study were obtained from the case-control study titled Determinants of Suicidal Behavior Conventional and Emergent Risk (DISCOVER), which was conducted to identify risk factors of suicidal behavior (39, 40). The study was approved by the Hamilton Health Sciences (#10-661) and St. Joseph's Healthcare (#11-3479) Research Ethics Boards. The study design for this paper is cross-sectional as data were taken from questionnaires administered at one time point. Study recruitment was completed from two city hospitals including Hamilton General Hospital, and St. Joseph's Healthcare, Hamilton where psychiatric inpatient services provided.

Participants

The inclusion criteria for the cases (individuals with suicide attempt) in this study were adult (18 years or older) participants that were admitted to hospital (the psychiatric or general hospitals), had a recent or past suicide attempt. The inclusion criteria for the controls in this study were psychiatric inpatients admitted at the same time as the cases with no history of suicide attempts and non-psychiatric inpatients without a history of suicide attempts. All study participants provided written informed consent and were interviewed face-to-face to conduct study related procedures. Participants were recruited from February 2011 to December 2014.

Variables

The socio-demographic characteristics included in this study were age, sex, ethnicity, marital status, current employment, and satisfaction with social support. Marital status was operationalized as those with a partner (currently married, common law, living with a partner) and those without a partner (never married, widowed, separated, divorced). Satisfaction with social support was measured using the Sarason Social Support Questionnaire (SSQ) short form, which asks participants how satisfied they were with the social support they were receiving on a six-point rating scale ranging from "very dissatisfied" to "very satisfied." (41). It asks participants to list up to 10 people who they can count on to be dependable, who can help them relax when under pressure, who accept their worst and best points, who really care about them, who can help them feel better, and who can console them. A social support score is generated by means of the number of people the participant has listed for each of the 6 items that were asked. The higher the number of the satisfaction with social support score, the greater the satisfaction of the participant. The satisfaction with social support score is generated by the means of the satisfaction ratings for all 6 items included in the SSQ (41). The Cronbach alpha for inter-reliability for this questionnaire is 0.97 (41).

Information about any stressful life events the participants experienced in the last year was also collected. Stressful life events included the dichotomous variables of marital separation, loss of job/retirement, loss of crop/business failure, violence, major intra-family conflict, major personal injury or illness, death/major illness of a close family member, death of a spouse, and other. These dichotomous variables were coded, where no occurrence of the stressful life event was coded as zero and the occurrence of a stressful life event was coded as one. These coded variables were then added to create a continuous stressful life events score.

Suicidal behavior was assessed using the occurrence of a suicide attempt and the level of suicidal intent. The occurrence of a suicide attempt was determined by self-reported suicide history data, which was then confirmed through access to medical records (39). The questionnaire used in the DISCOVER study to evaluate the level of suicidal intent was the Pierce Suicide Intent Scale (42). The Pierce Suicide Intent Scale is comprised of 12 questions that generate an output score of 0–22. A score of 0–3 on the questionnaire indicates low intent, 4–10 indicates medium intent, and 10+ indicates high intent (42). The Cronbach alpha value for the Pierce Suicide Intent Scale is 0.77 (43).

Statistical Analysis

Version 26 of SPSS (44) was used to conduct all descriptive, mediation, moderation, and interaction analyses. Descriptive statistics were used to summarize the demographic data of the study population. Continuous variables are presented as means with standard deviations, while dichotomous variables are summarized using percentages.

Our first objective was to explore whether the association between stressful life events and suicide attempts is mediated by level of perceived social support. Our mediation analysis was conducted in three steps, as follows:

1 First, we assessed the association between stressful life events score (independent variable) and suicide attempt (dependent variable) using a logistic regression model with age and sex included as covariates.
2 Second, we assessed the association between stressful life events score (independent variable) and social support score (mediator) using a linear regression model with age and sex included as covariates.
3 Third, we constructed a final logistic regression model with suicide attempt included as the dependent variable, and both social support score and stressful life events score as independent variables, adjusting also for age and sex. If social

support exerted a mediation effect, the association between stressful life events and suicide attempt would diminish as compared to that detected in step one of our analysis. We then applied Sobel's test to assess the statistical significance of the mediation effect using an online calculator (45).

Our second objective was to explore whether the association between stressful life events and suicide attempts is moderated by level of perceived social support. Our moderation analysis was conducted as follows: we created a continuous interaction term using the product of the stressful life events score and the social support score and tested this interaction in a logistic regression model using suicide attempt as the dependent variable. Our model was adjusted for age and sex, as well as the social support score, and the stressful life events score.

Our third objective was to explore whether the association between stressful life events and level of suicide intent is mediated by level of perceived social support. This mediation analysis was conducted using the same steps as described earlier:

1 First, we assessed the association between stressful life events score (independent variable) and level of suicide intent (dependent variable) using a linear regression model with age and sex included as covariates.

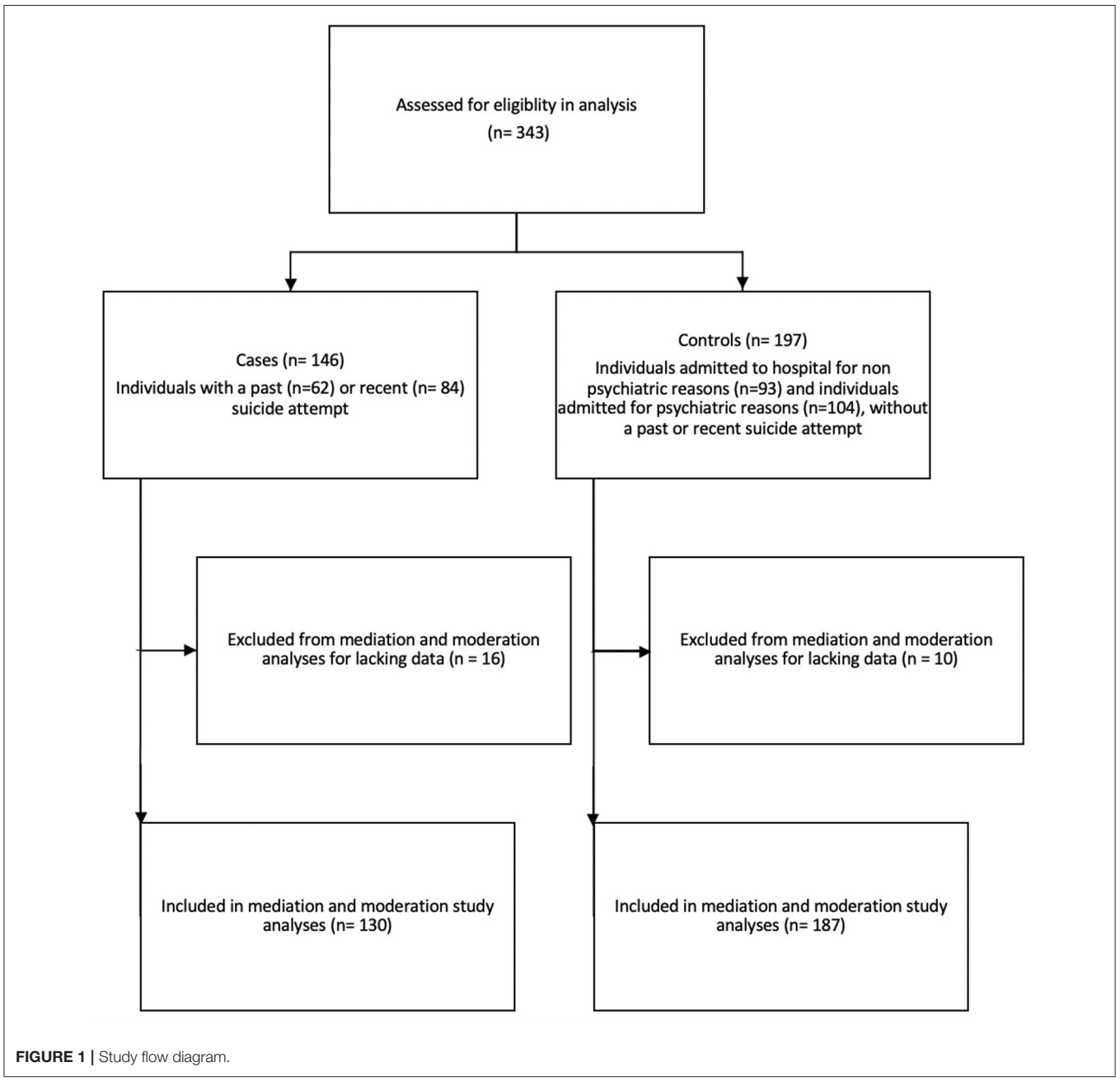

FIGURE 1 | Study flow diagram.

TABLE 1 | Demographic characteristics of participants with and without a history of suicide attempts.

Demographic variable	Total ($n = 343$)	Participants with a history of suicide attempts ($n = 146$)	Participants without a history of suicide attempts ($n = 197$)
Sex; % male	47.8	44.5	50.3
Mean Age in years (SD)	45.5 (15.4)	45.2 (14.7)	45.7 (15.9)
Ethnicity; % European[a]	81.2	92.5	72.8
Marital status; % with a partner[a]	34.9	26.9	40.6
Employment status; % currently employed[b]	35.6	23.3	44.7
Mean social support score (SD)	11.1 (10.2)	9.11 (8.88)	12.5 (10.8)
Mean satisfaction with social support score (SD)	6.9 (7.05)	7.58 (8.16)	6.36 (6.08)
Mean stressful life events score (SD)[c]	10.9 (1.6)	11.4 (1.53)	10.5 (1.52)
Marital separation[e]; % yes	9.4	12.2	7.5
Loss of job/retirement[e]; % yes	17.0	19.8	15.0
Loss of crop/business failure[e]; % yes	3.5	4.6	2.7
Violence[e]; % yes	11.9	16.0	9.1
Major intra-family conflict[e]; % yes	33.6	46.6	24.6
Major personal injury/illness[e]; % yes	37.1	52.7	26.2
Death or major illness of a family member[e]; % yes	34.3	38.9	31.0
Death of a spouse[e]; % yes	0.9	0.8	1.1
Other stressful life event[c]; % yes	37.5	44.6	32.6
Mean suicide intent score (SD)	-	14.2 (4.73)[d]	-

[a]*A total of 341 participants had data for this variable.*
[b]*A total of 342 participants had data for this variable.*
[c]*A total of 317 participants had data for this variable.*
[d]*A total of 115 participants had data for this variable.*
[e]*A total of 318 participants had data for this variable.*

2 Second, we assessed the association between stressful life events score (independent variable) and social support score (mediator) using a linear regression model with age and sex included as covariates.
3 Third, we constructed a final linear regression model with level of suicide intent included as the dependent variable, and both social support score and stressful life events score as independent variables, adjusting for age and sex. If social support exerted a mediation effect, the association between stressful life events and level of suicide would diminish as compared that detected in to step one of our analysis. Sobel's test was used to assess the statistical significance of the mediation effect (45).

Our fourth objective was to explore whether the association between stressful life events and level of suicide intent is moderated by the self-reported level of perceived social support. We created a continuous interaction term using the product of the stressful life events score and the social support score and tested this interaction in a linear regression model using level of suicidal intent as the dependent variable. Our model was adjusted for age and sex, as well as the social support score, and the stressful life events score.

For logistic regression analyses, we report odds ratios (OR) with 95% confidence interval (CI), and p-values. For linear regressions, we report unstandardized Beta-coefficients (B) with 95% CI, and p-values. For all analyses the alpha level of significance was set to $a = 0.05$. We assessed for multicollinearity using the variance inflation factor (VIF), where a VIF less than two was considered to be an acceptable cut-off.

RESULTS

Demographic Characteristics

Altogether, 343 individuals included in this study, 146 of whom were cases with a past or recent suicide attempt, and 197 of whom were controls (**Figure 1**). There were more women than men (women cases 55.5%, women control 49.7%) in the cases compared to the controls, and the cases were more likely to be without a partner (cases without partner 73.1%, controls without partner 59.4%). There was a larger proportion of individuals with European ethnicity seen in the cases group (92.5%) compared to the control group (72.8%). The mean social support score was 9.11 SD 8.88) compared to controls (12.5 SD 10.8), in contrast to the stressful life events score which was higher in cases (11.4 SD 1.53) compared to controls (10.5 SD 1.52). One of the highest reported stressful life events was "other stressful life event" where 44.6% of cases reported having other and 32.6% of controls reported having other stressors. Examples of these "other" stressors are "inability to find work," "financial stress," "having a baby," and "housing issues." The study participants' characteristics are provided in **Table 1.**

Perceived Social Support as a Mediator of the Association Between Stressful Life Events and Suicide Attempt

We found a significant association between stressful life events and suicide attempts, such that for each additional stressful life event, the odds of having a suicide attempt were 1.440 times greater (OR 1.440, 95% CI 1.440, 1.682, $p < 0.001$; **Table 2**). We also found a significant association between stressful life events and social support; each additional stressful life event was associated with a decrease in social support score (B −0.785, 95% CI −1.501, −0.068, $p = 0.032$). Our mediation analysis, which included both perceived social support and stressful life events as independent variables, revealed significant associations between both stressful life events (OR 1.414, 95% CI 1.209, 1.655, $p = 0.001$) and perceived social support (OR 0.967, 95% CI 0.942, 0.993, $p = 0.013$) and suicide attempt. The OR for stressful life events decreased from 1.440 in the first analysis to 1.414 in the mediation analysis, however, this effect did not reach the threshold of statistical significance when the Sobel's test was conducted (test statistic 1.64, $p = 0.100$). Details on the models used to conduct mediation analyses can be found in **Table 2.**

TABLE 2 | Logistic and linear regression results from mediation and moderation analyses with suicide attempts as the outcome[a].

	Predictors	Outcome	OR	95% CI	*p*
Model 1	Age	Suicide attempts	1.001	0.985, 1.016	0.928
	Female		1.298	0.813, 2.074	0.275
	SLEs[c]		1.440	1.440, 1.682	<0.001*
Model 2[b]	Age	Social support	−0.004	−0.078, 0.069	0.906
	Female		−0.454	−2.694, 1.787	0.691
	SLEs[c]		−0.785	−1.501, −0.068	0.032*
Model 3	Ag	Suicide attempts	1.001	0.985, 1.016	0.948
	Female		1.284	0.800, 2.061	0.301
	SLEs[c]		1.414	1.209, 1.655	<0.001*
	Perceived social support		0.967	0.942, 0.993	0.013*
Model 4	Age	Suicide attempts	1.000	0.985, 1.016	0.954
	Female		1.297	0.807, 2.085	0.282
	Perceived social support		0.901	0.726, 1.118	0.344
	SLEs[c]		1.324	1.031, 1.701	0.028*
	SLEs[c] × Perceived social support		1.007	0.987, 1.027	0.514
Sobel's test			**Sobel's test statistic**	**Standard error**	***p***
			1.64	0.016	0.100

[a]*Models 1 tests the independent association between SLEs and suicide attempts. Model 2 tests the independent association between SLEs and perceived social support. Model 3 represents the mediation analysis. Model 4 represents the moderation analysis.*
[b]*Unstandardized B values are reported for this linear regression.*
[c]*Stressful life events (SLEs).*
**Statistically significant at the 0.05 level.*

Perceived Social Support as a Moderator of the Association Between Stressful Life Events and Suicide Attempt

Perceived social support was not a moderator of the association between stressful life events and suicide attempt, as evidenced by a non-significant interaction effect between perceived social support and stressful life events (OR 1.007, 95% CI 0.987, 1.027, $p = 0.514$; **Table 2**).

Perceived Social Support as a Mediator of the Association Between Stressful Life Events and Level of Suicide Intent

We did not find a significant association between stressful life events and level of suicidal intent reported by participants (B 0.040, 95% CI −0.571, 0.652, $p = 0.896$; **Table 3**). No mediation effect of perceived social support could be detected (**Table 3**).

Perceived Social Support as a Moderator of the Association Between Stressful Life Events and Level of Suicide Intent

Perceived social support was not a moderator of the association between stressful life events and level of suicidal intent, as evidenced by a non-significant interaction effect between perceived social support and stressful life events (B −0.043, 95% CI −0.132, 0.046, $p = 0.343$; **Table 3**).

DISCUSSION

In this study, we explored the role of perceived social support as a mediator and as a moderator in the relationship between stressful life events and suicidal behavior. We identified that stressful life events were associated with increased risk of suicide attempts and social supported reduced the risk of suicide attempts, however social support did not mitigate the risk of suicide attempts when considered as an effect modifier between stressful events and suicide attempt. We used two outcome variables, the occurrence of suicide attempts and level of suicidal intent, to define suicidal behavior measures, and we did not detect any statistically significant mediation or moderation effects of perceived social support in the association between stressful life events and either of these outcome variables. Our findings are in contrast to a recent study by Yildiz et al. (32) that found perceived social support to mediate the relationship between stressful life events and suicide attempts in a sample of adolescents (32). Our contrasting finding suggests that mediation by perceived social support may not apply to this study sample of adults with suicide attempts admitted to psychiatric hospital, as the cited study was based on a general population sample with mean age of 15 years using different methods of assessing the exposure and outcome measures (32). Alternatively, Yildiz et al. included psychological distress as a partial mediator in the regression model used to assess the role of perceived social support, and the authors state that all variables in the model were imperative to the significance of the mediation (32), which presents the possibility that there may be reason to include a measure of psychological distress in

TABLE 3 | Linear regression results from mediation and moderation analyses with level of suicide intent as the outcome[a].

	Predictors	Outcome	*B*	95% CI	*p*
Model 1	Age	Level of suicidal intent	0.082	0.023, 0.141	0.007*
	Female		−0.613	−2.357, 1.130	0.487
	SLEs[b]		0.040	−0.571, 0.652	0.896
Model 2	Age	Social support	−0.004	−0.078, 0.069	0.906
	Female		−0.454	−2.694, 1.787	0.691
	SLEs[b]		−0.785	−1.501, −0.068	0.032*
Model 3	Age	Level of suicidal intent	0.082	0.023, 0.141	0.007*
	Female		−0.589	−2.334, 1.155	0.505
	SLEs[b]		0.021	−0.591, 0.634	0.945
	Perceived social support		−0.048	−0.145, 0.049	0.329
Model 4	Age	Level of suicidal intent	0.078	0.019, 0.138	0.010*
	Female		−0.615	−2.361, 1.132	0.487
	SLEs[b]		0.344	−0.565, 1.253	0.455
	Perceived social support		0.427	−0.567, 1.422	0.396
	SLEs[b] X perceived social support		−0.043	−0.132, 0.046	0.343

[a]*Models 1 tests the independent association between SLEs and level of intent. Model 2 tests the independent association between SLEs and perceived social support. Model 3 represents the mediation analysis. Model 4 represents the moderation analysis.*

[b]*Stressfull life events (SLEs).*

**Statistically significant at the 0.05 level.*

the regression model to adequately assess the mediation effects of perceived social support.

Although there is evidence for moderation by perceived social support (27, 28, 46), and indication in literature that the effect of stress on suicide differs according to differing perceived social support, this was not seen in our study. The studies looking at the moderation effects of perceived social support in the investigated association often included specific populations such as transgender youth (28), women with breast cancer (33), African children diagnosed with HIV (27), and as such, the moderating effect by perceived social support may not be present in our population of psychiatric inpatients with a history of suicidal behavior. Studies conducted in different populations used alternative measures to define perceived social support. For instance, the study on transgender youth used a perceived social support scale that limited responses to friends, significant others, and family (28), whereas the perceived social support measures used in our study do not limit the participant's responses to the type of individual providing the support. Thus, it may be important to evaluate perceived social support from different support figures within the psychiatric population and re-examine their moderating effects.

Despite not detecting mediating or moderating effects of perceived social support, we did find significant associations independently between stressful life events and suicide attempts, and stressful life events and perceived social support. The significance of the independent associations between stressful life events and suicide attempts (12–14), and stressful life events and perceived social support (30, 31), is consistent with what is seen in literature. Our findings lend further support for considering these factors both in statistical models and in clinical practice.

We did not find an association between stressful life events and level of suicidal intent, despite finding an association between stressful life events and suicide attempt. Although a high level of suicide intent is highly predictive of suicidal behavior as seen in literature (47), there is limited literature on the role of perceived social support in the association of stressful life events and level of suicidal intent specifically, which may provide reason as to why an independent relationship between stressful life events and suicidal intent was not established. Furthermore, there is more evidence for the association between stressful life events and severe forms of suicidal behavior such as suicide attempts, as evidenced by a review looking at the association between stressful life events and suicidal behavior in 95 independent studies (29). Thus, when investigating the role of perceived social support in this association, it may be necessary to define the outcome using specific definition of suicidal behavior such as suicide attempt.

LIMITATIONS

This is a cross sectional study limiting the inferences of the associations between stressors and suicide attempts. Furthermore, the stressful life events were reliant on self-report and subject to recall bias. Another limitation of this study is that the perception of social support is relative to the time of recruitment, whereas the participant's suicide attempt predates the time of recruitment and completion of the questionnaires. As such the reported perception of social support at the time of recruitment may have a different relevance on a suicide attempt that has occurred previously. Future directions may consider completing such assessments closer to the time of the suicidal behavior when feasible. An additional limitation regarding the stressful life events is that the scale used for data

collection did not have objective weightings associated with the listed events. Thus, it may be important for future research to explore these analyses while also giving weightings to the stressful life events as different life events may have varying levels of impact predates the time of recruitment and completion of the questionnaires relevance Previously. may consider completing such assessments closer to the time of the suicidal behavior when feasible additional not withstanding these limitations, the study provides further data into the role of stressful life events and perceived social support in the association with suicidal behavior in a high-risk group of patients with psychiatric disorders and suicide attempts admitted to psychiatric hospital.

CONCLUSION

This study explored the role of perceived social support in the association between stressful life events and suicidal behavior. We found that perceived social support did not act as a mediator or moderator in the investigated association, but there were significant independent relationships between stressful life events and perceived social support and stressful life events and suicide attempts. There is limited evidence on the association between stressful life events and perceived social support, and as such, our study adds to literature by providing evidence for this association in a psychiatric population. The results from this study also reinforce the importance of screening for variables such as stressful events and low perceived social support in the psychiatric population, in order to adequately assess risk for suicidal behavior. Future directions should include the investigation of the role of perceived social support as a mitigating factor in reducing the risk of suicide. Further investigations into the role of perceived social support in outcomes with different aspects of suicidal behavior will also provide clarification on the role of perceived social support in reducing suicidal behavior.

DATA AVAILABILITY STATEMENT

The raw data and related information supporting the conclusions of this article can be made available upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study was approved by the Hamilton Health Sciences (#10-661) and St. Joseph's Healthcare (#11-3479) Research Ethics Boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZS conceived the study and outlined study design and implementation. BP wrote the study manuscript, including the introduction, methods, results, and discussion. TR and MR contributed to the methods section and helped draft the methods and results sections of the manuscript. NS, NB-M, AH, CC, AD'E, LM, LT, and ZS provided feedback and edits for the manuscript. All authors have read and approved this manuscript.

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Emotion Reactivity and Suicide Risk in Patients With Depression: The Mediating Role of Non-Suicidal Self-Injury and Moderating Role of Childhood Neglect

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Background: The association between emotion reactivity (ER) and suicide risk has been confirmed in recent studies, especially in patients with depression. However, there is a lack of understanding of the underlying mechanism of the relation from ER to suicide risk among patients with depression. This study planned to examine a model of how ER, non-suicidal self-injury (NSSI), and childhood neglect (CN) interact to affect suicide risk in depressed patients.

Methods: Four hundred and ninety-six patients (64.5% female, mean age = 30.40 years, *SD* = 12.56) who have accomplished self-rating instruments of ER, NSSI, CN, and suicide risk were included.

Results: Findings showed that ER was positively connected with suicide risk, and NSSI partially mediated the above connection. Besides, CN moderated the mediation model, that is, the mediation effect was more pronounced in depressed patients with CN compared to depressed patients without CN.

Conclusions: It was concluded that there is a relationship among ER, NSSI, CN, and suicide risk in patients with depression, and it strengthens our knowledge of the mechanism behind suicide risk. Our findings emphasize that the identification of NSSI and CN should be considered when assessing the suicide risk of patients with depression, as well as the intervention focus on emotion regulation and support for patients.

Keywords: emotion reactivity, non-suicidal self-injury, suicide risk, childhood neglect, depression, moderated mediation

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INTRODUCTION

Suicide is an important public health issue, and it rose in occurrence rate, which has attracted the attention of all countries in the world. It is reported that more than 800,000 people committed suicide and lost their lives per year, making up 1.5% of the total number of deaths per year (1). Among all groups that are likely to commit suicide, depression is the most common group among suicide decedents, that is, individuals suffering from depression are at higher risk of suicide (2). Coincidently, previous

study has also confirmed that depressed patients experience higher rates of suicide (3). Suicide brings a huge psychological and economic burden to the family, society, and even the country (4). The prevalence and gravity of this public health problem have prompted substantial increases in research (5). Despite this, the rates of suicide have not significantly abated (6). Therefore, it is necessary to grasp the risk factors and the mechanism of suicide more comprehensively in order to carry out targeted prevention and intervention.

Emotion Reactivity and Suicide Risk

As a possible risk factor of suicide, emotion reactivity (ER) has been widely investigated by researchers (7). ER refers to three aspects of negative emotional experience, including emotional sensitivity, emotional intensity, and emotional persistence, which forms a part of personality traits and affects the individual's response to emotional stimulation (7). Theoretically, the suicide escape theory emphasizes that a high level of ER is accompanied by negative events that cannot be dealt with, and the pain caused by a high level of ER aggravates the possibility of suicide, that is to say, suicide is a behavior in order to release from the unbearable and painful mental state (8). From the perspective of empirical research, the research on the connection between ER and suicide risk also provides some evidence. Christopher (9) demonstrated the importance of ER with regard to suicide risk. Likewise, there was a significant correlation between higher ER and higher levels of suicidal thoughts and behaviors were highlighted (10). Another longitudinal study indicated that ER predicted suicide risk through depressive symptoms (11).

It can be said that there is an unusual relationship between ER and suicide risk. Nevertheless, neither the mediating mechanism nor the moderating mechanism has not been fully explored. The identification of influencing factors is essential to enhance our knowledge of suicide (12). Therefore, we put forward the study objectives that investigate a moderated mediation model of the relationship of ER to suicide risk, in which non-suicidal self-injury (NSSI) was considered as the mediator and childhood neglect (CN) as the moderator.

Emotion Reactivity, Non-Suicidal Self-Injury, and Suicide Risk

NSSI is conceptualized as taking intentional behavior without the intention of suicide to damage one's body (13), which is very common in patients with depression (14). In this present study, the reason why NSSI is considered as the mediator is mainly based on two reasons that ER may affect NSSI and NSSI may affect suicide risk. Relevant research also further confirmed the above two claims. On the one hand, subjects with a history of NSSI had a series of elevated ER manifestations (i.e., high sensitivity, high intensity, and persistence) (15), and high levels of ER intensify the likelihood of NSSI acts because NSSI does regulate higher ER states (16). Coincidently, Smith (17) underlined the importance of ER in clinical presentations of psychiatric patients, particularly when NSSI is present. On the other hand, so far, NSSI has been regarded as a precursor of suicide (18). NSSI is a kind of dependent coping strategies which lack perceived effectiveness. The failure of perceived effectiveness leads to long-term suffering or despair. The desire to escape and release may become stronger, and then aggravates the suicide risk (19). Similarly, another study suggests that an individual's perceived effectiveness in taking NSSI to release emotions or alleviate distress may have influence on suicide risk (20). A longitudinal study (21) demonstrated that identification and intervention of NSSI is a critical step to reduce the risk of ensuing suicide.

All in all, existing data have confirmed the association between ER and NSSI, and between NSSI and suicide risk. However, there are limited studies on NSSI functioning as mediator in the relation of ER to suicide risk. The above findings strengthen the confidence of this present study in exploring the role of NSSI as a mediating variable.

