MORTALITY OF PEOPLE WITH SEVERE MENTAL ILLNESS: CAUSES AND WAYS OF ITS REDUCTION

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MORTALITY OF PEOPLE WITH SEVERE MENTAL ILLNESS: CAUSES AND WAYS OF ITS REDUCTION

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Editorial: Mortality of people with severe mental illness: Causes and ways of its reduction

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Editorial on the Research Topic
Mortality of people with severe mental illness: Causes and ways of its reduction

Severe mental disorders (SMD) are associated with a variety of other illnesses and have poorer health outcomes and higher mortality than other non-communicable disease (1–3). People with severe mental disorders die on average 10–20 years earlier than the general population (4); this gap is increasing over time and recent data suggest that their standardized mortality ratios are higher than those previously reported (5). Only a minority of deaths of people with SMD are attributable to unnatural causes, such as suicide, homicide or accidents (6, 7): the majority of deaths are due to physical disorders, such as cardiovascular, respiratory and infectious diseases, diabetes mellitus and cancers (8, 9).

During the COVID-19 pandemic the mortality rates of patients with SMIs were even higher, due to physical complications of COVID-19 infection (10) and reduced access to care. Compared with the general population, people with SMI have a significantly higher risk of being infected by COVID-19, and of being hospitalized in intensive care units due to COVID-19 complications (11). This increased risk is due to several factors, including: (1) the presence of cognitive dysfunctions in people with SMI, which diminish compliance with preventive behavior (12); (2) the higher prevalence of comorbid medical conditions that are associated with severe forms of COVID-19 illness; (3) socioeconomic disadvantages, which result in unsafe working and living environments. Moreover, available data on COVID-19 infection suggest that people with severe mental disorders are more likely to be infected and die because of COVID-19 sequelae (13, 14). For these reasons, it has been advocated that patients with SMD should be given priority in programs of vaccination against COVID-19 (11, 15).

The increased morbidity and mortality in patients with severe mental disorders is also due to unhealthy lifestyle behaviors. Compared with the general population, patients with SDM have higher rates of sedentary behaviors, of tobacco smoking and of unhealthy diet (16, 17). Moreover, these patients are less likely to comply with appropriate interventions to correct unhealthy lifestyle behaviors and to seek medical help for physical diseases (18).

Among other factors that can contribute to the excess of morbidity and mortality in patients with severe mental disorders, various forms of stigma play an important role. Stigma leads to professionals' negative attitudes toward people with mental disorders, and to discrimination in the process of health care. Side-effects of many psychotropic medications and drugs are also contributing to the increased vulnerability to physical illness of people with SMD (19, 20).

More recently, the increased comorbidity between SMDs and physical disorders was seen as being related to common etiopathogenetic factors of SMD and other disorders, including the involvement of the immunological system, inflammation, and mitochondrial dysfunction (21). In fact, a low-grade systemic inflammatory state has been reported both in patients with SMD and in patients with metabolic syndrome, type 2 diabetes mellitus, moderate to severe obesity and hypertension (22).

Moreover, this evidence is further supported by the fact that interventions aimed at improving physical health activities or at rebalancing unhealthy as well as attention to diet habits in people with severe mental disorders are associated with a reduction of inflammatory state, through a reduction in blood levels of BDNF and pro-inflammatory cytokines, which leads to an improvement of health and a recovery from both physical and mental illnesses (23, 24).

From a public health perspective, the comorbidity between mental and physical disorders should be now considered a major health problem. Parallel to the public awareness of the magnitude of this problem, it became clear that a single discipline approach will not be able to identify effective solutions and that a multilevel approach, including the involvement of different health professionals and, stakeholders, patients and relatives, is needed for a proper long-term management of physical and mental health conditions.

The importance of lifestyle for the maintenance of physical and mental health led to the development of several psychosocial and behavioral interventions aiming at an improvement patients' physical health and dietary patterns and a reduction of alcohol abuse and tobacco smoking. The ultimate aims of these interventions were the reduction of cardiovascular risk factors and of the Body Mass Index (BMI). In addition to encouraging results, these studies also made it clear that that the improvement of physical health of people with severe mental disorders also leads to an improvement of mental health and progress in several other health-related domains, such as patients' empowerment, improved social contacts, and a reduction of the numbers of relapses and hospitalizations (16).

The focus of the Research Topic "*Mortality of People with Severe Mental Illness: Causes and Ways of its Reduction*" is to improve the understanding of the complex relationship between the higher rates of mortality and physical comorbidities of people with SMD and of risk factors and treatment strategies to improve the health and life of people with SMIs. All these issues have been addressed in the Research Topic. Six accepted papers are original research (4 are Original Research Papers and 2 are Brief Research Reports); moreover, the issue also includes 1 Review, 1 Policy and Practice Review paper, 1 Mini Review, 1 Perspective and 1 Case report paper, covering most aspects related to the management of physical comorbidity in patients with severe mental disorders.

Several papers included in this Research Topic delt with the clinical characterization of patients with severe mental disorders at risk of developing physical illnesses. The paper by Isella et al. focused on the role of resilience in a sample of patients who received an implantable cardioverter defibrillator; Sampogna et al. explored, in a sample of patients with SMD, the influence of recovery style on patients' engagement in healthy lifestyle behaviors, physical activity and improvement of dietary patterns. Baron et al. have addressed the issue of physical activity of patients with SMD, reporting that interventions associated with an improvement of physical activity levels can reduce patients' overall mortality. The paper by Berardelli et al. dealt with the relationship between lifestyle behaviors, mental health, and suicide risk and ideation.

The relationship among mental and physical health during emergencies have been addressed by De Hert et al. and by Medved et al. In particular, De Hert et al. provided an overview of published studies addressing the increased mortality rates of patients with SMD during the COVID-19 pandemic, while Medved et al. described the impact of the 2020 Croatian devastating earthquake on the physical and mental health of people with SMD Cuomo et al. focused on the inflammatory processes and on the association between inflammation and onset and maintenance of mental disorders showing an increase of a series of inflammatory markers in acute phase of patients with bipolar disorder, and the normalization of these indexes associated with the improvement of the patients' mental health status.

Four papers included in this Research Topic deal with interventions aiming at improving the physical health of people with severe mental disorders. Ventriglio et al. tested the efficacy of a psychosocial intervention providing information about the possible metabolic side effects of antipsychotics and their prevention and management. They reported that patients with SMD receiving the experimental intervention reported an improvement of BMI, a decrease in serum levels of fasting glucose, hemoglobin glycosylation and cholesterol, along with an improvement in mental health-related domains. The

challenges in the implementation of psychosocial interventions in routine practice has been addressed by Yuan et al. and by Kohn et al. In particular, Yuan et al. reported results of the implementation of interventions related to (1) weight loss; (2) tobacco smoking cessation; and (3) hypertension, dyslipidaemia and diabetes care, in a sample of patients with SMD. Kohn et al., in their original research paper, analyzed patients' and healthcare professionals' perspectives on somatic health in three psychiatric settings. They reported that stigma, communication difficulties among professionals and organizational difficulties (i.e., low availability of equipment, reduced building capacity, understaffing) are the most important factors hindering the achievement of satisfying levels of physical health in people with severe mental disorders.

Lastly, in their Policy and Practice Review, Falkai et al. present in overview of the activity of the "Munich/Augsburg consortium Precision in Mental Health (PriMe)," which will develop a global research framework aiming to deepen the understanding of comorbidities of patients with SMD and to identify and validate predictive markers of chronicity and mortality in in routine settings The PriMe Consortium will also aim to develop novel multimodal treatments, identify strategies to disseminate personalized treatments and ways to test their effectiveness, utility and scalability.

Taken together, the papers included in this Research Topic provide new knowledge and insights about the comorbidity of mental and physical disorders; they also highlight that much more work needs to be done. Over the past 10 years research on the complex interplay between mental and physical health has rapidly progressed and produced important evidence In the years to come, research should focus on the identification of protective factors that could reduce comorbidity of mental and physical disorders and reduce the mortality of people with severe mental disorders and on the acquisition of results which will allow the assessment of the value and cost-effectiveness of psychosocial interventions in dealing with the problems of comorbidity.

Author contributions

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

Conflict of interest

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

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BRIEF RESEARCH REPORT
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Resilience, Cardiological Outcome, and Their Correlations With Anxious-Depressive Symptoms and Quality of Life in Patients With an Implantable Cardioverter Defibrillator

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Background: Resilience is proven as a protective factor against the development of psychiatric disorders, and it has gained clinical relevance in the development and progression of cardiovascular pathology. The authors performed a longitudinal study on patients with implantable cardioverter defibrillator (ICD) with the primary aim to highlight the possible existence of a correlation between individual resilience capacity, depressive and anxiety symptoms, and quality of life in terms of outcomes. The secondary aim was to analyze the differences between patients with major cardiac events in the follow-up and patients without cardiac events with respect to the previous variables.

Materials and Methods: A total of 80 patients enrolled in the Cardiology Unit were evaluated at T_0 and during the follow-up through the following scales: the *14-item Resilience Scale* (RS-14), the *Hospital Anxiety and Depression Scale* (HADS), and the *World Health Organization Quality of Life-Brief Version* (WHOQOL-Bref).

Results: A significant linear correlation between resilience and all the areas of quality of life at T_0, T_1, and T_2 emerged. A negative correlation between resilience and anxiety and depressive symptoms emerged, as well as between depression and anxiety and quality of life. Patients with cardiac events during the follow up have shown a worse quality of life and the onset of anxiety-depressive symptoms over time, without changes to the resilience scores. Patients without cardiac events showed an increasing trend in resilience scores.

Discussion: Given the speed and simplicity of use of the RS-14 scale, it seems promising to further investigate the real clinical usefulness of this instrument in the cardiology field.

Keywords: implantable cardioverter defibrillator, resilience, anxiety, depression, life quality, screening, outcome

BACKGROUND

In recent years, resilience, defined as the "universal capacity which allows a person, group or community to prevent, minimize or overcome the damaging effects of adversity" (1), has gained clinical relevance in several medical disciplines, with particular attention to development and progression of chronic diseases. In fact, resilience not only moderates the link between risk factors and outcome but also allows maximizing the benefits coming from specific interventions, aimed at recovering from specific pathologies (2, 3). Indeed, resilience has proved itself effective in allowing a more rapid remission, increasing coping skills regarding one's condition and related treatments; this is also in line with current neuroscientific models (4–6). Regarding cardiovascular pathology, resilience is found to be particularly high in patients with coronary artery disease (7), although lower than the general population (8), and is associated with a better outcome (9) and a minor incidence of post-traumatic stress disorder symptoms (10). Some authors (5, 11) found that in cardiovascular population, psychological resilience seems to independently predict patients' mental and physical quality of life but has not been examined in relation to depression and in relation to the use of implantable cardioverter defibrillator (ICD).

Most patients undergoing ICD placement are able, within a span of variable time after the surgery, to recover their normal level of activity (12) with a good degree of satisfaction with the device (13). However, a significant percentage of patients could experience more relevant difficulties, which may persist for a prolonged time. The reported prevalence of common psychological and emotional disorders among carriers of ICD ranges from 15 to 60% (14, 15). The most represented diagnoses are anxiety disorders (24–87%), depressive disorders (9–15%), post-traumatic stress disorder (up to 20%), and adjustment disorders (16, 17).

The link between resilience and depressive symptoms is also well-known; several studies concluded that resilience is a protective factor against the development of psychiatric disorders, such as PTSD and depression (18, 19). Furthermore, negative effects and their reciprocal influences with resilience have been related to an increased risk of mortality in patients with cardiovascular disease (20, 21). In fact, there is an intrinsic relationship between psychological state and arrhythmic risk, demonstrated by the increased incidence of ventricular arrhythmias malignant in subjects with anxiety and depression (11).

Moreover, the psychological sequelae, experienced by ICD patients, may cause an impairment of their quality of life. The perception of a good quality of life in ICD carriers, defined as *"a multidimensional health outcome in which biological, psychological and social functioning are interdependent,"* should be taken into consideration as a success factor for the implant (22).

Given this premise, the authors performed a longitudinal study on 80 patients with ICD with the primary aim to highlight the possible existence of a correlation between individual resilience capacity and depressive and anxiety symptoms, using quality of life in terms of outcomes. The secondary aim was to analyze the differences between patients with major cardiac events (death, hospitalizations, incidence of arrhythmias, and ICD shocks) in the follow-up and patients without cardiac events with respect to the previous variables.

MATERIALS AND METHODS

The prospective observational study VC was conducted on 80 patients enrolled in the Cardiology Unit of the "ASST Sette Laghi—Ospedale di Circolo—Fondazione Macchi" of Varese. The study was approved by the Ethical Committee of Insubria on April 10, 2018 (study no. 22). This study observed regulatory and legal requirements (DL n.211, June 24, 2003, and DM December 17, 2004), according to the Declaration of Helsinki's ethical principles. Following the Institutional Review Board approval, all patients were specifically informed about the opportunity to participate in this study and signed a written specific consent before the enrollment. Data collected referred to the period between June 15, 2018 and June 30, 2019. Patients were evaluated at T_0, at the time of ICD implant, after 3 months (T_1), and after 12 months (T_2).

To be enrolled in the present study, patients had to fulfill the following inclusion criteria: patients aged between 18 and 85 years with indication to ICD implant, both in primary and secondary prevention; and willingness to sign the informed consent. Exclusion criteria were life expectancy <12 months, neurodegenerative diseases, moderate or severe cognitive impairment, moderate or severe intellectual disability, depressive and anxiety disorders diagnosis, previous or current psychopharmacology treatment at T_0, or abuse of alcohol or illicit substances. The following socio-demographic and clinical variables were taken into consideration: gender, age, education, marital status, employment, living conditions, past medical history, length of hospitalization, type of ICD, New York Heart Association (NYHA) (23) class, number of shocks after the implant, hospitalization, and access to the emergency room of cardiological relevance.

The following evaluation scales were administered at T_0 and during the follow up: the *14-item Resilience Scale*, which allows the assessment of resilience levels according to a two-factor structure (competence personal and self-acceptance) (24–26); the *Hospital Anxiety and Depression Scale* (HADS) that consists of 14 items, 7 of those for anxiety levels, whereas the others estimate depression grades, and that showed acceptable psychometric properties in several medical fields including cardiology (27, 28); and the *World Health Organization Quality of Life-Brief Version* (WHOQOL-Bref), shortened version of WHOQoL-100, which comprises four domains (physical health, psychological health, relationships, and environment) and allows an overall judgment on patients' quality of life and on general health (29, 30).

Collected data were analyzed using SPSS Version 22.0 (IBM Corp., Armonk, NY, 2013). Continuous variables were represented by mean ± deviation standard or median ± standard error in case of non-Gaussian distribution. The qualitative

TABLE 1 | Socio-demographic and clinical characteristics.

	Total
Gender	
Male	60 (80%)
Female	15 (20%)
Age	
Mean	69 ± 10.49
Education	
None	1 (1.3%)
Primary school	26 (34.7%)
Junior high school/High school	6 (60%)
Bachelor's degree	3 (4%)
Marital status	
Unmarried	4 (5.3%)
Married	58 (77.3%)
Divorced	6 (8%)
Widowed	7 (9.4%)
Employment	
Unemployed	14 (28.6%)
Employed	10 (20.4%)
Retired	25 (51%)
Living condition	
No caregiver	69 (92%)
Caregiver	6 (8%)
Familiarity for serious mental illness	0
Past medical history	
Hypertension	59 (78.67%)
Previous myocardial ischemia	50 (66.67%)
Respiratory pathologies	19 (25.33%)
Neoplastic pathologies	11 (14.67%)
Neurologic pathologies	12 (16%)
Minor psychiatric disorders	4 (5.33%)
NYHA class T0	
Class I	40 (53.33%)
Class II	27 (36%)
Class III	7 (9.33%)
Class IV	1 (1.33%)

variables were represented by frequencies and distributions of frequency. Once the normal distribution of the scores obtained at the RS-14 was confirmed, comparison of means by ANOVA test was performed; given the non-normality of other data (Lilliefors $p < 0.05$) the Mann-Whitney test was used. The evaluation of the existence of a possible correlation between resilience and other continuous variables collected was made through the calculation of Pearson's R and R2. Authors also performed a multivariate regression considering resilience, depression, and anxiety as independent variables and WHOQOL-Bref scores as dependent variables. The possible existence of a variation of resilience and other psychological variables over time was subsequently assessed, using the ANOVA test for paired data and the Wilcoxon Matched Pairs Test for non-Gaussian data. A p value < 0.05 was considered statistically significant.