Childhood Neglect as a Moderator

High levels of ER are closely related to a series of negative behaviors, including NSSI, whether in the general population or in depressed patients (15, 16, 22). Consequently, ER may be an important factor for NSSI (15). Nevertheless, we need to realize that NSSI is not an inevitable result for depressed patients with higher ER. In fact, there may be some specific factors behind the relationship between ER and NSSI, thereby affecting NSSI. To date, few studies have explored the risk factors behind the relationship between ER and NSSI, so it is impossible to identify and intervene the risk factors. As a form of childhood adversities, CN has the greatest impact on depressed patients (23). CN refers to caregivers' failure to provide for the development and well-being in terms of health, nutrition, emotional development, shelter, or safe living conditions, including physical neglect and emotional neglect (24). Previous surveys found that two-fifths of Chinese have CN experiences (25), and this proportion is higher among patients with mental illness. This present study plans to examine the moderating role of childhood neglect (CN) in the paths from ER to suicide risk.

According to the social learning theory, affected by the family environment and family atmosphere, children will involuntarily regard their parents as the object of imitation to learn their parents' reactivity and regulation ways (26). Children who have experienced CN tend to exhibit hyper-reactivity to negative emotions as a result of acquiring negative affect and poor regulation strategies from their parents (27). In brief, CN plays an important role in the emotional processing of patients with depression (28). The dilemma of emotional processing partly impels the depressed patients to turn to coping strategies that can help them quickly extricate themselves from negative emotions (17). Empirical studies indicated that individuals with CN result in a lower registration of sensory input as well as hypersensitivity toward negative life events (29) and are more likely to take negative coping strategies such as NSSI, especially those with depression who have limited ability to regulate high levels of ER (30, 31). Therefore, CN may act as a key role in the relationship between ER and NSSI. Considering the special functions of CN (32), it is very important to have the ability to deal with the experience of CN in order to reduce the occurrence of adverse consequences (e.g., NSSI and suicide).

This Study

Foreign studies have surveyed the relation between ER, NSSI, CN, and suicide risk, respectively (15, 18, 33, 34), including the samples of depression (10). Unfortunately, under the background of China, there are few studies on the exploration of the relationship between the four variables mentioned above, let alone the exploration of mediators or moderators. Even in these few extant studies in China, there is a relatively lack of studies involving samples of mental disorders. Most of the samples are from the general population such as students, and the characteristics of these samples may be different from those of depressed samples. The present study evaluated a moderated mediation model among a Chinese sample of patients with depression to figure out the associations between ER, NSSI, CN, and suicide risk. Specifically, the following assumptions were made in this study: (A_1) ER would positively correlated with suicide risk; (A_2) NSSI would serve as a mediator in the association from ER to suicide risk; and (A_3) CN would serve as a moderator in the association from ER to suicide risk. In other words, participants with CN scoring higher in ER are estimated to display higher risk of NSSI and, in turn, higher suicide risk compared with to participants without CN.

METHODS

Participants

A total of 496 patients with depression who were hospitalized and treated in two top psychiatric hospitals in Beijing from June 2019 to November 2021 were selected as the participants. Inclusion criteria were as follows: (1) ICD-10 diagnosis of depression; (2) clinical stability [during the first 3 months of the study, patients did not increase their drug dosing by more than 50% (35)]; (3) over 18 years; (4) able to comprehend the study illustrations and willing to signed informed consent. For exclusion criteria, this study did not allow any situation that may be detrimental to the completion and accuracy of this investigation, including previous brain organic diseases, previous history of other mental diseases or current comorbidity, intellectual disability, hearing impairment, or severe acute and chronic diseases.

Procedures

First, the researchers involved in the study were trained uniformly. Before collecting the data, the researchers would ask the respondents about their willingness to participate in the study and inform them that they could voluntarily choose whether to take part in this study or not. After the permission of the respondents, the researcher would explain the purpose, method, and significance of this study, and then the respondents signed the informed consent. Secondly, the respondents were arranged in a quiet room, and the researchers were completed by the respondents independently. During the period, if the respondents have any question, the researchers gave objective explanation one by one. Finally, after the respondents completed the questionnaire, the researchers collected the questionnaire on the spot. The researchers observed and judged the emotional reaction of the respondents; when necessary, they assisted doctors and nurses to give the respondents necessary psychological counseling in time. A total of 508 questionnaires were sent out and 496 were returned, with a response rate of 97.6%. All of the participants were given a small gift to compensate for the time they spend filling out the questionnaire after filling out the questionnaire. This study enlisted the approval of the Research Ethics Committees of Peking Union Medical College (2019-18-K7).

Measures

Demographic Data

Self-designed General Information Questionnaire was used to collect demographic and clinical data of each respondent, including age, gender, education, marriage, employment, residence, family structure, and duration of illness.

Suicidal Risk

The Suicide Behaviors Questionnaire-Revised (SBQ-R) (36) was applied to evaluate suicidal risk, consisting of four items that the previous suicidal ideation or behavior, the suicidal ideation within 1 year, the threat of suicide, and the future suicide attempts. The total score of SBQ-R is 3–18. Higher scores reveal a higher suicide risk. Zhao translated the scale into Chinese (37), which proves that it has good reliability and validity. The Cronbach's α of the SBQ-R was 0.70 in the present study.

Emotion Reactivity (ER)

The 21 Emotion Reactivity Scale (ERS) (7) was employed to measure three aspects of ER: sensitivity (10 items; e.g., "I tend to get angry easily," "I am a sensitive person"), intensity (7 items; e.g., "I experience emotions strongly," "I get so upset and I cannot think straight"), and persistence (4 items; e.g., "It takes me much longer than most people to calm down when I am upset"). For each item, the responses followed a 5-point Likert scoring system, which range from 0 ("not at all like me") to 4 ("completely like me"). A higher score reflects a higher level of ER. Good inner reliability and convergent validity were displayed in ERS (7). The Chinese version of the scale has been translated by Yang (7). The Cronbach's α ranged from 0.70 to 0.92 (38).

Non-Suicidal Self-Injury (NSSI)

Wan et al. developed The Non-suicidal Self-injury Questionnaire (NSSI-Q) (39). It consists of 12 items, including two aspects: first 7 items consist of NSSI without serious body injury; last 4 items consist of NSSI with serious body injury. The incidence of 12 types of NSSI of each respondent over the last 12 months were surveyed by this questionnaire, which involves pinching, scratching, hitting hard objects with head/fist, etc. For each item, the responses followed a 5-point Likert scoring system, which range from 0 ("never") to 4 ("always"), with a total score between 0 and 48. As a self-rating scale for NSSI, good reliability and validity were presented (39). In this study, the Cronbach's α of NSSI-Q was 0.82. In order to improve the model fit and stability, we adopted the parceling method to parcel the 12 items into 3 parcel (40, 41).

Childhood Neglect (CN)

The Adverse Childhood Experience International Questionnaire (ACE-IQ) was developed by WHO (42) in 2016, which was a

retrospective self-report measure of childhood trauma for people aged 18 years and older. An ACE score was implemented by adding up the number of ACEs reported. The frequency scoring method was used for this analysis, which refers to the final scores including the summation of the types of ACE reported that were defined in the WHO guidelines based on the frequency (42). Ho et al. (43) has translated the ACE-IQ into Chinese, and the Cronbach's α was 0.83. The Abuse and Neglect domain subscales consist of physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect, and we used the items of physical and emotional neglect to assess patient's childhood neglect. The Cronbach's α of the subscale is 0.72 in this study.

Data Analysis

This study follows the principle that data should be normally distributed by skewness and kurtosis testing before any analysis can be performed (44). The results indicated that the skewness and kurtosis of all the data are in the acceptable range. First, we employed descriptive analysis to examine the prevalence of NSSI and suicide risk, likewise the bivariate correlations between the above variables (A_1). Second, NSSI that functioned as mediator in this connection from ER to suicide risk was tested (A_2). We employed the bootstrap procedure with 1,000 iterations in order to examine NSSI as the mediator (45). A bootstrapping method that can produce a point estimation and 95% bias-corrected (BC) confidence intervals (CI) was adopted to test the pathway of statistical meaning. When the 95% CIs of the point estimation did not cover 0, indirect effects revealed significant statistical meaning ($p < 0.05$). Finally, we tested the CN functioned as the moderating role in the relation between ER and NSSI (A_3). We employed four common standards to assessed the model fitting degrees, including comparative fit index (CFI), tucker-Lewis index (TLI), the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA). TLI > 0.95, CFI > 0.95, SRMR < 0.06, and RMSEA < 0.06 represent the good fitting degree of the model. Descriptive analyses and model testing were performed in SPSS 22.0 and Mplus 7.4.

RESULTS

Descriptive Analysis

The demographic data of 496 participants were displayed in **Table 1**. The average age of the respondents was 30.40 years ($SD = 12.56$), 64.5% were female. Most of the respondents got bachelor (university and above) at least and 61.9% of the respondents were single. In terms of employment status, the number of the respondents in employment and unemployment was roughly similar, accounting for 47.2 and 49.2%, respectively. Most of the respondents (66.5%) came from urban areas. Family structure was approximately equally distributed, with 50.4% single child family and 49.6% multiple children family. The majority of respondents had been ill within 3 years (57.5%).

In terms of SBQ-R, the total score of 496 participants was 8.61 ± 4.72. Specifically, 230 respondents (46.4%) scored 3–7, 140 respondents (28.2%) scored 8–12, and 126 respondents (25.4%) scored 13–18. With respect to NSSI, the final sample comprised 303 (61.1%) adult patients accompanied with NSSI in the past year. Of the 303 patients who committed NSSI, 76 (25.1%) had only one type of NSSI and 227 (74.9%) had more than one type of NSSI. "Deliberately hitting hard objects with fist" (33.5%), "Deliberately pinching oneself" (25.4%), and "Deliberately hitting hard objects with head" (25.4%) were the most prevalent method of NSSI, respectively. The prevalence of neglect was 71.0% among 496 patients, including 12.5% of physical neglect and 58.5% of emotional neglect.

TABLE 1 | Demographic and clinical characteristics of the sample ($N = 496$).

Variables	*M* (SD) or *n* (%)
Age, years, mean (SD)	30.4 (12.56)
Gender: female	320 (64.5)
Education	
Elementary school and below	6 (1.2)
Junior/high school graduate	179 (36.1)
University and above	311 (62.7)
Marital status	
Single	307 (61.9)
Married	154 (31)
Divorced or widowed	35 (7.1)
Employment status	
Employed	234 (47.2)
Unemployed	244 (49.2)
Retired	18 (3.6)
Residence	
Urban	330 (66.5)
Rural	166 (33.5)
Family structure	
Single child family	250 (50.4)
Multiple children family	246 (49.6)
Duration of illness (years)	
<3	285 (57.5)
3–5	74 (14.9)
5–10	70 (14.1)
>10	67 (13.5)

Preliminary Analyses

Table 2 indicates the descriptive statistics of related variables, including means, standard deviations (*SD*), skewness, kurtosis, and the bivariate correlation analysis between above variables. ER was positively connected with suicide risk, NSSI, and CN, with correlation coefficients of 0.731, 0.547, and 0.438, respectively ($p < 0.001$). Meanwhile, suicide risk was positively connected with NSSI ($r = 0.588$, $p < 0.001$) and CN ($r = 0.443$, $p < 0.001$). NSSI was positively linked to CN ($r = 0.441$, $p < 0.001$). The prima facie evidence for the assumed moderated mediation model was offered by the findings of the above correlation analysis.

Test of Mediation

To test the mediation assumption, a structural equation model was applied to verify whether NSSI mediated the connection from ER to suicide risk. The fitting degrees of this model were

TABLE 2 | Bivariate correlations between and descriptive statistics of study variables.

	1	2	3	4
ER	1			
Suicide risk	0.731***	1		
NSSI	0.547***	0.588***	1	
CN	0.438***	0.443***	0.441***	1
Mean	29.139	8.669	3.889	NE
SD	16.570	4.797	6.034	NE
Skewness	0.678	0.402	2.327	NE
Kurtosis	−0.211	−1.061	6.251	NE

NSSI, non-suicidal self-injury; ER, emotion reactivity; CN, childhood neglect; NE, non-existent (Similarly hereinafter).
****p < 0.001 (Similarly hereinafter).*

TABLE 3 | Regression results for conditional direct effect and conditional indirect effects.

Predictor	β	*p*	LLCI	ULCI	R^2
NSSI					36.7
ER	0.606	<0.001	0.526	0.676	
Suicide risk					56.2
ER	0.513	<0.001	0.422	0.608	
NSSI	0.318	<0.001	0.204	0.406	

Standardized regression coefficients were reported.

allowable, $\chi^2 = 45.123$, $df = 32$, $\chi^2/df = 1.41$, $p = 0.062$, RMSEA = 0.029, CFI = 0.995, TLI = 0.994, SRMR = 0.021. As presented in **Table 3**, ER directly affects suicide risk ($\beta = 0.513$, $p < 0.001$) and NSSI ($\beta = 0.606$, $p < 0.001$). The path from NSSI to suicide risk demonstrated statistical significance ($\beta = 0.318$, $p < 0.001$), with high levels of NSSI predicting high levels of suicide risk. The indirect effect from ER to suicide risk mediated by NSSI was significant [$\beta = 0.193$, $p < 0.001$, BC 95% CI (0.130, 0.252)]. The mediation effect of NSSI made up 27.3% of the total effect. In conclusion, ER is directly or indirectly associated with suicide risk through NSSI. The whole model explains the variance of 56.2% in suicide risk.

Test of Moderated Mediation

After determining that NSSI mediated the relation from ER to suicide risk, we examined the possibility that this relationship was moderated by CN. For the purpose of illustration, we also investigated NSSI as a function of ER and CN through simple slope graph. Functions are graphed for two levels of ER: 1 SD above the mean and 1 SD below the mean. As displayed in **Figure 1**, the interaction of ER and CN had an effect on NSSI ($\beta = 0.021$, SE = 0.008, $p = 0.007$). More precisely, ER had a higher indirect conditional effect on suicide risk through NSSI among subjects with CN ($B = 0.580$, SE = 0.054, 95%CI = 0.469–0.680, $p < 0.001$) than subjects without CN ($B = 0.490$, SE = 0.073, 95%CI = 0.334–0.622, $p < 0.001$). A high level of ER was a determinant of NSSI, but this effect was more pronounced among respondents with CN. Thus, the explanation for this moderating effect was confirmed. And the path coefficients for the moderated mediation model can be seen in **Figure 2**.

DISCUSSION

This study tested a model of how ER, non-suicidal self-injury (NSSI), and childhood neglect (CN) interact to affect suicide risk in depressed patients. The findings revealed that ER was significantly and positively correlated with suicide risk, and that this correlation was mediated by NSSI to some extent. In addition, CN moderated the above mediating effects. Next, we will try to make further discussion and explanation based on the main findings in this study.

Overall our findings supported our assumptions. First of all, the total score of SBQ-R was 8.61 ± 4.72, which accords with the scale developer's explanation that 8 was the most valuable partitioned scores on the SBQ-R for clinical populations (36). In terms of NSSI, the prevalence of NSSI was 61.1%, which was lower than Preyde's study (77%) (46). One possibility to explain the discrepancies in estimates of the detection rate of NSSI is different scales, sample sources, and size adopted in research. Another possibility is culture backgrounds. NSSI is regarded as a very obscure topic in China. Individuals with NSSI and their families are afraid to talk about the experience publicly because they are afraid of losing face. It can stop participants and their families from disclosing their experiences of NSSI (47). Additionally, our data suggested that hitting, pinching, and scratching was the top 3 reported method of NSSI, which was similar to a study (48). Moreover, reporting of multiple NSSI behaviors was found in the majority of participants. All of these distributional characteristics illustrate the depth and breadth of NSSI among Chinese depressed patients. The incidence of CN reached 71%, suggesting that CN is not

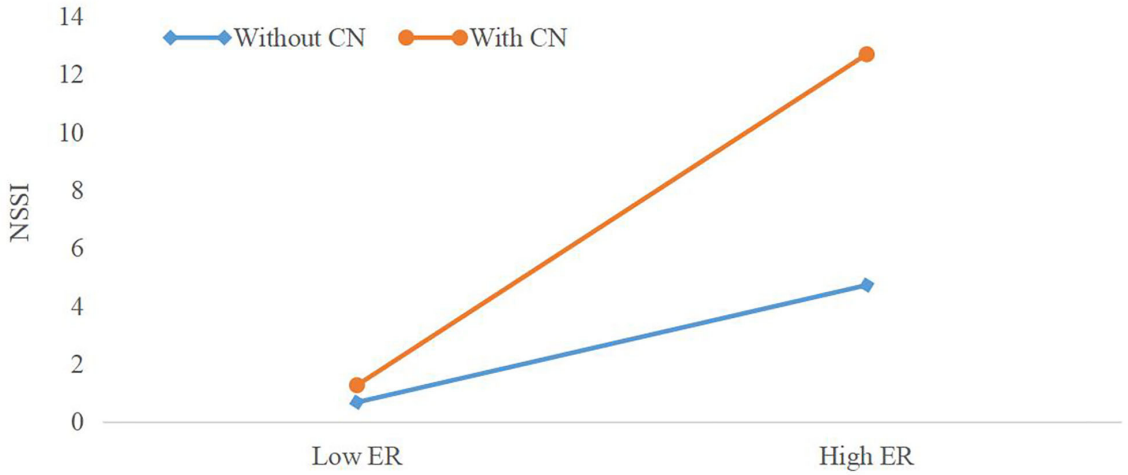

FIGURE 1 | The moderating effect of childhood neglect between emotion reactivity and non-suicidal self-injury. Functions are graphed for two levels of emotional reactivity: 1 SD above the mean and 1 SD below the mean. ER, emotion reactivity; NSSI, non-suicidal self-injury; CN, childhood neglect.

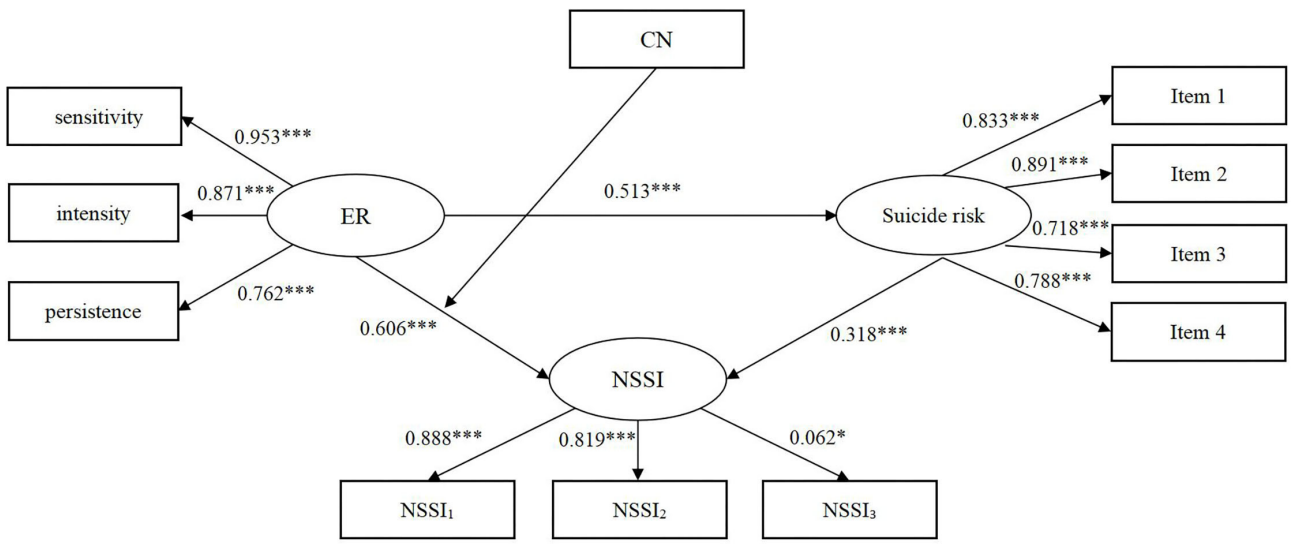

FIGURE 2 | Path coefficients for the moderated mediation model. The coefficient of the regulatory effect in the model were not displayed (The regulatory variables included in this study are classified variables). The moderation effect has been tested using the interaction term below. ER, emotion reactivity; NSSI, non-suicidal self-injury; CN, childhood neglect; Item I, previous suicidal ideation or behavior; Item 2, suicidal ideation within 1 year; Item 3, threat of suicide; Item 4, future suicide attempts; $NSSI_1$, deliberately pinching oneself; deliberately scratching oneself; deliberately hitting hard objects with head; deliberately hitting hard objects with fist; $NSSI_2$, deliberately hitting oneself with a fist, palm, or hard object; deliberately biting oneself; deliberately pulling own hair; deliberately stabbing oneself; $NSSI_3$, deliberately cutting oneself; deliberately scalding oneself; deliberately rubbing own skin; deliberately carving words on the skin (excluding tattoos). $^{***}p < 0.001$; $^{*}p < 0.05$.

optimistic in China, and it is urgent to pay attention to it and take countermeasures.

Next, in line with previous research, our results presented that depressed patients who are at high levels of ER generally show higher suicide risk (49, 50). As a part of temperament, ER has an impact on the reasons and ways of individual's reaction to emotional experiences (10), and such effect may last through early adulthood before stabilizing in the later life (51). High levels of ER (i.e., more sensitive, intense, and persistent response to emotional experiences) may lead to adverse reactions of adaptation by interfering with cognitive and behavioral inhibitory control, thus aggravating the emotional state of negative aversion, thus increasing suicide risk (52). In fact, the impact of ER on the suicide risk is more significant in patients with depression because they experience more negative emotions and psychological distress than the general population (53). Besides, strong ER to daily stress interferes with emotion expression and regulation to some extent (54, 55), especially in

depressed patients who is weak in regulating and responding to emotions (56), whereas emotion dysregulation may be at the core of suicidality for individuals with clinical samples (57).

Further, NSSI partially mediated the association between ER and suicide risk. That is, ER was not only directly and positively correlated to suicide risk, but also NSSI mediated the association. A high level of ER can be regarded as an early warning signal when an individual is ineffective in coping with external pressure, which indicates that an individual is ineffective in coping with negative emotions for a long time (52). As such, individuals who were accompanied with high levels of ER are supposed to have limited ability to recognize and implement coping strategies for bearing misery or solving problems, and thereby are eager to release themselves from the aversive experiences and negative emotions quickly by adopting the negative coping strategy of NSSI (17, 58). Also, it is proved that NSSI is an effective method that helps individuals to regulate their negative emotional experiences in the short term (59). In particular, it needs to be mentioned that the negative emotion regulation ability of patients with depression is limited, and the short-term benefit of emotion regulation is the most attractive for them (60). NSSI just meets their short-term, urgent needs. More importantly, NSSI was classified as a prelude to suicide (18). If the depressed patients fail to achieve the expected effect due to the limited ability of NSSI to regulate emotions, they will feel hopeless and helpless, and then resort to suicide (61). In addition, the participation of NSSI produces a series of negative self-perception (e.g., low self-esteem, low self-efficacy, self-criticism) (62, 63), which further aggravates the desire of suicide.

Finally, CN moderated the indirect effect of ER on suicide risk through NSSI. Specifically, it suggests that high levels of ER may have a greater impact on NSSI in participants with CN experience. CN as the moderator was similar to a study that the association between ER and NSSI was stronger in patients with CN experience than in patients without CN experience (64). As a kind of chronic stress, CN is often interdependent with impoverished social and emotional environments, affecting the physical and psychological development and adaptability of individuals, hindering the development of normal emotional skills (65), and possibly leading to a blunted pattern of ER (66). For instance, according to the social information processing model, CN can result in alterations in two initial steps of the information processing. That is, hyper-reactivity to negative emotional experiences in children suffered from CN is more likely to happen (31). Similarly, CN increases the possibility of insecure attachment, and high sensitivity to negative experiences, emotional dysregulation, and self-regulation difficulties resulted from the patterns of disturbances in attachment (67). Failure to regulate emotions in a state of high ER can cause helplessness, self-blame, pessimism, and even self-hatred attributional style in individuals who have experienced CN (68). This attributional style may well increase vulnerability to employing self-punishment as a self-management technique, with NSSI as one such technique, such that NSSI becomes a strategy to relieve stress and misery caused by self-blaming/criticizing cognitions (69). Notably, depressed patients are bad at emotion regulation, which makes them lack of self-regulation when facing stressful life events in the future (70), and in turn, easy to be in a high level of ER state, thus adopting stress reduction behaviors (e.g., NSSI) that act as a form of avoidance to escape from feelings and thoughts associated with stressful life events (71).

LIMITATIONS

Compared with the previous studies, this current study has several strengths. We selected two top and wide radiation scope psychiatric hospitals in China to recruit subjects, and for the first time comprehensively explored the ER, suicide risk, NSSI, and CN of patients with depression in Chinese context, as well as the relationship behind them. Despite of these merits, we are ought to acknowledge several limitations in this study. First, As the capital of China, Beijing attracted patients around the country instead of only Beijing natives. China has a large population and only two hospitals may not represent the whole country. Thus, we still propose to carry out multicenter studies in the future. Our findings should be cited with caution. Second, we adopted self-rating instruments that display a good reliability, but the results may be influenced by social desirability, respondent bias, and recall bias. Consequently, expert opinions or other objective evidence are necessary to complement self-rating instruments so as to obtain comprehensive and objective models of suicide risk in which the differences between subjective and objective information could be analyzed. Finally, an exploration of testing the temporal and/or causal relationship cannot be achieved because this current study employed the design of cross-sectional. It is indispensable to apply the longitudinal and/or quasi-experimental method to strengthen the credibility of the results.

IMPLICATIONS

Despite these limitations, the findings have implications for practice and research. Firstly, emotion regulation strategies that concentrate on reappraisal, acceptance, and suppression need to be emphasized to overcome elevated ER (31). Additionally, it is our responsibility to realize the importance of employing support-seeking resources from families, teachers, and friends that can buffer the influence on ER (72). For NSSI, hospitals should not be the only place to identify NSSI, but should extend the ability of perceptive identification toward NSSI to communities and even families (73). Of course, the above-mentioned ability of perceptive identification toward NSSI cannot be separated from the training for staffs and educators. As for CN, it is necessary for clinical staff to conduct psychological assessment on patients to whether they have CN experiences and whether they need help. Clinical staff can help patients relive how they felt at the time by discussing their CN experience with them, helping them to identify their thoughts and emotions in order to reshape their beliefs, rather than blaming the CN experience

on themselves. Importantly, regular psychological counseling, family visits, parent-child psychotherapy, and intervention centered on community resources also need to be carried out to form a linkage intervention mechanism for patients' CN experiences (74).

In terms of implications for future research, future research can continue to explore other variables that may affect the relationship between ER and suicide risk, in which NSSI can also be taken into account, and more potential links have been found. What is more, future related research should not be limited to CN, but expand to other types of childhood adversities, such as physical abuse, sexual abuse, family dysfunction, etc. For example, a recent study (75) revealed that childhood adversities was related to negative repetitive thinking (e.g., worry and rumination) in adulthood, while negative repetitive thinking may be related to an increase of depressive symptom severity and suicidal ideation. Therefore, future research may also explore the role of negative repetitive thinking in the association between childhood adversities, ER, and depression/suicidal ideation.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committees of Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LW and HZ designed the study. LW and JL collected the data. LW and QC analyzed the data. LW was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Inflamed Mind: Multiple Genetic Variants of *IL6* Influence Suicide Risk Phenotypes in Interaction With Early and Recent Adversities in a Linkage Disequilibrium-Based Clumping Analysis

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Background: Understanding and predicting suicide remains a challenge, and a recent paradigm shift regarding the complex relationship between the immune system and the brain brought attention to the involvement of inflammation in neuropsychiatric conditions including suicide. Among cytokines, IL-6 has been most frequently implicated in suicide, yet only a few candidate gene studies and without considering the effect of stress investigated the role of *IL6* in suicidal behaviour. Our study aimed to investigate the association of *IL6* variation with a linkage disequilibrium-based clumping method in interaction with childhood adversities and recent stress on manifestations along the suicide spectrum.

Methods: One thousand seven hundred and sixty-two participants provided information on previous suicide attempts, current suicidal ideation, thoughts of death, and hopelessness, and were genotyped for 186 variants in *IL6*. Early childhood adversities were recorded with an instrument adapted from the Childhood Trauma Questionnaire, recent life events were registered using the List of Threatening Life Events. Following a 3-step quality control, logistic and linear regression models were run to explore the effect of genotype and gene-environment interactions on suicide phenotypes. All regression models were followed by a clumping process based on empirical estimates of linkage disequilibrium between clumps of intercorrelated SNPs. Interaction effects of distinct types of recent life events were also analysed.

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Results: No clumps with significant main effects emerged, but we identified several clumps significantly interacting with childhood adversities on lifetime suicide attempts, current suicidal ideation, and current thoughts of death. We also identified clumps significantly interacting with recent negative life events on current suicidal ideation. We reported no clumps with significant effect on hopelessness either as a main effect or in interaction with childhood adversities or recent stress.

Conclusion: We identified variant clumps in *IL6* influencing suicidal behaviour, but only in interaction with childhood or recent adversities. Our results may bring us a step further in understanding the role of neuroinflammation and specifically of IL-6 in suicide, towards identifying novel biological markers of suicidal behaviour especially in those exposed to stressful experiences, and to fostering the adaptation of a new paradigm and identifying novel approaches and targets in the treatment of suicidal behaviour.

Keywords: *IL6*, inflammation, suicide, suicide attempt, suicide ideation, childhood adversities, recent stress, gene-environment interaction

INTRODUCTION

In spite of advances in neurobiology and neuropsychiatry, understanding and predicting suicide remains a challenge. Several clinical, psychosocial and socio-demographic risk factors and prognostic indicators for suicidal behaviour (1) have now been identified, however, with a low predictive value (2) and often even of a non-modifiable nature. Thus, more objective markers, especially biomarkers, and possibly reflecting modifiable processes, are imminently needed to improve prediction, risk screening and assessment, as well as to develop efficient methods for prevention and intervention. Furthermore, we need better insight into the neurobiological processes to offer a novel understanding of pathophysiology of suicide and identify new treatment targets and approaches (3).

While there has been a long-standing view that the brain is isolated from the peripheral immune system, recently a paradigm shift happened based on understanding of the multiple layers of immune surveillance in the central nervous system (4). Peripherally produced cytokines may cross the blood-brain barrier conveying signals to CNS, and with cytokines that are secreted locally by microglia, astrocytes and endothelial cells in the brain play a relevant role in the development and maintenance of brain function (5). While mental illnesses are not immunological disorders, the immune system potentially participates in subgroups of symptoms across multiple psychiatric disorders (4). Previous systematic reviews concluded that neuroinflammation may play a crucial role in the pathophysiology of suicidal behaviour including ideation, attempts and suicidal death. Still, more detailed knowledge of pathophysiological mechanisms underlying suicidal behaviour are needed including the possible mediators and moderators of inflammatory response that enhance vulnerability or resilience to suicide (6).

Proinflammatory states with higher levels of proinflammatory cytokines in blood, CSF and post-mortem brain are associated with different forms of suicidal behaviour and ideation (3, 7–14), suggesting that cytokine activation may impact suicidal behaviour in vulnerable individuals. Among cytokines, IL-6 is most frequently associated with suicidal behaviours (15), and assessment of IL-6 level is increasing in behavioural and psychosocial research due to its role in orchestrating inflammatory response and association with mental and physical health outcomes (16).

The majority, about 90% of suicidal behaviour occurs in the context of psychiatric disorders (17), but only a small minority, about 5% of psychiatric patients die by suicide, which suggests that beyond genetic and biochemical factors, environmental factors and stressors, as well as a dysfunction of the stress response system resulting in a maladaptive stress response also play a role in the emergence of suicide (18). The fact that the stress response is strongly associated with the immune system also supports that inflammation is one promising candidate for furthering our understanding of suicidal behaviours (3, 19, 20). Psychosocial stress is associated with upregulated gene expression and systemic inflammation markers, especially *IL6* (21). Thus, genetic variability in the expression of inflammatory markers in response to stress may contribute to increased vulnerability. In spite of this, only very few studies investigated the association of variation in *IL6* gene with suicidal behaviour. Furthermore, even those focused only on candidate variants, and did not consider the context of current or early stressors and adverse experiences.

As suicidal death is, fortunately, a relatively rare event, for clinical research other manifestations along the suicidal continuum are used as proxies, including suicidal ideation on non-lethal attempts which are strong predictors of the occurrence of subsequent completed suicide (22).

Thus, our present study aimed to investigate the impact of variation along the *IL6* gene with a linkage disequilibrium-based clumping method in interaction with early childhood adversities and recent negative life events on multiple manifestations of suicide including lifetime suicide attempts and current suicidal ideation in a larger European general population sample.

METHODS

Sample

Volunteers aged 18–60 from Budapest and Greater Manchester were recruited to participate in the NewMood study (New Molecules in Mood Disorders, Sixth Framework Program of the European Union LHSM-CT-2004-503474) without receiving any compensation *via* advertisements, an online platform, and general practices. After providing written informed consent, participants received a saliva-based genetic sampling kit for genotyping and a questionnaire pack, consisting of a detailed background evaluation and multiple sub-units for in-depth phenotyping of several depression-related markers and endophenotypes (23, 24). Of the NewMood dataset, comprehensive mapping to enable exclusion of related individuals and those with incomplete relevant phenotypic and genotypic data yielded the present sample of 1,762 unrelated adults with self-reported European ethnic white origin, who were genotyped for the *IL6* gene.

Ethical approval was obtained from both local ethics committees (North Manchester Local Research Ethics Committee, Manchester, UK, and Scientific and Research Ethics Committee of the Medical Research Council, Budapest, Hungary). The study was carried out in accordance with the Declaration of Helsinki.

Phenotyping

Phenotypes Related to the Suicide Spectrum

In the present study we focused on four suicide- and suicide risk-related phenotypes in order to grab a larger part of the suicidal behaviour spectrum, including previous suicide attempts, current suicidal ideation, and markers of current suicide risk including hopelessness and thoughts of death.

Previous lifetime suicide attempt (SUIC) was based on self-report providing a dichotomous variable. Current suicidal ideation (SI-BSI03) was evaluated using item 3, "Thoughts of ending your life" of the Brief Symptom Inventory (BSI) (25). Hopelessness (H-BSI18), a well-established independent risk factor of suicide was evaluated using BSI item 18 "Feeling hopeless about the future," while thoughts of death (ToD-BSI21) were measured using BSI item 21 "Thoughts about death and dying." These variables were scored on a scale from 0 to 4 ("Not at all" to "Extremely") based on severity during the prior week to the assessment.

Measures of Environmental Stressors

To be able to evaluate gene-environment interactions contributing to the emergence of the measured suicidal behaviours, we assessed two types of environmental stressors, including childhood adversities (CHA) and recent negative life events (RLE). Childhood trauma and adversity (CHA) was assessed with an instrument derived from the Childhood Trauma Questionnaire (CTQ) (26) using the sum of four items on parental emotional abuse, physical abuse, and parental neglect, expanded by two more items on parental loss, as validated previously (24). Recent negative life events (RLE) occurring within 1 year prior to the assessment were recorded *via* the List of Threatening Experiences (27) encompassing four types of life events related to intimate relationships, financial difficulties, personal problems such as health-related or legal difficulties, and the social network (28).

Genotyping

Participants provided buccal mucosa cells *via* a genetic sampling kit including a cytology brush (Cytobrush plus C0012, Durbin PLC) sent by mail to detect DNA. Extraction of genomic DNA was carried out according to the protocol of Freeman et al. (29). Genotyping was performed using Illumina CoreExom PsychChip. Genotyping was carried out in accordance with ISO 9001:2000 quality management requirements, and was blinded regarding phenotype.

Variant annotation was carried out based on the GRCh37/hg19 human assembly. For the purpose of phasing SHAPEIT was used to estimate additional haplotypes, followed by imputation of missing genotypes *via* IMPUTE2. This process yielded 186 SNPs on the *IL6* gene with boundaries extended by 10 kilobase (kb) pairs at both sides.

Statistical Analyses

Genotyping provided a dataset including 1,762 individuals genotyped for 186 SNPs in the *IL6* gene (with boundaries extended by 10 kb) in the NewMood database. For SNPs we applied a 3-step quality control protocol including calculation of Hardy-Weinberg Equilibrium (HWE; $>1 \times 10^{-5}$), missingness rates (MF; <0.05), and minor allele frequencies (MAF; >0.01) along the criteria suggested by Coleman et al. (30). For quality control purposes and main effect/interaction models Plink v1 0.9 was used. 86 SNPs survived quality control and were entered into analyses.

Logistic and linear regression models were applied to explore the effect of genotype and gene-environment interactions on lifetime suicide attempts (SUIC) as a dichotomous variable and on current suicidal ideation (SI-BSI03), hopelessness (H-BSI18) and current thoughts of death (ToD-BSI21) as continuous outcome variables, respectively. First, main effects of genetic variation on all phenotypes were analysed (**Supplementary Table 1**), followed by gene-environment interaction models with early childhood adversities (CHA) in case of suicide attempts (SUIC), current suicidal ideation (SI-BSI03), hopelessness (H-BSI18) and current thoughts of death (ToD-BSI21) (**Supplementary Table 2**); and with recent negative life events (RLE) in case of current suicidal ideation (SI-BSI03), hopelessness (H-BSI18) and current thoughts of death (ToD-BSI21) (**Supplementary Table 3**).

Next, all regression models, including main effect and interaction, were followed up by a clumping process using the CLUMP function in Plink. Clumping is a statistical method for yielding clumps of intercorrelated SNPs based on empirical estimates of their linkage disequilibrium (LD), stepping beyond independent significance levels, identifying connected SNPs and

their index or top SNP (the one with the highest significance). The four parameters used for clumping were as follows: (1) maximum *p*-value of the clump's top SNP was 0.001; (2) maximum *p*-value for secondary SNPs was 0.05; (3) minimum LD R^2 was 0.5; and (4) physical distance threshold was 250 kilobases.

As secondary analyses, we also analysed the interaction effects of different types of recent life events including financial difficulties (RLE-financial), personal problems (RLE-personal), intimate relationship problems (RLE-relationship), and social network disturbances (RLE-social) (28) on current indicators of suicide risk. Intercorrelations between the subscales have also been previously reported, and were either negligibly weak or non-significant (31).

All analyses were run according to additive, dominant, and recessive models. In all statistical models, population (Manchester or Budapest), gender and age were entered as covariates. In addition, in the case of gene-environment interaction models, the main effects of both the SNP and the stressors (CHA/RLE) were also included as covariates.

Nominal significance threshold was set at $p < 0.05$. Bonferroni-method was used to correct for multiple comparisons. Assuming 33 models [in main effect: 4 outcome variables (SUIC/SI-BSI03/H-BSI18/ToD-BSI21), × 3 genetic models (additive/dominant/recessive) = 12 models; in interaction: 1 outcome variable (SUIC) × 1 environmental variable (CHA) × 3 genetic models (additive/dominant/recessive) = 3; and 3 outcome variables (SI-BSI03/H-BSI18/ToD-BSI21) × 2 environmental variables (CHA/RLE) × 3 genetic models (additive/dominant/recessive) = 18 models] the corrected significance threshold was set at $p = 0.0015$. For the secondary analyses, assuming 36 models [3 outcome variables (SI-BSI03/H-BSI18/ToD-BSI21) × 4 environmental variables (RLE intimate/financial/personal/social) × 3 genetic models (additive/dominant/recessive) = 36 models], significance threshold was set at $p = 0.0014$. The main steps of genotyping and the statistical analyses are illustrated in **Figure 1**.

In the above analyses, Plink v1.90 was used to calculate missingness rate (MR; <0.05), Hardy-Weinberg equilibrium (HWE; $>1 \times 10^{-5}$) and minor allele frequency (MAF; >0.01) as part of quality control steps prior to the analyses; for clumping; and for building linear and logistic regression models to test for main and interaction effects of genetic variation in the *IL6* gene. Analyses were supported by scripts individually written in R 3.0.2 (R Core Team, 2013). R was also used to illustrate the effects of significant findings (version 4.0.3 with the ggplot2 package). Descriptive statistics were run using IBM SPSS Statistics 25.

All data used in the study were openly shared and are available in the Figshare depository at https://figshare.com/s/6d0f6f781466c78a7c0a.

RESULTS

Description of the Sample

Descriptive statistics of the analysed sample are shown in **Table 1**.

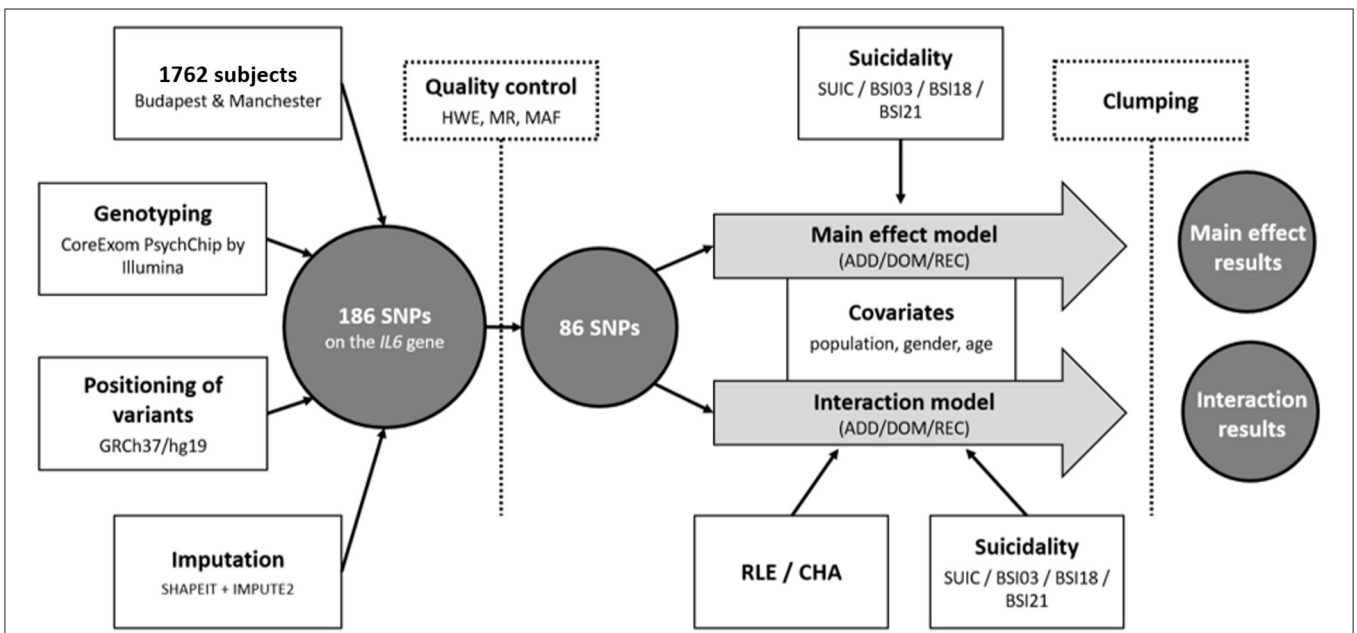

FIGURE 1 | Sample, methodology and statistical analyses used to investigate effect of *IL6* gene variations on lifetime suicide attempts (SUIC) and suicide items of the Brief Symptom Inventory (BSI) both in main effect models and in interaction with proximal (recent negative life events) and distal (childhood adversities) stressors. SNP, Single Nucleotide Polymorphism; SUIC, lifetime suicide attempts; BSI, Brief Symptom Inventory; SI-BSI03, current suicidal ideation ("Thoughts of ending your life"); H-BSI18, current hopelessness ("Feeling hopeless about the future"); ToD-BSI21, current thoughts of death ("Thoughts about death and dying"); RLE, Recent negative Life Events; CHA, Childhood Adversity; HWE, Hardy-Weinberg Equilibrium; MR, Missing Rate; MAF, Minor Allele Frequency; ADD, additive model; DOM, dominant model; REC, recessive model.

TABLE 1 | Characteristics of the sample.

	N	%		
Total	1,762			
Gender				
Male	504	28.60%		
Female	1,258	71.40%		
Lifetime suicide attempt	208	11.80%		
	Minimum	**Maximum**	**Mean**	**SD**
Age	18	60	32.56	10.47
SI-BSI03 Current suicidal ideation	0	4	0.34	0.86
H-BSI18 Hopelessness	0	4	0.95	1.31
ToD-BSI21 Current thoughts of death	0	4	0.67	1.16
RLE	0	8	1.21	1.27
CHA	0	16	3.28	3.34

BSI, Brief Symptom Inventory; RLE, recent negative life events; CHA, childhood adversity; SD, standard deviation.

Main Effect of *IL6* Variation on Lifetime Suicide Attempts, Current Suicidal Ideation, Current Hopelessness, and Current Thoughts of Death

Logistic regression models with SUIC (for lifetime suicide attempts) and linear regression models with SI-BSI03, H-BSI18, and ToD-BSI21 (for suicidal ideation and other markers of current suicidal risk) identified several individual SNPs reaching nominal significance threshold, however, as all *p*-values exceeded the maximum threshold specified for clumping ($p = 0.001$), clumps could not be identified.

Effects of Early Childhood Adversities in Interaction With *IL6* Variation on Lifetime Suicide Attempts, Current Suicidal Ideation, Current Hopelessness, and Current Thoughts of Death

Logistic regression models on the interaction between *IL6* and childhood adversities on lifetime suicide attempts yielded three significant clumps (one for additive and two for dominant models), surviving correction for multiple testing (**Table 2**; **Figure 2**). In the additive model, a clump containing three SNPs emerged with rs2069835 as the top SNP and the minor C allele as a protective allele ($p = 0.0004$; **Figure 2A**). In the dominant models, one identified clump contained four SNPs with rs2069835 as the top SNP and the minor C allele as a protective allele ($p = 0.0004$; **Figure 2B**), while the other contained 3 SNPs, with rs1880241 as the top SNP and the minor G allele as a risk allele ($p = 7.08 \times 10^{-5}$; **Figure 2C**).

Linear regression models on the interaction between *IL6* and childhood adversities on current suicidal ideation (SI-BSI03) yielded three significant clumps (two for additive and one for dominant models) all consisting of one SNP each, surviving correction for multiple testing (**Table 3**; **Figure 3**). In the additive model, one identified clump contained rs2069837 with the minor allele G as a risk allele ($p = 0.0006$; **Figure 3A**). Furthermore, one clump containing only one SNP, rs7458109, was significant in both additive and dominant models, with the minor C as a risk allele ($p = 0.0006$ and $p = 0.0004$ for additive and dominant models, respectively) (**Figures 3B,C**).

Linear regression models on the interaction between *IL6* and childhood adversities on current hopelessness (H-BSI18) yielded no significant clumps.

Linear regression models on the interaction between *IL6* and childhood adversities on current thoughts of death (ToD-BSI21) yielded three significant clumps (one for additive, dominant and recessive models) surviving correction for multiple testing (**Table 4**; **Figure 4**). In case of the additive model, a clump containing 24 SNPs with rs1474348 as top SNP and the minor C allele as a protective allele emerged ($p = 0.0005$; **Figure 4A**). In case of the dominant model, a clump containing 5 SNPs with top SNP rs4719714 and the minor T allele as a risk allele was found ($p = 0.0007$; **Figure 4B**). In the recessive model, a clump containing 19 SNPs with rs2069845 as top SNP and the minor G allele as a protective allele was identified ($p = 0.0002$; **Figure 4C**).

Effects of Recent Negative Life Events in Interaction With *IL6* Variation on Current Suicidal Ideation, Current Hopelessness, and Current Thoughts of Death

Linear regression models on the interaction between *IL6* and recent negative life events (RLE) on current suicidal ideation (SI-BSI03) yielded three significant clumps (one for dominant and two for recessive models) surviving correction for multiple testing (**Table 5**; **Figure 5**). In the dominant model, a clump containing seven SNPs with top SNP rs4719713 and the minor G allele as a risk allele was identified ($p = 0.0003$; **Figure 5A**). In the recessive model, one identified clump contained 4 SNPs with top SNP rs7805828 and the minor A allele as a protective allele ($p = 7.39 \times 10^{-5}$; **Figure 5B**); while the other clump contained six SNPs with top SNP rs60056354 and the minor T allele as a protective allele ($p = 0.0007$; **Figure 5C**).

No significant clumps emerged in linear regression models on the interaction between *IL6* and recent negative life events (RLE) either on current hopelessness (H-BSI18), or current thoughts of death (ToD-BSI21).

Effects of Distinct Types of Recent Negative Life Events in Interaction With *IL6* Variation on Current Suicidal Ideation, Current Hopelessness, and Current Thoughts of Death

Linear regression models on the interaction between *IL6* and recent negative life events related to financial problems (RLE-financialC2) on current suicidal ideation (SI-BSI03) yielded two significant clumps surviving correction for multiple testing, one of which was significant in both additive and dominant models. In the additive and dominant models, a clump containing three SNPs with top SNP exm609179 and the minor A allele as a risk

TABLE 2 | Interaction effects between *IL6* variation and childhood adversities on lifetime suicide attempts.

***IL6* × CHA: lifetime suicide attempts**

SNP	OR	SE	95%CI	Minor allele	Risk/protective	*p*
ADDITIVE MODEL						
rs2069835	0.47	0.21	0.31–0.72	C	Protective	0.0004
rs13438415	0.52	0.21	0.35–0.79	A	Protective	0.0020
rs2069824	0.53	0.22	0.35–0.81	C	Protective	0.0032
DOMINANT MODEL						
rs1880241	2.04	0.18	1.44–2.90	G	Risk	0.0001
rs62449494	1.94	0.18	1.38–2.74	G	Risk	0.0002
rs7805828	2.01	0.18	1.42–2.83	A	Risk	0.0001
rs2069835	0.46	0.22	0.30–0.70	C	Protective	0.0003
rs7801617	0.64	0.22	0.41–0.99	A	Protective	0.0439
rs13438415	0.51	0.21	0.33–0.77	A	Protective	0.0014
rs2069824	0.51	0.22	0.34–0.79	C	Protective	0.0022

Top SNP of each clump are marked in bold, member SNPs in each clump are listed under the top SNP. P-values surviving corrections for multiple testing are shown. CHA, childhood adversity; OR, odds ratio; SE, standard error; 95%CI, 95% confidence interval.

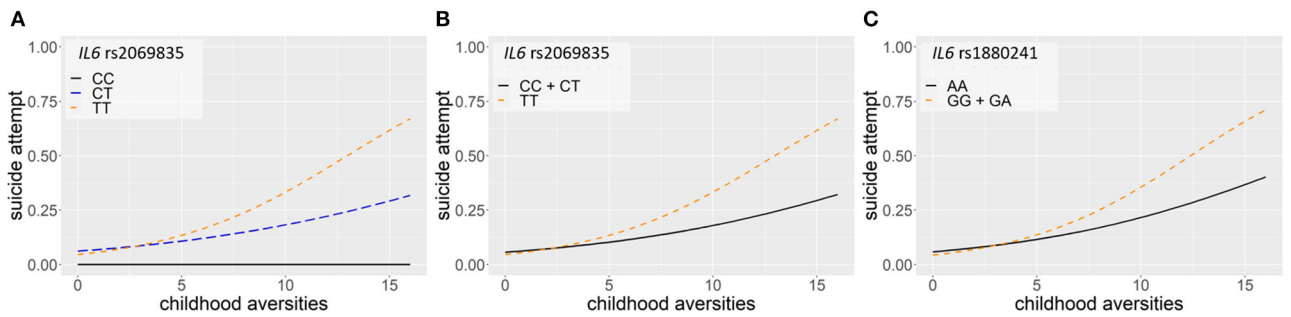

FIGURE 2 | Logistic regression models on the interaction between *IL6* and childhood adversities on history of lifetime suicide attempts yielded three significant clumps (one for additive and two for dominant models), surviving correction for multiple testing. In the additive model, a clump containing three SNPs emerged with rs2069835 as the top SNP and the minor C allele as a protective allele ($p = 0.0004$) **(A)**. In the dominant model, a clump containing 4 SNPs with rs 2069835 as the top SNP and the minor C allele as a protective allele ($p = 0.0004$) **(B)**, and another clump containing 3 SNPs, with rs1880241 as the top SNP and the minor G allele as a risk allele ($p = 7.08 \times 10^{-5}$) **(C)** was identified. The figure was generated for illustration purposes using R.

TABLE 3 | Interaction effects between *IL6* variation and childhood adversities on current suicidal ideation.

***IL6* × CHA: current suicide risk**

SNP	Beta	SE	95%CI	Minor allele	Risk/protective	*p*
Current suicidal ideation (SI-BSI03)						
ADDITIVE MODEL						
rs7458109	0.48	0.14	0.21–0.76	C	Risk	0.0006
rs2069837	0.30	0.09	0.13–0.48	G	Risk	0.0006
DOMINANT MODEL						
rs7458109	0.51	0.14	0.23–0.79	C	Risk	0.0004

Top SNP of each clump are marked in bold, other SNPs in each clump are listed under the top SNP. P-values surviving corrections for multiple testing are shown. SE, standard error; 95%CI, 95% confidence interval.

allele was identified ($p = 0.0002$), while in the recessive model a clump with 15 SNPs including top SNP rs1554606 and the minor T allele as a protective was found ($p = 0.0002$). In interaction with life events related to personal problems (RLE-personalC3) linear regression identified one clump in the *IL6* gene which survived correction for multiple testing in both additive and dominant models, containing 6 SNPs including top SNP rs34328912 with the minor C allele as a risk allele ($p = 0.0003$). Life events related

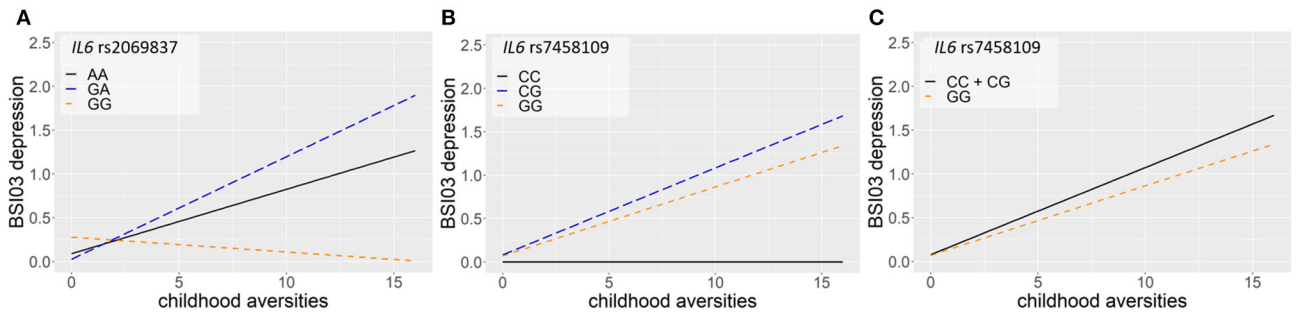

FIGURE 3 | Linear regression models on the interaction between *IL6* and childhood adversities on current suicidal ideation (SI-BSI03) yielded three significant clumps, consisting of one SNP each. In the additive model, one identified clump contained rs2069837 with the minor allele G as a risk allele ($p = 0.0006$) **(A)**. Furthermore, one clump containing also one SNP, rs7458109, was significant in both additive and dominant models, with the minor C as a risk allele ($p = 0.0006$ and $p = 0.0004$ for additive and dominant models, respectively) **(B,C)**. The figure was generated for illustration purposes using R.

to intimate relationships (RLE-intimateC1) or social network (RLE-socialC4) did not interact with *IL6* variation on current suicidal ideation.

On the other hand, recent intimate relationship-related life events and social network-related life events interacted with *IL6* variation on current thoughts of death (ToD-BSI21). In case of recent intimate relationship life events (RLE-intimateC1) two interacting clumps surviving significance for multiple testing were identified. The clump included 16 SNPs in the additive and 14 SNPs in the dominant model; top SNP was rs7802307 for both models with the minor T allele as a protective allele ($p = 0.0008$ and $p = 0.0009$ for additive and dominant models, respectively). There was also a significant interaction between *IL6* variation and recent life events related to the social network (RLE-socialC4) according to the recessive model surviving correction for multiple testing yielding one clump including 2 SNPs with top SNP rs7802307 and the minor T allele as a protective allele ($p = 0.0005$). In case of current thoughts of death (ToD-BSI21), no significant interaction effects emerged in case of the other two types of life events, financial problems (RLE-financialC2) or personal problems (RLE-personalC3).