TABLE 2 | Psychological variables at T_0, T_1 and T_2.

	T_0	T_1	T_2
RS-14 (mean)	85.52 ± 9.61	88.00 ± 9.40	87.61 ± 5.55
HADS-d (median)	5 ± 0.74	2 ± 0.60	4 ± 0.58
HADS-a (median)	6 ± 0.63	3 ± 0.61	4 ± 0.58
WHOQoL-Bref (mean)			
Global	55.25 ± 2.97	50.00 ± 2.76	62.50 ± 2.67
Physical health	66.07 ± 1.40	71.41 ± 1.44	69.65 ± 2.28
Psychological	70.83 ± 1.33	70.83 ± 1.32	70.83 ± 1.41
Social relationship	70.85 ± 1.74	66.67 ± 1.60	66.67 ± 1.70
Environment	65.61 ± 1.90	65.63 ± 1.34	68.75 ± 1.27

RESULTS

Participation in the study was proposed to 80 patients; 75 patients (93.75%) signed the informed consent with subsequent enrollment. At T_1, 7 patients dropped out of the study because they did not want to be assessed thorough the questionnaires. At T_2, among the 37 patients recruited for this last phase of study, one patient died not for cardiovascular problems, and 36 completed the follow-up. Socio-demographic and clinical characteristics of samples are listed in **Table 1**.

The hospitalization lasted between 3 and 68 days, with a median of 6 days (95% CI = 8–13 days). Most patients (89.33%) were discharged at home, whereas 8 patients (10.67%) were admitted to a cardiological rehabilitation center after hospital discharge. Implant complications occurred in 5 patients (6.67%): in two cases the cause was arrhythmic, two were on a hemorrhagic basis, and one on an infectious basis. The ICD was implanted in primary prevention in 59 patients (78.67%), while in the remaining 21.33% ($n = 16$) in secondary prevention for sustained ventricular arrhythmias (68.75%; $n = 11$) or cardio-circulatory arrest (31.25%; $n = 5$). Forty patients (53.33%) received a single/dual chamber defibrillator, 40% ($n = 30$) a biventricular defibrillator, whereas the remaining 6.67% ($n = 5$) a subcutaneous device. **Table 2** shows changes of the considered psychological variables during the study period (**Table 2**).

By comparing intra-individual's modification of RS-14 score at T0 and during the follow-up, no statistically significant differences emerged ($p = 0.06$).

Regarding the HADS scores, anxious symptomatology improved at the first follow-up after 3 months ($p = 0.008$), though it worsened again after 12 months ($p = 0.007$). On the contrary, depressive symptoms underwent a progressive improvement between T_0 and T_1 ($p = 0.002$) then remained stable over time. Regarding the WHOQoL global score, no statistically significant differences were observed between T_0 and T_1 ($p = 0.37$), whereas it has improved at the second follow-up after 12 months ($p = 0.002$); no statistically significant differences were observed in the Physical Health and Psychological domains' score over the study period. In the Social Relationship domain, patients' scores worsened at the first follow-up ($p = 0.027$), showing no further variation after 12 months. Lastly, a statistically significant difference was observed

TABLE 3 | Correlation between RS-14 and the other psychological variables.

	r	*p*-value
WHOQoL-Bref (T0)		
Global	0.30	0.009
Physical health	0.44	<0.0001
Psychological	0.56	<0.0001
Social relationship	0.34	0.0003
Environment	0.19	0.09
HADS-a	−0.42	0.0004
HADS-d	−0.66	<0.0001

in the Environment domain, with a clear improvement after 12 months from the implant ($p = 0.03$).

A significant linear correlation was found between resilience (RS-14) and all areas of quality of life (WHOQoL-Bref), except for the Social Relationship domain, during the whole study period. In greater detail, this correlation appeared stronger for Physical Health and Psychological domains (**Table 3**). Furthermore, a strong inverse correlation between resilience levels and anxious-depressive symptoms emerged from data analysis; these results remained constant over time during the subsequent follow-up (**Table 3**).

At the first outpatient visit to check ICD functioning (T_1), it emerged that two patients received a shock from the device; one patient had been appropriately shocked for the onset of sustained ventricular tachycardia, whereas for the other the shock was inappropriate for the onset of atrial fibrillation. By consulting the hospital software, it was also found that 13.24% of patients had one or more accesses to the emergency department or admissions to the cardiology department. In greater detail, 66.67% of the patients had one access only, whereas the remaining 33.33% had two or more accesses. The main causes of hospitalization were arrhythmias (22.22%), heart failure (44.44%), myocardial infarction (11.11%), and other cardiac causes (22.22%).

At T_2, ICD shocks had been recorded for four patients: two patients received appropriate shocks for the onset of sustained ventricular tachycardia, whereas one patient received three inappropriate ICD shocks for the onset of supraventricular tachycardia. It was also found that 27.03% of patients had made one or more visits to the emergency room or admissions to cardiology department. Leading causes of hospitalization were the presence of arrhythmias (30%) and the onset of heart failure (30%), followed by myocardial infarction (20%) and other cardiac causes (20%).

In the group of patients that concluded the follow-up with events, an improvement has been observed during the whole study period in the Psychological, Social Relationship, and Environment domains, whereas other psychological variables did not show statistically significant variations. No statistically significant differences were found in patients without events (**Table 4**).

Comparing the group of patients, those with events (device shocks and/or hospital admissions for cardiac causes) and those without events, it was found that at time T_1 the patients with cardiac events presented on average increased levels of anxiety (3 ± 0.41 vs. 5 ± 1.27; $z = -1.90$; $p = 0.06$) and a significant reduction in the overall quality of life (62.50 ± 2.28 vs. 43.75 ± 6.57; $z = 2.67$; $p = 0.008$). Similar results were found at T_2: patients with cardiac events had on average a worse overall quality of life (62.50 ± 3.29 vs. 50.00 ± 4.85; $z = 2.79$; $p = 0.009$); furthermore, patients with events show worse scores in the Environmental domain compared to those without cardiac events and/or hospitalization (68.75 ± 2.07 vs. 59.37 ± 3.07; $z = -2.99$; $p = 0.005$). No further statistical differences had been observed in the two groups.

A multivariate regression considering resilience, anxiety, and depression as independent variables and WHOQOL-Bref as the dependent one was performed at each time point of the study.

At T_0, an association between the physical ($b = 0.45$; $p = 0.0001$), psychological ($b = 0.47$ $p < 0$ 0001 areas), and environmental areas ($b = 0.30$; $p = 0.02$) of the WHOQOL-Bref emerged. No independent variables and global and social quality of life were identified. Anxiety was characterized as an independent modifier of the physical area ($b = -0.28$; $p = 0.02$) and depression as an independent modifier of the psychological area ($b = -0, 26$; $p = 0.03$). At T_1, the multivariate analysis showed that resilience was independently associated with the physical areas ($b = 0.28$; $p = 0.019$), with the social one ($b = 0.50$; $p = 0.0001$), and the psychological one ($b = 0.48$; $p < 0.0001$) of the WHOQOL-Bref. Anxiety ($b = -0.27$; $p = 0.016$) and depression ($b = -0.28$; $p = 0.04$) were also related to the physical and psychological areas (anxiety: $b = -0.23$; $p = 0.01$; depression: $b = -0.28$; $p = 0.009$), while the environmental area showed a correlation only with depression ($b = -0.40$; $p = 0.022$). At T_2, no significant findings emerged.

DISCUSSION

Despite the success of cardiac defibrillator implantation for the prevention of sudden cardiac death and in terms of cardiological outcome, there is a growing demand not only to improve the general mortality and safety of patients, but also their quality of life (14). Many patients with ICD experience high degrees of distress in the period immediately before and after the implant, but most of them are usually able to quickly return to normal activities and report feelings of relief. Cardiac events, however, can worsen the individual response to the implant. The purpose of this work was therefore to describe the complex interaction between underlying cardiological disease, ICD implantation, and individual factors of stress vulnerability and resilience on a real clinical sample, in order to better understand the psychological variables on which to intervene in order to obtain a better adaptation and an increase in the quality of life. In fact, emotion regulation has emerged as one of the most important personal competencies in modulating the risk of psychopathological burden (31, 32). Moreover, as in other clinical fields, better health outcomes could also be predicted using the pharmacogenetic information through pharmacogenetic testing as part of routine

TABLE 4 | Changes in psychological variables in patients without and with events (ICD shocks and/or hospitalization).

	T_0	T_1	T_2	T_0-T_2	*p*-value
Changes in psychological variables in patients without events					
RS-14 (mean)	84.45 ±11.17	84.73 ±10.00	86.18 ±5.04	$t = 0.59$	0.57
HADS-d (median)	3 ±1.42	3 ±1.32	4 ±0.82	$z = 0.77$	0.44
HADS-a (median)	6 ±1.15	4 ±1.26	5 ±1.30	$z = 0.12$	0.91
WHOQoL-Bref (mean)					
Global	50.00 ±4.85	50.00 ±5.61	50.00 ±5.93	$z = 0.84$	0.07
Physical health	60.71 ±4.03	67.86 ±3.32	64.29 ±4.43	$z = 0.46$	0.65
Psychological	58.33 ±4.93	70.80 ±2.97	70.83 ±2.60	$z = 1.94$	0.05
Social relationship	66.70 ±3.05	66.67 ±2.41	66.67 ±2.19	$z = 2.03$	0.04
Environment	59.37 ±3.07	65.63 ±2.74	68.75 ±2.12	$z = 2.52$	0.011
Changes in psychological variables in patients with events					
RS-14 (mean)	86.00 ±9.06	89.44 ±8.97	88.24 ±5.75	$t = 1.29$	0.21
HADS-d (median)	5 ±0.87	3 ±0.65	4 ±0.69	$z = 2.28$	0.02
HADS-a (median)	6 ±0.77	2 ±0.70	4 ±0.62	$z = 1.56$	0.12
WHOQoL-Bref (mean)					
Global	62.50 ±3.29	62.50 ±3.06	62.50 ±2.79	$z = 1.38$	0.17
Physical health	71.43 ±2.30	71.43 ±2.14	71.43 ±2.61	$z = 0.69$	0.49
Psychological	70.80 ±2.37	75.00 ±2.49	70.83 ±1.73	$z = 0.89$	0.37
Social relationship	75.00 ±2.16	75.36 ±2.41	76.12 ±2.19	$z = 1.99$	0.17
Environment	68.75 ±2.07	65.63 ±1.48	68.85 ±1.53	$z = 1.38$	0.16

clinical care in the management of cardiovascular disease (33–35). In general, it is possible to observe that in the year following an ICD implant, patients need a period of adaptation, against which various internal and external factors intervene, with consequences both on a psychological level and on the quality of life. After a year an overall improvement was observed in both aspects; however, for patients who presented problems of a cardiac nature during the observation period, such recovery appears more difficult and slower, also in relation to elements of reinforcement and negative expectations related to body, health, and future. Patients with cardiac events during the follow-up have shown a worse quality of life and the onset of anxiety-depressive symptoms over time, without changes to the resilience scores. Patients without cardiac events showed an increasing trend in resilience scores. Good resilience skills can instead promote faster activation of effective coping strategies, thus allowing faster remission, as confirmed in other works (4). From these results, the need to propose an early screening in order to identify the patients most at risk of developing not only physical but also psychological complications emerges (36, 37). The tests used in the present work have proved to be useful in this regard; in particular, the presence of high levels of resilience, measured through the RS-14, was found to be statistically significantly correlated to better perception of life quality and lower levels of anxiety and depression. This correlation was maintained both at baseline and in the follow-up. It also showed no variability in individual scores at either follow-up, thus confirming it to be an individual characteristic, independent of external factors. An early definition of the resilience level of each patient before implantation of a defibrillator could be a useful tool in predicting the most vulnerable subjects and therefore guaranteeing the possibility of greater attention to their psychological well-being and guarantee them a targeted psychological support path.

Although it is not possible to define a statistically significant correlation between baseline levels of resilience and the onset of major cardiac events, due to the limited number of cardiac events that occurred in the follow-up period, the trend followed by our data encourages us to continue collecting data on this topic. Furthermore, given the speed and simplicity of use of the RS-14 scale, it seems promising to also further investigate the real clinical usefulness of this instrument in the cardiology field. The main limitation of this study is the total sample size. A further limitation is represented by the recruitment during the cardiological visit coinciding with the implantation of the ICD; this situation could in fact affect the patient's emotional state and represent a confounding factor in the responses to the questionnaires. Another limit of the study could be represented by the lack of collection of information regarding coping strategies, personality traits, and cognitive styles of the patients enrolled. The strengths of this study are represented by the perspective-longitudinal structure and by the double approach, intra-individual and between groups. This allowed an optimal evaluation over time of the psychophysical state of the patients. The sample examined also belongs to the real-world and is strongly representative of the population receiving a defibrillator implant. The literature shows little data in this field and our work appears innovative and a source of desirable future insights. This work confirms the need for a more careful assessment of the psychological needs and expectations

of patients who undergo an ICD implant, especially in the presence of organic complications; it would be desirable to carry out a screening before implantation to identify the most vulnerable patients and direct them to a targeted path that may include professionals dedicated to the treatment of psychological complications as well as physical ones. Given the speed and simplicity of use of the RS-14 scale, it seems promising to further investigate the real clinical usefulness of this instrument in the cardiology field.

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 Ethics Committee of ASST-Settelaghi, Varese. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC, BC, and RD contributed to conception and design of the study. CI, CD, and FC organized the database. CI and AG performed the statistical analysis. GL and AG wrote the first draft of the manuscript. FC, MI, IC, and CD wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Biomarkers, Inflammation, and Bipolar Disorder: Association Between the Improvement of Bipolar Disorder Severity and the Improvement in C-Reactive Protein Levels After 7 Days of Inpatient Treatment

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Introduction: Compared to the general population, people with severe mental illness (SMI) have a poorer health status and a higher mortality rate, with a 10–20-year reduction in life expectancy. Excess mortality and morbidity in SMI have been explained by intertwined components. Inflammatory processes could increase the morbidity and mortality risk in patients with bipolar disorder (BD) because of a bidirectional interaction between BD and conditions related to inflammation. This pilot study aimed to evaluate the relationship between C-Reactive-Protein (CRP) and bipolar disorder severity.

Methods: A retrospective observational study was conducted on 61 hospitalized patients with bipolar disorder. CRP was measured at admission to inpatient treatment (T0) and after seven days from the admission (T1). Clinical Global Impression for Depression, Mania and Overall Bipolar Illness were recorded at T0 and T1. Comparisons among the recorded CRP values were determined through the paired *t*-test. Correlations between CRP and CGI scores were determined through Spearman's correlation coefficient at T0 and T1.

Results: A statistically significant decrease in CRP values was observed after 7 days of hospitalization ($p < 0.001$) and positive significant correlations emerged between CRP and CGI scores at T0 and T1.

Conclusion: Patients admitted to the inpatient unit reported a statistically significant decrease of CRP values during the first 7 days of treatment. Although the direction of the relationship between BP severity and inflammation status continues to remain unclear, this study showed a relationship between the improvement of bipolar disease symptoms and the improvement of the inflammatory marker CRP.