In case of hopelessness (H-BSI18), no significant interaction effects were found with any recent life event subtypes.

In silico Characterisation and Functional Prediction of Identified Top IL6 SNPs as Well as SNPs in the Clumps Showing a Significant Effect on Suicidal Behaviours

Genomic location of significant SNPs and top SNPs identified in the clumping procedure are shown in **Figure 6**. Figures are based on diagrams generated by LDlink, LDmatrix Tool (https://ldlink.nci.nih.gov/?tab=ldmatrix).

To detect the functional effect of the top significant SNPs, we utilised FuncPred (https://snpinfo.niehs.nih.gov), and SNPNexus (https://www.snp-nexus.org/v4/guide/#cons), including DeepSea to predict significance of predicted chromatin effect and evolutionary conservation; FunSeq2 to calculate a non-coding score for the identified variants; GWAVA to calculate functional probability, and Genomic Evolutionary Rate Profiling. Results are shown in **Supplementary Tables 4–12** separately for all analyses where significant clumps were identified.

DISCUSSION

Our study investigated the effect of multiple variants in the *IL6* gene with a linkage disequilibrium-based clumping method on different manifestations along the suicide spectrum, including lifetime suicide attempts as well as current suicide ideation and markers of current risk such as thoughts of death and hopelessness. We identified no clumps of variants with a main effect on any of the investigated phenotypes. However, significant effects of several clumps of SNPs were identified in interaction with environmental stressors in several models. In case of lifetime suicide attempts, in interaction with early childhood adversities we identified 3 clumps, one in an additive and two in dominant models, with rs206985 emerging as top SNP in both models. In case of current markers of suicide risk, in interaction with childhood adversities we identified 3 clumps influencing current suicidal ideation (with rs7458109 as top SNP in both additive and dominant models) and three clumps influencing current thoughts of death. In case of current ideation we also identified 3 clumps of variants interacting with recent negative life events, with top SNP rs4719713. Our results suggest that *IL6* variation influences suicidal behaviour and risk but only in interaction with environmental stress. The validity of our findings is further supported by the fact that while we focused on a single gene, we investigated the combined effects of all 186 SNPs of *IL6* available in the NewMood genetic database clumped based on linkage disequilibrium, but without prior theoretical selection of only a few candidate variants.

The Effect of IL-6 on Brain and Behaviour

Cytokines are a heterogeneous group of regulatory polypeptides, released by immunocompetent cells such as lymphocytes and macrophages, playing a role in host defence and repair processes of tissues. and besides being able to cross the blood-brain barrier by active transport, are also produced in the brain by

TABLE 4 | Interaction effects between *IL6* variation and childhood adversities on current thoughts of death.

***IL6* × CHA: current suicide risk**

SNP	Beta	SE	95%CI	Minor allele	Risk/protective	*p*
Current thoughts of death (ToD-BSI21)						
ADDITIVE MODEL						
rs1474348	−0.15	0.04	−0.24 to −0.07	C	Protective	0.0005
rs6461662	−0.09	0.04	−0.18 to −0.01	G	Protective	0.0273
rs6963591	−0.09	0.04	−0.18 to −0.01	A	Protective	0.0315
rs6963866	−0.09	0.04	−0.18 to −0.01	C	Protective	0.0290
rs1546762	−0.09	0.04	−0.18 to −0.01	C	Protective	0.0314
rs1546763	−0.09	0.04	−0.18 to −0.01	G	Protective	0.0314
rs4719713	−0.09	0.04	−0.18 to −0.01	G	Protective	0.0302
rs1880241	0.09	0.04	0.01 to 0.17	G	Risk	0.0240
rs1880242	−0.10	0.04	−0.18 to −0.01	G	Protective	0.0213
rs2002792	0.11	0.04	0.02 to 0.19	G	Risk	0.0142
rs7802307	−0.15	0.04	−0.23 to −0.06	T	Protective	0.0009
rs1800795	−0.15	0.04	−0.24 to −0.07	C	Protective	0.0006
rs2069832	−0.15	0.04	−0.24 to −0.07	A	Protective	0.0006
rs1474347	−0.15	0.04	−0.24 to −0.07	C	Protective	0.0005
rs1554606	−0.15	0.04	−0.23 to −0.06	T	Protective	0.0006
rs2069845	−0.15	0.04	−0.23 to −0.06	G	Protective	0.0005
rs7787893	−0.13	0.04	−0.22 to −0.05	A	Protective	0.0019
rs35436671	−0.13	0.04	−0.22 to −0.05	G	Protective	0.0023
rs12700390	−0.13	0.04	−0.22 to −0.04	G	Protective	0.0030
rs12700391	−0.13	0.04	−0.22 to −0.04	C	Protective	0.0030
rs7781534	−0.13	0.04	−0.22 to −0.04	A	Protective	0.0031
rs4722168	−0.13	0.04	−0.22 to −0.04	G	Protective	0.0033
rs1581497	−0.13	0.04	−0.22 to −0.05	C	Protective	0.0028
rs1829927	−0.13	0.04	−0.22 to −0.04	G	Protective	0.0031
DOMINANT MODEL						
rs4719714	0.22	0.06	0.09 to 0.34	T	Risk	0.0007
rs56728381	0.21	0.06	0.09 to 0.34	C	Risk	0.0008
rs73683966	0.20	0.06	0.08 to 0.33	G	Risk	0.0016
rs73683967	0.20	0.06	0.08 to 0.33	G	Risk	0.0013
rs10499563	0.21	0.06	0.09 to 0.34	G	Risk	0.0008
RECESSIVE MODEL						
rs2069845	−0.27	0.07	−0.42 to −0.13	G	Protective	0.0002
rs7802307	−0.25	0.08	−0.40 to −0.10	T	Protective	0.0012
rs1800795	−0.27	0.08	−0.42 to −0.12	C	Protective	0.0005
rs2069832	−0.26	0.08	−0.41 to −0.11	A	Protective	0.0007
rs1474348	−0.26	0.08	−0.41 to −0.11	C	Protective	0.0006
rs1474347	−0.26	0.08	−0.41 to −0.11	C	Protective	0.0006
rs1554606	−0.27	0.07	−0.42 to −0.13	T	Protective	0.0002
rs7787893	−0.23	0.08	−0.37 to −0.08	A	Protective	0.0028
rs35436671	−0.23	0.08	−0.38 to −0.07	G	Protective	0.0041
rs12700390	−0.22	0.08	−0.38 to −0.06	G	Protective	0.0056
rs12700391	−0.22	0.08	−0.38 to −0.06	C	Protective	0.0056
rs7781534	−0.22	0.08	−0.38 to −0.07	A	Protective	0.0054
rs4722168	−0.22	0.08	−0.38 to −0.07	G	Protective	0.0053
rs1581497	−0.22	0.08	−0.38 to −0.07	C	Protective	0.0049
rs1829927	−0.22	0.08	−0.38 to −0.07	G	Protective	0.0054

Top SNP of each clump are marked in bold, other SNPs in each clump are listed under the top SNP. P-values surviving corrections for multiple testing are shown. SE, standard error; 95%CI, 95% confidence interval.

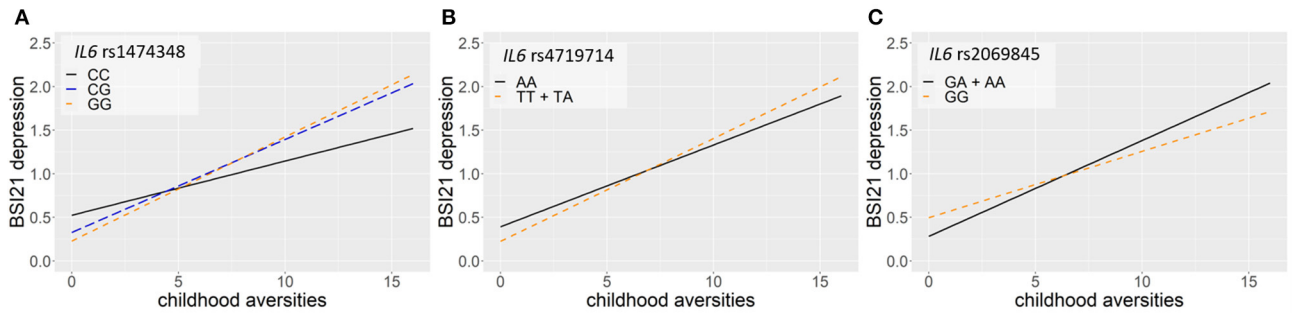

FIGURE 4 | Linear regression models on the interaction between *IL6* and childhood adversities on current thoughts of death (ToD-BSI21) yielded three significant clumps. In case of the additive model, a clump containing 24 SNPs with rs1474348 as top SNP and the minor C allele as a protective allele emerged ($p = 0.0005$) **(A)**. In case of the dominant model, a clump containing 5 SNPs with top SNP rs4719714 and the minor T allele as a risk allele was found ($p = 0.0007$) **(B)**. In the recessive model, a clump containing 19 SNPs with rs2069845 as top SNP and the minor G allele as a protective allele was identified ($p = 0.0002$) **(C)**. The figure was generated for illustration purposes using R.

TABLE 5 | Interaction effects of *IL6* variation and recent negative life events on current markers of suicidality.

***IL6* × RLE: current suicide risk**

SNP	Beta	SE	95%CI	Minor allele	Risk/protective	*p*
Current suicidal ideation (SI-BSI03)						
DOMINANT MODEL						
rs4719713	0.27	0.07	0.12 to 0.42	G	Risk	0.0003
rs6461662	0.27	0.07	0.12 to 0.42	G	Risk	0.0003
rs6963591	0.27	0.07	0.12 to 0.42	A	Risk	0.0003
rs6963866	0.27	0.07	0.12 to 0.41	C	Risk	0.0004
rs1546762	0.27	0.07	0.12 to 0.42	C	Risk	0.0003
rs1546763	0.27	0.07	0.12 to 0.42	G	Risk	0.0003
rs1880242	0.27	0.07	0.12 to 0.42	G	Risk	0.0003
RECESSIVE MODEL						
rs7805828	−0.32	0.08	−0.48 to −0.16	A	Protective	7.39E-05
rs62449494	−0.31	0.08	−0.47 to −0.15	G	Protective	0.0002
rs1880241	−0.19	0.08	−0.34 to −0.04	G	Protective	0.0146
rs2002792	−0.29	0.08	−0.44 to −0.14	G	Protective	0.0002
rs60056354	−0.38	0.11	−0.61 to −0.16	T	Protective	0.0007
rs367801961	−0.38	0.11	−0.61 to −0.16	A	Protective	0.0007
rs35610689	−0.39	0.12	−0.63 to −0.16	G	Protective	0.0018
rs34880821	−0.39	0.12	−0.63 to −0.16	A	Protective	0.0012
rs66543531	−0.40	0.12	−0.63 to −0.16	T	Protective	0.0011
rs6954667	−0.39	0.12	−0.62 to −0.16	A	Protective	0.0008

Top SNP of each clump are marked in bold, other SNPs in each clump are listed under the top SNP. P-values surviving corrections for multiple testing are shown. SE, standard error; 95%CI, 95% confidence interval.

neurons, astrocytes and activated microglial cells, thus providing a direct link with the immune system (32). Cytokines are increasingly recognised as messenger molecules, that modulate neuroendocrine functions, participate in neuroinflammatory and neurodegenerative processes, and have also been implicated in neurodevelopmental disorders and in the neurobiology stress-related conditions such as mood disorders or suicide (6, 15, 33, 34). Proinflammatory cytokines IL-6, IL-1, and TNF-alpha appear to be the most relevant considering their actions in the brain (34), and one of their most remarkable and relevant characteristics is their pleiotropy to bind different cell target types (6).

IL-6 is a pleiotropic cytokine mediator of immune reactions with functions including production of acute phase proteins in liver, B-lymphocyte proliferation and differentiation, osteoclast activation, and fever induction in brain. There are two types of IL-6 signalling: the anti-inflammatory or classical pathway, and the proinflammatory pathway or transsignalling way. IL-6 binds to membrane-bound IL-6R in the classical pathway, and to soluble IL-6R in the proinflammatory pathway. The proinflammatory

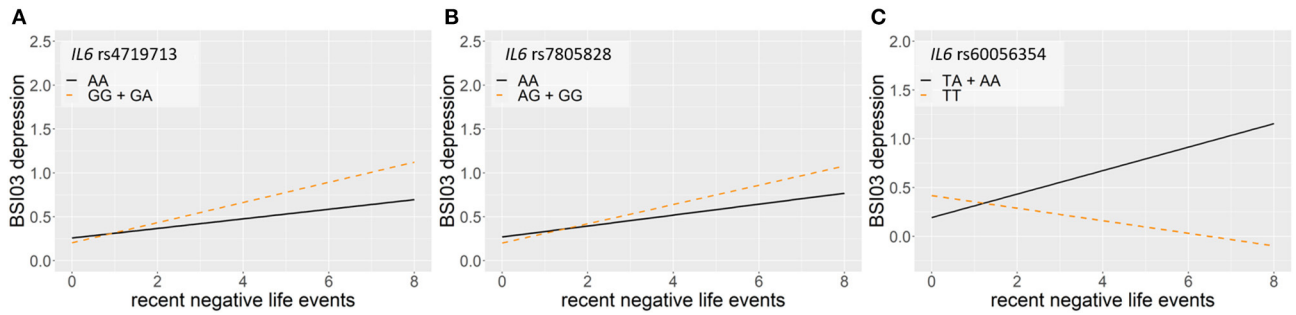

FIGURE 5 | Linear regression models on the interaction between *IL6* and recent negative life events (RLE) on current suicidal ideation (SI-BSI03) yielded three significant clumps. In the dominant model, a clump containing seven SNPs with top SNP rs4719713 and the minor G allele as a risk allele was identified ($p = 0.0003$) **(A)**. In the recessive model, one identified clump contained 4 SNPs with top SNP rs7805828 and the minor A allele as a protective allele ($9 = 7.39 \times 10^{-5}$) **(B)**; while the other clump contained six SNPs with top SNP rs60056354 and the minor T allele as a protective allele ($p = 0.0007$) **(C)**. The figure was generated for illustration purposes using R.

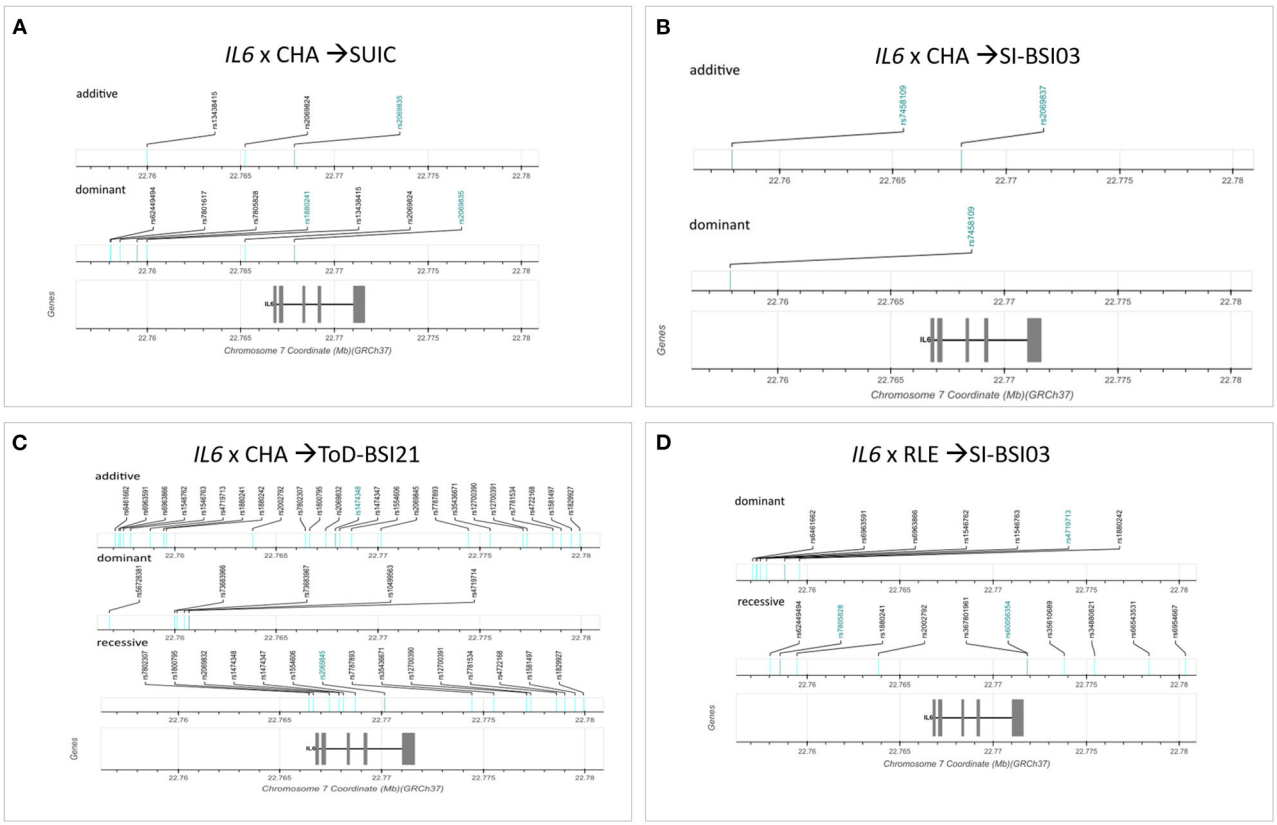

FIGURE 6 | Genomic location of significant clumps of SNPs in the *IL6* gene influencing suicidal phenotypes in interaction with different types of stress. Logistic regression models on the interaction between *IL6* and childhood adversities on lifetime suicide attempts yielded three significant clumps (one for additive and two for dominant models) **(A)**. Linear regression models on the interaction between *IL6* and childhood adversities on current suicidal ideation (SI-BSI03) yielded three significant clumps (two for additive and one for dominant models) all consisting of one SNP each **(B)**. Linear regression models on the interaction between *IL6* and childhood adversities on current thoughts of death (ToD-BSI21) yielded three significant clumps **(C)**. Linear regression models on the interaction between *IL6* and recent negative life events (RLE) on current suicidal ideation (SI-BSI03) yielded three significant clumps **(D)**. Top SNPs are marked with blue for each clump. The exons are marked with grey rectangles on the gene. Figures are based on diagrams generated by LDlink, LDmatrix Tool (https://ldlink.nci.nih.gov/?tab=ldmatrix).

pathway is used by various cell types within the brain (34). IL-6 can directly bind to receptors on neurons in the central nervous system and has been shown to directly impact generation of action potentials, which may influence changes in emotion and behaviour including increased risk for suicidal intent and behaviour (35).

Cytokines including IL-6 contribute to changes in the brain and behaviour *via* several mechanisms. Cytokine receptors, including IL-6 receptors can be found in specific brain regions and can thus have a direct effect on neuronal function and induce specific effects on behaviour and emotion; for example, IL-6 receptors are located on serotonin neurons in the medulla oblongata, hypothalamus, hippocampus, cerebellum, and prefrontal cortex. Cytokines also modulate concentration and function of monoamine neurotransmitters and especially serotonin and metabolites in various brain regions implicated in the pathophysiology of suicide including the prefrontal cortex, hippocampus and amygdala (5, 14). Cytokines also induce changes in the function of the HPA-axis, the other major system implicated in suicidal behaviour (14). Furthermore, inflammation and increased cytokine levels are also associated with activation of the kynurenine pathway (36) with downstream production of metabolites with effects on glutamate neurotransmission (37). Ultimately, disruption of regulatory corticostriatal circuits as a consequence of increased cytokine levels lead to abnormalities in executive function, emotion regulation, hopelessness and impulsivity contributing to suicide vulnerability (38). However, given their role in the central nervous system, cytokines including IL-6 quite likely exert a profound influence *via* their effect on foetal and later neurodevelopment (39).

The Effect of *IL6* Gene on Suicidal Behaviour

Genetic component of suicidal behaviour is estimated at 43% (40) with 30–50% for a broader suicidality phenotype (41). In a previous GWAS, strongest candidate genes of suicidal behaviour were linked to inflammatory response (42), and recent studies identifying top ranking molecular markers predicting suicidal ideation lead to 8 genes including *IL6* (besides *SAT1, SKA2, SLC4A4, KIF2C, MBP, JUN,* and *KLHDC3*) (16, 43, 44). The imbalance between anti- and proinflammatory cytokines in suicidal behaviour also suggests that cytokine genes may be putative contributors of suicide risk (45), with heritability for IL-6 levels estimated in twin studies ranging between 0.25 and 0.26 when taking into account confounding factors such as BMI (46).

IL6 gene in humans is mapped to region p15-21 on chromosome 7. It includes four introns, five exons, encoding a precursor protein with a total length of 212 amino acids, yielding a 186-amino acid mature segment and a 28-amino acid signal sequence (34). A very recent study using an SNP-based correlation and Mendelian randomisation approach showed a consistent association between increased IL-6 signalling using different genetic proxies and suicidality (47).

In spite of its suspected role in suicidal behaviour, only a few studies directly investigated genetic variation in *IL6* in association with suicide. One study assessed two variants in suicide attempters, completers and controls, selected based on previous studies showing their role in *IL6* expression regulation (48, 49). While no difference was found in rs2069845 allele frequencies in the three groups, the C allele of promoter-based rs1800795, possibly influencing histone acetylation and transcription factor binding and associated with higher IL-6 levels (48, 49), was more common in completed than attempted suicide, and was also associated with the lethality of suicide attempts (45) suggesting that higher IL-6 levels may mediate this association. Interestingly, in a previous study the G allele of rs1800795 was found to be neuroprotective considering its role on hippocampal volume in healthy subjects (50). Considering that smaller hippocampal volume predicts suicide attempts in depressed patients (51), this association may account for one of the effects of *IL6* gene on suicide risk.

Remarkably, both of the candidate variants rs2069845 and rs1800795 investigated by the study of Eftekharian et al. emerged as members of significant clumps in our present analyses, which, in contrast, investigated all 186 SNPs available in the NewMood database without hypothesis-based variant pre-selection. However, in our analyses the mentioned variants did not influence suicidal behaviours as a main effect, but only in interaction with environmental events, and rs1800795 showed an opposite effect, as in our study the C allele appeared as a protective variant.

Effects of *IL6* Variation on Suicidal Behaviour in Interaction With Environmental Stress

Our finding that effect of *IL6* variation was only observable in those exposed to some forms of environmental influences, either early traumas or recent negative life events, falls in line with previous observations that in several psychiatric conditions, including depression (31, 52–55), genetic factors do not directly influence manifestations, but rather exert their effects *via* influencing sensitivity towards environmental factors, and it seems to be the case also for both suicide and inflammation.

Stress has a well-known impact on neuropsychiatric disease which may in part be mediated *via* immunological mechanisms especially in the case of mood and anxiety disorders (4). Exposure to stressful life events and social stressors such as social defeat, loss, separation or rejection may cause impairments in various aspects of immune function, including stress-related changes in cytokine levels and function, and proinflammatory cytokine upregulation in both human and animal models (56). Inflammation increases threat-related neural sensitivity to negative social experiences to enhance sensitivity to threats to well-being or safety in order to avoid them, and also enhances reward-related neural sensitivity to positive social experiences to increase approach-related motivations towards others who might provide support and care (56). Psychological stress in clinical studies leads to elevated inflammation (57), with IL-6 levels up to four times higher in chronic stress compared to no stress (34, 58–61). Acute stress (62) and life-event related stress (63) also correlates with increased blood IL-6 levels (34).

Genetic variability likely interacts with environmental stressors leading to increased inflammatory markers in genetically susceptible individuals (14). However, only a few studies looked at the GxE effect in the background of increased IL-6 levels in the face of stress, and no previous studies investigated the effect of *IL6* variation on suicidal manifestations

in a GxE approach. In one study, older adults losing a spouse did not only show a two-fold increase IL-6 levels, but this effect was moderated by the G allele of candidate variant rs1800795 in the *IL6* gene (64), the same variant implicated in the aforementioned candidate gene study on the association between *IL6* SNPs and suicide (45), and identified also in our analyses in two variant clumps. Similarly to the study of Schultze-Florey et al. in our models rs1800795 interacted with environmental influences, but with early childhood adversities rather than recent life events. Furthermore, in line with the results of Schultze-Florey et al. the C allele which was associated with an unchanged IL-6 level in the face of stress emerged as a protective allele in our models. Finally, we observed no main effect of this variant, similarly to the results of Schultze-Florey et al. where genotypes alone did not account for observed differences in circulating IL-6 in bereaved subjects and non-bereavers (64).

While this SNP did not show an effect in our study in interaction with recent stress, we found several clumps of variants interacting with negative life events occurring in the past year on current suicidal ideation. We could not identify clumps of variants interacting with recent stress on other suicide risk markers such as current thoughts of death or hopelessness. However, as specific genes and variants may mediate the effects of only specific types of stressors (53–55, 65), we also looked at the interaction between *IL6* variation and distinct recent stress types. Our models identified separate variant clumps significantly interacting with recent financial problems or personal problems on suicidal ideation, and with intimate relationship problems and social network problems on current thoughts of death, which once again suggests that different types of stressors may exert their effect *via* the mediation of different genetic variants.

Effects of *IL6* Variation on Suicidal Behaviour in Interaction With Childhood Adversity

Early life adversity has been described as a major contributor to enhanced vulnerability to lifetime suicide (66). Childhood maltreatment affects immune response predisposing to heightened inflammatory states lasting into adult life with long-term consequences on both brain and behaviour (67), including abnormal cortisol stress responses, persistently increased levels of inflammatory cytokines including IL-6 and TNFα, low-grade elevations in other proinflammatory markers such as CRP, as well as greater inflammatory responses to later psychosocial stress (68). In a study investigating depressed patients raised inflammatory gene expression including cytokine-producing genes was linked to childhood adversity coupled with high suicide risk, and reduced gene expression was observed in those without childhood adversity and low suicide risk, suggesting the involvement of the immune system as a mediator between childhood adversity and increased suicide risk through a long-lasting activation of inflammation (69). In our study, variation in *IL6* showed robust interaction effects with childhood adversity on both lifetime suicide attempts and current suicidal ideation and current thoughts of death, emphasising the role of inflammation and as well as the role of *IL6* variation in predisposing to suicide risk in those exposed to early adversities, which might be exploited for risk screening and identification of those particularly in need of preventive interventions. As mentioned before, it is also notable that we identified in our clumps two variants previously investigated in association with suicide in candidate variant studies, providing further support to their putative role.

Hopelessness Is Not Associated With Variation in the *IL6* Gene

Hopelessness has long been identified as one of the key and independent risk factor of suicidal behaviour (70). In our study we found no association between *IL6* variation and hopelessness, either as a main effect or in interaction with recent stress or childhood adversities. This is surprising in the light of previous studies which found positive correlations between IL-6 levels and hopelessness in serum and saliva samples taken at different times of the day (71), reported associations between hopelessness and IL-6 levels in depressed patients (72), and found that adolescents exhibiting higher levels of hopelessness reflecting cognitive vulnerability responded with higher increase of IL-6 levels to laboratory-based acute stress (73).

Functional Prediction and Effects of Identified Variants in Previous Studies

While in our study we focused on the effects of linkage disequilibrium-based clumps of variants in the *IL6* gene rather than on single SNPs, and used top SNPs only to characterise the identified significant clumps, several of the member SNPs of significant clumps have previously been implicated in the literature in association with possibly relevant phenotypes.

Most importantly, as mentioned above, rs1800795, a member of two significant clumps interacting with childhood adversities on current thoughts of death, have previously been implicated in association with suicide (45), although with another direction; and with higher circulating IL-6 levels for G allele carriers in interaction with recent stress (64), which corresponds to our results where the minor C was associated with a protective effect. It is also noteworthy that in another study we have previously reported that the rs1800795 in interaction with recent stress increased depression risk and had an impact on depression severity (74). These convergent findings underscore the role of this particular variant in mediating the effects of stress on suicide and related phenotypes. rs1800795 has also been associated with a number of somatic conditions including cancer, inflammatory and autoimmune disorders. rs1800795 is located in the putative promoter of *IL6* and affects binding of transcription factors GATA1, GATA2, and YYI as well as NF1 and Sp1 (49) with likely functional consequences as reflected by the positive associations for this variant in divergent studies.