Keywords: bipolar disorder, inflammation, CRP, C-reactive protein, biomarker, inpatients

INTRODUCTION

The morbidity, mortality, and suffering associated with severe mental disorders are not only a result of psychiatric symptoms and their attendant dysfunction (1). Medical disease and medical risk factors are common in patients with mental illness in general and in patients with bipolar disorder (BD) in particular. Physical illness affects the course, severity, and treatment of bipolar disorder (2–6), and lead to even greater morbidity, mortality, and disability (7).

Many physical illnesses have been cited as highly prevalent in patients with bipolar disease, the most common of which are obesity, cardiovascular disease, diabetes, and thyroid disease. Since patients with bipolar disorder spend most of their time in the depressive phase of the illness, there is often a loss of the discipline and motivation required to reduce such physical risk factors.

Katon has established a clear relationship between depression and several negative health behaviors including poor diet, excessive eating, smoking, abuse of substances, and a sedentary lifestyle (8). For example, mortality due to cardiovascular disease has been reported as doubled in patients with BD (9). Moreover, abnormalities in the homeostatic balance between the sympathetic and the parasympathetic systems, with loss of heart rate variability (HRV), sympathoadrenal activation, hypothalamic-pituitary-adrenal (HPA) axis activation, immune system dysregulation resulting in a pro-inflammatory status, platelet activation, and endothelial dysfunction have been observed in many patients with BD, major depressive disorder (MDD), and other psychiatric disorders (10). The study of inflammatory biomarkers and their change in the different phases of BD may contribute to the research about the etiology and treatment of BD (11).

Many studies have identified neuroinflammatory mechanisms of bipolar disorder (BD), showing how these mechanisms may impact the disease progression and the effectiveness of drug treatment.

For instance, a correlation between autoimmune processes and increased expression of psychiatric disorders is supported by the increased risk of patients with systemic autoimmune diseases developing BD (12). Although such chronic immune dysfunction appears to contribute significantly to developing comorbidities in BD, the direction of this cause-effect relationship is still unclear. Specifically, it is not yet clear whether BD increases the risk for immune dysfunction or whether a pre-existing inflammatory condition increases the risk of BD. The most recent hypothesis suggests a bidirectional interaction between BD and conditions related to inflammation and that these reinforce each other; moreover, specific genetic and environmental factors contribute to increasing the risk (13).

Several biologic mechanisms may contribute to the increased mortality risk from natural causes found among patients with bipolar disorder, such as dysregulation of the hypo-thalamic-pituitary-adrenal axis; the dysregulation of the autonomic nervous system may also lead to insulin resistance and may worsen metabolic syndrome (14), and pharmacological treatment.

Measuring neuroinflammation through pro and anti-inflammatory cytokines should determine a positive increase in the treatment of bipolar disorder. Rosenblat et al. hypothesized a simultaneous trend in mood levels, cognitive functions, and inflammatory markers in patients with bipolar disorder (13). According to this scheme, cytokine levels increase chronically and can increase both during depressive and manic episodes. Specifically, Fernandes et al. showed an increase in C reactive protein (CRP) more markedly in the acute phase of mania (15, 16), while Klaus Munkholm et al. showed an altered leukocyte component in patients with bipolar disorder compared to the healthy control group on a sample of 300 blood draws (17).

High levels of CRP have been found in various psychiatric disorders but particularly in schizophrenia, depressive disorders, bipolar disorder (18). Scientific evidence has found a correlation between high levels of C-reactive protein and manic states, while more uncertain data are those concerning euthymic and depressive states (19), although some studies show the increase, decrease or absence of variations of CRP during the various phases of the disease (14). The role of C-reactive protein in the neuro-progression of the disease remains unclear.

This retrospective pilot work aimed to evaluate the relationship between the improvement of the acute symptoms of bipolar disorder and the improvement of the inflammatory marker levels C-reactive protein in hospitalized patients.

MATERIALS AND METHODS

This observational study aimed to retrospectively evaluate the relationship between the inflammatory marker CRP and bipolar disorder severity. The study was approved by the University of Siena and Area Vasta - South-East Institutional Review Board - Ethics Committee (num. ID17856; Approval Date: 05/02/2021).

Consecutive patients were enrolled according to the following criteria: (1) a diagnosis of bipolar disorder according to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5]; (2) age $\geq$ 18 years; (3) length of hospital stay longer than 8 days; (4) voluntary participation, ability to understand and sign consent information. Exclusion criteria were: (1) Primary diagnosis of schizophrenia, schizophrenic form disorder, schizoaffective disorder, and delusional disorder; (2) NeuRodegenerative disorders, intellectual disability, neurological diseases, history of head injury; (3) Any clinical condition that could interfere with the reliability of the assessment, such as: current infection, recent surgery, trauma, burns, neoplastic processes, joint rheumatism such as rheumatoid arthritis and rheumatic polymyalgia, autoimmune diseases such as SLE, inflammatory bowel disease, pelvic inflammatory disease, myocardial infarction, appendicitis, pancreatitis, cholangitis, pyelonephritis, gout, and tuberculosis; (4) Pharmacological treatment in progress with anti-inflammatories or corticosteroids doses.

Patients were treated with standard of care medications for bipolar disorder, mainly consisting of a mood stabilizer and/or an antipsychotic combined, when necessary, with other medications such as antidepressants, benzodiazepines, or other hypnotics.

TABLE 1 | Patients characteristics.

	Median (IQR) or *N* (%)
N. Patients	61
Age, years	50 (38–63)
Sex	
Female	42 (68.9%)
Male	19 (31.1%)
Diagnosis	
Bipolar disorder (type I)	30 (49.2%)
Bipolar disorder (type II)	31 (50.8%)
Other psychiatric comorbidities	9 (14.8%)
Physical comorbidities	13 (21.3%)
BMI	25.3 (22.1–27.2)
Underweight (<18.5)	4 (6.6%)
Normal (18.5–22.9)	16 (26.2%)
Overweight (23.0–24.9)	9 (14.8%)
Obese (≥25.0)	32 (52.5%)
Smoking	31 (50.8%)

Endpoints

Blood tests were collected at admission to inpatient treatment (T0) and after 7 days from the admission (T1).

Blood Tests and Psychometric Scales

CRP was collected for all patients at T0 and T1. CRP values higher than 0.5 mg/dL were considered as abnormal values. Clinical Global Impression (CGI) for Depression, Mania and Overall Bipolar Illness were registered at T0 and T1.

Statistical Analysis

Descriptive statistical analyses are presented as mean ± standard deviation or median and interquartile range for continuous variables and frequencies and percentages for qualitative variables. Comparisons were determined through the paired *t*-test. Correlations between CRP and CGI scores were determined through Spearman's correlation coefficient at T0 and T1. Statistical significance was set at 5% ($p < 0.05$). STATA17 (StataCorp, College Station, TX, USA) was used for all statistical analyses.

RESULTS

Sixty-one patients (42 females and 19 males, median age 50 years, IQR: 38–63 years) were enrolled and included in the study. Thirty patients were affected by bipolar disorder type I, 31 patients by bipolar disorder type II. Other psychiatric comorbidities were present in 9 patients. Thirteen patients reported significant physical comorbidities. Complete patients' characteristics are reported in **Table 1**.

Mean CRP significantly decreased during hospitalization (mean CRP at admission: 0.60 ± 0.24 mg/dL; mean CRP after 7 days: 0.42 ± 0.17 mg/ dL; $p < 0.001$; no missing values). Positive correlations emerged between CRP and CGI scores at T0 and T1 as reported in **Table 2**.

DISCUSSION

We found that patients admitted to the inpatient unit reported a reduction of CRP during the first 7 days of supervised treatment, in synch with the improvement of their acute symptoms of bipolar disorder. Our results confirm those already reported in other studies in which CRP detected in the various stages of bipolar disorder disease was higher in untreated patients, possibly due to a direct protective role of medication treatment (i.e., mood stabilizers or atypical antipsychotics) against the patient's inflammatory state or due to the improvement in bipolar disease related to the use of appropriate medications (15, 16). For instance, Van den Ameele et al. found that untreated patients with BD showed disease-related inflammatory cytokine alterations, while patients in a state of euthymia and receiving a treatment with mood stabilizers such as lithium, had similar values to healthy controls, this suggesting a role of medications such as lithium in normalizing the immune system (20).

This study has several limitations. First, the observation period was short, and we were unable to report on the longer-term changes of CRP, for instance during the euthymia period. Second, the concentration of baseline CRP exhibited a large interindividual variability. Third, the sample size was small. Fourth, we were unable to establish if the decrease in CRP was specifically related to specific medications or were instead due to other factors (i.e., admission to the hospital). Finally, possible confounding effects on the CRP serum caused by minor comorbidities were not considered.

Because of the factors above, we were unable to establish if the decrease in inflammatory markers was primarily a direct effect of the medications that were prescribed during inpatient stay, or may also be related to other factors, such as the inpatient admission itself, psychoeducation, and the consequent improvement in circadian rhythms and daily routine. Indeed, the positive correlation between CRP and a higher degree of symptoms severity could be related to the activation of the stress response induced by symptoms such as increased psychomotor activity and lack of sleep, via complex interplay of endocrine, nervous, and immune mechanisms that involve activation of the sympathetic-Adreno-Medullar (SAM) axis, the Hypothalamus-Pituitary-Adrenal (HPA) axis, and the immune system (21). Nonetheless, our results confirm a relationship between CRP and clinical status, with a decrease in CRP as patients' acute symptoms improved. A recent paper evaluated the association between inflammation and specific symptoms of depression and suggested symptom-specific rather than generalized effects of inflammation on depression (22).

Studying the relationship between the improvement of the acute symptoms of bipolar disorder and the reduction of the C-reactive protein levels may hypothesize new clinically-oriented research: (1) whether and how much an early improvement of inflammatory markers indicates the efficacy of a new treatment; (2) whether and which anti-inflammatory

TABLE 2 | Spearman's correlation coefficient at T0 and T1.

	CRP T0	**CGI OBI T0**	**CGI Depression T0**	**CGI Mania T0**
CRP T0	1.0000			
CGI OBI T0	0.7607*	1.0000		
CGI Depression T0	0.4017*	0.3871*	1.0000	
CGI Mania T0	0.8811*	0.7185*	0.4517*	1.0000
	CRP T1	**CGI OBI T1**	**CGI Depression T1**	**CGI Mania T1**
CRP T1	1.0000			
CGI OBI T1	0.3330*	1.0000		
CGI Depression T1	0.6609*	0.2661*	1.0000	
CGI Mania T1	0.4998*	0.4249*	0.4708*	1.0000

*$p < 0.05$.

treatments can reduce bipolar disorder symptoms; and (3) if the decrease of inflammatory markers is directly correlated with an improvement of bipolar disorder symptoms or if the improvement of inflammatory markers indicates the change of a third factor (e.g., an infection, a change in microbiota, etc.) that is correlated with the symptoms of bipolar disorder and that may become a future target of bipolar disorder treatment.

Specifically, a pooled analysis of population-based cohort studies, reported that higher concentrations of CRP were strongly associated with the presence of four physical symptoms (loss of energy, sleep problems, changes in appetite, fatigue) and one cognitive symptom (lack of interest in doing things). Following these suggestions, future studies could further investigate the relationship between inflammatory markers, such as CRP, and specific symptoms of bipolar disease.

CONCLUSIONS

A significant decrease in CRP was observed in patients admitted to the inpatient unit during the first 7 days of treatment, as their symptoms of bipolar disorder improved. It remains to be established which specific factor contribute to the decrease in CRP and whether the decrease of CPR is related to an improvement of bipolar disorder symptoms or vice-versa.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Siena and Area Vasta - South-East Institutional Review Board - Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC, DK, and AF contributed to conception and design of the study. AS organized the database. GB and AS performed the statistical analysis. AC, DK, and SB wrote the first draft of the manuscript. AG and GB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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BRIEF RESEARCH REPORT
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Use of Psychoeducation for Psychotic Disorder Patients Treated With Modern, Long-Acting, Injected Antipsychotics

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Introduction: There is an increased risk of adverse metabolic effects of some modern antipsychotic drugs, and concern that long-acting, injected preparations of them may increase such risk. We now report on clinical and metabolic outcomes in patient-subjects diagnosed with affective and non-affective psychotic disorders following exposure to psychoeducation on metabolic risks of modern antipsychotics followed by treatment with long-acting atypical injected antipsychotics over 6-months.

Materials and Methods: 85 psychotic disorder outpatients (42 affective [AP]; 43 non-affective [NAP]) at the University of Foggia were treated with long-acting, injected, second-generation antipsychotics in association with a set of psychoeducational sessions concerning general health and potential effects of antipsychotic drug treatments. They were evaluated at baseline and six months.

Results: Initially, NAP subjects reported higher ratings of positive and negative symptoms than AP subjects, were more likely to receive risperidone or paliperidone, with higher CPZ-eq doses of antipsychotics (294.0 ± 77.8 vs. 229.3 ± 95.8 mg/day), and shorter QTc electrocardiographic recovery intervals. During the 6-month follow-up, ratings of treatment-adherence improved through overall (+8.75%), and symptom-ratings decreased (−7.57%) as did Body-Mass Index (−2.40%; all $p \leq 0.001$). Moreover, serum levels of fasting glucose, hemoglobin glycosylation, cholesterol and prolactin concentrations all decreased, with little difference between subjects with AP vs. NAP.

Discussion and Conclusions: A psychoeducational program was associated with consistent improvement in psychotic symptoms and several metabolic and physiological measures, as well as with treatment-adherence during six months of treatment with long-acting, injected, second-generation antipsychotics, in association with both affective and non-affective psychotic disorders.

Keywords: long-acting antipsychotics, psychotic disorders, metabolic changes, psychoeducation, treatment-adherence

INTRODUCTION

Major mental disorders are associated with increased risk of morbidity and mortality due to the illnesses themselves and their treatments (1). The prevalence of metabolic syndrome (MS) among schizophrenia patients may range 37-63% with a relative risk (RR) of 2–3 in patients compared to general population, as well as MS in bipolar disorder patients ranges 30–49% with a RR of 1.5-2 (2). Consequently, it has been largely described an increased risk of death from medical causes in schizophrenia and 20% (10–15 years) shorter lifespan (2, 3); similarly, affective psychoses are associated with higher standardized mortality ratios from medical causes than general population ranging 1.9-2.1 (2, 3). Many factors including poor life-style and food intake, poor attention to health needs and side effects of psychotropic drugs may impact on the metabolic outcome of patients affected by psychoses (3). Currently, the employment of second- and third- generation antipsychotics, such as serotonin- dopamine antagonists or dopamine partial agonists, are clinically preferred since are more effective on negative, affective and cognitive symptoms of psychosis (4). Nonetheless, newer antipsychotics may induce increases in body-weight, insulin- resistance with long- term adverse physiological effects including type−2- diabetes mellitus, hypertension and dyslipidemia, in addition to obesity (4–6). Also, it has been largely described that the prevalence of metabolic syndrome in patients treated with antipsychotics is approximately 40% (33.8–42.1%) in contrast to rates of 10.4–12.2% among psychosis un-medicated patients: some atypical antipsychotics such as olanzapine and risperidone were associated to higher weight gain among non-clozapine second generation antipsychotics, as well as risperidone and amisulpride were responsible for increasing serum prolactin (7).

These metabolic issues are potentially life-threatening effects and need to be carefully assessed and treated by clinicians (8, 9). Also, strategies of prevention need to be employed and awareness regarding their own general health needs to be addressed among these patients (10). International organizations have proposed guidelines for screening and preventing metabolic issues in patients treated with antipsychotics suggesting physical monitoring and psycho-education in the long-term treatment (11, 12).

Physical activity may be a relevant therapeutic intervention for people with severe mental disorders and life style-related medical issues: this has been confirmed among schizophrenia-spectrum disorders patients as well as those affected by major depressive disorder and bipolar disorder (2). In addition, life-style factors such as tobacco smoking, unhealthy dietary patterns, poor sleep, together with poor physical activity have been found to be associated to higher risk of mental illness and poorer outcome of illness: these data suggest that life-style factors need to be addressed within mental health care (12).

We describe the impact of a repeated, systematic, prospective psycho- educational intervention on clinical and metabolic outcomes of patients affected by stable affective (APs) and non-affective psychoses (NAPs) treated with long-acting atypical antipsychotics over 6-months. We compared psychopathology and medical parameters of interest between the diagnostic groups at baseline and at the end of the program aimed at increasing awareness of the general health, improving diet and exercise, and limiting obesity and other side effects.

MATERIALS AND METHODS

Subjects

85 outpatients affected by Affective Psychoses ($n = 42$; APs: Schizoaffective Disorders, Not Otherwise Specified Psychoses) and Non-Affective Psychoses ($n = 43$; NAPs: Schizophrenia, Delusional Disorders) attending the Unit of Psychiatric at University of Foggia and treated with long-acting atypical antipsychotics, at stable doses, have been recruited and assessed at intake (T1) and 6 months (T2) for psychopathology, treatments, adherence, and monitored for anthropometric and electrocardiographic measures. Also, they received a systematized, repeated psycho-education about physical health. Diagnoses met DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), confirmed with the Mini-International Neuropsychiatric Interview (MINI) performed by consensus of experienced clinicians (AV, AP, and SI) (13, 14). This is a real-world study based on a straightforward clinical assessment with easy and reliable tools.

Patients were voluntarily recruited, clinically treated and followed at the Psychiatric Outpatient Services of University of Foggia Medical Center in 2014–2018, as part of an approved PhD Program in Clinical and Experimental Medicine at University of Foggia. All participants provided written, informed consent and the intervention was approved by the Medical Center Ethical Review Committee. Acutely psychiatrically or medically ill patients were excluded and we recruited those reporting a stable phase of illness in the previous three months and treated with a stable long-acting antipsychotic treatment clinically determined and followed for six months.

Assessment and Monitoring Procedures

Patients were assessed and monitored at intake (T1) and 6 months (T2) of follow-up, employing standardized methods. Clinical assessment, treatment selection and physical monitoring have been run by psychiatrists (AV, AB, VS, EM), whereas psychoeducation and rating scales have been delivered by two expert psychologists (AP, SI). Required information was gathered at intake and repeatedly during the follow-up. Electrocardiograms (with the record of QTc interval) were performed at intake and final visit as well as anthropometrics (height, weight, waist circumference, body mass index [BMI]), vital signs (blood pressure and pulse rate) and serum assays (serum lipids, carbohydrates, prolactin) which were carried out consistently by the University Medical Center clinical laboratory.

Antipsychotic drug- doses were converted to mg/day chlorpromazine-equivalents according to suggested conversion formulas (15, 16). Adherence to treatment was rated with the 30-item Drug Attitude Inventory (DAI-30) at intake and six months (17). Psychopathology including positive, negative and general symptoms were rated with the Positive and Negative Syndrome Scale (PANSS) (18) and the Brief Psychiatric

Rating Scale (BPRS) (19) at intake and six months; each investigator has been trained in order to employ the tools correctly and levels of inter-rater agreement were calculated (κ-statistic $\geq$0.94).

Psychoeducational Program

The repeated, systematic, prospective psycho- educational intervention was provided to all subjects once/month in conjunction with the administration of monthly long-acting injectable treatment. It included six sessions concerning psychiatric and general health, diet, exercise, weight-control, current treatment, following methods recommended by Littrell and colleagues (20). Patients were also trained to regularly measure vital signs (blood pressure, pulse rate) anthropometric parameters (weight, body-mass index [BMI], waist circumference) and advised about food-selection, healthy diets, daily physical exercise. Motivational modules regarding daily activity were performed.

In this trial no control condition was included.

Data Analysis

Data analyses were performed with standard, commercial, statistical software (Statview®; SAS Institute, Cary, NC; Stata®, StataCorp, College Station, TX). Data were presented as means or percentages (including %-changes) with 95%- Confidence Intervals- or standard deviations (as %-changes), compared between diagnosis by ***t***-test or χ^2. We also carried out repeated-measures ANOVA to evaluate changes in parameters of interest over time. Findings are considered statistically significant with two-tailed $p \leq 0.05$.

TABLE 1 | Subject characteristics at intake.

Measures	Means [95%CI]			*p*-value
	Non-affective psychoses	Affective psychoses	All pychoses	
Number (n)	43	42	85	-
Female (%)	30.2 [17.2–46.1]	52.4 [36.4–68.0]	41.2 [30.6–52.4]	**0.048**
Age (years)	43.8 [39.6–48.0]	40.3 [36.7–43.9]	42.0 [39.3–41.7]	0.212
Married (%)	9.30 [2.59–22.1]	21.4 [10.3–36.8]	15.3 [8.40–24.7]	0.142
Employed (%)	6.98 [1.46–19.9]	19.1 [8.60–34.1]	12.9 [6.64–22.0]	0.117
Initial morbidity ratings				
PANSS (total)	63.2 [53.9–72.5]	50.4 [44.7–56.1]	56.9 [51.4–62.4]	**0.022**
BPRS (total)	42.3 [37.9–46.7]	36.9 [33.1–40.7]	39.6 36.7–42.5[]	0.068
Antipsychotic use (%)				
Risperidone-LAI	27.9 [15.3–43.7]	9.52 [2.66–22.6]	18.8 [11.2–28.8]	**0.030**
Paliperidone-LAI	72.1 [56.3–84.7]	42.9 [27.7–59.0]	57.6 [46.4–68.3]	**<0.001**
Olanzapine-LAI	0.00 [0.00–0.00]	16.7 [6.97–31.4]	8.24 [3.38–16.2]	**0.005**
Aripiprazole-LAI	0.00 [0.00–0.00	31.0 [17.6–31.4]	15.3 [8.40–24.7]	**<0.001**
Mean dose (CPZ-eq mg/day)	294 [270–318]	229 [199–259]	262 [242–282]	**0.001**
DAI-30 score	10.9 [10.2–11.6]	11.1 [10.4–11.8]	11.0 [10.5–11.5]	0.765
Body-mass index (BMI, kg/m^2)	28.4 [26.7–30.1]	28.1 [26.0–30.2]	28.2 [26.9–29.5]	0.792
Waist circumference (cm)	103 [98.3–108]	101 [95.7–106]	102 [98.5–105]	0.668
Blood pressure & pulse				
Systolic (mm Hg)	119 [116–122]	122 [118–126]	118 [116–120]	0.262
Diastolic (mm Hg)	76.8 [74.2–79.4]	75.3 [72.4–78.2]	76.3 [74.4–78.2]	0.191
Pulse rate (per min)	85.7 [82.6–88.8]	83.4 [79.6–85.6]	83.4 [81.5–85.3]	0.399
QTc interval (msec)	407 [398–416]	420 [413–427]	413 [407–419]	**0.020**
Carbohydrates (serum)				
Fasting blood glucose	94.7 [90.1–99.3]	94.3 [89.4–99.2]	94.5 [91.2–97.8]	0.897
Hemoglobin glycosylation (%)	6.28 [6.02–6.55]	6.15 [5.96–6.34]	6.09 [6.03–6.15]	0.442
Serum lipids (mg/dL)				
Triglycerides	143 [124–162]	150 [120–180]	146 [129–163]	0.710
Total cholesterol	188 [178–198]	196 [184–208]	192 [184–200]	0.335
Low-density cholesterol (LDL)	125 [117–133]	123 [110–136]	124 [117–131]	0.859
High-density cholesterol (HDL)	45.9 [42.5–49.3]	49.8 [45.7–54.3]	47.8 [45.1–50.5]	0.150
Serum prolactin (μg/L)	45.1 [34.6–55.6]	40.4 [27.9–52.9]	42.8 [34.8–50.8]	0.563

Boldface*: Factors significantly different at intake by diagnostic type, by t-test or χ^2 ($p < 0.05$).*

PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; CPZ-eq, chlorpromazine-equivalent mg/day; DAI-30, 30-item Drug Attitude Inventory.

RESULTS

Sample Characteristics at Intake

85 adult outpatients affected by Affective Psychoses (n = 42; APs: Schizoaffective Disorders, Not Otherwise Specified Psychoses) and Non-Affective Psychoses (n = 43; NAPs: Schizophrenia, Delusional Disorders) were recruited in the 2014–2018 period, treated and followed for six months. Those with NAPs or APs included 30.2 and 52.3% women respectively (p = 0.048), with overall age-at-intake of 43.8 ± 12.2 vs. 40.3 ± 11.6 years. Demographic characteristics were similar through the diagnostic subgroups (**Table 1**). Psychopathological symptoms rated with PANSS and BPRS scales were slightly higher among NAPs vs. APs patients (63.2 ± 30.3 vs. 50.4 ± 18.2 [PANSS; p = 0.022] and 42.3 ± 14.4 vs. 36.9 ± 12.3 [BPRS; $p = 0.068$]).

Long-acting treatments, clinically selected, were exclusively based on SDA agents (injectable- risperidone [27.9%] and - paliperidone [72.0%]) for NAP patients and also included olanzapine and aripiprazole for AP patients ranking: paliperidone (42.8%)> aripiprazole (30.9%) > olanzapine (16.6%)> risperidone (9.52%) (p = 0.000). Average daily doses of antipsychotic (all converted to chlorpromazine-equivalent milligrams for comparison) were much higher among NAP vs. AP patients (294.0 ± 77.8 vs. 229.3 ± 95.8; $p = 0.001$).

Baseline anthropometrics, serum parameters and vital signs were somewhat similar between diagnostic groups and recorded QTc electrocardiographic interval was slightly higher among AP vs. NAP patients (419.9 ± 22.3 vs. 406.6 ± 29.2; p = 0.020) (**Table 1**).

Follow-Up Assessment

Measures changes from baseline (T1) were recorded after 6 months (T2) of follow-up and psycho- educational program. Changes were computed as means ± standard deviations (not shown) but also presented in a more informative manner as %-changes with standard deviations: *[(parameter at T1- parameter at T2)/ parameter at T1]*100*. Findings for all cases (N = 85) at 6-months showed a significant improvement of adherence-rate (DAI-30; +8.75%), reduction of psychopathological ratings (−7.57 % at PANSS and −6.45 % at BPRS), decrease of BMI (-2.40%) as well as QTc Interval (-0.20%), fasting glucose (−2.54%), hemoglobin glycosylation (−3.47%), total cholesterol with an increase of high density lipoproteins (−3.98 and +34.8 % respectively), reduction in serum prolactin (-4.81%) ($0.000 \leq p \leq 0.002$). Measures changes have shown little differences among diagnoses. PANSS score decreased highly among NAP vs. AP patients (−9.54 vs. −3.76%) as well as hemoglobin glycosylation (−3.84 vs. −2.76%), QTc interval (−0.209 vs. −0.203%) and serum prolactin (−4.97 vs. −4.49%) ($0.006 \leq p \leq 0.035$) (**Table 2**). Finally, we computed changes in measures among the different long-acting treatments over time: all measures did not differ among the treatments ($0.068 \leq p \leq 0.981$; not shown).

DISCUSSION AND CONCLUSION

This study aimed to test the impact of a psychoeducational program on general health among 85 patient-subjects diagnosed with clinically stable affective and non-affective psychoses treated with long-acting, injected, second-generation drugs,

TABLE 2 | Changes of measures over six months of long-acting antipsychotic treatment and psychoeducation.

Measures	Changes (%) with SD					
	All cases		*p*-values	Non-affective psychoses	Affective psychoses	*p*-values
PANSS score	−7.57	9.44	**<0.001**	−9.54 [9.03]	−3.76 [9.19]	**0.006**
BPRS score	−6.45	9.68	**<0.001**	−6.36 [11.3]	−6.63 [5.09]	0.079
DAI-30 score	+8.75	5.93	**<0.001**	+9.36 [5.86]	+7.58 [5.98]	0.194
BMI (kg/m^2)	−2.40	4.77	**<0.001**	−2.33 [5.31]	−2.77 [3.58]	0.227
Waist (cm)	−58.0	36.6	0.646	−59.0 [34.0]	−56.2 [41.6]	0.185
QTc	−0.20	0.01	**0.002**	−0.20 [0.01]	−0.20 [0.01]	**0.039**
Diastolic BP	+0.71	14.6	0.841	+0.71 [13.6]	+0.70 [16.8]	0.064
Systolic BP	+2.71	12.2	0.135	+2.04 [11.2]	+4.00 [14.2]	0.661
Pulse rate	+2.05	16.3	0.605	+2.35 [15.7]	+1.49 [17.8]	0.594
Fasting glucose	−2.54	8.30	**0.001**	−3.15 [7.36]	−1.36 [9.89]	0.953
Hemoglobin glycosylation	−3.47	3.87	**<0.001**	−3.84 [3.59]	−2.76 [4.34]	**0.007**
Total cholesterol	−3.98	9.54	**<0.001**	−3.33 [9.87]	−5.24 [8.92]	0.557
LDL cholesterol	−0.87	0.27	0.265	−0.86 [0.25]	−0.89 [0.30]	0.858
HDL cholesterol	+34.8	55.1	**<0.001**	+27.2 [46.7]	+49.3 [67.0]	0.186
Triglycerides	−12.41	44.0	0.166	−11.8 [44.6]	−13.4 [43.6]	0.871
Serum prolactin	−4.81	11.0	**0.000**	−4.97 [13.3]	−4.49 [4.43]	**0.035**

The 85 APs and NAPs patient-subjects were assessed clinically at baseline and 6 months, changes in measures were tested by repeated measures ANOVA.
SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; CPZ-eq, chlorpromazine-equivalent mg/day; DAI-30, 30-item Drug Attitude Inventory; BMI, Body-Mass Index; HDL, High-Density Lipids (cholesterol). LDL, Low-Density Lipids.
***Boldface**: Factors significantly different.*

as determined by treating physicians. Changes in clinical, anthropometric and physiological measures over six months of treatment exposure were measured.

Clinicians preferred risperidone and paliperidone antipsychotics for the long-term treatment of patient-subjects diagnosed with schizophrenia or other non-affective psychoses, possibly due to their relatively high affinity at dopamine D_2-receptors and their reported benefits on both positive and negative psychotic symptoms (21). Olanzapine and aripiprazole were preferred with affective psychoses since they may have mood-stabilizing effects (22). Subjects with non-affective psychoses were also given relatively high CPZ-eq doses of antipsychotics. Among few initial differences between subjects with affective and non-affective disorders, the QTc electrocardiographic interval was slightly higher with affective disorders (**Table 1**). It is of interest that patients recruited in the study were not affected by serious cardiological conditions and a small number of subjects were taking anti-hypertensive drugs (27.2%; not described for heterogeneity of data). Variations of QTc intervals among patients may also reflect an additional individual variability (23).

By six-months of treatment that involved close clinical follow-up and continued psychoeducational intervention was associated with several moderate, but favorable changes (**Table 2**). These include improved adherence ratings, even above those expected with injected, long-acting drugs: this reflects the evidence that joining a psycho-educational program may increase the personal awareness about illness and improve patients' attitudes regarding its treatment (24). Also, improvements in psychotic-symptoms ratings (PANSS and BPRS) may reflect benefits of the medication provided and perhaps added benefits associated with the psychoeducational intervention aimed to increase patients' *insight* (25). Improvements in BMI, carbohydrates, hemoglobin glycosylation, serum lipids and prolactin concentration may in part reflect changes in life-style, diet and physical exercise, all as encouraged by the psychoeducation intervention (26). In addition, participants' attitudes toward medications and their adherence to scheduled injections improved as reflected in ratings with the DAI-30.

Limitations

Cause-and-effect relationships involved in the observed changes are not clear without a control condition lacking psychoeducation. In fact, the comparison with a control-group of patients treated with long-acting medications with no psychoeducation (as well as patients treated with oral antipsychotics and psychoeducation) would add more evidence on the cause-and-effect relationships between their clinical outcomes and psychoeducational intervention. Also, it is notable that differences in baseline measures and their changes with treatment related to the type of psychotic illness were somewhat negligible (**Tables 1**, **2**). This study is limited by the relatively small number of subjects, only 6 months of treatment and follow-up, the lack of a comparison condition without a psychoeducational component, and lack of blinding to diagnosis and treatment. Nonetheless, similar improvements in clinical and metabolic status of severe mentally ill patients given the same psycho-educational program have been confirmed in our previous study conducted in 2014 (3).