Rs7801617, a member SNP in a clump significantly interacting with childhood adversities on previous suicide attempts has previously been implicated in response to escitalopram in the GENDEP study (75). Another SNP in the same clump, rs2069824, has also been associated with treatment response in major depression and suggested to be a candidate for further

investigation (76). These results may once again converge with our findings suggesting further studies on the association of these *IL6* variants with the efficacy of antidepressants in reducing the risk of suicidal behaviour.

Rs1880241, a top SNP of a clump significantly interacting with childhood adversities on lifetime suicide attempts has been found to be related to level of circulating CRP in a study revealing a protective effect of CRP on schizophrenia and a risk effect of CRP on bipolar disorder (77). IL-6 is an upstream stimulator of CRP production (35, 47), and many of its effects on relevant phenotypes may be mediated by CRP. Finally, rs4719714, top SNP of a clump significantly interacting with childhood adversities on current thoughts of death have been implicated in association with fatigue and sleep disturbances (78, 79).

Several of our identified variants have been implicated in other conditions such as somatic illnesses, references to these and results of functional prediction are shown in **Supplementary Tables**. However, the functional consequences or the effect on cytokine levels or function in case of the majority of these variants are unknown.

Clinical Utility of the Involvement of *IL6* Variation in Suicidal Behaviour and Implications for Further Research

Understanding the role of inflammation and the contribution of the *IL6* gene has several potential clinical implications. *IL6* genotype may be utilised as a potential biomarker to identify specific subgroups of depressed patients with increased vulnerability for inflammation; and to detect at-risk subjects especially following early childhood adversities or recent stress and possibly target them with preventive measures focusing on inflammation (6). In this regard it is important that besides anti-inflammatory agents, psychological therapies, such as cognitive-behaviour therapy (80) or supportive-expressive dynamic psychotherapy (SEDP) has been shown to decrease IL-6 levels (81), without the side-effects of pharmacological agents, making subjects who carry the risk variants and exposed to stress suitable candidates for such intervention. The association of *IL6* genotype with the efficacy of such therapies on decreasing both IL-6 levels and suicide risk might also be tested. One further important question arising partly from our study is that whether childhood adversities in interaction with *IL6* genotype have a harmful effect on multiple measures of suicide risk, then how viable it is to offset or remediate the dire consequences of childhood trauma and maltreatment (67) before the onset of clinical symptoms by psychosocial or pharmacological interventions focusing on inflammation.

Besides finding potential biomarkers of acute and long-term suicide risk, a novel approach to treatment of suicide with novel treatment targets is also needed, especially as current treatments focus solely on treating the primary psychiatric diagnosis (5). Specific effects of cytokines on emotion and behaviour in different brain areas could be exploited for more optimal treatment targets, by identifying upstream triggers of inflammation and downstream neurobiological effectors and moderators conveying vulnerability or resilience (5). There is significant therapeutic promise in addressing different facets of the immune system (4), and immunotherapies may be helpful for depressed patients with low-grade inflammation or associated risk factors or suicide (47). Besides potential new targets, several anti-inflammatory treatments clinically approved for other indications might be tested in suicidal patients. Once more, use of potential biomarkers such as *IL6* variation may help identify those who may benefit from such agents even in the face of the abovementioned limiting factors.

Limitations

Several limitations of our study must be taken into account when interpreting the impact of our results. First, lifetime suicide attempts, as well as both early childhood adversities and recent life events occurring in the past year were retrospectively assessed based on self-report, and are thus subject to recall and reporting biases. Current suicidal ideations, thoughts of death and hopelessness are similarly self-reported. Second, assessment of childhood adversity and recent negative life events does not take into consideration the differing severity and subjective impact of individual life events. Thirdly, we could not exclude the contribution of depression to our suicidal phenotypes. Finally, besides *IL6*, *IL6R* encoding the IL-6 receptor is also very important in determining IL-6 levels and functions, thus variation in this gene should also be covered by future broader studies to understand the impact of *IL6*. Nevertheless, our study also has several strengths, including consideration of several variants without hypothesis-based candidate SNP selection along the *IL6* gene with a linkage disequilibrium-based clumping method, employing different manifestations of suicidal behaviour along the suicide spectrum as phenotypes, and using a GxE paradigm with two etiologically different types of stressors.

CONCLUSION

In conclusion, our study investigating the role of variation in the *IL6* gene with a linkage disequilibrium-based clumping approach identified several clumps of SNPs that influence both the risk of suicide attempts and current suicidal ideation and thoughts of death. Our results may bring us a step further in understanding the role of inflammation and specifically of IL-6 in suicidal behaviour, and identify novel biological markers of suicide risk especially in those exposed to stressful experiences, as well as to foster the adaptation of a new paradigm and identify novel approaches and targets in the treatment of suicidal behaviour.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found online in the FigShare repository: https://figshare.com/s/6d0f6f781466c78a7c0a.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by North Manchester Local Research Ethics Committee; and Scientific and Research Ethics Committee of the Medical Research Council, Budapest, Hungary. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG, JB, GB, and GJ designed and conceptualised the study and collected the data. SS, DG, NE, and ZG participated in statistical analyses. DT carried out *in silico* functional analyses. XG, JB, and DT wrote the first draught of the manuscript. SS and ZG created figures. All authors participated in interpreting the data, developing further and final versions of manuscript, and contributed and have approved 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.2021.746206/full#supplementary-material

Supplementary Table 1 | Individual main effects of the investigated *IL6* variants on lifetime suicide attempts (SUIC), current suicidal ideation (SI-BSI03), hopelessness (H-BSI18), and current thoughts of death (ToD-BSI21).

Supplementary Table 2 | Individual interaction effects of the investigated *IL6* variants and childhood adversities (CHA) on lifetime suicide attempts (SUIC), current suicidal ideation (SI-BSI03), hopelessness (H-BSI18), and current thoughts of death (ToD-BSI21).

Supplementary Table 3 | Individual interaction effects of the investigated *IL6* variants and recent life events (RLE) on current suicidal ideation (SI-BSI03), hopelessness (H-BSI18), and current thoughts of death (ToD-BSI21).

Supplementary Table 4 | Functional prediction results for SNPs in the significant clump emerging in interaction with childhood adversities (xCHA) on lifetime suicide attempts (SUIC) in the additive model.

Supplementary Table 5 | Functional prediction results for SNPs in the two significant clumps emerging in interaction with childhood adversities (xCHA) on lifetime suicide attempts (SUIC) in the dominant model.

Supplementary Table 6 | Functional prediction results for SNPs in the two significant clumps emerging in interaction with childhood adversities (xCHA) on current suicidal ideation (SI-BSI03) in the additive model.

Supplementary Table 7 | Functional prediction results for SNPs in the significant clump emerging in interaction with childhood adversities (xCHA) on current suicidal ideation (SI-BSI03) in the dominant model.

Supplementary Table 8 | Functional prediction results for SNPs in the significant clump emerging in interaction with childhood adversities (xCHA) on current thoughts of death (ToD-BSI21) in the additive model.

Supplementary Table 9 | Functional prediction results for SNPs in the significant clump emerging in interaction with childhood adversities (xCHA) on current thoughts of death (ToD-BSI21) in the dominant model.

Supplementary Table 10 | Functional prediction results for SNPs in the significant clump emerging in interaction with childhood adversities (xCHA) on current thoughts of death (ToD-BSI21) in the recessive model.

Supplementary Table 11 | Functional prediction results for SNPs in the significant clump emerging in interaction with recent life events (xRLE) on current suicidal ideation (SI-BSI03) in the dominant model.

Supplementary Table 12 | Functional prediction results for SNPs in the two significant clumps emerging in interaction with recent life events (xRLE) on current suicidal ideation (SI-BSI03) in the recessive model.

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The Correlation of Reduced Fractional Anisotropy in the Cingulum With Suicide Risk in Bipolar Disorder

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Objective: This study aims to investigate the significant alterations in brain white matter integrity in individuals with bipolar disorder (BD) who had attempted suicide by applying a tract-based spatial statistics (TBSS) approach with tensor-based spatial normalization.

Methods: A TBSS approach with novel tensor-based registration was used to compare the white matter fractional anisotropy (FA) between 51 individuals with BD, of whom 19 had attempted suicide, and 43 healthy controls (HC). The suicide attempt was assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS). In addition, we also investigated the correlations of FA values with clinical measures in BD, including illness duration, and the severity of depression and anxiety measured by the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA), respectively.

Results: A significant reduction of FA value in the hippocampal cingulum was observed in BD individuals who had attempted suicide compared with those who had not. For the genu/body of the corpus callosum, inferior fronto-occipital fasciculus, uncinate fasciculus, and anterior thalamic radiation, the reductions in FA values were significantly greater in both BD subgroups who attempted suicide and who did not, compared to HC. The correlation analysis showed that the illness duration of attempters was correlated to the FA value of the genu of the corpus callosum, while the HAMD and HAMA scores of non-attempters were relevant to the FA of the superior longitudinal fasciculus.

Conclusion: The observation that white matter integrity was altered in the hippocampal cingulum in BD individuals who attempted suicide suggested that this brain area may be the neurobiological basis of suicide attempts. Our findings also support the involvement of white matter (WM) microstructure of frontal–subcortical circuits in the neurobiological mechanism of BD. In addition, the illness duration of patients with attempted suicide may have an effect on the altered integrity of the corpus callosum.

Keywords: bipolar disorder, cingulum, fractional anisotropy, suicide attempt, tract-based spatial statistics

INTRODUCTION

Suicide attempt is defined as a non-fatal, self-inflicted, potentially life-threatening behavior with an intent to die (1), which is also reported to be associated with a poor quality of life (2). It has been reported that bipolar disorder (BD) has a high lifetime risk for suicide attempts and suicide completion. Specifically, 25–56% of individuals with BD present at least one suicide attempt during their lifetime, and ∼15–19% of individuals with BD die from suicide (3). It has been demonstrated that a previous suicide attempt is a robust predictor of future completed suicide (4), suggesting that the occurrence of suicide attempts may be an important intervention point for predicting and preventing suicide. However, in view of the subjectivity and non-specificity of the sociodemographic and clinical information of suicide attempts, it is of great significance to try to elucidate the neural basis underpinning suicide attempts in BD.

Non-invasive neuroimaging studies are qualified to explore the neurophysiological basis of suicide attempts at a neuroanatomical level. Recently, growing evidence has brought about a dysconnectivity hypothesis that suicide may be related to inefficient or anomalous white matter (WM) pathway (5, 6). By providing a measurement of water diffusion in tissues, diffusion tensor imaging (DTI) can be used to detect alterations in the microstructural architecture of cellular membranes (7). As the most commonly used DTI parameter, fractional anisotropy (FA) primarily reflects the directionality and integrity of WM fibers. Decreased FA signifies less anisotropic diffusion and thus reduced microstructural integrity (8).

Previous studies have reported that suicide behavior may be associated with inefficient WM pathway. In particular, the corpus callosum, which has frequently been reported to be abnormal in individuals with BD (9, 10), is suggested to be preferentially involved in suicide. For example, the integrity of the corpus callosum is altered in BD individuals who had a history of attempted suicide (6) or suicidal ideation (11). However, the anomaly of the corpus callosum may be just significant in BD but not in suicide attempters (12, 13). Likewise, suicide attempters with BD showed FA differences in uncinate fasciculus (UF) (14) and frontal WM (15, 16) compared to non-attempters. The WM integrity of these brain areas was also found to be abnormal in the comparison between BD and healthy controls (HC) (17–19).

Although the neuroimaging studies above explored the suicide-related brain regions, the analytical methods previously used had some limitations. For example, the voxel-based morphology (VBM) that requires data smoothing would cause a partial volume effect. Although standard tract-based spatial statistics (TBSS) studies avoid the limitation of VBM by projecting volumetric data onto a WM skeleton (20), they just used the tensor-derived information (i.e., FA) for registration (21), which may affect the accuracy of the alignment without the information of WM direction. A recently developed tensor-based spatial normalization method available in DTI-TK software (http://dti-tk.sourceforge.net/) has been applied to provide registration optimization and avoid errors that may arise in the application of standard TBSS. Thus, in the present study, we will apply this method to investigate the WM tracts in suicide attempters with BD.

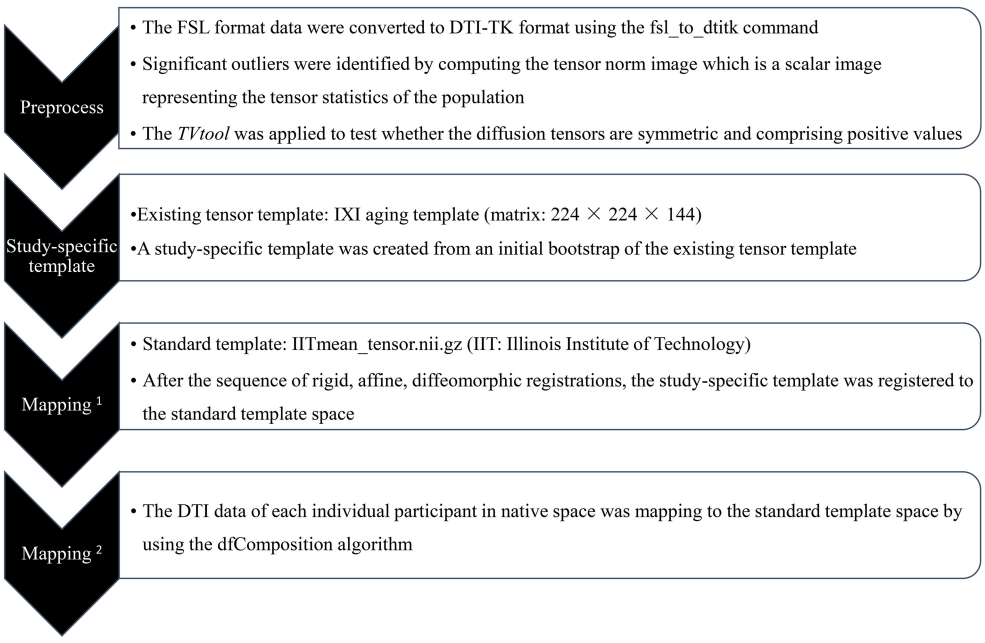

FIGURE 1 | Flow diagram of tract-based spatial statistics (TBSS) registration process followed by DTI-TK tutorials.

The primary objective of our study was to apply an optimized TBSS approach to determine whether there are FA differences of the major WM tracts between subgroups of BD individuals who have, and have not, attempted suicide, and HC. We also sought to investigate whether disrupted integrity of WM was associated with clinical measurements.

METHODS AND MATERIALS

Participants

Fifty-one patients diagnosed with BD were all recruited from the Fourth People's Hospital of Chengdu. Diagnoses and suicide history were assessed in all patients by two licensed clinical psychiatrists (Wang XL and Feng C) using a structured clinical interview according to DSM-IV-TR criteria and the Columbia-Suicide Severity Rating Scale (C-SSRS, available at www.cssrs.columbia.edu), respectively. A self-injurious behavior without suicidal intent was excluded from being recorded as attempted suicides, and accordingly, 19 BD individuals were classified as having attempted suicide (attempters) and 32 as never having an attempted suicide (non-attempters). Most attempters had attempted suicide only once, but three of them had attempted at least three times. In the non-attempters group, 15 participants had suicide ideation. The severity of depression, mania, and anxiety was measured by the Hamilton Depression Rating Scale (HAMD), Young Mania Rating Scale (YMRS), and Hamilton Anxiety Rating Scale (HAMA), respectively. A comparison group of HC was recruited through advertising, and all were screened using the non-patient edition of the Structured Clinical Interview for the DSM-IV-TR (SCID-I-NP), to exclude any psychotic disorder. None of the HC had attempted suicide or had a family history of major mood or psychotic disorder as assessed by using the Family History—Research Diagnostic Criteria (22). For all participants, the following exclusion criteria were also applied: (i) age under 18 or over 60 years old, (ii) serious medical conditions that could affect brain structure, (iii) loss of consciousness >5 min, and (iv) contraindication to MR imaging. The study was approved by the Research Ethics Committees of West China Hospital of Sichuan University and the Fourth People's Hospital of Chengdu, and fully informed written informed consent was obtained from all participants.

MRI Acquisition

MR imaging was performed on a 3.0-T Tim Trio MRI system (Siemens Healthineers, Erlangen, Germany) equipped with an eight-channel head coil. For DTI, a spin-echo planar imaging sequence was used with the following acquisition parameters: repetition time (TR) = 6,800 ms, echo time (TE) = 93 ms, field of view (FOV) = 230 × 230 mm^2, matrix = 128 × 128, slice thickness = 3 mm, 50 slices, and no gap. The diffusion-sensitizing gradients (b = 1,000 s/mm^2) were applied along 20 non-collinear directions, and a reference image with no diffusion weighting (b_0 image) was also acquired.

Data Processing and Analysis

The MR images were inspected to exclude those with structural abnormalities and significant head motion, then the raw DICOM data were converted into NIFTI format using dcm2nii for inputting to the FMRIB Software Library 6.0.1 (FSL, FMRIB Image Analysis Group, Oxford, UK) (23, 24). The diffusion tensor was computed from the eddy current-corrected DTI data using DTIfit, and a mask was obtained by running the BET algorithm on the $b = 0$ images. Next, the data were co-registered using DTI-TK software [http://dti-tk.sourceforge.net/, (25, 26)] as described by Wang et al. (27). The steps comprising this process are shown in the flow diagram (**Figure 1**). So far, the main registration work that corresponds to the standard TBSS step of registration has been completed.

TABLE 1 | Demographic and clinical characteristics of participants.

Characteristics	Bipolar disorder subjects		Control subjects (n = 43)	F/χ^2	p
	Attempters (n = 19)	Non-attempters (n = 32)			
Age (years), mean (SD)	33 (12.2)	32 (12.7)	32 (10.4)	0.084	0.92
Range of age	18–58	18–58	20–52		
Sex, women/men (% women)	5/14 (26%)	22/10 (69%)	20/23 (47%)	8.972	0.01
Handedness, right/left (% right)	18/1 (95%)	29/3 (91%)	43/0 (100%)		
Disease duration (years)	9.2 (7.1)	7.9 (9.3)		0.54	0.59
HAMD score, mean (SD)	10.7 (8.8)	8.7 (6.1)		0.89	0.38
HAMA score, mean (SD)	10.5 (9.6)	9 (7.9)		0.58	0.56
YMRS score, mean (SD)	8.1 (9.5)	5 (6.7)		1.22	0.23
Lifetime psychosis (%)	4 (21.1)	8 (25.0)			
Family history of psychiatry (%)	9 (47.4)	11 (34.4)			
Clinical subtype: BD I/BD II	15/4	23/9			
Mood state					
Euthymia	10	15			
Depression	4	14			
Mania/hypomania	4	4			
Mixed state	1	0			
Unmedicated* (%)	3 (15.8)	3 (9.4)			
Medications (%)					
Lithium carbonate	5 (26.3)	6 (18.8)			
Anticonvulsants	0	3 (9.4)			
Atypical antipsychotics	10 (52.6)	26 (81.3)			
Benzodiazepines	6 (31.6)	7 (21.9)			
SSRI	6 (31.6)	10 (31.3)			
SNRI	3 (15.8)	5 (15.6)			
Mood stabilizers	11 (57.9)	21 (65.6)			
Comorbidity (%)					
Alcohol use disorder	1 (5.3)	1 (3.1)			
Cannabis abuse	1 (5.3)	0			
Obsessive compulsive	0	1 (3.1)			
Anxiety disorder	6 (31.6)	8 (25.0)			

**Not treated with medication for at least 2 weeks. HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Scale; YMRS, Young Mania Rating Scale; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors.*

The subsequent steps in DTI-TK were to generate the spatially normalized high-resolution (i.e., isotropic spatial resolution of isotropic 1 mm^3) maps of mean FA skeleton and the 4D FA data. The processes comprise the following steps: (1) the spatially normalized data were resampled to a matrix of 182 × 218 × 182 for which the corresponding voxel size is 1 × 1 × 1 mm^3; (2) the mean tensor was generated from the individual high-resolution DTI data, and maps of the mean FA and mean FA skeleton computed; (3) the FA data of each individual and the mean FA and mean FA skeleton were transformed to MNI space; and (4) all FA data were merged into a 4D volume, which was used to create a combined binary 3D mask. At this point, the preparation of all the data for analysis has been completed. Finally, the aligned FA data of all individuals were projected onto the mean FA skeleton map to obtain a "skeletonized" FA map, which was thresholded at a level of 0.25.

Statistical Analysis

First, potential differences in age and sex between the two BD subgroups and the HC group were analyzed by one-way analysis of variance (ANOVA) and chi-square tests, respectively. Next, the FSL tool for non-parametric permutation inference (i.e., randomize) was used to carry out the between-group statistical comparison of the 4D skeletonized FA images using a voxel-wise generalized linear model (GLM) with 5,000 permutations per test. The comparisons that were analyzed include attempters vs. HC, non-attempters vs. HC, and attempters vs. non-attempters. The permutation, or randomization method, is appropriate to use when the null distribution of the data is not known, which can be the case when, for example, the noise of the data does not follow a Gaussian distribution, as is often the case with MRI data (28). In order to assess cluster significance, a so-called threshold-free cluster enhancement (TFCE) approach was used (29) to calculate the *p*-value for each voxel after controlling for whole-brain family-wise error (FWE). Clusters were considered significant at a corrected $p < 0.05$, with sex and age added as covariates. Finally, the FSL routine named "atlasquery" was applied to automatically identify which WM fiber tracts with the statistically significant voxels corresponded to the Johns Hopkins University DTI-based white-matter atlases (30).

TABLE 2 | TBSS results of attempters, non-attempters, and healthy controls.

White matter tract	MNI coordinates of cluster peak (mm)			Number of voxels	Difference	*p*	Breakdowns
	x	*Y*	*z*				
Attempters vs. non-attempters							
R cingulum (hippocampus)	22	−25	−21	29	Attempters < non-attempters	0.003*	R cingulum (hippocampus)
R cingulum (hippocampus)	25	−22	−25	12	Attempters < non-attempters	0.004*	R cingulum (hippocampus)
Attempters vs. controls							
Genu of corpus callosum	13	1	31	5,182	Attempters < controls	0.002	Body of corpus callosum
							Genu of corpus callosum
							R inferior fronto-occipital fasciculus
							R anterior thalamic radiation
							R uncinate fasciculus
Genu of corpus callosum	−20	43	3	1,410	Attempters < controls	0.006	Genu of corpus callosum
							L anterior thalamic radiation
							L inferior fronto-occipital fasciculus
							L uncinate fasciculus
L inferior fronto-occipital fasciculus	−27	33	1	427	Attempters < controls	0.013	L inferior fronto-occipital fasciculus
							L uncinate fasciculus
							L anterior thalamic radiation
Non-attempters vs. controls							
Genu of corpus callosum	16	56	−8	13,420	Non-attempters < control	∼0	Genu of corpus callosum
							Body of corpus callosum
							R inferior fronto-occipital fasciculus
							L inferior fronto-occipital fasciculus
							L anterior thalamic radiation
							R anterior thalamic radiation
							L uncinate fasciculus
R superior longitudinal fasciculus	31	−87	12	925	Non-attempters < control	0.012	R superior longitudinal fasciculus
R superior longitudinal fasciculus	41	4	16	694	Non-attempters < control	0.008	R superior longitudinal fasciculus
R superior longitudinal fasciculus	50	−12	23	167	Non-attempters < controls	0.016	R superior longitudinal fasciculus

**p-value was uncorrected. JHU, JHU white-matter tractography atlas; R, right; L, left.*

Correlations Between Clinical Parameters and FA Values

Since the attempter subgroup contained a significantly greater proportion of females than the non-attempter subgroup, a two-tailed, two-sample *t*-test was applied to determine whether FA values differed with respect to sex. Subsequently, a partial correlation analysis was performed to investigate if potential correlations exist between clinical measurements and FA values in the attempter and non-attempter subgroups using sex as a covariate. The clinical measurements included illness duration, HAMD score, YMRS score, HAMA score, and lithium medication.

RESULTS

Group Comparisons

The demographic and clinical information regarding the three groups of participants (i.e., attempters, non-attempters, and HC) is presented in **Table 1**. No significant difference was observed in the mean age of the participants among the three groups ($F = 0.084$, $p = 0.92$). There was a significant difference in the sex ($\chi^2 = 8.972$, $p = 0.011$; pairwise comparisons: attempters vs. non-attempters, $p = 0.003$, attempters vs. HC, $p = 0.135$, and non-attempters vs. HC, $p = 0.055$).

Compared to HC, FA was significantly reduced in the genu/body of the corpus callosum, bilateral inferior fronto-occipital fasciculus, left UF, and bilateral anterior thalamic radiation in both attempters and non-attempters (**Table 2** and **Figures 2A,B**). For non-attempters there was also a significant reduction in the right superior longitudinal fasciculus compared to HC. When compared between two BD subgroups, FA was significantly reduced in the right hippocampal cingulum in attempters compared to non-attempters (uncorrected $p < 0.005$; **Table 2** and **Figure 3**).

Clinical Correlations

The illness duration of attempters was correlated to the FA value of the genu of the corpus callosum ($r = -0.695$, $p = 0.003$) ($p < 0.05$; **Figure 4**). Both HAMD ($r = 0.405$, $p = 0.024$) and HAMA ($r = 0.521$, $p = 0.003$) scores of non-attempters were correlated to the FA value of the superior longitudinal fasciculus. No significant correlation was observed between FA values and sex, YMRS score, and lithium exposure in attempters or non-attempters.

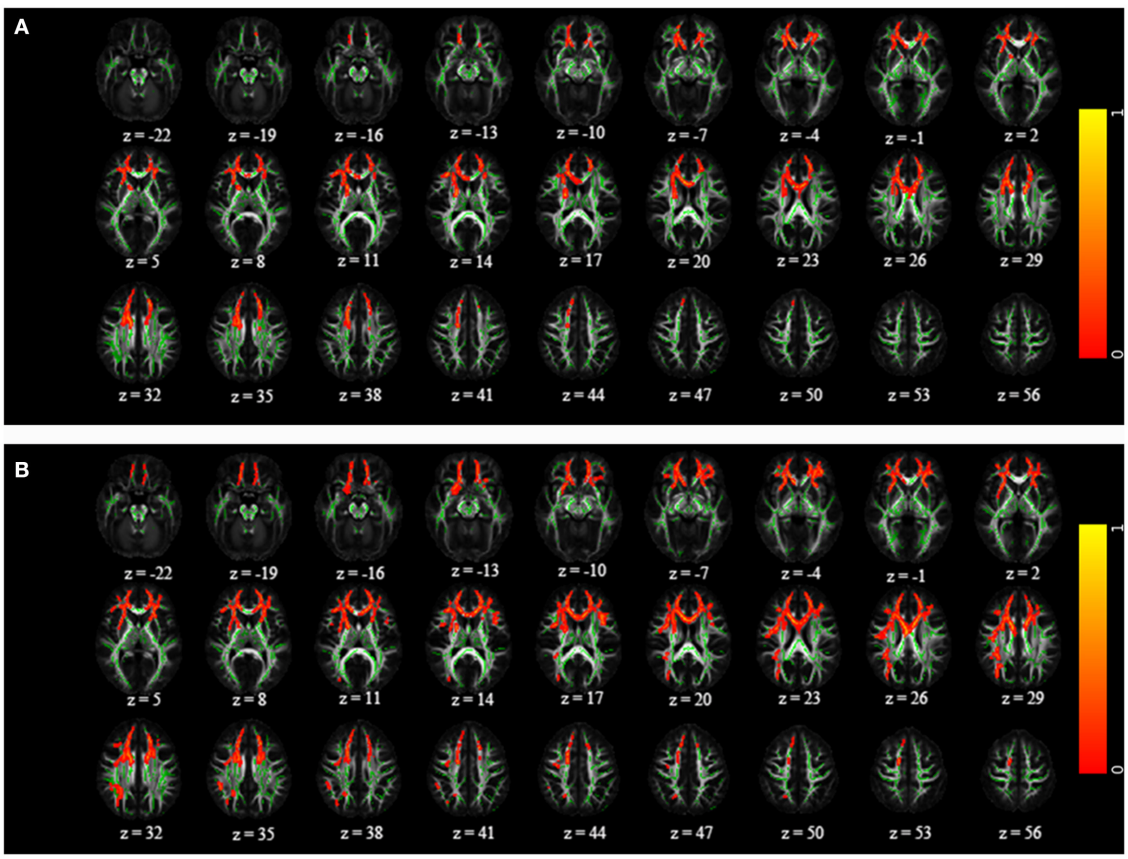

FIGURE 2 | Comparison of statistically significant differences (corrected $p < 0.05$) between **(A)** attempters and healthy controls and **(B)** non-attempters and healthy controls on one axial slice in IIT-mean space. The mean fractional anisotropy (FA) skeleton is shown in green, and regions with higher FA values are shown in red. The color bar provides 1-*p* values.