In conclusion, the findings suggest favorable changes in clinical and metabolic status among severely ill psychotic outpatients treated with modern, long-acting, injected antipsychotic drugs combined with close clinical follow-up and ongoing psychoeducation. We suggest that such interventions may contribute to improving clinical and medical outcomes in psychotic disorders and limit mortality-risk, and conclude that they require further, controlled testing.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study involving human participants has been reviewed and approved by University of Foggia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AV and AB: each authors has contributed to the development of the report. AV, AP, VS, EM, and SI: reviewing clinical and pharmacy records. AV, JC-M, and JT: analyzing data. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Importance of Suicide Risk Formulation in Schizophrenia

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Suicide is a cause of early mortality in nearly 5% of patients with schizophrenia, and 25–50% of patients with schizophrenia attempt suicide in their lifetime. Evidence points to numerous individual, clinical, social, and psychological risk factors for suicide in patients with schizophrenia. Although recognizing suicidal risk factors in schizophrenia is extremely important in suicidal risk assessment, we have recently witnessed a change in suicide risk management that shifts the focus from suicide risk assessment to suicide risk formulation. Suicide risk formulation is dependent on the data gathered in the suicide risk assessment and assigns a level of suicide risk that is indispensable for the choice of treatment and the management of patients with a high suicidal risk. In this article, we extend the suicide risk formulation model to patients with schizophrenia. Suicide risk formulation results from four different areas that help clinicians collect as much information as possible for the management of suicidal risk. The four distinct judgments comprise risk status (the risk relating to the specific group to which the patient belongs), risk state (the risk for the person compared with his baseline or another reference point in the course of his life), available resources (on whom the person can count during a crisis) and foreseeable events (which can exacerbate the crisis). In schizophrenia, the suicide risk formulation model allows the clinician to evaluate in depth the clinical context of the patient, the patient's own history and patient-specific opportunities for better choosing and applying suicide prevention strategies.

Keywords: suicide risk, schizophrenia, prevention strategies, risk formulation, risk assessment

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SUICIDE RISK FORMULATION IN SCHIZOPHRENIA

Suicidal behavior in schizophrenia is an underestimated event, with 25–50% of these patients attempting suicide in their lifetime (1–3). It is also a frequent cause of early mortality, affecting nearly 5% of patients with schizophrenia (4, 5). Suicide may occur at any time during the clinical course of schizophrenia, although several studies have suggested that the highest suicide risk occurs during the first 10 years of illness (6, 7). Previous studies have reported numerous individual, clinical, social, and psychological risk factors for suicide in patients with schizophrenia (8, 9). Furthermore, schizophrenic patients who attempt suicide typically use lethal and violent methods requiring urgent medical attention and hospitalization (10).

Due to the importance of this outcome in patients with schizophrenia, suicide risk formulation and management are essential skills for clinical practice (11, 12). Many strategies can be used to

prevent suicide, and awareness of suicide risk factors in patients with schizophrenia is necessary to manage suicide risk better (13).

Many factors associated with suicide in schizophrenia have been identified, but attempts to identify high-risk patients have so far produced too many false positives to be clinically useful. Suicide prevention strategies can be improved by assessing several suicide risk factors simultaneously. Although recognizing that suicidal risk factors in schizophrenia are extremely important, we have recently witnessed a change in suicide risk management that shifts the focus from suicide risk assessment to risk formulation. Suicide risk formulation is a process by which the clinician forms a judgment about the patient's suicide risk based on data collected during the suicide risk assessment, and suicide risk formulation would seem to be indispensable for treating and managing a suicidal crisis (14, 15). Pisani et al. (16) supported this paradigm shift, and they pointed to the necessity for rethinking the formulation of suicide risk from a predictive to a preventive perspective. The authors discussed that, usually in clinical practice, the assessment of suicide risk had been based on the expression "low," "moderate," or "high" risk, and they argued that this type of assessment had poor reliability and validity (16). The model proposed by those authors provides for a risk assessment that does not use a categorical approach. According to those authors, suicide risk formulation is based on four different areas that help clinicians collect as much information as possible to manage suicide risk. The four distinct judgments involved in suicide risk formulation comprise: risk status (the risk relating to the specific group to which the patient belongs), risk state (the risk of the person compared with his baseline or another reference point in the course of his life), available resources (on whom the person can count during a sudden crisis) and foreseeable events (which can exacerbate the crisis). This model redefines the concept of suicide risk formulation as a concise, empirically-based summary of a patient's immediate distress and resources at a specific moment and place (16).

In this article we extend the suicide risk formulation model to patients with schizophrenia. In schizophrenia, the suicide risk formulation model allows the clinician to evaluate in depth the clinical context of the patients, the patient's own history, and patient-specific opportunities for better application of suicide prevention strategies.

SUICIDE RISK STATUS IN SCHIZOPHRENIA

The evaluation of the risk status compares suicide risk factors in a patient relative to other patients in a given population. For this reason, risk status is expressed using comparative forms such as "higher than," "similar to," or "lower than" in relation to a relevant comparison group. These factors tend to be more enduring (i.e., fixed, historical, and static), comprising patients demographic features. Other risk factors are mainly involved in the acute phase of schizophrenia and in the remission phase (16).

Demographic features, such as Caucasian race, male sex, younger age, and being unmarried, seem to be associated with increased suicide risk in patients with schizophrenia and are considered long-term status risk factors (17–20). Recently, Dickerson et al. (21) studied 733 patients with a schizophrenia spectrum disorder in order to examine the role of different variables in suicide risk. This study found that being Caucasian (vs. African American) and male was associated with higher hazard rates for suicide. Furthermore, a meta-analysis and meta-regression of 96 studies (22) confirmed that being male was consistently associated with suicide in patients with schizophrenia but a protective factor against suicidal attempts. The authors explained this result as consistent with the "gender paradox" phenomenon (23) in which females present higher rates of suicidal ideation and non-lethal behavior than do males. Suicide mortality is typically lower for females than for males, probably because women are more likely to use less lethal methods than do men. Regarding the relationship between age and suicidal risk in schizophrenia, several studies have demonstrated that younger patients have an increased likelihood of attempting suicide (24–26).

Furthermore, studies on marital status and suicide risk indicate that being married is a protective factor for suicidal risk, and married patients indeed have more family support than patients who are not married (27). Finally, the prevalence of suicide risk in patients with schizophrenia differs across countries (28). For example, several studies have demonstrated that patients with schizophrenia who live in high-income countries were more likely to attempt suicide than those in the low- and middle-income countries. Furthermore, patients who live in North America or Europe and Central Asia present a higher prevalence of suicide attempts than patients in South Asia, sub-Saharan Africa, East Asia, and Pacific areas (28). Differences in socio-cultural and economic contexts (such as societal discrimination and stigma) and the prevalence of substance abuse (such as alcohol and cocaine) may explain these differences (29–32).

Through the model of suicide risk formulation, previous suicide attempts are among the essential enduring risk status factors for suicidal behavior (33–35). Furthermore, repeated attempts exponentially increase the risk of a lethal act (36, 37). A multicenter randomized trial conducted by Fleischhacker et al. (the ZODIAC Study) (38) analyzed 18,254 patients with schizophrenia to understand better the features of completed and attempted suicide in this population. The results confirmed that previous suicide attempts were the strongest predictor of completed suicide and future suicide attempts. In addition, using logistic regression, Li et al. (39) examined 64 inpatients with schizophrenia and found that previous suicide attempts were an independent risk factor for suicide and useful for better suicide risk formulation.

Other enduring suicide risk factors that play an important role in suicide risk formulation include adverse childhood experiences (ACEs). It has been postulated that ACEs are nearly three times more frequent in patients with schizophrenia and other psychoses than in the general population (40). Adverse childhood experiences that include physical, sexual and emotional abuse, as

well as neglect, are present in about 30% of the general population and can impair the individual's sense of security (e.g., substance-abusing parents, divorce, incarceration of a family member, etc.) (41). Is well-known that ACEs increase the risk of mental health consequences in adulthood, including depression, anxiety, psychosis, post-traumatic stress disorders, dissociative disorders, and personality disorders (42). In patients with schizophrenia, ACEs have been associated with the development of psychotic episodes (43), an earlier onset of schizophrenia (43), a higher incidence of positive and negative symptoms (44–49) and a higher risk of suicidal behavior (43, 45, 46, 50, 51). Several studies have proposed that the risk of developing psychosis is higher in patients exposed to multiple ACEs. A possible explanation is that repeated exposure to adverse experiences increases mesolimbic dopamine reactivity, causing delusions and hallucinations (40, 52–56). Several studies have reported an association between negative childhood experiences and suicidal risk in psychiatric patients (57–59). Consistent with these findings, Hassan et al. found that patients with schizophrenia who had experienced ACEs were more likely to attempt suicide than patients who did not report ACEs. Moreover, recently Prokopez et al. (60) studied 100 patients with schizophrenia and observed that multiple ACEs were associated with a higher frequency of suicide attempts. Notably, the authors observed that men and women with various adverse experiences during childhood reported more suicidal ideation and a higher frequency of at least one suicidal attempt. The women with multiple ACEs had a higher number of suicide attempts.

Family functioning, that is, the ability to adapt oneself to changes determined by the levels of cohesion, flexibility, and communication within a family, is often compromised in families of individuals with schizophrenia and is an important enduring factor in suicide risk formulation (61–63). Moreover, it seems that disrupted relationships with family members may increase suicide risk (64–67). For example, in a sample of 263 patients with schizophrenia spectrum disorders, Chang et al. (68) found that suicidal behavior was associated with poorer family relationships. In addition, a study by Demir (69), that analyzed 350 psychiatric outpatients, found a significant association between suicidal behavior and abnormal emotional expression by a family member who exhibited excessive, hostile, and judgmental emotions toward the psychiatric patient.

Among other factors involved in suicide risk status, premorbid functioning in psychotic disorders influences clinical and functional outcomes (70). For example, in a study by Pompili et al. (71), good premorbid functioning increased the risk of completing suicide. The authors explained this result as being consistent with the "demoralization syndrome" (72), in which a good level of functioning and insight into the illness may cause hopeless feelings and suicidal thoughts (73). Conversely, Bakst et al. (74), who assessed premorbid functioning in a sample of 444 individuals with a first psychotic episode, found that a higher likelihood of suicide attempts before the first psychiatric hospitalization was associated with poorer premorbid functioning. Nevertheless, when the sample was divided into two groups (schizophrenia vs. other psychoses), the association was no longer significant in the patients with schizophrenia. In contrast, the association remained significant in the patients with other psychoses. The authors interpreted this result by taking into account the heterogeneous phenomenology of schizophrenia.

Different clinical features associated with schizophrenia can be enduring suicide status risk factors. The age of schizophrenia onset has a crucial role in understanding the developmental and distinctive features (i.e., genetic and environmental antecedents) of the disorder that appear in early adulthood and become chronic and impairing (75). Early-onset schizophrenia is associated with a poorer prognosis and worse psychological, social and biological outcomes (76, 77). In particular, suicide risk seems to be associated with an early onset of schizophrenia, as confirmed by Vinokur et al. (78) in a study of 138 patients with schizophrenia. Moreover, in a British follow-up investigation (79), most suicides occurred within the first 2 years of the onset of the psychotic disorder. A study by Castelein et al. (80) that followed 424 patients with schizophrenia for 20 years found that the percentage of deaths that was from suicide declined over time from 11.0 to 2.4%. Thus, although higher suicide rates have been identified in younger patients, suicide risk remains stable throughout life in individuals with schizophrenia (2). Several authors also reported that a longer illness duration was significantly associated with lifetime suicide attempts (81, 82). Recently, Chang et al. (68) showed that a longer illness duration was one predictor of lifetime suicide attempts in a sample of 263 patients with schizophrenia. Dai et al. (83) replicated this result by comparing 908 patients with schizophrenia with suicide attempts to those without suicide.

Status factors involved in the suicide risk formulation in the acute phase of schizophrenia include the type of psychotic symptoms and categorization of schizophrenia, depressive symptoms and hopelessness, alcohol abuse, anxiety symptoms, insomnia, and illness insight. Evidence regarding the predictive value of positive and negative symptoms on suicide risk is still conflicting (80, 84, 85). Andriopoulos et al. (86) found that both positive and negative symptoms were increased in individuals with suicide ideation (vs. those without suicide ideation). Gill et al. (87) examined 42 individuals at high risk for psychosis and found a significant association between suicide ideation and negative symptoms.

However, the association between specific subtypes of schizophrenia and suicide risk is still controversial. The review conducted by Pompili et al. (33) found no significant differences in suicide risk according to the classical categorization of schizophrenia as catatonic, hebephrenic, or undifferentiated. On the other hand, paranoid schizophrenia seems associated with a higher suicide risk, probably as a result of the later age at onset (88). Possible explanations for the increased risk of suicide associated with increased age at onset of illness in patients with paranoid schizophrenia might include the stress these patients face, the deterioration in cognitive functioning, and having had a family and occupation during their early adult years (36, 89). Furthermore, a relation between command hallucinations and suicide risk has been postulated, but the data are still controversial. Fenton et al. (89), in a long-term follow-up study, observed that patients with schizophrenia who died by suicide presented lower negative symptom severity upon admission

and more often had two positive symptoms (suspiciousness and delusions) than patients without suicidal behaviors (89). Repeated psychiatric hospitalizations are a common feature of patients with schizophrenia due to the disease's chronic nature and poor medication adherence (90).

Moreover, re-hospitalization seems to be strongly associated with suicidal ideation and behaviors, as Fleischhacker et al. (38) highlighted in their study of potential baseline risk factors for attempted suicide in 18,154 patients with schizophrenia. The results showed that a history of more than five hospitalizations was, alongside previous suicide attempts, the most substantial variable associated with attempted suicide. Zhang et al. (91) assessed 520 inpatients with schizophrenia and compared suicide attempters and non-attempters. They found that patients who had attempted suicide reported significantly more frequent hospitalizations, and a logistic regression analysis confirmed that suicide attempts were associated with more hospitalizations.

An additional factor in evaluating suicide risk status in schizophrenia is patient insight into the illness. Most researchers have defined insight as being comprised of at least three domains: awareness of the disease, awareness of the need for treatment, and awareness of the consequences of the disorder (92). Some studies (93, 94) have demonstrated that hopeless awareness of the severity of the disorder (schizophrenia) was one of the most important predictors of completed suicide in patients with psychotic disorders. However, it is still uncertain whether insight was directly related to suicide or mediated by its influence on hopelessness. Several studies have demonstrated that illness awareness is associated with increased suicide risk in patients with schizophrenia (95–97). In a recent study of 100 psychiatric inpatients, Berardelli et al. (98) reported that patients with higher scores on the insight-high dimension had a 1.35 greater odds of having a higher suicide risk, indicating that greater illness insight is involved in suicide risk.

Current depressive disorders were strongly associated with suicide in patients diagnosed with schizophrenia (99, 100). More than 50% of patients who died by suicide had symptoms of depression at the time of the suicide (8), and it has been suggested that a depressive disorder may trigger suicidal behavior in vulnerable patients with schizophrenia (36). In addition, *hopelessness* is an important risk factor in people diagnosed with schizophrenia (101), even in the absence of a concomitant depression (94). Several studies have also reported that symptoms of demoralization in patients with schizophrenia are related to suicide risk (73). Depressive symptoms occur in different phases of the psychosis, including prodromal, acute, and post-psychotic phases (102–104). It has been proposed that depressive dimensions are intrinsic to schizophrenia psychopathology, in positive, negative, and disorganized symptom clusters (104). The close linkage between psychotic symptoms and depression, especially in the prodromal phase, suggested that depression in schizophrenia may be the severe end of a dimension of affective dysregulation from adolescence progressing to the early stages of psychosis as the illness crystalizes (105). Furthermore, depression could be a psychological reaction to the diagnosis of schizophrenia and its implications for patients' lives or could be related to early risk factors such as a childhood trauma (103). Addressing psychotic depression is important not only in suicide formulation but also for schizophrenia management as it is related to relapse, greater substance-related problems, poorer life satisfaction, mental functioning, family relationships, and medication adherence (106).

Substance abuse is a common phenomenon among individuals with schizophrenia (107). Up to 50% of patients with schizophrenia exhibit either alcohol or illicit drug dependence, and more than 70% are nicotine dependent (108). In particular, heavy cannabis abuse has been reported to be a stressor, eliciting relapse in patients with schizophrenia and related disorders (109). Although it is difficult to compare the relative impact of different mental health problems with suicide risk, alcohol and drug use disorders have been strongly linked to suicide risk (110, 111). Multiple potential links, including genetic vulnerability, treatment side effects, and psychosocial factors, have been discussed as possible pathways (112). One explanation for the increased incidence of substance use in patients with schizophrenia is the self-medication hypothesis (113). Individuals with a substance use disorder (i.e., a diagnosis of either alcohol or drug abuse or dependence) are almost six times more likely to report a lifetime suicide attempt than those without a substance use disorder (114). In addition, evidence has suggested that alcohol abuse is a predictor of suicide (7, 115). However, some authors have suggested that alcohol abuse may be associated with suicide attempts but not with completed suicide (116). As for drug abuse, most studies have reported an association with increased suicide risk (117) and impulsiveness (118). In particular, abuse of stimulants (cocaine, amphetamine) increase the risk of attempted suicide (119).

Anxiety symptoms are highly prevalent in schizophrenia and occur in up to 65% of patients (120, 121). Anxiety symptoms are strongly associated with depressive symptoms, somatization, and feelings of guilt in patients with schizophrenia (122, 123). Panic attacks have also been associated with suicide risk in schizophrenia (120). However, although anxiety symptoms do not discriminate suicide ideators from attempters, anxiety symptoms significantly predict general suicidality in schizophrenia (124). Patients with schizophrenia and anxiety symptoms have a lower quality of life but higher insight into their illness than those without anxiety symptoms (124).

In a case-control study, Pompili et al. (125) suggested the role of insomnia as a suicide risk factor. Previous research on the relationship between suicide and sleep disturbances has noted that those patients with schizophrenia who exhibited suicidal behavior presented increased overall rapid eye movement (REM) activity (126).

Other schizophrenia related factors, mainly present in the remission phase, are involved in suicide risk status including loss of confidence in pharmacotherapy, fear of further mental breakdown and fear of acute symptomatology.

Finally, risk status is the assessment of different enduring risk factors based on the clinical context and patient population, on the patient's history, and on patient-specific opportunities for prevention.

SUICIDE RISK STATE IN SCHIZOPHRENIA

Suicide risk refers to a person's current risk compared with his/her own risk at baseline or at another set point in time. Factors involved in risk state are more dynamic and related to the moment-to-moment clinical status of patients. Together, risk status and risk state allow clinicians to understand the patient's current vulnerability among their population, context, and time. The risk state formulation focuses on temporal changes and on the effect of the distress on the patient's life. The state risk factors that are mainly involved in the acute phase of schizophrenia include the presence of suicide ideation or recent suicide behavior, recent loss, social isolation, new hospitalizations, loss of faith in treatment, excessive treatment dependence, awareness of the illness, and social alienation (16).

The presence of suicidal ideation during the acute phase of schizophrenia must be carefully evaluated during the clinical interview. With the aid of appropriate psychometric tools, recent stressors and precipitant events represent important dynamic factors capable of modifying the suicide risk state. Among the various stressors, recent loss is often considered a state risk factor for suicide in patients with schizophrenia (1, 22, 99). Gallego et al. (127) investigated 3,322 patients diagnosed with schizophrenia and affective disorders and reported a significant association between recent financial or relational loss and current suicide attempts. In a sample of 180 patients with first-episode psychosis, Fedyszyn et al. (128) demonstrated that one of the most vital risk factors for suicide was a recent negative event, such as a traumatic or stressful experience. Social isolation, which consists of disrupted or non-existent interpersonal contacts and relationships, is a well-known suicide risk factor in schizophrenia (129–131). Recently, several papers have further addressed this relationship. For example, Bornheimer et al. (132) investigated the relationship between social isolation, psychosis, and suicide ideation and found a mediating effect of social isolation in the relationship between psychosis and suicide ideation. In addition, the authors identified an indirect path between positive symptoms (hallucinations and delusions) and suicide ideation through social isolation. Conversely, several studies have shown the protective role of social support in reducing suicide risk (133–135). Social support increases feelings of belongingness and prevents negative appraisals after stressful events, and the presence of individuals can physically prevent suicide attempts. However, only a few studies have analyzed the role of poor social support in suicide risk in schizophrenia spectrum disorders. Xie et al. (50) reported a significant negative correlation between social support and suicide ideation in a sample of patients with schizophrenia. In a study of 212 patients with schizophrenia, Pješčić et al. (136) found a higher prevalence of poor social support and social isolation in patients with suicide ideation.

The state risk formulation also evaluates several features related to schizophrenia and its treatment during the acute and remission phases of the illness, including recent discharge from a psychiatric ward and fear of a new hospitalization. Current discharge from a psychiatric ward as a risk factor for suicide was noted in a recent study (137) that reported a suicide rate of 178 per 100,000 person-per year within the first 3 months after discharge. Moreover, the lack of adequate outpatient healthcare seems to increase suicide risk (137). Erlangsen et al. (138) assessed 248 suicides in Denmark between 1990 and 2006 and identified recent discharge as a significant risk factor for suicide. Waiser et al. (139) examined 2,881 patients with schizophrenia through a survival analysis method. They found that ∼32% of suicides occurred within 6 months after psychiatric hospitalization, with the rate rising to 48% within 1 year. Lastly, Lopez-Morinigo et al. (140) analyzed 426 suicides (71 patients with schizophrenia spectrum disorder and 355 controls) and demonstrated a significant association between recent hospital discharge and completed suicide in the schizophrenia group. In a systematic review by Hawton et al. (8), agitation or motor restlessness seemed to be associated with suicide risk in patients with schizophrenia during the acute phase of the illness.

It is well-known that schizophrenia can modify many facets of patients' experience, including language, emotion and intersubjectivity, all factors related to social alienation. Therefore, these symptoms of schizophrenia should be understood as human psychopathological phenomena and not only as sub-products of a malfunctioning brain (141). Disturbances in both language, emotion and social interactions in patients with schizophrenia have received some research attention. However, little attention has been paid to these dimensions' subjective experience, particularly the personal meaning for patients with schizophrenia (142). Their language, emotion and encounters with other people has been poorly investigated. Furthermore, hyper-reflexivity, which refers to a type of intensified self-consciousness, diminished self-affection that represents a decline in consciousness of oneself as the subject of experience, and alteration of interactions with the world are other important dimensions involved in a loss of vital contact with reality in patients with schizophrenia (143). Schizophrenia should be viewed as a disorder of the person and not only of the brain. We can understand the importance of a suicide risk formulation based on the evaluation of subjective dimensions and external-social dimensions that are strongly connected to suicide risk (16).

In the acute phase of the illness, patients with schizophrenia may voluntarily decide to enter in a hospital if their symptoms are severe and painful. Awareness of the severity of psychotic symptoms and the fear of a new hospitalization can affect the patient's mental state, increasing hopelessness, helplessness and social isolation, all risk factors for suicide. Furthermore, clinicians can decide to commit a patient involuntarily. The decision to involuntarily commit an individual has become more challenging due to rapid changes in health care. It is important to remember that patients who are forced into treatment may develop a sense of distrust toward treatment providers and family members, which can delay recovery in the long run and can increase suicide risk. Alongside the increased awareness of symptoms, fear of the ineffectiveness of drug therapies and fear of becoming dependent on the various treatments can also increase the risk of suicide of patients with schizophrenia (144).

Among the various acute symptoms of schizophrenia, agitation seems to be involved in suicide risk. Pompili et al. (125) conducted a retrospective case-control study comparing 20 patients with schizophrenia who died by suicide with 20 living

controls and found that agitation and motor restlessness was much more common in the suicides Furthermore, the guidelines drafted by the European Psychiatric Association (145) highlight the role of agitation in affecting suicidal behavior in patients with schizophrenia. Suicide risk also seems to be associated with poor adherence to treatment as shown in several studies (8, 146). For example, Hering and Erkens (147) analyzed 603 patients with schizophrenia. They observed a four-fold increased risk of suicide in the group that interrupted treatment with antipsychotic drugs compared with the group that continued treatment. In addition, Novick et al. (148) reported that, of the 6,731 patients in the study, 28.8% of the sample was non-adherent to treatment, and this feature was associated with suicide attempts. Consistent with this, Ward et al. (149) analyzed 3,291 patients with schizophrenia, and their results demonstrated that good adherence was a protective factor against suicide.

Antipsychotic medications are known to be associated with several movement disorders, acute side effects, late-onset side effects, tardive dyskinesia, and extrapyramidal symptoms (EPSs). The latter include acute dystonia and parkinsonism which can be present also in the remission phase of schizophrenia (150). In a double-blind, randomized controlled multicenter trial on 298 patients with first-episode schizophrenia who were in treatment with risperidone or haloperidol, suicide ideation was associated with akathisia, suggesting that EPSs may have a promoting effect in suicide risk (151). However, the findings of Reutfors et al. (150) demonstrated a lower suicide risk in patients with a history of EPSs. The authors explained their results by noting that these patients were characterized by better adherence to treatment, higher dosages, and a prevalence of polypharmacy.

Other suicide state factors include the presence of medical disorders and poor mental health conditions (152). Patients with schizophrenia present higher mortality rates, probably due to the presence of a medical disorder and unhealthy lifestyle behaviors, in addition to psychiatric impairment and psychotropic medication use. The presence of physical comorbidity, the need for new pharmacological treatments and specialist visits, and fear of the prognosis and for the quality of life could increase the psychological fragility of patients, thereby becoming state risk factors.

In conclusion, the factors involved in risk state are dynamic and malleable and relate more to moment-to-moment clinical status in the acute phase of schizophrenia. Together, risk status and risk state allow clinicians to understand better an individual's current vulnerability in this population, context, and time.

AVAILABLE RESOURCES AND FORESEEABLE CHANGES IN SCHIZOPHRENIA

A suicide risk formulation model based only on a categorical label for suicide risk state requires detailed additional information in order to plan risk prevention and the management of the patient. A complete suicide risk formulation, in combination with estimates of risk state and risk status, permits an assessment of the patient's available resources and future foreseeable changes (16).

Available resources are defined as resources immediately accessible to the patient and clinicians to support them during suicide crises in the acute phase of the illness. Recognizing the available resources for patients is different from assessing suicide protective factors, which often refer to general and epidemiologic factors known to decrease suicide risk across populations and are not immediately available during an acute suicidal crisis. In this sense, clinicians have to focus on the personal variables of each patient (coping strategies, resilience) and relational variables such as social support available during the acute phase of the crisis (16). Furthermore, when applying this model to patients with schizophrenia, the clinician, when identifying available resources, must consider the presence of psychotic symptomatology, patient insight, and factors that reduce collaboration between the patient and the resources.

Foreseeable changes are stressors that can increase or decrease suicide risk in the acute phase of schizophrenia. However, not all stressors increase suicide risk. Therefore, in the formulation of suicide risk, it is important to understand what makes an ordinary stressor a trigger for suicide (153). To better investigate the role of the various stressors, clinicians should investigate the subjective meaning or consequence of the stressor for the patient. In schizophrenia, foreseeable changes comprise the presence of substance use, school disciplinary action, inpatient discharge and social and relationship difficulties.

Furthermore, return to a conflictual environment after hospitalization and changes in pharmacotherapy are other

TABLE 1 | Suicide risk formulation in schizophrenia.

Suicide risk status	Suicide risk state	Available resources	Foreseeable changes
• Socio-demographic features	• Comorbid psychiatric disorders	• Coping strategies	• Subjective meaning of the stressor
• Previous suicide attempts	• Insomnia	• Resilience	• Presence of substance abuse
• Adverse childhood experiences	• Recent losses	• Social support	• School disciplinary actions
• Family conflicts	• Social isolation	• Insight	• Inpatient discharge
• Premorbid functioning	• Recent discharge from a psychiatric ward	• Absence of psychotic symptomatology	• Social difficulties
• Early onset schizophrenia	• Agitation/motor restlessness	• Good collaboration with the clinician	• Conflictual environment
• Repeated psychiatric hospitalizations	• Poor compliance		• Changes in pharmacotherapy
• Higher insight levels	• Extra-pyramidal symptoms		
• Positive/negative symptoms			
• Longer duration of illness			

foreseeable changes that need to be assessed. To better understand suicide risk in schizophrenia, it is also important to assess whether symptoms are increasing or decreasing and the meaning of these changes for the patient. The assessment of anger, impulsivity, isolation, depression, demoralization, and hopelessness is necessary for immediately implementing suicidal risk prevention strategies. Finally, the level of engagement between the clinician and the patient, the relationship with the clinician, and the degree to which the patient's report has been honest, reliable, and credible are other essential factors (153) (**Table 1**).

SUICIDE RISK FORMULATION AND SUICIDE PREVENTION STRATEGIES IN SCHIZOPHRENIA

Suicide prevention in patients with schizophrenia is a complex phenomenon. Inadequate knowledge of suicide risk factors in patients with schizophrenia negatively affects the ability of clinicians to recognize patients at risk for suicide. Clinicians need to have better knowledge of suicide-related knowledge and suicide risk formulation in order to identify patients with high suicide risk. Careful assessment and management of psychotic symptoms, comorbid depression, hopelessness, demoralization symptoms and substance use disorders are also necessary to prevent suicide in patients with schizophrenia.

Several pharmacological and non-pharmacological strategies are available to reduce suicide risk in patients with schizophrenia. Undoubtedly enhancing adherence with medications is essential for alleviating psychotic and non-psychotic symptoms in schizophrenia. Patient-related features involved in the adherence with medications include demographic characteristics, newly starting treatment, younger age at onset of illness, alcohol dependence and other illicit substance use, homelessness, low levels of involvement in social activities, independent housing, and financial constraints (154). Lack of family support for adherence, or having no family, further contribute to non-adherence. Significantly higher IQs, executive functioning, memory, and verbal learning/fluency are also factors involved in medication adherence (155, 156). Medication non-adherence is associated with an increased risk for relapse of psychosis, persistent symptoms, and suicide attempts (157), making it indispensable to enhance adherence with medications.

Studies suggest that antipsychotic medications, including clozapine, risperidone, olanzapine and quetiapine, may reduce mortality and suicide risk in schizophrenia (158, 159). In 2002, the U.S. Food and Drug Administration (FDA) approved clozapine for decreasing suicide risk in patients with schizophrenia. Studies have suggested that atypical antipsychotic may be more effective than the use of typical antipsychotics (146, 160). Evidence for the ability of clozapine therapy to reduce suicidal behaviors has been highlighted in several studies since the late 1990s. Meltzer and Okayli (161) observed 88 neuroleptic-resistant patients treated with clozapine for 0.5–7.0 years and reported decreased suicidal behavior. Walker and Diforio (162) noted that suicidal behavior decreased in patients with current clozapine treatment compared with past users. Reinstein et al. (163), in a retrospective study of 295 patients, confirmed that clozapine treatment reduced suicide risk during continuous drug administration. More recently, Meltzer et al. (164), in a multicenter, randomized, international, 2-year study comparing the risk for suicidal behavior in patients treated with clozapine *vs.* olanzapine, observed that suicidal behavior was significantly less frequent in patients treated with clozapine. Several studies conducted by Tiihonen et al., confirmed that antipsychotic medication in general, particularly clozapine, was associated with lower suicide risk (165, 166). Furthermore, the same author observed that long-term treatment with antipsychotic drugs is associated with lower mortality, and clozapine seems to produce substantially lower mortality than any other antipsychotics (166). However, some antipsychotics, including clozapine and haloperidol and other antipsychotics, may increase the risk of depression (167). Tiihonen et al. (168) investigated whether using benzodiazepines, antidepressants, or multiple concomitant antipsychotics was associated with mortality in patients with schizophrenia. Their results demonstrated that the use of 2 or more antipsychotics was not associated with increased mortality. In contrast, antidepressant use was not associated with a higher risk for mortality and was associated with markedly fewer suicides. However, benzodiazepine use was associated with an increased risk of suicidal and non-suicidal deaths. Haukka et al. (169) observed that olanzapine, and to some degree clozapine, tended to perform well for suicide risk; which is in line with a review on the potential anti-suicidal effects of atypical antipsychotic (167). Taipale et al. (170) investigated the risk of attempted and completed suicide in patients with schizophrenia. The authors confirmed that clozapine is the only antipsychotic associated with a decreased risk of suicide. Several studies have also demonstrated that olanzapine, an atypical antipsychotic similar to clozapine, could effectively reduce depression and suicide risk in patients with schizophrenia (171, 172).