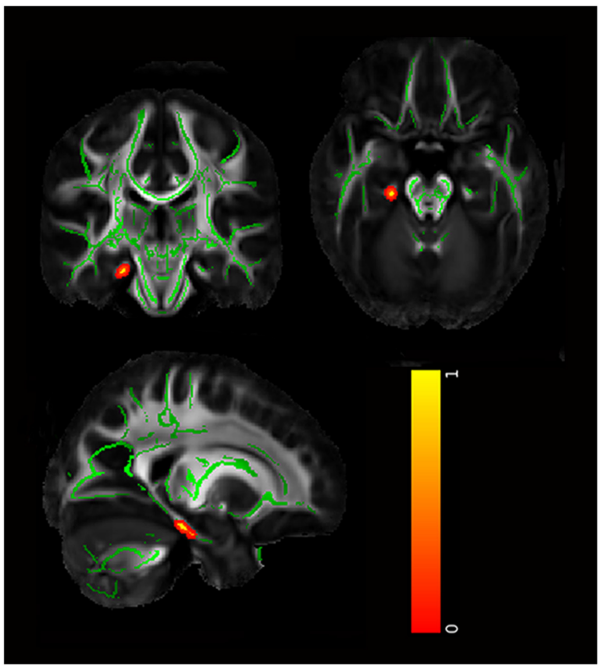

FIGURE 3 | The significant differences in attempters compared with non-attempters (uncorrected $p < 0.005$). The mean FA skeleton is shown in green, and regions with higher FA values are shown in red. The color bar provides 1-p values.

DISCUSSION

By using a TBSS approach with tensor-based registration, we demonstrated that FA was significantly reduced in the hippocampal cingulum of individuals with BD who had attempted to commit suicide compared with those who had not. We found that both attempters and non-attempters with BD had significantly reduced FA in the genu/body of the corpus callosum, inferior fronto-occipital fasciculus, UF, and anterior thalamic radiation when compared with HC. In addition, FA in the right superior longitudinal fasciculus was found significantly reduced only in non-attempters compared to HC. The illness duration of attempters was correlated to the FA value of the genu of the corpus callosum.

Consistent with our finding of reduced FA in the hippocampal cingulum in attempters compared to non-attempters, Ho et al. (31) reported that FA reduction in the cingulum-hippocampus tracts could be used as a predictor of suicidal ideation. Yurgelun-Todd et al. (32) also found that the right cingulum FA had a positive correlation with current suicidal ideation and impulsivity. From another point of view, the hippocampal cingulum is part of the so-called cingulum tract that carries information from the cingulate gyrus to the hippocampus, and our observation that reduced FA was found in attempters compared to non-attempters may indicate that attempted suicide is associated with abnormal hippocampal structure. For example, reduced gray matter volume in the hippocampus has been reported in suicidal mood disorder patients (33, 34). This anomaly has also been found in two reports that showed reduced gray matter volume in the hippocampus of BD individuals who have attempted suicide compared to those who have not (14, 16). In addition, some investigators found that FA value in the cingulum fibers could be a supplementary marker to the volume of the hippocampus (35).

The FA abnormalities in the corpus callosum, UF, inferior fronto-occipital fasciculus, and anterior thalamic radiation were ubiquitous in BD and not specific in the suicide attempter subgroup, which was in keeping with other DTI studies (36–38). It is known that all these regions are considered to be key components in the frontal–subcortical circuits (39). These circuits connect specific areas of the frontal cortex (i.e., dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex) with the basal ganglia and thalamus and are thought to be involved in mediating emotional and cognitive processing (40, 41). Almost two decades ago, Strakowski et al. (42) proposed that abnormalities in frontal–subcortical circuits may significantly contribute to symptoms experienced by individuals with BD. This view was further supported by the findings of two task-related fMRI studies (43, 44). Furthermore, studies of single-photon emission computerized tomography revealed significant functional disruption and metabolic abnormalities of frontal–subcortical circuits in BD by single-photon emission computerized tomography (45) and magnetic resonance spectroscopy imaging (46).

In addition, the current study found reduced FA in the superior longitudinal fasciculus only in the non-attempters compared to HC. One of the possible explanation may be that a lower proportion of non-attempters were exposed to lithium. In an attempt to obtain further insight, we extracted the FA values of all the tracts that showed significant differences between individuals with BD and HC and investigated the relationship with lithium exposure. This analysis revealed that the FA values are significantly higher in the lithium group than the non-lithium group ($t = -2.54$, $p = 0.021$), suggesting that the higher lithium exposure in the attempter group was counteracting the reduction of FA to a certain extent.

The result of the correlation analysis showed that the FA value of the superior longitudinal fasciculus was significantly correlated with the severity of depression and anxiety in non-attempters. Similarly, the anomaly of the superior longitudinal fasciculus in non-attempters may be correlated with the medication of lithium, and the positive correlation might be interpreted as the aggressive treatment in patients with more severe depression or anxiety. Thus, we presumed that the superior longitudinal fasciculus could be rapidly repaired after treatment. This inference needs to be further confirmed through prospective longitudinal research. Moreover, we also observed that the attempters with longer illness duration showed a lower FA value in the genu of the corpus callosum. This result suggested that the integrity loss in the genu of the corpus callosum would get progressively worse as the illness progresses. This result also suggested that the newly diagnosed individuals may not be spared from this integrity loss.

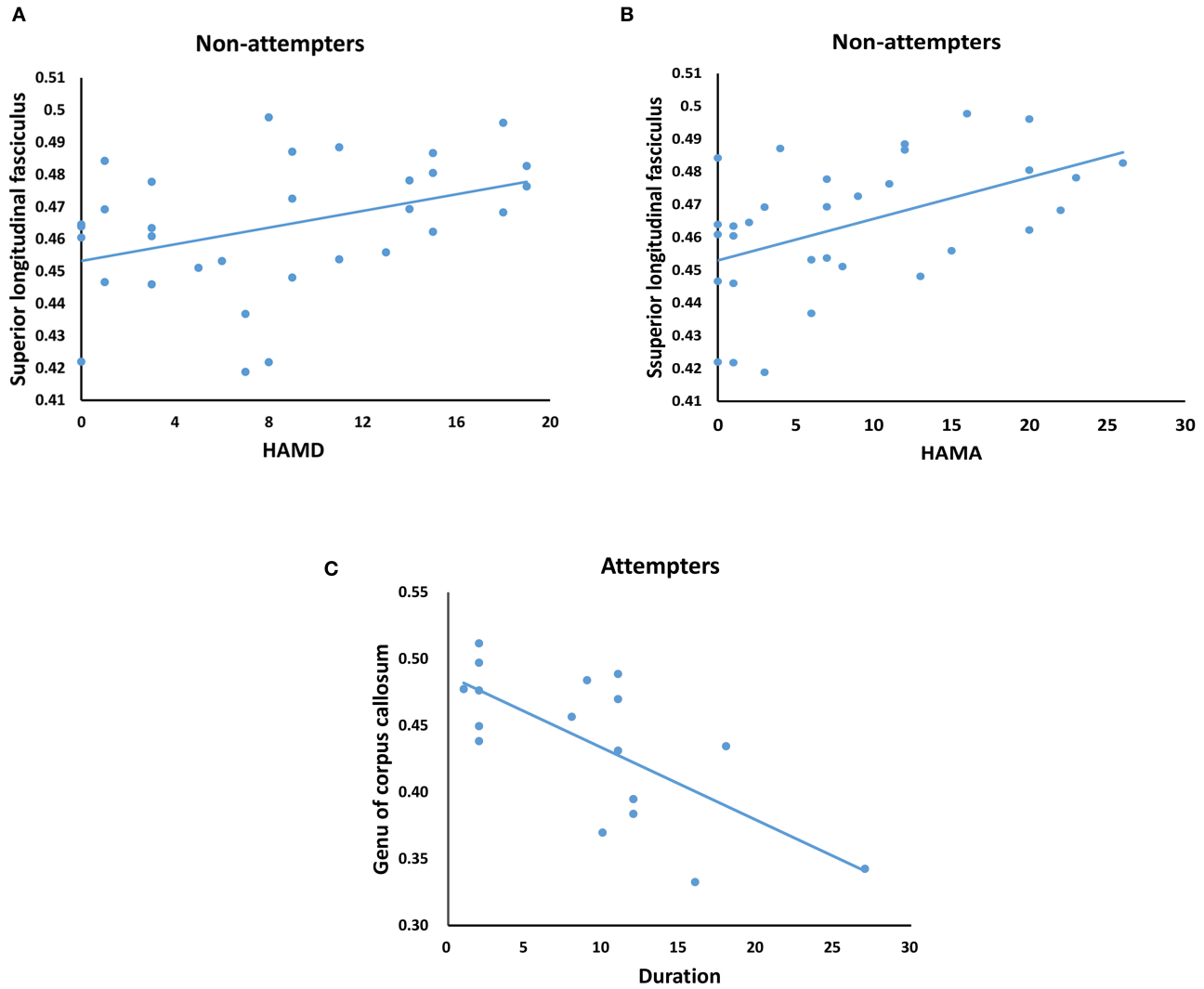

FIGURE 4 | Correlations between clinical measurements and FAs in attempters and non-attempters. **(A,B)** The HAMD score **(A)** and HAMA score **(B)** of non-attempters were positive correlated with the FA value of superior longitudinal fasciculus. **(C)** The illness duration of Attempters was negative correlated with the FA value of genu of corpus callosum. Significant at $p < 0.05$.

There are several limitations that must be considered in interpreting the findings of the present study. Firstly, the relatively high number of females in attempters compared to non-attempters may have potential influences, although sex was included as a covariate in the analyses. Secondly, there was heterogeneity in illness subtypes and mood states in the patient group, which may also bias the current findings. Thirdly, the significance of the reduction in FA in attempters compared to non-attempters did not pass the test for the effect of multiple comparisons, and further research need to be performed to explore this finding. Fourthly, a high variation was observed in FA values of the WM tracts in individuals with BD, which may be related to recruiting BD individuals with different severities of illness and correspondingly taking different medications. In future studies, it would be necessary to separate individuals according to different clinical subtypes and mood states of BD, taking into account the possible effects of different medications, especially lithium. Moreover, it is better to explore white matter integrity with more potential metrics such as AD, RD, or MD. Finally, because of the cross-sectional nature of our study, the observed effects cannot be interpreted as being causative.

CONCLUSIONS

Our study suggests that the hippocampal cingulum may be the neurobiological basis underlying attempted suicide of BD individuals. The observation of reduced FA in the frontal–subcortical circuit in both attempters and non-attempters with BD potentially sheds light on the neural basis of BD. In addition, the illness duration of suicide attempters may have an effect on

the altered integrity of the corpus callosum. We recommended that functional MRI could be applied together with DTI in future studies to determine the functional significance of abnormal WM integrity in BD individuals who have attempted suicide.

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 West China Hospital of Sichuan University and the Fourth People's Hospital of Chengdu. Written informed consent to participate in this study was provided by the participants.

AUTHOR CONTRIBUTIONS

ZJ contributed to the conception and design of the study. XW, FT, CF, XL, and SY contributed to the acquisition of data. FT, XW, and NR contributed to the analysis and interpretation of data. FT, XL, and NR contributed to the drafting and revising of the paper. FT and ZJ had full access to all data and take responsibility for the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Suicidal Behavior in Fibromyalgia Patients: Rates and Determinants of Suicide Ideation, Risk, Suicide, and Suicidal Attempts—A Systematic Review of the Literature and Meta-Analysis of Over 390,000 Fibromyalgia Patients

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Background: Suicide is a leading cause of death worldwide, affecting ∼800,000 people every year. Fibromyalgia is an extremely prevalent rheumatic disease with a predisposition for comorbid anxiety and depression, which are known risk factors for suicidal behavior. Suicidality and relevant risk factors for suicidal behavior have not been thoroughly studied in patients with fibromyalgia.

Objectives: To investigate the risk of suicidal ideation and attempts in patients with fibromyalgia.

Methods: A systematic review and meta-analysis was conducted and reported according to the "Preferred Reporting Items for Systematic reviews and Meta-analyses" (PRISMA) standards. Also, the gray literature was extensively searched.

Results: Thirteen studies were included in the present systematic review and meta-analysis, including 394,087 fibromyalgia patients. Sample size ranged from 44 to 199,739 subjects, mean age ranged from 45.8 to 54.5 years while the female percentage with fibromyalgia ranged from 17.1 to 100.0%. The overall suicide ideation prevalence was 29.57% (95%CI 1.84–72.07), with an OR 9.12 of (95%CI 1.42–58.77), ranging from 2.34 (95%CI 1.49–3.66) to 26.89 (95%CI 5.72–126.42). Pooled suicide attempt prevalence was 5.69% [95%CI 1.26–31.34], with an OR of 3.12 [95%CI 1.37–7.12]. Suicide risk was higher with respect to the general population with an OR of 36.77

(95%CI 15.55–96.94), as well as suicide events with an HR of 1.38 (95%CI 1.17–1.71). Determinants of suicidality were found to be: employment status, disease severity, obesity and drug dependence, chronic pain and co-morbidities, in particular depression, anxiety, poor sleep, and global mental health. However, in some cases, after adjusting for psychiatric conditions, the threshold of statistical significance was not achieved.

Conclusion: Fibromyalgia patients are particularly prone to suicide, in terms of ideation, attempt, risk and events, warranting a pre-emptive screening of their mental health status. Given the few studies available, the high amount of heterogeneity, the evidence of publications bias and the lack of statistical significance when adjusting for underlying psychiatric co-morbidities, further high-quality studies should be conducted.

Clinical Trial Registration: ClinicalTrial.gov, identifier 10.17605/OSF.IO/Y4BUE.

Keywords: fibromyalgia, suicidal ideation and attempt, PRISMA guidelines, systematic review, meta analysis

INTRODUCTION

Suicide is a leading cause of mortality worldwide, accounting for 1.4% of premature deaths. According to the World Health Organization (WHO), in 2015, ∼800,000 deaths were due to suicide, roughly estimating as one person every 40 seconds (1). Suicide is a complex, multi-factorial phenomenon, deriving from the interaction between individual characteristics and environmental factors. Suicide attempts and ideation may be antecedents of suicide and as such, represent important predictors of suicidal behaviors (2). Suicidality includes a diverse and dynamic spectrum, ranging from death wishes and suicidal thoughts to suicide attempts and completed suicides.

Most suicidal behaviors and suicides occur in patients with underlying psychiatric diseases (1), including depression and mood disorders (3), substance abuse and dependence (4), schizophrenia and other psychoses (5), anxiety (6), personality disorders (7), eating disorders (8) and trauma-related disorders (9). Co-occurrence of suicide and organic mental disorders which are characterized by neurological impairment and dysfunction, such as multiple sclerosis (10) and epilepsy (11), is also frequently reported.

Among physical illnesses, chronic conditions such as asthma (12) and renal failure (13), significantly increase the risk of suicidality (1). Fibromyalgia is a chronic condition, characterized by widespread, musculoskeletal pain, morning stiffness, hypersensitivity to physical and physiological stimuli, sleep disorders and prominent fatigue. It is the second most common musculoskeletal condition, affecting 0.2–6.6% of the population worldwide (14), with a higher prevalence rate among women (in the range 2.4–6.8%) (15). As a chronic pain disorder, fibromyalgia patients suffer from high rates of comorbid anxiety and depression, which, as previously mentioned, are well-known risk factors for suicidal behaviors (16–18).

Suicidality has been well-studied with relation to other chronic pain conditions, however there is a dearth of information with regard to suicidality amongst fibromyalgia patients. Although several large-scale studies have reported a statistically significant increased risk of suicide among fibromyalgia patients, these findings were not replicated in subsequent studies. Therefore, we conducted the present systematic review and meta-analysis with the aim of evaluating the risk of suicidal ideation, behavior, attempts and events amongst patients with fibromyalgia.

MATERIALS AND METHODS

Study Protocol and Design

The study protocol of the present systematic review and meta-analysis was conducted in accordance with the "Preferred Reporting Items for Systematic reviews and Meta-Analyses–Protocol" (PRISMA-P) guidelines (19). The study protocol is available upon formal request to the Corresponding Authors. It has been registered in the "Open Science Framework" (OSF) database (Registration Code 10.17605/OSF.IO/Y4BUE).

Research Team

The team involved in the process was multi-disciplinary and comprised of several members, including an expert of research methodology, biostatistics, and epidemiology (NLB), experts in the field of psychology and psychiatry (WC, NLB, HD, DA), experts in the field of rheumatology (AW, HA, DMG, and MA) and experts in the field of internal medicine (HA).

Review Aim and Purposes

The research question was generated after an extensive consultation of the research team. The review questions were: (i) What are the suicidal ideation, attempt and event rates among fibromyalgia patients? (ii) What are the main determinants of suicidal behavior among fibromyalgia patients?

The study's aim was to synthesize the existing scholarly literature concerning suicide rate among fibromyalgia patients and its determinants. Findings were presented by means of charts, tables and figures, together with a detailed, narrative report of the literature.

Literature Search

Several scholarly databases, including PubMed/MEDLINE, Scopus, ISI/Web of Science (WoS), were searched, using a

string of proper keywords, such as "fibromyalgia" and "suicide" (and synonyms), connected by Boolean operators. Wild card option (truncated keywords) and Medical Subject Headings (MeSH) terms were used where appropriate. Research strategy was adapted for each database, modifying the string of keywords accordingly. Gray literature was mined performing an extensive search of Google Scholar and Directory of Open Access Journals (DOAJ). Conference abstracts and proceedings were assessed as well. Relevant available reviews on the study topic were not included in the present systematic review and meta-analysis, yet were thoroughly evaluated with the goal of discovering additional potentially eligible studies. Further details about search strategy are reported in **Supplementary Table 1**.

Reference lists of potentially eligible studies were consulted in order to reduce the risk of missing relevant articles. Furthermore, target journals were hand-searched for potentially relevant studies. Artificial Intelligence techniques (such as Natural Language Processing (NLP)-based approaches) were utilized to facilitate and aid screening and selection process.

Literature search was carried out on May 31, 2019.

Inclusion Criteria

- Studies meeting the following PICOS criteria were considered for inclusion:
- P (patient, problem or population): fibromyalgia patients;
- I/E (intervention/exposure or phenomenon of interest): suicidality/suicidal behavior (in terms of suicide risk, suicidal ideation, attempt and event);
- C (comparison, control or comparator): any comparator (fibromyalgia patients *vs.* general population or patients suffering from other diseases);
- (outcome/outcomes of interest): prevalence/incidence and determinants of suicidality/suicidal behavior among fibromyalgia patients, within the conceptual framework of the "ideality to action" framework; and
- Study design/characteristics: original observational articles, prevalence/incidence studies.

Furthermore, the following criteria were taken into consideration:

- Time: no time filter/restraint (scholarly databases searched from inception); and
- Languages: no language filter/restraint (that is to say, all the full complement of languages available). In case of inclusion of non-English articles, they were acquired in full-text and translated by expert translators with expertise in the field of medicine and related health-allied disciplines.
- The reader is referred to **Supplementary Table 1** for further details.

Exclusion Criteria

Studies not meeting the above-mentioned PICOS criteria were excluded (**Supplementary Table 1**). More in detail, exclusion criteria were:

- P: patients with fibromyalgia as co-morbidity and not as the main diagnosis;
- I/E: fibromyalgia patients without suicidal behavior;
- C: cases vs. controls;
- O: studies not reporting outcome(s) of interest or with insufficient details to compute them; and
- S: review articles, letter to editor, editorial, expert opinion, commentary, clinical case reports or series; and interventional studies (including clinical trials).

Studies excluded with reasons were noted and reported (**Table 1**).

TABLE 1 | List of studies excluded with reasons.

Study excluded with reason	Reason for exclusion
Amir et al. (17)	Not meeting inclusion/exclusion criteria
Liu et al. (20)	Not meeting PICOS criteria (FM as a co-morbidity and not as the main diagnosis)

FM, fibromyalgia.

Data Extraction

The following data were retrieved: namely, study publication year, country, sample size, and main characteristics of the recruited sample (age, female percentage, educational level, employment and marital status, and disease activity). Data were extracted independently by two reviewers. Data extraction was pilot-tested on a sample of five articles randomly selected from the pool of included studies. In case of disagreement between reviewers, a third author was consulted and acted as a final referee. For further details, the reader is referred to **Supplementary Table 2**.

Study Appraisal

Methodological quality of the included studies was critically appraised using the Newcastle-Ottawa scale (NOS) (21). This tool explores three dimensions: namely, study selection (in terms of representativeness of the sample and the reliability of its recruitment method), comparability of the recruited sample with other studies in literature, and outcome(s) (in terms of its/their assessment, adequate follow-up, and sufficient follow-up duration).

Meta-Analysis

Meta-analysis was conducted using the commercial software "Comprehensive Meta-analysis" (CMA version 3.0) and MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). Rates were pooled together computing the effect size (ES) with its 95% confidence interval (CI). For prevalence figures, the logit transformation approach was utilized in the current meta-analysis, being one of the possible approaches for pooling together raw prevalence data. The following equation was used to compute the *logit* transformation *l*:

$$l = \ln\left(\frac{p}{1-p}\right)$$

where p is the prevalence proportion.

Variance was computed using the following equation:

$$Var\left(l\right) = \frac{1}{N \bullet p} + \frac{1}{N \bullet (1-p)}$$

where N is the study population size.

The pooled *logit* transformation was subsequently back-transformed to a proportion utilizing the following equation:

$$p = \frac{e^{l}}{e^{l}+1}$$

Heterogeneity among studies was quantified carrying out the I^2 and Q statistics. If $I^2 > 50.0\%$, heterogeneity was considered statistically significant and the random-effect model was utilized instead of the fixed-effect model. To investigate the sources of heterogeneity, meta-regression analyses (both uni-variate and multi-variate) were carried out, based on study publication year, country, sample size, quality, and main characteristics of the recruited sample (age, female percentage, educational level, employment and marital status, and disease activity) as moderators. In order to assess the stability and reliability of our findings, cumulative analysis was performed, removing one study per time and verifying the impact on the pooled ES. Sensitivity analysis based on study publication year, country, sample size and quality was performed. Publication bias was studied visually inspecting the funnel plot and carrying out the Egger's regression test. In case of the presence of publication bias, the "true" ES was estimated using the Duval and Tweedie's trim-and-fill method.

All figures with $p < 0.05$ were considered statistically significant.

RESULTS

Systematic Review

As pictorially shown in **Figure 1**, the initial search yielded a pool of 18,397 items. After removing duplicates, 18,101 studies were screened for potential inclusions. Studies were excluded in accordance with the exclusion criteria reported in **Supplementary Table 1** (17, 22).

Finally, 13 studies (20, 23–34) (**Table 2** and **Supplementary Table 3**) have been included in the present systematic review and meta-analysis, investigating a total sample of 394,087 fibromyalgia patients. Sample size ranged from 44 (29) to 199,739 (24) subjects: mean age ranged from 45.8 (32) to 54.5 (29) years while female percentage ranged from 17.1 (29) to 100.0% (20). Marital status ranged from 38.6 (30) to 86.3% (31). The percentage of subjects who had completed primary school ranged from 38.6 (29) to 61.5% (31), while the unemployment rate ranged from 5.6 (31) to 13.6% (26). Five and four studies were carried out in Spain (26, 29–31, 33), and in the USA (24, 27, 28, 34), respectively, whereas the remaining four studies were performed in Denmark (25), Canada (23), Taiwan (32) and Israel (20). Seven studies (23–25, 27, 28, 32, 34) were database-based, while three (26, 30, 31) and three (20, 29, 33) were cross-sectional and case-control studies, respectively. No longitudinal studies could be found. The diagnosis of fibromyalgia was mostly based on the 1999 ACR criteria, with the exception of two studies, one of which utilized the 2010 ACR criteria (27), and the second (34) which utilized machine learning techniques, and combined diagnostic criteria, clinical expertise and textual information from clinical charts and medical records. The diagnosis of suicidality was made by asking *ad hoc* questions in two studies (23, 26), or utilizing structured, validated, and reliable psychometric tools in seven studies (20, 25, 26, 29–31, 33). One study (24) did not report sufficient details about methodology adopted, while one study (34), as also previously mentioned for the diagnosis of fibromyalgia, deployed an ensemble of techniques, combining machine learning approaches, literature review and clinical expertise. Three studies (27, 28, 32) evaluated suicide event (categorized in completed suicide, suicide attempt, and non-suicidal self-inflicted injury).

The majority of studies demonstrated an increased risk of suicidal behavior amongst fibromyalgia patients, however these findings were not replicated in three studies included in this meta-analysis (20, 23, 28). When evaluating the determinants of suicidality among fibromyalgia patients, poor sleep quality was identified as a predictor of suicidality by several studies (26, 29–31). Triñanes and co-workers (31) and other studies, demonstrated depression and in particular, cognitive depression symptoms such as those identified by the Beck Depression Inventory (BDI) Self-Blame sub-scale, to be closely related to suicidal ideation. Additional risk factors reported were age (32), employment status (26), occupation (32), disease severity (26), obesity (34), psychological traits such as perceived burdensomeness, thwarted belongingness and poor marital adjustment (33) and drug dependence (34).

Study Appraisal

Concerning the methodological quality of the included studies, one (20), five (24, 26, 29, 31, 33), three (25, 27, 30), one (23) and three (28, 32, 34) were deemed of fair, fair-to-moderate, moderate, moderate-to-high and high quality, respectively.