A study of 339 patients with psychotic disorders found that both olanzapine and risperidone were effective for the treatment of psychotic symptoms. However, only olanzapine produced a seven-fold lower risk of suicidal behaviors (173). In addition, olanzapine demonstrated a more significant anti-suicidal effect than haloperidol (174) and was similar to risperidone (175). Furthermore, quetiapine has been shown some potential effects for reducing suicidal risk, not only in patients with schizophrenia (167). Evidence about other atypical antipsychotic drugs on suicidal risk remains very limited. Whether all specific antipsychotics effectively prevent completed suicides also remains unclear. Long-Acting Injectable Antipsychotics (LAIs) have several advantages in terms of efficacy, safety and tolerability in treating schizophrenia. A better understanding of whether LAI treatment may decrease suicide risk by indirectly acting on a range of risk factors for suicide specific to patients with schizophrenia is of significant clinical importance. Pompili (176) suggested that long-acting injections of second-generation antipsychotics can be an effective

treatment strategy to improve medication adherence and prevent suicide risk.

Furthermore, in addition to antipsychotics, other psychotropic medications, such as antidepressants and mood stabilizers, are often used in for patients with schizophrenia (177). Research suggests that the use of antidepressants together with antipsychotic drugs has been associated with a decrease in all-cause mortality, including suicide (169). However, Tiihonen et al. (165), in a large cohort study, observed that antidepressant treatment increases the risk of suicide attempts but not of completed suicides and death. In addition, a cohort study noted that antidepressant use in schizophrenia, compared with no use, was associated with a significant reduction in risk of completed suicide (166). However, two systematic reviews of randomized controlled trials confirmed the increased risk of self-harm or suicidal attempts related to selective serotonin uptake inhibitors (SSRIs) (160, 178).

Mood stabilizers have been used to augment the effects of antipsychotic drugs in patients with schizophrenia. Mood stabilizer medications may also effectively reduce depression, aggression and impulsivity in patients with schizophrenia when administered with antipsychotic therapy. Together with clozapine, lithium is the only drug showing anti-suicidal properties in bipolar and major affective disorders (171). A comprehensive meta-analysis of the effect of lithium in reducing suicide risk reported that both completed and attempted suicide were reduced by nearly five-fold, or 80% (179). Recently, several studies have suggested that lithium treatment reduces suicide attempts, suicides, hospitalization for suicide attempts, and other suicide spectrum disorders, compared with patients treated with other mood stabilizers (180–182). Although the beneficial effects of lithium on suicide risk in affective disorders are well-documented (183), data on whether this extends to patients with schizophrenia or schizoaffective disorder are lacking (184). The potential of other mood-stabilizing agents, such as lamotrigine, which has established antidepressant activity, is less well-understood than that of lithium, valproate or carbamazepine.

Non-pharmacological strategies are also crucial in the management of suicide risk in patients with schizophrenia. Psychosocial interventions, reality-orientated therapies, cognitive-behavioral therapy, cognitive remediation, supportive therapy, education and family intervention can be used together with pharmacological therapies in order to reduce suicide risk in patients with schizophrenia. Interventions such as vocational rehabilitation, social skills training, and supportive employment may also reduce social isolation and feelings of hopelessness, decreasing suicidality.

A few studies have examined the impact of specific psychotherapeutic and psychosocial interventions on suicide risk in patients with schizophrenia (36). Evidence suggests that supportive psychotherapeutic interventions that discuss acute symptoms, depression and hopelessness, daily difficulties, medications, adverse effects, social isolation, and stigma are necessary non-pharmacological suicide prevention strategies in patients with schizophrenia (185). Findings of a recent meta-analysis that examined 11 studies showed a statistically significant treatment effect of psychosocial interventions for suicide spectrum disorders individuals with psychosis (132).

Reviews and meta-analyses of cognitive behavior therapy (CBT) for psychosis have reported positive results for various symptoms (186, 187). A randomized controlled trial of cognitive behavioral therapy (CBT) for 90 patients with schizophrenia found that cognitive behavioral therapy was related to a significant reduction in suicidal ideation at the end of the psychotherapy and 9 months after the therapy (188). Additionally, psychodynamic treatments have been proposed to reduce suicide risk in patients with schizophrenia (189). Overall, clinicians should consider a phenomenological approach when treating suicidal individuals, pointing to the inner experience of the wish to be dead of each unique individual, avoiding the limitation of treating only single diagnostic entities (190, 191).

CONCLUSIONS

Suicide in schizophrenia is a complex phenomenon that represents an ongoing challenge in clinical practice. This overview shows that suicide risk in schizophrenia is influenced by a variety of demographic, clinical, psychological, social, cultural, and environmental factors. However, identifying high-risk patients only with simple techniques of suicide assessment has so far produced too many false-positive results to be clinically helpful.

Suicide prevention strategies can be improved by simultaneously assessing and examining multiple risk factors and applying the suicide risk formulation model. Therefore, therefore, the aim of the suicide risk formulation model in schizophrenia is not the prediction but rather the formulation of a complete picture of the person. Promoting communication and collaboration between professionals, patients, and families should reduce suicide risk in the short term and in the long term. Structuring a targeted intervention plan that includes pharmacological and non-pharmacological strategies seems indispensable for managing suicide risk in patients with schizophrenia.

For psychiatrists and other clinicians working with patients with schizophrenia, arriving at a clear formulation of a patient's level of risk, based on a synthesis of clinical and non-clinical information, is a core competency for assessing and managing suicide risk. In addition, in clinical settings, the suicide formulation model allows for the prevention of future suicidal behavior and leading to practical safety and crisis response plans, which are the main objective of suicide prevention.

AUTHOR CONTRIBUTIONS

MP and IB: conceptualization. MP, IB, and ER: methodology. IB, DE, SS, and ER: data curation. IB and ER: writing-original draft preparation. DL and MP: writing, review, and editing. All authors contributed to the article and approved the submitted version.

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COVID-19-Related Mortality Risk in People With Severe Mental Illness: A Systematic and Critical Review

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Background: Increasing clinical evidence suggests that people with severe mental illness (SMI), including schizophrenia spectrum disorders, bipolar disorder (BD), and major depressive disorder (MDD), are at higher risk of dying from COVID-19. Several systematic reviews examining the association between psychiatric disorders and COVID-19-related mortality have recently been published. Although these reviews have been conducted thoroughly, certain methodological limitations may hinder the accuracy of their research findings.

Methods: A systematic literature search, using the PubMed, Embase, Web of Science, and Scopus databases (from inception to July 23, 2021), was conducted for observational studies assessing the risk of death associated with COVID-19 infection in adult patients with pre-existing schizophrenia spectrum disorders, BD, or MDD. Methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results: Of 1,446 records screened, 13 articles investigating the rates of death in patients with pre-existing SMI were included in this systematic review. Quality assessment scores of the included studies ranged from moderate to high. Most results seem to indicate that patients with SMI, particularly patients with schizophrenia spectrum disorders, are at significantly higher risk of COVID-19-related mortality, as compared to patients without SMI. However, the extent of the variation in COVID-19-related mortality rates between studies including people with schizophrenia spectrum disorders was large because of a low level of precision of the estimated mortality outcome(s) in certain studies. Most studies on MDD and BD did not include specific information on the mood state or disease severity of patients. Due to a lack of data, it remains unknown to what extent patients with BD are at increased risk of COVID-19-related mortality. A variety of factors are likely to contribute to the increased mortality risk of COVID-19 in these patients. These include male sex, older age, somatic comorbidities (particularly cardiovascular diseases), as well as disease-specific characteristics.

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Conclusion: Methodological limitations hamper the accuracy of COVID-19-related mortality estimates for the main categories of SMIs. Nevertheless, evidence suggests that SMI is associated with excess COVID-19 mortality. Policy makers therefore must consider these vulnerable individuals as a high-risk group that should be given particular attention. This means that targeted interventions to maximize vaccination uptake among these patients are required to address the higher burden of COVID-19 infection in this already disadvantaged group.

Keywords: severe mental illness, schizophrenia, bipolar disorder, major depressive disorder, mortality, COVID-19

BACKGROUND

People with severe mental illness (SMI), including schizophrenia (SZ) (lifetime prevalence: 0.7%), bipolar disorder (BD) (lifetime prevalence: 0.4–1.1%), and major depressive disorder (MDD) (lifetime prevalence: 15–18%) (1–3), have a two to three times higher mortality rate than the general population (4–7). This mortality gap translates into a 10–20 years shortened life expectancy (6, 8) and appears to be widening (9).

It is well-known that the majority of deaths in individuals with SMI are due to physical diseases, predominantly cardiovascular diseases (8, 10). Non-medical factors, including unhealthy lifestyles, disparities in physical health care, and stigmatizing attitudes toward people with SMI, contribute to the higher risk of death (11–13). Disease-related factors, such as unawareness of physical problems and challenges in appraising health information due to cognitive deficits, delusions, and, in general, lower educational attainment and health literacy (11, 14–18), as well as the use of psychotropic medication (antipsychotics, antidepressants, and mood stabilizers) (4, 10, 12) may further increase the risk of physical comorbidities.

Research has shown that several respiratory viruses, including human coronaviruses, can have neuroinvasive properties (19). The central nervous system (CNS) is also a potential target for the SARS-CoV-2 virus, because angiotensin-converting enzyme 2 (ACE 2) receptors, used by the virus to enter the cells, are equally expressed in glial cells and neurons in the brain (20–23). Although there is still no convincing evidence for direct neuropathogenic effects of SARS-CoV-2 (24, 25), COVID-19 infection can cause CNS damage (26–28). In a prospective autopsy cohort study, extensive inflammatory changes, affecting both white and gray matter, were detected in the brain of patients with lethal COVID-19. This inflammatory response was most pronounced in the olfactory bulbs and medulla oblongata. Results of this study suggest that CNS changes are due to a maladaptive immune response, rather than the consequence of a direct virus-induced effect, given that viral presence was low at late stages of COVID-19 (29). The first longitudinal imaging study (which had not been peer reviewed as of Oct 13, 2021), comparing structural and functional brain scans acquired from individuals before and after SARS-CoV-2 infection (n = 401) with scans from a well-matched control group (n = 384), demonstrated brain atrophy, mainly in the limbic regions with direct neuronal connectivity to the primary olfactory and gustatory system, in addition to a more diffuse loss of gray matter. These authors suggested that the observed brain changes may be due to a direct virus effect, or to neuroinflammation, following viral infection and initiating chronic neuronal dysfunctions (30).

Different pathogenic pathways may be involved (31). One of the proposed mechanisms is that the SARS-CoV-2 virus enters the CNS through the neuronal retrograde route. In this case the virus infects neurons in the periphery and uses the olfactory nerve pathway to gain access to the CNS and cause infections of immune-functioning microglia or astrocytes in the CNS (19, 30). This, however, does not rule out a pathway from the nose to the brain by other mechanisms (such as the vascular route). A review by Uversky et al. (20) stated that there are at least seven candidate routes the SARS-CoV-2 virus can use to reach the CNS.

Nevertheless, because of these findings concerns have been raised regarding the neuroinvasive effect of COVID-19 infection in patients with pre-existing neuropsychiatric disorders, in particular in SMIs, which are often already characterized by a systemic pro-inflammatory state (32, 33). According to one review, 0.9–4% of individuals infected with SARS-CoV-2 develop psychotic spectrum disorders (34). A retrospective cohort study reported the following numbers (<6 months after acute infection): 0.9% in COVID-19 infection without hospitalization, 2.9% after hospitalization, and 7% after COVID-19-related encephalopathy (28). However, some of these cases probably are due to COVID-19-related psychosocial stress or treatment (e.g., steroid treatment in patients with COVID-19) (34, 35).

Recently, five systematic reviews and meta-analyses (36–40), assessing the risk of COVID-19-related mortality in patients with a psychiatric disorder, have demonstrated that people with SMI have a higher COVID-19-related mortality risk, compared to general population controls, and even compared to people with other psychiatric disorders. This risk remained high after adjustment for age, sex, and other confounders. Although these reviews have been thoroughly conducted, certain methodological limitations may hinder the accuracy of their research findings. Most of these reviews did not use a comprehensive search strategy for COVID-19 (36–39), or did not include the Embase database (36, 37, 40). Several of these reviews not only included laboratory-confirmed COVID-19 cases, but also patients where the SARS-CoV-2 infection was based on a clinical diagnosis made by physicians (36, 37, 39), or did not make this clear in their methodology section (40). Furthermore, reviews reporting

mortality data on mood disorders did not distinguish unipolar and BDs (although most of the included studies in these reviews relied on electronic medical records that do not allow a fine-grained analysis of clinical variables) and/or pre-existing from post-infection or comorbid disorders [e.g., (38)]. Finally, a thorough discussion part is also missing in most of these reviews.

AIM OF THE STUDY

To overcome the above-mentioned limitations a novel systematic literature search was conducted to assess the risk of death associated with COVID-19 infection in people with SMI (schizophrenia spectrum disorders, BD, and MDD), compared with patients without SMI, or without any psychiatric disorder, and a thorough discussion part was provided.

METHODS

Search Strategy

A comprehensive literature search, using the PubMed, Embase, Web of Science, and Scopus databases (from inception to July 23, 2021), was conducted without language restriction for studies reporting data on the risk of death associated with COVID-19 infection in adult patients with schizophrenia spectrum disorders, BD, or MDD, compared with controls (patients without a SMI or without a psychiatric disorder). Two of the authors (JD and MD) and two experienced biomedical information specialists worked closely together to construct effective search strings for the different databases. Full search strategies are available as **Supplementary Material 1**. Duplicates were removed using EndNote X9 and Rayyan QCRI (JD). After removing duplicates, titles and abstracts were screened by JD. Articles that were deemed potentially relevant according to the selection criteria were selected. JD and MD independently reviewed the full text of the selected articles and assessed their eligibility. They also attempted to identify additional studies through a systematic search of the reference lists of selected articles and of previously published systematic reviews/meta-analyses.

Selection Criteria

Inclusion criteria were:

(i) Published, peer-reviewed, original studies,
(ii) Population-based observational studies, including case-control, cohort, or cross-sectional studies,
(iii) Studies including patients with laboratory-confirmed COVID-19 cases (i.e., a positive real-time reverse transcription-polymerase chain reaction test),
(iv) Studies including patients with a clinically confirmed pre-existing SMI (i.e., schizophrenia spectrum disorders, BDs, and/or unipolar depression), using a widely-accepted standardized disease coding system, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), and
(v) Studies reporting COVID-19-related mortality outcomes [i.e., odds ratio, risk ratio, hazard ratio (HR), or associated metrics] and comparing COVID-19-related mortality risks of SMI patients with non-SMI patients, or patients without a psychiatric disorder.