Meta-Analysis

Rates of suicidal ideation were derived from 4 studies and ranged from 1.08% in the study by McKernan et al. (34) to 54.6% in the study by Jimenez-Rodríguez and co-authors (29). In particular, passive suicidal ideation ranged from 39.7 to 41.0%, whereas active suicidal ideation ranged from 8.3% in the study by Calandra and collaborators (30) to 13.6% in the study by Jimenez-Rodríguez et al. (30). Pooled rate for suicidal ideation, active and passive suicidal ideation resulted 29.57% [95%CI 1.84–72.07], 39.86% [95%CI 35.14–44.72], and 9.00% [95%CI 6.44–12.16], respectively. In the last 2 cases (active and passive suicidal ideation), heterogeneity was low and statistically not significant and, therefore, fixed-effect model was applied, whereas for the overall suicidal ideation rate due to the significant amount of heterogeneity ($Q = 819.97$, $I^2 = 99.63\%$ [95%CI 99.51–99.73], $p < 0.001$), the random-effect model was performed. OR was derived from 3 studies and ranged from 2.34 ([95%CI 1.49–3.66], $z = 3.71$, $p < 0.001$) in the study by Ratcliffe and co-workers (23) to 26.89 ([95%CI 5.72–126.42], $z = 4.17$, $p < 0.001$) in the study

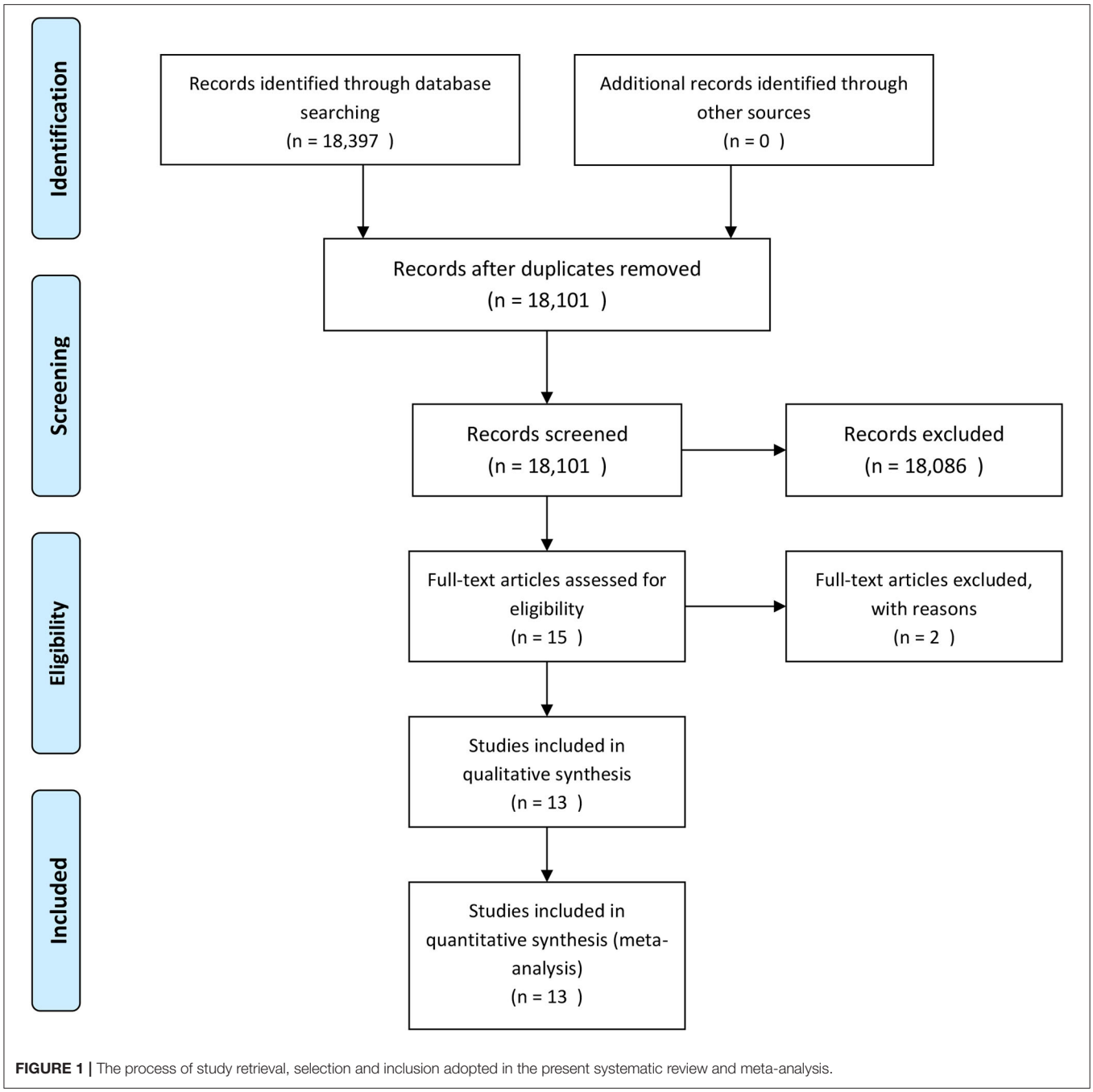

FIGURE 1 | The process of study retrieval, selection and inclusion adopted in the present systematic review and meta-analysis.

by Jimenez-Rodríguez and co-authors (29). Due to the highly statistically significant heterogeneity ($I^2 = 83.27$), the random-effect model was applied. Pooled OR resulted 9.12 ([95%CI 1.42–58.77], $z = 2.33$, $p = 0.020$), when not adjusting for psychiatric co-morbidities. However, due to the presence of publication bias, the "true" ES resulted 2.34 ([95%CI 0.48–11.52], not statistically significant). Correcting for confounding factors, the pooled OR resulted 7.60 ([95%CI 0.72–80.17], $z = 1.69$, $p = 0.092$). Once again, evidence of publication bias could be detected. Performing the trim-and-fill analysis, the "true" OR yielded 1.21 ([95%CI 0.15–9.83], not statistically significant). Interestingly, it was not statistically significant in both cases.

For suicidal attempt, rates were derived from 2 studies and ranged from 16.7 [95%CI 11.5–22.9] in the study by Calandre and co-authors (26) to 0.4 [95%CI 0.3–0.5] in the study by McKernan and co-workers (34). Due to the highly statistically significant heterogeneity ($Q = 92.27$, $I^2 = 98.9$ [95%CI 97.8–99.5], $p < 0.001$), the random-effect model was performed. The overall pooled ES resulted 5.69 [95%CI 1.26–31.34]. OR resulted 3.12 [95%CI 1.37–7.12] as computed in the study by Ratcliffe and

TABLE 2 | Main characteristics of included studies.

Authors	Year	Country	Study design	Sample size	Gender	Age	Suicidal variable studied	Epidemiological findings	Main findings
Amir et al. (20)	2000	Israel	Cross-sectional, case-control study	51 outpatients randomly chosen from 600	F 100%	48.96 ± 8.41	Suicide risk	44.5 ± 8.4 SRS score	No differences in terms of suicide risk with general population and other patients (RA, LBP)
Ratcliffe et al. (23)	2008	Canada	Retrospective database-based study (data drawn from the Canadian Community Health Survey Cycle 1.2 file) study	595	NR	NR	SI, SA	OR ranging from 1.21 [95%CI 0.68–2.18] to 2.34 [95%CI 1.49–3.66] for SI, OR ranging from 1.27 [95%CI 0.54–3.01] to 3.12 [95%CI 1.37–7.12] for SA	No significant SI and SA OR after adjusting for psychiatric conditions and/or other co-morbid chronic pan conditions
Cheng et al. (24)	2009	USA	Retrospective database-based study	199,739	NR	NR	Suicide risk	Incidence 31/100,000 person/years for SB, OR 3.5 for SB	Increased suicide risk among FM patients
Dreyer et al. (25)	2010	Denmark	Retrospective-prospective database-based study (data drawn from the hospital database and from the Danish Mortality Register)	1,269 (1,353 out of an initial list of 1,361)	F 93.2%	58.2% in the range 30–49 years	Suicide event	8 suicide events (SMR 10.5 [95%CI 4.5–20.7] for all patients, 4 suicide events (SMR 6.5 [95%CI 1.8–16.7] for confirmed FM patients, 2 suicide events (SMR 19.6 [95%CI 2.2–70.8] for possible FM patients	Increased suicide risk at the time of diagnosis until 5 years after the diagnosis
Calandre et al. (26)	2011	Spain	Cross-sectional study	180 out of 795 (completion rate of 22.6%)	F 97.8%	51 ± 8.5 [22–74]	SA	30 (16.7%) for SA (21 (70%) by drug poisoning); 20 (66.7%) one SA, 5 (16.7%) two SA and 5 (16.7%) reported three SA	Higher SA rate with respect to general population
Wolfe et al. (27)	2011	USA	Retrospective database-based study (data drawn from the Wichita nonparticipant group file and from the NDB)	8,186	F 93.9%	50.5 ± 12.4	Suicide risk	OR 3.31 [95%CI 2.15–5.11] with respect to general population	Increased suicide risk

(Continued)

TABLE 2 | Continued

Authors	Year	Country	Study design	Sample size	Gender	Age	Suicidal variable studied	Epidemiological findings	Main findings
Ilgen et al. (28)	2013	USA	Retrospective database-based study (data drawn from the VA National Patient Care Database and the NDI database)	79,359	F 17.1%	NR	Suicide risk	HR 1.45 [95%CI 1.16–1.81], $p < 0.001$; HR 1.16 [95%CI 0.92–1.44], $p = 0.09$	No significant suicide risk when correcting for psychiatric conditions
Jimenez-Rodríguez et al. (29)	2014	Spain	Cross-sectional, case-control study	44	F 93.2%	54.5 ± 12.7	Active and passive SI, suicide risk	18 (41%) for passive SI, 6 (13.6%) for active SI, 36 (81.8%) for risk of suicide, OR 26.89 [95%CI 5.72–126.42] for SI, OR 48.0 [12.93–178.21] for suicide risk	Higher SI and suicide risk with respect to controls
Calandre et al. (30)	2015	Spain	Cross-sectional study	373	F 94.6%	49 ± 8.6	SI	148 (39.7%) for passive SI, 31 (8.3%) for active SI	Higher SI rate among FM patients
Triñanes et al. (31)	2015	Spain	Cross-sectional study	117	F 100%	49.09 ± 9.26 [22–80]	SI (generally passive)	38 (32.5%) for SI	Higher SI rate among FM patients with respect to general population
Lan et al. (32)	2016	Taiwan	Retrospective nationwide database-based, matched case-control study (data drawn from the Longitudinal Health Insurance Database, a subset of the NHIRD)	95,150	F 58.4%	45.8 ± 17.2	Suicide event	347 suicide events (4.16/10,000 person-years). Crude HR 1.58 [95%CI 1.38–1.83] and adjusted HR 1.38 [95%CI 1.19–1.60] for suicide event	Increased suicidal behaviors among FM patients, with an overall mild-to-moderate risk of suicide events
Lafuente-Castro et al. (33)	2018	Spain	Case-control study	38 without SI, 15 with SI	F 96.0%	52 ± 8.2	SI, suicide risk	OR 19.054 [95%CI 2.405–150.935] for SI, OR 30.055 [95%CI 10.247–100.269] for suicide risk	Increased suicidal behaviors among FM patients
McKernan et al. (34)	2018	USA	Retrospective database-based	8,879	F 90.9%	57[a]	SI, SA	96 for SI, 34 for SA	Increased suicidal behaviors among FM patients

CI, confidence interval; F, female; FM, fibromyalgia; HR, hazard ratio; LBP, low back pain; NDB, National Data Bank for Rheumatic Diseases; NDI, National Death Index; NHIRD, National Health Insurance Research Database; NR, not reported; OR, odds ratio; RA, rheumatoid arthritis; SA, suicide attempt; SB, suicidal behaviour; SI, suicide ideation; SMR, standardized mortality ratio; SRS, Suicide Risk Scale; VA, Veterans Affairs.

[a] *Median.*

colleagues (23). However, statistical significance was lost, when adjusting for psychiatric co-morbidities (OR 1.27 [95%CI 0.54–3.01]).

For suicide risk, OR ranged from 30.06 ([95%CI 10.25–100.27], $z = 5.85$, $p < 0.001$) in the study by Lafuente-Castro et al. (33) to 48.0 ([95%CI 12.93–178.21], $z = 5.78$, $p < 0.001$) in the study by Jimenez-Rodríguez et al. (29). Pooled OR resulted 36.77 ([95%CI 15.55–96.94], $z = 8.21$, $p < 0.001$). In terms of HR, suicide risk resulted 1.45 ([95%CI 1.16–1.81], $p < 0.001$) as computed in the study by Ilgen and collaborators (28). However, statistical significance was lost when adjusting for psychiatric conditions (HR 1.16 [95%CI 0.92–1.44], $p = 0.09$).

Concerning suicide event, HR resulted 1.38 [95%CI 1.17–1.71], adjusting for psychiatric conditions, as computed in the study by Lan et al. (32). Incidence of suicide events among fibromyalgia patients was 31/100,000 person/years, as computed in the study by Cheng and co-workers (24). Mortality OR resulted 3.31 [95%CI 2.15–5.11] with respect to general population, as reported in the study by Wolfe and co-authors (27). Standardized mortality rate was 10.5 [95%CI 4.5–20.7], as reported by Dreyer and colleagues (25). All these values were not adjusted for underlying psychiatric conditions (24, 25, 27).

Relevant forest plots are shown in **Figure 2** and tabulated in **Table 3**.

DISCUSSION

Fibromyalgia is a chronic pain syndrome closely associated with psychiatric comorbidities, sleep disturbances and fatigue, which all contribute to a detrimental effect on quality of life. The close link between fibromyalgia and depression, a known risk factor for suicide, has supported the theory that fibromyalgia patients may have a higher risk of suicidal ideation and behavior, however, contrasting findings have been reported in the literature. The findings from our large-scale and rigorously conducted systematic review and meta-analysis indicate that while fibromyalgia patients do have an overall increased risk of

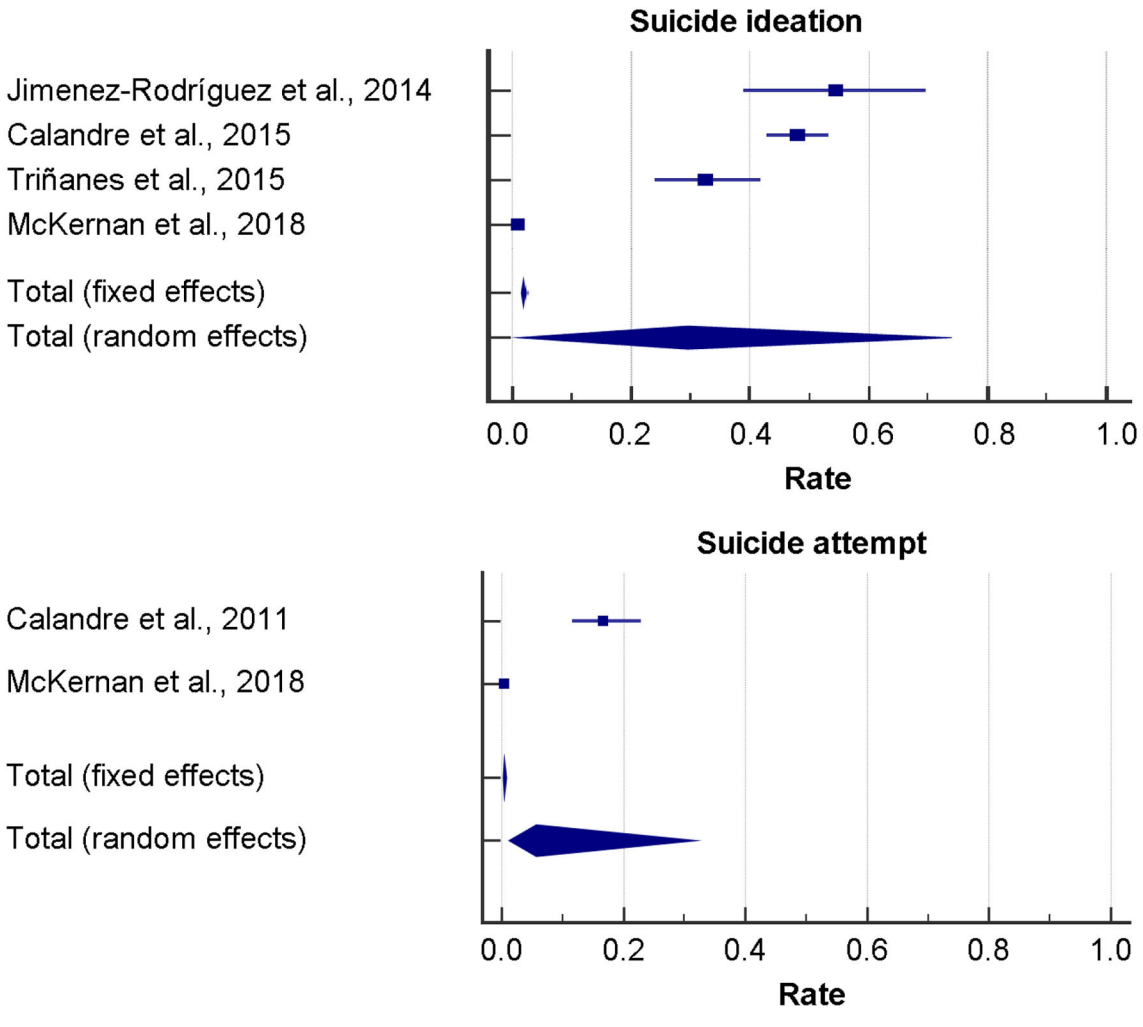

FIGURE 2 | Forest plots of suicide ideation and attempt rates among fibromyalgia patients.

TABLE 3 | The main findings of the systematic review and meta-analysis on suicidality among fibromyalgia patients.

Variable	Results
Suicide ideation	Overall suicide ideation rate 29.57% [95%CI 1.84–72.07]; 1.08–54.6%
	Passive suicide ideation rate 39.86% [95%CI 35.14–44.72]; 39.7–41.0%
	Active suicide ideation rate 9.00% [95%CI 6.44–12.16]; 8.3–13.6%
	OR 9.12 [95%CI 1.42–58.77]; 2.34 [95%CI 1.49–3.66]–26.89 [95%CI 5.72–126.42]
	OR 7.60 [95%CI 0.72–80.17] adjusted for psychiatric conditions
Suicide attempt	Rate 5.69% [95%CI 1.26–31.34]; 0.38–16.67%
	OR 3.12 [95%CI 1.37–7.12]
	OR 1.27 [95%CI 0.54–3.01] adjusted for psychiatric conditions
Suicide risk	OR 36.77 [95%CI 15.55–96.94]; 30.06 [95%CI 10.25–100.27]–48.0 [95%CI 12.93–178.21]
	HR 1.45 [95%CI 1.16–1.81]
	HR 1.16 [95%CI 0.92–1.44] adjusted for psychiatric conditions
Suicide event	HR 1.38 [95%CI 1.17–1.71]
	Incidence 31/100,000 person/years
	Mortality OR 3.31 [95%CI 2.15–5.11]
	SMR 10.5 [95%CI 4.5–20.7]

CI, confidence interval; HR, hazard-ratio; OR, odds-ratio; SMR, standardized mortality rate.

suicidal behavior and attempts, this association may be due to the confounding presence of chronic and psychiatric comorbidities.

Several studies have demonstrated the relationship between chronic pain syndromes and suicide. Interestingly, it appears that while the physical characteristics of pain, such as intensity and type, are of importance, it is rather the emotional, psychological interpretation of pain that significantly impacts and drive suicidality (35, 36). In the study by Calandre et al. (30) included in this review, physical pain was only weakly associated with suicidal ideation in fibromyalgia patients. In another included study, which compared suicidal ideation and attempts between fibromyalgia patients and patients with lower back pain, the risk was greater for fibromyalgia patients, despite similar mean pain intensity scores for both groups (29). This suggests that personality traits and behaviors commonly associated with fibromyalgia, such as neuroticism and catastrophizing, predispose fibromyalgia patients to distorted pain perception and further amplifies their suicidality risk (17, 36, 37).

When evaluating the relationship between fibromyalgia and suicidality, it is important to note the association between fibromyalgia with several well-known suicidal risk factors, such as female gender, psychiatric comorbidity and sleep disturbance. Additionally, it is important to address the significant impact of demographic and socioeconomic factors on suicidality, such as marital and employment status, which are also known to be lower in fibromyalgia patients (33). While conducting this systematic review, we found that disease severity, employment status and comorbidities such as obesity, drug dependence, anxiety, poor sleep, global mental health and in particular, depression, were all important negative factors which contributed to the overall risk of suicide in fibromyalgia patients. As noted before, when the confounding effect of the comorbidity factors was evaluated, fibromyalgia was not shown to have an independent association with suicidal ideation and attempts. Thus, it may be inferred that it is not the chronic condition of fibromyalgia *alone* which leads to a higher risk of suicidality, yet rather the impact of the comorbidities, mainly psychiatric, which drives the increased risk. However, it remains to be seen whether the presence of fibromyalgia may augment the suicidal risk effect conferred by psychiatric illness, mainly depression. It has been hypothesized that the fibromyalgia syndrome is the results of a neurogenic neuroinflammatory reaction in which physical and psychological trauma trigger CNS sensitization and subsequently, widespread pain and mood disorders. Major depressive disorder has also been recently linked to immune system activation in the CNS, which raises the possibility of a combined detrimental neuroinflammatory impact leading to an increased risk of suicidality in fibromyalgia patients with depression (38). Another theory indicates the important role of serotonergic neurotransmission, which has been demonstrated to be decreased in fibromyalgia patients and independently associated with an increased risk of suicide (32, 39, 40).

Although thorough, this meta-analysis demonstrates the paucity of information existing in the literature regarding suicidality amongst fibromyalgia patients. Furthermore, the low quality of evidence should be noted. With the only exception of the investigation conducted by Dreyer et al. (26), the majority of the studies included in this meta-analysis were retrospective and/or cross-sectional, and as such, impeded our ability to determine a causal association between suicidality and fibromyalgia. Moreover, despite the critical importance of taking psychological comorbidities into account, only five studies adjusted for co-morbid chronic conditions and only six investigations adjusted for co-occurring psychiatric disorders. Nevertheless, this systematic review and meta-analysis sheds light upon the important confounding effect of said comorbidities when assessing the relationship between fibromyalgia and suicidal ideation and behaviors.

Our study's major strength relies on its methodological rigor, transparency and reproducibility as a systematic review and meta-analysis conducted in accordance with the PRISMA guidelines, in addition to the extensive literature search, cross-checking and cross-referencing we conducted. However, our study suffers from several limitations, which should be properly recognized. The major shortcoming was the small number of studies retained for each outcome, which precluded the possibility of running meta-regressions based on different co-factors and co-variates, such as study design, diagnostic criteria utilized for fibromyalgia and suicidality/suicidal behaviors, use of validated tools or self-report questionnaires, and further stratifying according to underlying chronic and/or psychiatric co-morbidities. Moreover, it is noteworthy that the largest sample size included in the present systematic review and meta-analysis

(34) could not be adequately controlled for diagnostic criteria and quality. Another limitation was the high amount of heterogeneity and the presence of publication bias, which calls for caution when interpreting and generalizing the present findings. Nevertheless, our study demonstrates the importance of further elucidating and determining suicidality risk factors. Given the complex, non-linear, multi-factorial etiopathogenesis of suicidal behaviors, longitudinal studies are warranted. Also, the use of structural equation modeling could be particularly effective, considering the reciprocal relationship among the variables, in order to avoid "ceiling effects."

CONCLUSIONS

The present systematic review and meta-analysis has practical implications for rheumatologists, who should be aware of the clinically relevant suicide risk among fibromyalgia patients. We found that fibromyalgia is associated with an increased rate of suicidality, in terms of ideation, attempt, risk and events, warranting a pre-emptive screening of their mental health status. However, in some cases, after adjusting for psychiatric conditions, the threshold of statistical significance was not achieved. Given the few studies available, the high amount of heterogeneity and the evidence of publications bias, further high-quality studies should be conducted, with a focus on longitudinal studies.

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 authors.

AUTHOR CONTRIBUTIONS

MA, NB, DM, and HA: conceptualization. AW, AK, DM, YY, DA, and HA: data curation. NB: formal analysis and methodology. MA and HA: supervision. MA, AK, YY, and HA: writing—original draft. MA, NB, AK, YY, AW, DM, DA, and HA: writing—review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.629417/full#supplementary-material

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The Role of Oxidative Stress in Suicidal Behaviour Among Bipolar Patients: A Cross-Sectional Study in a Malaysian Sample

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Background: Oxidative stress markers are found to be linked with depression and suicide attempts in bipolar disorder (BD), although the role of DNA damage as a marker of suicidal ideation and attempt has yet to be determined. We aim to investigate the association between DNA damage and suicidal behaviour, i.e., suicidal ideation and suicide attempt, among suicidal ideators in BD patients while accounting for clinical and psychosocial risk factors.

Methods: A cross-sectional study was conducted in the Universiti Kebangsaan Malaysia Medical Centre on 62 consecutive BD patients diagnosed using the M.I.N.I. Neuropsychiatric Interview and 26 healthy control participants. Socio-demographic and clinical assessments were performed using the Columbia Suicide Severity Rating Scale (C-SSRS) for lifetime suicidal ideation and attempt, Quick Inventory of Depressive Symptomatology (QIDS) for depression severity, Clinical Global Impression for Bipolar Disorder (CGI-BD) for illness severity [both mania (CGI-Mania) and major depressive episode (CGI-MDE)], Social Readjustment Rating Scale (SRRS) for change in life events, and Barratt Impulsiveness Scale (BIS) for behavioural impulsivity. The degree of DNA damage in peripheral blood samples was determined using a standard protocol of comet assay.

Results: Multivariable logistic regression revealed higher scores of CGI-MDE as the sole significant factor for lifetime suicidal ideation (OR = 1.937, 95% CI = 1.799–2.076). Although initial bivariate analysis showed a significant association between DNA damage, malondialdehyde (MDA), catalase (CAT), and suicidal behaviour, the findings were not seen in multivariable logistic regression. Bivariate subgroup analysis showed that moderate and severe DNA damage ($p = 0.032$ and $p = 0.047$, respectively) was significantly associated with lifetime suicide attempts among lifetime suicidal ideators.

The study is the first to look at the connexion between DNA damage and suicidal risk in bipolar patients. It is limited by the small sample size and lack of information on illicit substance use.

Conclusions: More severe DNA damage was significantly associated with lifetime suicide attempts among lifetime suicidal ideators in BD. However, the severity of depression was found to be independently associated with lifetime suicidal ideation *per se* rather than DNA damage in BD. Larger prospective studies are required to ascertain the potential of DNA damage as a biomarker for the transition from suicidal ideation to a suicide attempt.

Keywords: suicidal ideation, suicide attempt, suicide, suicidal behaviour, oxidative stress, biomarkers, DNA damage, bipolar disorder

INTRODUCTION

Suicide is a common endpoint for many individuals with severe psychiatric illnesses. It account for 1.4% of all deaths worldwide and is a significant cause of mortality in bipolar disorder (BD) (1). Recent research has found that 20% of BD patients die by suicide, with 20–60% of them having at least one suicide attempt in their lifetime (2).

The presence of suicidal ideation is a recognised risk factor for more serious suicidal acts (3). However, previous studies have found that not all suicidal ideators progress to attempted or completed suicide. A retrospective chart review by Busch et al. (4) showed that only 39% of patients eventually committed suicide, and most of them were depressed (4). Chan et al. (5) found that 24% of suicidal ideators with unipolar or bipolar depression transitioned to a suicide attempt within a year (5). Therefore, it is clinically pertinent to identify suicide attempters among suicidal ideators given attempted suicide being one of the most robust predictors of eventual suicide (6). Established risk factors for suicidal ideation among BD patients include the severity of hopelessness, irritability directed inwards, and hostility (7). The risk for a suicide attempt is increased in the presence of the following factors: previous suicide attempt, comorbid alcohol abuse, recently been discharged from the hospital, depression, mixed features, and psychotic mania (8).

May and Konskly's meta-analysis has shown that clinical risk factors for suicidal ideators are different from those for suicide attempters; i.e., depression and hopelessness predict suicidal ideas well but not suicide attempts (9). This difference is one of the challenges in the process of predicting suicidal behaviour in clinical settings; i.e., which suicidal ideators will subsequently attempt suicide? Thomas Joiner has introduced the concept of capability for suicide in his interpersonal-psychological theory of suicide (ITPS); i.e., a suicide attempter has developed the capability to overcome the fear of attempting suicide via the habituation to pain, injury, and death (10, 11). This type of ideation-to-action framework has been employed in the process of understanding the progression of a suicidal idea to potentially lethal attempts from the clinical perspective (12). Nevertheless, this model is based solely on clinical factors, and it does not incorporate the measurable biological markers. Also, mental illness appears to play a lesser role in suicide in Asia, while the accessibility to lethal suicide means and acute life stressors appears to be more important as compared with the Western counterpart (13). Some lethal methods for suicide used by the Asian population include charcoal burning, pesticide poisoning, ingestion of native poisonous plants, self-immolation, and jumping (14).

Oxidative stress, a group of measurable biological markers, has been implicated in the pathophysiology of BD. A meta-analysis by Brown et al. (15) stated that increased lipid peroxidation (LP) and nitric oxide (NO) levels, as well as DNA and RNA damage, are commonly found in BD (15). In addition, oxidative stress biomarkers are also shown to be associated with suicide attempts in bipolar depression, which includes NO metabolites (NOx), lipid hydroperoxides, and plasma total antioxidant potential (16). Schiavone et al. have suggested high NOX2-derived oxidative stress may have a role in predicting suicide (17). In the study of Moraes et al. (18), they cannot find any association between oxidative stress and suicidal behaviour, which can be predicted by early life trauma (18). In another study, the NO level and advanced oxidation protein products (AOPP) correlate positively to the intensity of suicidal ideation, and the number of lifetime suicide attempts correlates positively with advanced glycoxidation end products (AGE) and dityrozine (DT), while it correlates negatively with catalase (CAT) (19). A meta-analysis indicates that inflammatory neurotoxicity, nitro-oxidative stress, and lowered neuroprotection explain partly the increased suicidal ideation and attempts among psychiatric patients, which is more in suicide attempters (20).

There is still a knowledge gap with regard to our understanding of the role of oxidative stress markers in more comprehensive risk models of suicidal behaviour incorporating established clinical and psychosocial factors, particularly in terms of differentiating suicide attempters from non-attempters within a high-risk group of BD patients with suicidal ideation, especially in Asian populations. Therefore, the objective of this study is to investigate the association between oxidative stress biomarkers and suicidal behaviour, i.e., suicidal ideation and suicide attempt, among suicidal ideators in BD patients while taking into consideration the interplay of clinical and psychosocial risk factors for suicidal behaviour.

METHODS

Participants

A cross-sectional study of a total sample of 88 study participants that included 62 consecutive BD inpatients and outpatients and 26 healthy controls from the age group range from 19 to 74 years old was conducted between July 2015 to November 2017 in one of the university hospitals in Malaysia. The diagnosis of BD was confirmed with M.I.N.I. Neuropsychiatric Interview (MINI 7.0) using the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) criteria, in either English (21) or Malay version (22). The patient must be able to communicate in both English or Malay language and give written consent. Exclusion criteria were as follows: clinically too ill to be interviewed, delirium, dementia, mental retardation, anaemia or other blood diseases, inflammatory/rheumatological diseases, metabolic or cancer-related diseases, pregnancy, or refusal to participate in the study. Eligible healthy controls were recruited according to the following inclusion criteria: no lifetime diagnosable psychiatric conditions, no lifetime suicidal ideation, stable medical conditions, and written consent for the study. Exclusion criteria for healthy control included the following: registered staff or student of Universiti Kebangsaan Malaysia Medical Centre (UKMMC), having anaemia or other blood diseases, inflammatory/rheumatological diseases, metabolic, or cancer-related diseases and pregnancy. Age and gender matching for healthy controls was not feasibly performed due to logistic challenges. However, age and gender were accounted for in the multivariable logistic regression analysis. Socio-demographic information, i.e., age, gender, ethnicity, marital status, education level, employment, religion, smoking status, psychotropic medication, and antioxidant use, was collected using a self-reported questionnaire. Columbia Suicide Severity Rating Scale (C-SSRS), an interviewer-rated questionnaire, was used to assess for lifetime suicidal ideation (defined as a "yes" answer in item 3 in the lifetime suicidal ideation section of C-SSRS, i.e., the presence of active suicidal ideation in a lifetime regardless of the intention to carry out) and attempt (defined as a "yes" answer in the column of lifetime actual of attempt in the section of suicidal behaviour in C-SSRS). C-SSRS was suitable for assessment of both suicidal ideation and behaviour given the good convergent and divergent validity for suicidal ideation, i.e., strong correlation to suicide item of Montgomery–Åsberg Depression Rating Scale (MADRS) ($r = 0.799$, $p < 0.0001$; Cohen's d = 2.657) and weak correlations against somatic depression items, i.e., sleep ($r = 0.021$, $p > 0.05$; Cohen's d = 0.042) and hunger ($r = 0.042$, $p > 0.05$, Cohen's d = 0.084). There were high sensitivity and specificity for suicidal behaviour, i.e., 100% sensitivity and specificity for actual suicide attempts (23). The Malay version of C-SSRS was linguistically validated (24).

Disease severity of BD was assessed with clinician-rated Clinical Global Impression for Bipolar Disorder (CGI-BD) and self-rated Quick Inventory of Depressive Symptomatology (QIDS). CGI-BD, an improved version of the original CGI, which was more suitable for the assessment of BD, was used to assess both the severity of manic (CGI-Mania) and major depressive episode (CGI-MDE) (25). A higher CGI-Mania score indicated more severe mania, while a higher CGI-MDE score indicated more severe depression.

The QIDS was a self-reported questionnaire with high internal consistency and concurrent validity for the severity of major depressive episode (MDE) (26). The translation of QIDS into the Malay language was done using the "2 forward, 2 backward" technique. Forward translation from the original English version to the Malay version was performed by a master-level clinical psychologist and a biomedical science research officer with established research experience in the reliability and validity of psychological rating scales. The two translated versions were combined using the best wording based on the consensus, and face validity was assessed by a consultant psychiatrist (A) and a doctorate-level clinical psychologist (C). The combined forward translated Malay version was sent for backward translation into English by two medical undergraduates with training in research including translation of rating scales in psychiatry, and the two backward-translated versions were combined by another consultant psychiatrist (B). Subsequently, face validity of the Malay-translated version was assessed by the two consultant psychiatrists (A and B) and the clinical psychologist (C). Preliminary pilot reliability analysis of QIDS Malay version in 10 patients with an MDE showed good internal consistency, i.e., Cronbach alpha of 0.849. A higher QIDS score indicated more severe depression.

Social Readjustment Rating Scale (SRRS) was a self-rated questionnaire for change in life events. Good concordance (Spearman's rho 0.97–0.91) was demonstrated between the Malaysian and American populations (27). The Malay version translated by Othman (28) had been widely used in the Malaysian population with depression (28–30). A higher SRRS score indicated more changes in life events.

Barratt Impulsiveness Scale (BIS) was used to examine behavioural impulsivity (31). The Malay version of BIS was validated locally in an unpublished dissertation with good internal consistency (Cronbach alpha of 0.77) and test–retest reliability (Spearman rho 0.77) (32). A higher BIS score indicated more behavioural impulsivity.

Ethical approval was obtained from UKMMC Research and Ethics Committee [Approval Number GUP-2014-048].

Blood Sampling

Peripheral blood measuring 15 ml was sampled within 24 h of the clinical interview in heparinized tubes for the analysis of superoxide dismutase (SOD), glutathione reductase (GPx), CAT activities, and malondialdehyde (MDA) concentrations, as well as for assessment DNA damage using comet assay (CA). The samples were sent to the laboratory for biochemical analysis upon sampling. The samples were initially centrifuged at 1,008 *g* for 10 min at 4°C to separate the red blood cells (RBCs) from the plasma. The RBC pellets were washed three times with 0.9% ice-cold NaCl and centrifuged at 1,008 *g* for another 10 min before being stored in the freezer with a temperature of −80°C until the time of analysis. Meanwhile, the plasma layer was transferred into Eppendorf tubes for MDA analysis.

Superoxide Dismutase Activity Analysis

The activity of SOD was analysed based on the methods by Beyer and Fridovich (33). Blood samples were mixed with an equal volume of distilled water to prepare haemolysates. The haemolysate (20 μl) was added to 1 ml of substrate solution that was made up of 50 mM of phosphate buffer, 0.2 M of L-methionine, 1.72 mM of nitro blue tetrazolium, and 1% Triton X-100. This mixture was then reacted with 10 μl of riboflavin in a brightly illuminated aluminium foil-lined box containing two 20-W Sylvania GroLux fluorescent lamps for 7 min. A control tube was run simultaneously, and the absorbance was measured at 560 nm. One unit of SOD equals the amount of enzyme needed to inhibit the rate of reduction of nitro blue tetrazolium by 50% at 25 °C and pH 7.8.

Glutathione Reductase Activity Analysis

The activity of GPx was analysed based on the methods by Paglia and Valentine (34). Firstly, the haemolysates (200 μl) were diluted with 0.8 ml of distilled water and mixed with 1 ml of cyanmethemoglobin reagent. Then it was added to a substrate mixture that was made up of 0.05 M of phosphate buffer, 5 mM of ethylenediamine tetraacetate, 1.125 M of sodium azide, 8.4 mM of reduced nicotine adenine dinucleotide phosphate (NADPH), 10 U/ml of GPx, and 0.15 M of reduced glutathione. Subsequently, 0.1 ml of H_2O_2 (2.2 mM) was added into 2.9 ml of the reaction mixture, followed by a change in absorbance for 5 min at 340 nm. A control tube was also run simultaneously. One unit of Px equals the amount of enzyme that was needed to oxidise 1 μmol of NADPH to $NADP^+$ per min at 25°C and pH 8.0.

Catalase Activity Analysis

The activity of CAT was analysed based on the methods by the team of Aebi (35). Initially, the haemolysate was prepared with 50 mM of phosphate buffer. Then 1 ml of H_2O_2 (30 mM) was added to 2 ml of enzyme solution to initiate a reaction. The change in absorbance was read against a blank that contained 1 ml of phosphate buffer. One unit of CAT equals the amount of enzyme needed to decompose 1 μmol of H_2O_2 per second at 25°C at pH 7.0.

Malondialdehyde Concentration

The concentration of MDA was measured based on the methods by Pilz et al. (36). Firstly, 25 μl of 1,1,3,3-tetraethoxypropane 95% was dissolved in 100 ml of distilled water to prepare an MDA standard of 1 mM of stock solution. Then 1% sulfuric acid was diluted with the prepared MDA standard to yield final concentrations of 10, 5, 2.5, and 1.25 nmol/ml to obtain the standard curve for the determination of MDA in total.

Comet Assay

Assessment of DNA damage was performed using a standard protocol for CA (37, 38). A mixture of 5 μl of whole blood with 70 μl of 0.6% low melting point agarose was prepared at about 37°C and rapidly pipetted onto a fully frosted microscope slide coated with a layer of 80 μl of normal-melting-temperature agarose (0.6%). Coverslip was removed after the solidification process, and the slides were immersed in cold lysing solution (2.5 M of NaCl, 100 mM of $Na_2EDTA{\cdot}2H_2O$, 10 mM of Tris-HCl, and sodium sarcosinate, adjusted to pH 10.0 with solid NaOH; and the volume was made up of 1 L of dH_2O) for 1 h in the refrigerator. The slides were then incubated in freshly prepared electrophoresis buffer (60 ml of NaOH and 10 ml of EDTA were made up of 2 L of cold dH_2O) at 10°C and a depth of 0.25 cm for 20 min. Electrophoresis of DNA was carried out at 1–10°C for 20 min using 25 V with the current adjusted to 300 mA, followed by buffer neutralisation with 0.4 M of Tris (pH 7.5) for two times. Slides were drained, and 30 μl of EtBr (0.2 mg/ml) was added. Slides were placed in a humidified air-tight container in a refrigerator to prevent drying of the gel and analysed immediately after the excess liquid was blotted. Coded slides were examined at ×200 magnification using a fluorescence microscope (AxioCam MRC, Carl Zeiss, Germany) whereby 500 randomly selected non-overlapping cells on each slide were analysed microscopically by categorising cells as undamaged cells without a tail (Grade 0 = CA0), cells with a tiny tail (Grade 1 or mild damage = CA1), cells with a dim tail (Grade 2 or moderate damage = CA2), cells with a clear tail (Grade 3 or severe damage = CA3), and only tail (Grade 4 or maximally damage = CA4). A total damage score for each slide was calculated by multiplying the number of cells assigned to each grade of damage by the numeric value of the grade and summing overall grades, giving a maximum possible score of 2,000, corresponding to 500 cells at grade 4 (CA total) (39).

Statistical Analysis

The statistical analysis was performed using Statistical Product and Service Solution version 20 (SPSS 20). Statistical differences were analysed using the chi-squared test and Mann–Whitney U-test given the non-normally distributed data. The independent variables with continuous data included age, body mass index (BMI), CGI-Mania, CGI-MDE, QIDS, BIS, SRRS, SOD, GPx, CAT, MDA, CA 0, CA 1, CA 2, CA 3, CA 4, CA 5, and CA Total, when the independent variables with categorical data included gender (female = 1), ethnic (Malay = 1), marital status (non-married = 1), education level (higher educational level = 1), employment (working = 1), religion (Muslim = 1), smoking status (yes = 1), and antioxidant use (yes = 1).

A multivariable binary logistic regression was carried out using lifetime suicidal ideation compared with that without dependent variables.

RESULTS

The clinical characteristics of BD patients are outlined in **Table 1**.

Table 2 describes the demography, clinical details, and the severity of DNA damage among BD patients with and without suicidal ideation and healthy control. The characteristics of the three groups were similar in terms of age ($p = 0.114$), gender ($p = 0.133$), ethnicity ($p = 0.661$), marital status ($p = 0.738$), religion ($p = 0.949$), and smoking status ($p = 0.135$). Missing data for antioxidant use were 18.2%, and smoking status was 39%.

Among the BD patients, 50% (27 subjects) had lifetime suicidal ideation, and 22.22% (12 subjects) had lifetime suicide attempts. A significantly higher proportion of female gender ($p < 0.034$), higher score of CGI-MDE ($p < 0.001$), higher

score of QIDS ($p < 0.001$), higher frequency severe DNA damage (CA 3) ($p < 0.032$), maximal DNA damage (CA 4) ($p < 0.038$), higher level of MDA ($p < 0.005$), and higher level of CAT ($p < 0.003$) were seen in the group with lifetime suicidal ideation compared with the healthy control using non-parametric univariate analysis. BIS ($p = 0.927$) and SRRS ($p = 0.801$) were not significantly different between the groups.

TABLE 1 | Clinical characteristic of BD patients.

Characteristics	*N* (%) (Total = 62)
Treatment with lithium	12 (19.35%)
Treatment with atypical antipsychotics	53 (85.48%)
Treatment with anticonvulsants	33 (53.23%)
Bipolar 1 disorder	47 (75.81%)
With mixed features	9 (14.52%)
With chronic medical illness (diabetes mellitus, hypertension, dyslipidaemia)	21 (33.87%)
With lifetime suicidal ideation	27 (43.55%)
With lifetime suicide attempt	16 (25.81%)

BD, bipolar disorder.

After the female gender, CGI-MDE, QIDS, CA 3, CA 4, MDA, and CAT were controlled using multivariable binary logistic regression with ENTER mode (lifetime suicidal ideation as dependent variable), only CGI-MDE was significantly associated with lifetime suicidal idea (**Table 3**). Higher CGI-MDE was associated with lifetime suicidal ideation among the subjects (OR = 1.937, 95% CI = 1.799–2.076, $p = 0.017$, Cox and Snell $R^2 = 0.278$; Nagelkerke $R^2 = 0.387$) as shown in **Table 3**.

In the subgroup of BD patients with lifetime suicidal ideation (27 subjects), 44.44% (12 subjects) had lifetime suicide attempts. Bivariate subgroup analysis revealed a significantly higher frequency of moderate DNA damage (CA 2) ($p = 0.032$) and severe DNA damage (CA 3) ($p = 0.047$) among BD patients with lifetime suicidal ideation and lifetime suicide attempts as

TABLE 2 | Differences in demographics, clinical characteristics, and oxidative stress between case (BD patients with lifetime suicidal ideation) and control (BD patients without lifetime suicidal ideation and healthy control) ($n = 88$).

	BD patients with lifetime suicidal ideation, $n = 27$	Control, $n = 61$		*p*-Value
		BD patients without lifetime suicidal ideation, $n = 35$ (IQR or %)	Healthy control, $n = 26$ (IQR or %)	
Age (years), median (IQR)	38 (13)	40 (29)	33 (15)	0.680*
BMI, median (IQR)	26.25 (9.58)	25.6 (6.4)	22.64 (5.25)	0.412*
Smoking, *n* (%)	8	10	2	0.776**
Antioxidant use, *n* (%)	11	21	11	0.785**
Female, *n* (%)	**21**	**18**	**14**	**0.034****
Malay, *n* (%)	12	20	10	0.818**
Non-married, *n* (%)	17	20	14	0.614**
Higher education, *n* (%)	19	20	24	0.794**
Working, *n* (%)	14	22	21	0.138**
Muslim, *n* (%)	13	20	12	0.817*
CGI-Mania, median (IQR)	1 (3)	4 (4)	1 (0)	0.921*
CGI-MDE, median (IQR)	**3 (3)**	**1 (1)**	**1 (0)**	**<0.001***
QIDS, median (IQR)	**9.5 (10)**	**6 (9)**	**2 (4)**	**<0.001***
BIS, median (IQR)	67 (13)	68.5 (13)	66.5 (13)	0.927*
SRRS, median (IQR)	300 (241)	333 (424)	263 (214)	0.801*
CA 0, median (IQR)	180 (206)	129.5 (200)	366 (113)	0.210*
CA 1, median (IQR)	163 (84)	172.5 (88)	173 (113)	0.225*
CA 2, median (IQR)	97 (126)	109 (175)	5 (13)	0.073*
CA 3, median (IQR)	**36 (48)**	**32 (48)**	**1.5 (5)**	**0.032***
CA 4, median (IQR)	**10 (22)**	**11 (15)**	**0 (2)**	**0.038***
CA Total, median (IQR)	524 (121)	525.5 (114)	525.5 (27)	0.351*
MDA, median (IQR)	**4.59 (1.95)**	**4.49 (1.62)**	**2.23 (0.32)**	**0.003***
SOD, median (IQR)	1.58 (0.92)	1.25 (0.8)	1.52 (1.02)	0.623*
CAT, median (IQR)	**0.45 (0.06)**	**0.44 (0.08)**	**0.38 (0.07)**	**0.005***
GPx, median (IQR)	5.1 (3.39)	4.87 (1.67)	5.57 (2.08)	0.568

*IQR, interquartile range; BMI, body mass index; CGI-Mania, Clinical Global Impression for manic episode; CGI-MDE, Clinical Global Impression for major depressive episode; QIDS, Quick Inventory of Depression Symptomatology; BIS, Barratt Impulsiveness Scale; SRRS, Social Readjustment Rating Scale; CA, comet assay; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione reductase; BD, bipolar disorder. *Mann–Whitney U-test. **Chi-squared test. Bolded item, $p < 0.05$.*

TABLE 3 | Effects of demographic factors, clinical factors, and oxidative stress on lifetime suicidal ideation using multivariate binary logistic regression analysis.

Variable	OR	SE	95% CI		*p*-Value	Wald (df = 1)
			Lower	Upper		
Female	0.448	0.643	0.127	1.578	0.211	1.563
CGI MDE	**1.937**	**0.277**	**1.126**	**3.331**	**0.017**	**5.705**
QIDS	1.035	0.067	0.908	1.179	0.609	0.261
CA 3	0.989	0.015	0.961	1.018	0.451	0.568
CA 4	1.014	0.030	0.955	1.075	0.655	0.200
MDA	1.356	0.253	0.826	2.224	0.229	1.450
CAT	1,644.754	5.524	0.033	82843092.54	0.180	1.797
Constant	**0.002**	**2.579**			**0.017**	**5.692**

Cox and Snell $R^2 = 0.278$; Nagelkerke $R^2 = 0.387$. OR, odds ratio; df, degree of freedom; CGI-MDE, Clinical Global Impression for major depressive episode; QIDS, Quick Inventory of Depression Symptomatology; CA, comet Assay; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase. Bolded item, $p < 0.05$.

TABLE 4 | Differences in the degree of DNA damage (quantified by comet assay) between lifetime suicidal ideators with previous suicide attempt and without previous suicide attempt.

	Lifetime suicidal ideator with lifetime attempt		*p*-Value*
	Yes, *n* = 12 Median (IQR)	No, *n* = 15 Median (IQR)	
CGI-MDE	4 (2)	2 (3)	0.059
CGI-Mania	1 (3)	2 (3)	0.516
QIDS	9.5 (7)	8 (13)	0.631
SRRS	314.5 (218)	287 (506)	0.943
BIS	67.5 (13)	67 (16)	0.792
CA 0	147.5 (139)	241 (254)	0.075
CA 1	170 (83)	139 (82)	0.347
CA 2	**129 (152)**	**63 (190)**	**0.032**
CA 3	**48 (54)**	**31 (39)**	**0.047**
CA 4	10 (17)	10 (24)	0.719
CA Total	511 (117)	533 (122)	0.648

*IQR, interquartile range; CGI-Mania, Clinical Global Impression for manic episode; CGI-MDE, Clinical Global Impression for major depressive episode; QIDS, Quick Inventory of Depression Symptomatology; BIS, Barratt Impulsiveness Scale; SRRS, Social Readjustment Rating Scale; CA, comet assay. *Mann–Whitney U-test. Bolded item, $p < 0.05$.*

compared with those with lifetime suicidal ideation but never attempted suicide (**Table 4**). Socio-demographic and clinical independent variables were non-significant factors ($p \geq 0.05$).

DISCUSSION

Suicidal Behaviour, Clinical, and Social Factors

After significant covariates using multivariable binary logistic regression were controlled, clinician-rated depression severity (CGI-MDE) emerged as the independent significant factor associated with lifetime suicidal ideation. Our findings suggest that clinician-rated rather than self-reported severity of depression may be more clinically useful in identifying suicidal ideation among bipolar patients. However, this is in contrast to a study of Oquendo et al. (40), which found that subjective rather than clinician ratings of depression severity predicted future suicidal acts. Oquendo's study included both bipolar and unipolar depression patients, in which we postulate that the latter may have been more forthcoming in terms of self-reported depression severity. Hence, in the process of assessment of suicidal behaviour, the choice of clinician vs. self-reported assessment of depression severity may require consideration of the type of diagnosis, i.e., unipolar or bipolar depression.

In our study, traditional risk factors including gender, marital status, and education level were not found to be associated with suicidal ideation. In addition to that, impulsivity was not found to be different between the groups with suicidal ideation. Despite extensive studies, the role of impulsivity in predicting suicidal behaviour was still not conclusive due to conflicting findings (41). Nevertheless, these findings need to be interpreted with caution given the small sample size of the study.

Oxidative Stress Biomarkers and Suicidal Behaviour

A higher degree of DNA damage was seen among the group with lifetime suicidal ideation compared with those without suicidal ideation *per se*. However, DNA damage did not remain as a significant factor after controlling for severity of depression in which the latter merged as the sole independent factor associated with suicidal ideation from the multivariable analysis. A possible explanation for this finding may lie in the relationship between the positive correlation of the severity of DNA damage with the severity of BD, which is congruent with the findings of Andreazza et al. (42). Raza et al. (43) proposed the pathophysiology of major psychiatric disorders with oxidative stress, i.e., that DNA damage causes dysfunctional DNA repair that results in abnormal neurotransmission and impaired neuroplasticity on top of dysfunctional energy metabolism in the brain (43). Nevertheless, the causal relationship between DNA damage and suicidal behaviour still requires more in-depth longitudinal study for definitive conclusions. Such findings may herald the potential utility of DNA damage as a biomarker

of suicidal behaviour in enhancing the predictive value of existing clinical assessments of suicide risk. In addition, future research is required to elucidate the mechanism(s) underlying the relationship between DNA damage and suicidal behaviour. This may have implications in terms of discovering novel therapeutic targets for suicide prevention.

Lifetime suicide attempts have been found to correlate negatively with the CAT level, i.e., a lower CAT value, although it is not specific to BD patients (19). Nevertheless, the role of CAT in the suicidal behaviour of BD patients may be attributed to its positive correlation with the severity of bipolar depression (44). Although MDA is found to be higher in depression and treatment-resistant BD (44–46), there is limited information on its role in suicidal behaviour.

Interestingly, we demonstrated that the severity of DNA damage was the only significant factor that differentiated suicide attempters from non-attempters among BD patients with lifetime suicidal ideation, albeit in a very small subgroup of patients ($n = 12$). We postulate that in this population of patients who are on the more severe spectrum of suicidal behaviour, oxidative stress levels, i.e., DNA damage, may be more indicative of the extent of bipolar illness pathology in comparison with a cross-sectional measure of depression severity. Future longitudinal studies are warranted to clarify the relationship between DNA damage as a potential oxidative stress biomarker of the transition from suicidal ideation to suicide attempt in BD in view of the cross-sectional nature of our current study, which limits any conclusive inference into the temporal progression of ideation attempt. In addition to a study of Vargas et al. (16), which found an association between oxidative stress markers and suicide attempts in BD, other studies have also shown some evidence of the role of oxidative stress markers besides DNA damage in completed suicides. NOX2 is found to be significantly higher in the cortex of suicide victims (17). In line with that, the NO synthase gene variant has been shown to be more susceptible to violent suicidal behaviour (47). A significant correlation is also found between redox ions and DNA damage in the brain regions of the BD suicide victims (48). Polymorphism in glutathione-*S*-transferases M1 (GSTM1) and T1 (GSTT1), an important gene modifying the body's antioxidant capacity, has also been implicated as a risk factor for higher risk of suicidal behaviour among anxious smokers (49). Nevertheless, most of the studies are not able to provide information about the transition from suicidal ideation to a suicide attempt.

Lithium, Body Mass Index, Antioxidant, Smoking, and Oxidative Stress

Antioxidant use, lithium use, smoking status, and obesity have an important influence on the oxidative stress biomarkers and might be confounding factors to the severity of DNA damage in our study. Although there were limitations in terms of missing data (i.e., missing data for antioxidant use is 18.2% when smoking status is 39%), there was no significant difference between the two groups for the mentioned four factors. Interpretation of the result needs to take this factor into consideration. Several antioxidant compounds have been found to be a potential agent to be adjunctive therapy to treat BD, including chelated mineral formula, L-tryptophan, magnesium, folic acid, omega-3, and *N*-acetylcysteine (NAC) (50–53). Omega-3 fatty acid supplementation is also shown to reduce surrogate markers of suicidal behaviour, although the study is carried out on small sample size (54). With more understanding about oxidative stress in BD patients, a specific agent may be potentially developed to target and treat suicidal behaviour, in conjunction with the traditional treatment regime.

Only a small number of the patients in this study were on lithium (16.67%, i.e., nine of the BD patients), which is an established effective suicide-reduction agent in BD patients. Lithium has been shown to reduce LP and hence reducing oxidative stress in BD patients (55). The anti-inflammatory effect of lithium is also being proposed to involve the inhibition of glycogen synthase kinase-3 (GSK3) pathway, which is linked with the suicidal endophenotypes of aggression, impulsivity, and depression traits (56).

The median BMI of the group of lifetime suicidal ideation was touching the line of overweight, i.e., BMI 25. It is important to note that obesity increases the risk of suicidal behaviour (57) and also has a significant association with a higher level of oxidative stress (58, 59). Hence, obesity might be a potential target of intervention for the prevention of suicidal behaviour.

Vargas et al. have found out that smoking behaviour has an effect on both oxidative stress and suicide attempts (16). Significantly higher levels of NOx, fibrinogen, advanced oxidative protein product, and lower levels of TRAP are seen among depressed smokers compared with non-smoker non-depressed people, and also more frequent suicide attempts (60). This might imply that smoking cessation may be a potential target to reduce both suicidal behaviour and oxidative stress.

Strength

To the best of our knowledge, DNA damage in bipolar patients connected with redox state and suicide risk has not been described yet. As CA is a relatively cost-effective biochemical analysis, the findings of this study highlight the possibility of using basic oxidative stress analysis to elucidate suicidal behaviour further.

Limitations

Cross-sectional study design limits the interpretation of the causal relationship of this association, i.e., the progression from suicidal ideation to attempt cannot be demonstrated. The small sample size subjects this study to potential type 2 error. Multiple testing increases the possibility of type 1 error. Another limitation is that the information on illicit substance use is not captured systematically using specific measurement tools, although our clinical interview only found that one of the BD patients has a significant substance use issue. In addition, the Malay versions of QIDS and SSRS do not have full-scale validation. The pharmacological treatments reported in **Table 1** (i.e., lithium, atypical antipsychotics, and anticonvulsants) were not considered as variables in the

performed logistic regression due to the imbalance between medicated BD patients (overrepresented) and non-medicated healthy controls (underrepresented). This is a limitation of our study, as the type of pharmacological treatment is an important confounding variable. Recommendations for future research to address such a study limitation include adequately powered sample sizes and stratification for study participants with and without pharmacological treatments.

CONCLUSION

Our study findings suggest that DNA damage may be a potential candidate as a biomarker of suicidal behaviour, in particular differentiating suicide attempters from non-attempters among suicidal ideators in BD. However, the cross-sectional nature and relatively small sample size of our study are limitations that preclude any definitive conclusions with regard to the temporal and causal relationship between DNA damage and suicidal behaviour in BD. Larger prospective studies are necessary to elucidate the mechanism of DNA damage in the transition from ideation into suicide attempt, which in turn would bear clinical implications to the early detection and prevention of the progression of suicidal behaviour in BD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universiti Kebangsaan Malaysia Medical Centre Research and Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL, NM, JG, HA, NA, SShah, SF, SShar, SM, TM, AA, WW, and LC: study conception and design. JL, NM, JT, SSu, SShar, GG, FM, and LC: conducting the research. JL, NM, JT, SShah, SSu, and LC: drafting of the manuscript. All authors: approval of the final manuscript.

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