Studies that did not include patients with pre-existing SMI (thus studies where COVID-19 may have been an antecedent to the onset of the SMI disorder), a control group, COVID-19-related mortality outcomes, original data, or were not peer-reviewed and published (preprints, conference papers), as well as case reports, reviews, meta-analyses, and studies where SMI mortality outcomes were grouped with those for non-SMIs, or studies where COVID-19 was not ascertained according to laboratory testing were excluded.

This systematic review adhered to the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (41). We did, however, not register our protocol prior to submitting the manuscript for publication.

Data Extraction

Data from the included studies were extracted from each article by JD to collect the following information:

(i) Study characteristics: author information, publication year, country where the study was conducted, study design (cross-sectional, cohort or case-control, prospective vs. retrospective), time period studied during the COVID-19 pandemic,
(ii) Patient characteristics: primary diagnoses included in the study, sample sizes of SMI patients and controls, mean/median age (years), and sex distribution,
(iii) Outcome measure: adjusted and unadjusted mortality data (odds ratio, risk ratio, HR, or associated metrics with 95% confidence interval estimates), and
(iv) Covariates in adjusted risk.

Assessment of Risk of Bias

The quality of each observational study was rated using the Newcastle-Ottawa Scale (NOS), whereby a higher score indicated higher methodological quality and lower risk of bias. The NOS was adapted for cross-sectional data.

RESULTS

Search Strategy

The original search in the PubMed (n = 131), Embase (n = 1,133), Web of Science (n = 105), and Scopus (n = 77) databases yielded a total of 1,446 reports. Of these, 265 duplicate reports were removed. Overall, 37 references of published studies were selected as potentially eligible, of which 12 original records met the inclusion criteria. One record, identified through cross-referencing and which fulfilled the inclusion criteria, was added, resulting in a total of 13 original records. The results of the study selection are shown in the PRISMA flow diagram (see **Figure 1**).

Study and Patient Characteristics

Study and patient characteristics, as well as mortality data and covariates are presented in **Table 1**. Median age of SMI patients across studies ranged from 40 to 66 years and was

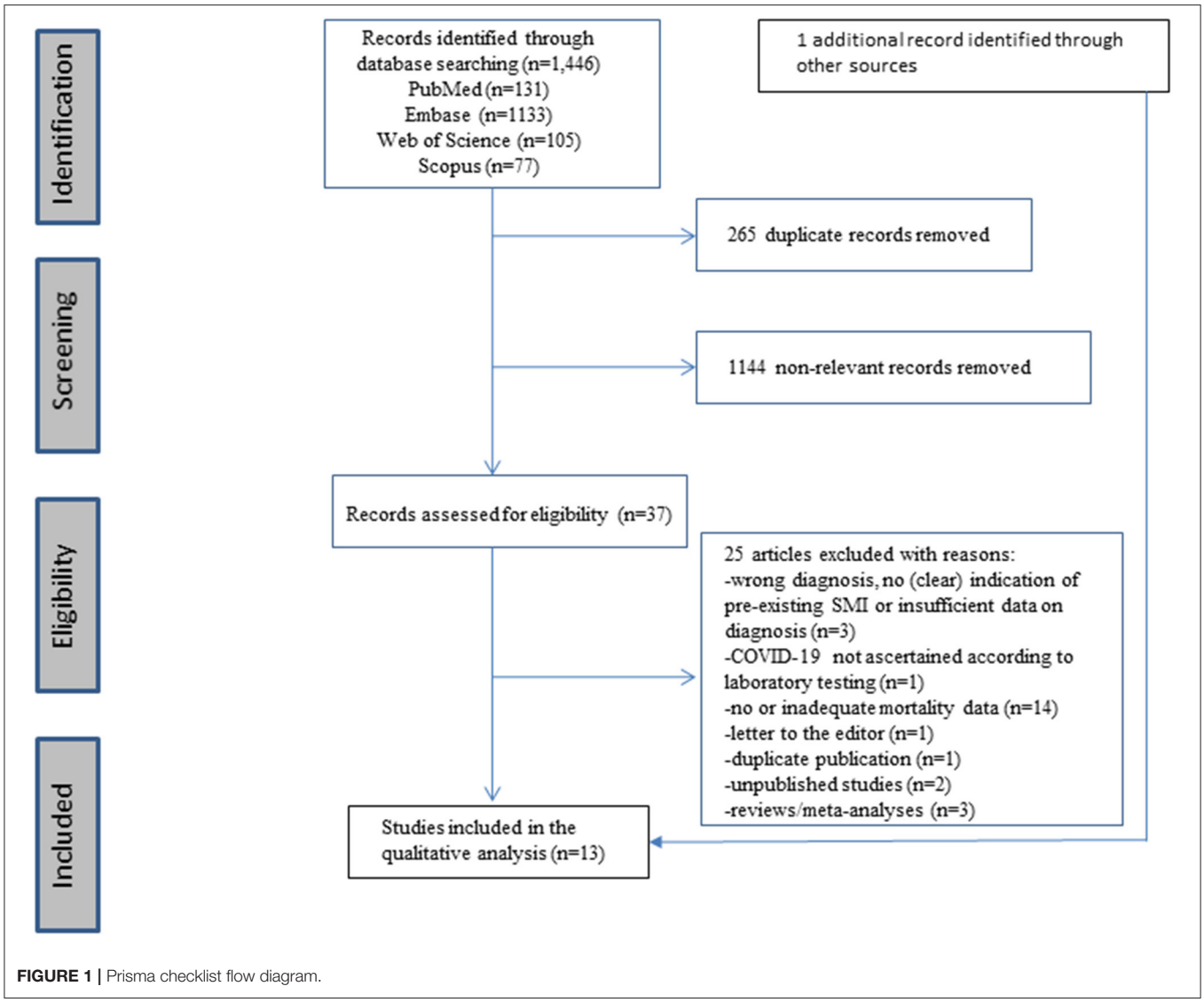

FIGURE 1 | Prisma checklist flow diagram.

not reported in nine studies. Two studies were carried out in Denmark, two in France, one in Israel, one in South Korea, two in Spain, one in the U.K., and four in the U.S. Severe mental illness was almost exclusively categorized according to ICD classification criteria. In the French and Israeli studies only patients with schizophrenia (spectrum disorders) were analyzed. The U.S. study of Egede et al. (46) analyzed exclusively data of BD patients.

Quality Assessment

Data on study quality are presented in **Supplementary Material 2**. Methodological quality was high in nine studies, and moderate in four studies.

Study Results

For studies analyzing mortality data separately for patients with schizophrenia spectrum disorders, BD and MDD, fully adjusted risks (= adjusted for demographic factors and one or more comorbidities or other covariates) ranged from 1.30 to 4.36 for schizophrenia spectrum disorders, and from 2.04 to 2.68 for depression. Only two studies (42, 46) reported COVID-19-related mortality data separately for patients with BD. In the study of Egede et al. (46), including exclusively BD patients, a HR of 2.67 (95% CI: 1.07–6.67) was found, while Barcella et al. (42) did not find a significant HR [adjusted HR = 1.94 (0.97–3.90)] in the fully adjusted model. A variety of factors were likely to contribute to the increased mortality risk of COVID-19 in these patients. These included male sex, older age, and somatic comorbidities, as evidenced by the reduction of the unadjusted risk after adjusting for these demographic factors and comorbidities. However, as even after this adjustment the risk of COVID-19-related mortality was still increased, other factors also seem to play a primordial role (see **Table 1**).

TABLE 1 | Study characteristics and mortality data of the included studies (33, 42–53).

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Barcella et al. (42)	Denmark	Cohort study	February 27 2020–January 2 2021	Schizophrenia spectrum disorders (F20–29) BD (F30, 31, 38) Unipolar depression, including MDD (F32–34, F39) (ICD-8 and ICD-10) Controls = patients without psychiatric disorder	Schizophrenia spectrum disorders (n = 984) vs. controls (n = 127,281) BD (n = 485) vs. controls (n = 127,281) Unipolar depression (n = 3,764) vs. controls (n = 127,281)	40 (median) 48.8% 45.3 (median) 37.3% 44 (median) 30.8%	**Standardized average RR: 2.29 (1.36–3.22)** **Unadjusted HR:4.12 (2.64–6.43)** **Adjusted HR:2.41 (1.53–3.79)** **Standardized average RR: 1.87 (1.12–3.12)** **Unadjusted HR:3.34 (1.66–6.70)** Adjusted HR:1.94 (0.97–3.90) **Standardized average RR: 1.92 (1.39–2.44)** **Unadjusted HR:2.63 (1.97–3.52)** **Adjusted HR:2.04 (1.52–2.74)**	Age, sex, highest obtained education, income, ischemic heart disease, congestive heart failure, cerebrovascular disease, CKD, HP, peripheral artery disease, DM, COPD, asthma, substance abuse, and malignancy

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Nemani et al. (43)[†]	U.S.	Retrospective cohort study	March 3 2020–May 31 2020	Schizophrenia spectrum disorders (F20, 22, 23, 25, 28, 29) Mood disorders -Unipolar depression, including MDD F32, 33, 34, 39 -BD F30, 31 (ICD-10) Controls = patients without psychiatric disorders, with the exception of patients with organic mental disorders, mental disorders due to substance use, mental retardation, and disorders of psychological development.	Lifetime SZ vs. controls: 75/6,349 Lifetime mood disorders vs. controls: 564/6,349 Recent SZ vs. controls: 46/6,349 Recent mood disorders vs. controls: 374/6,349	N/A	**Unadjusted OR: 2.93 (1.75–4.92)** **Demographically adjusted OR: 2.87 (1.62–5.08)** **Fully adjusted OR: 2.67 (1.48–4.80)** **Unadjusted OR: 1.82 (1.45–2.29)** Demographically adjusted OR: 1.25 (0.98–1.61) Fully adjusted OR: 1.14 (0.87–1.49) **Unadjusted OR: 2.84 (1.47–5.52)** **Demographically adjusted OR: 3.13 (1.50–6.54)** **Fully adjusted OR: 2.67 (1.26–5.69)** **Unadjusted OR: 2.19 (1.69–2.84)** **Demographically adjusted OR: 1.52 (1.13–2.03)** Fully adjusted OR: 1.27 (0.94–1.73)	Demographically adjusted: age, sex, race Fully adjusted (demographically + medical risk factors): age, sex, race, smoking status, HP, heart failure, myocardial infarction, DM, CKD, COPD, and cancer

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Tzur Bitan et al. (44)	Israel	Retrospective cohort study	March 2020–October 2020	SZ (ICD-9 or ICD-10) (F20) Controls = people without schizophrenia randomly drawn from the general population	642 patients vs. 709 controls	51.51 (mean, SZ) 51.37 (mean, controls) 61%	**Non-adjusted OR: 3.14 (1.34–7.36) Adjusted OR (95% CI): 3.27 (1.39–7.68)**	Age, sex
Jeon et al. (45)	South Korea	Retrospective cohort study	1 December 2019–15 May 2020	Schizophrenia spectrum disorders (ICD-10) (F20–F29) Mood disorders (BD+ MDD) (ICD-10) (F30-F39) Controls = patients without a psychiatric disorder	159 patients vs. 628 controls 273 patients vs. 1,060 controls	N/A	Adjusted OR: 2.25 (0.36–14.03) Adjusted OR (95% CI): 2.33 (0.96–5.66)	Cohort matched by age, sex, and Charlson Comorbidity Index with up to four people without mental disorder and adjusted for type of insurance, medical history of DM and pneumonia, and use of β-blockers and anticonvulsants
Egede et al. (46)	U.S.	Cross-sectional analysis	March 20–July 10 2020	BD (ICD-9 and ICD-10) (F30.1–F30.4, F30.9, F31.1–F31.6, F31.73–F31.78, F31.9) Controls = patients without a psychiatric disorder	38 patients vs. 1,330 controls	52.3 (mean) 29.7%	**Non-adjusted HR: 2.83 (1.15–6.96) Demographically adjusted HR: 2.63 (1.07–6.49)** **Fully adjusted HR: 2.67 (1.07–6.67)**	Gender, age, race/ethnicity, location, and primary payor, tobacco use, and BMI.

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Fond et al. (47)	France	Case-control study	February 27 2020–May 4 2020	SZ (F20,22,25) (ICD-10) Controls = patients without a psychiatric disorder	15 patients vs. 1,077 controls	66 (median) 73.3%	**Non-adjusted OR: 3.80 (1.19–12.20)**	
							Adjusted OR: 4.36 (1.09–17.44)	Age, sex, smoking status, obesity, Charlson Comorbidity Index
							Adjusted OR: 4.28 (1.07–17.20)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, hydroxychloroquine
							Adjusted OR: 4.33 (1.08–17.34)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, hydroxychloroquine-azithromycin combination
Fond et al. (48)	France	Cohort study	February 1 2020–June 9 2020	SZ (F20,22,25) (ICD-10) Controls = patients without a SMI	823 patients vs. 49,927 controls	48.8%	**Unadjusted OR: 1.25 (1.05–1.49) Adjusted OR: 1.30 (1.08–1.56)** Significant interaction between SZ and age (p = 0.0006): SZ patients between 65 and 80 years have a significantly higher risk of death than controls of same age [**+7.89%; Adj. OR: 1.62 (1.28–2.06)**]	Age, sex, social deprivation, smoking status, overweight and obesity, Charlson Comorbidity Index, origin of the patient, hospital category, number of hospital stays for COVID-19, geographical areas of hospitalization

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Reilev et al. (49)	Denmark	Cohort study	February 27 2020–May 19 2020	SMI=SZ (F20), schizoaffective disorder (F25), or BD (F30,31)(ICD-10) Controls = patients without a SMI	76 patients vs. 11,046 controls	N/A	**Non-adjusted OR: 3.8 (2.1–7.0)** **Demographically adjusted OR: 2.5 (1.2–5.1)** Fully adjusted OR: 1.9 (0.9–3.9)	 Age, sex Age, sex, and number of comorbidities
Poblador-Plou et al. (50)	Spain	Retrospective cohort study	March 4 2020–May 17 2020	Mood disorders (ICD-9-CM) Controls = patients without a psychiatric disorder	202 patients vs. 569 controls	N/A	Adjusted OR: 1.38 (0.98–1.95) (men with mood disorder) **Adjusted OR: 1.46 (1.12–1.91) (women with mood disorder)**	Age Age
Yang et al. (33)	U.K.	Retrospective cohort study	January 31 2020–July 26 2020	MDD (ICD-9 or ICD-10) Psychotic disorders (ICD-10) Controls = non-psychiatric patients	22,352 patients vs. 398,662 controls 1,431 patients vs. 419,583 controls	N/A	**Adjusted OR: 2.68 (2.03–3.54)** **Adjusted OR: 3.50 (1.70–7.17)**	Adjusted for birth year, sex, race or ethnicity, Townsend deprivation index, educational attainment, annual household income, BMI, smoking status, and history of chronic cardiac disease, DM, COPD, CKD, and asthma.

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Castro et al. (51)	U.S.	Retrospective cohort study	February 15 2020–May 24 2020	Mood disorders (MDD and BD) (ICD-10) Controls = individuals without a psychiatric disorder	717 patients vs. 2,271 controls	N/A	Mortality risk ≥ hospital *day* 12 **Unadjusted HR: 2.16 (1.54–3.02) Demographically adjusted HR: 2.00 (1.42–2.82)** **Fully adjusted HR: 1.54 (1.05–2.25)** Mortality risk< hospital *day* 12 Unadjusted HR: 1.17 (0.91–1.50) Demographically adjusted HR: 1.08 (0.83–1.39) Fully adjusted HR: 0.88 (0.65–1.18)	Age, sex, race, ethnicity, admission site (academic medical center compared with community hospital), socioeconomic status, and Charlson comorbidity index
Diez-Quevedo et al. (52)	Spain	Retrospective cohort study	March 1 2020–November 17 2020	Mood disorders (ICD-10) Controls = patients without mood disorders	279 patients (mood disorder) vs. controls	N/A	**Adjusted HR: 1.52 (1.13–2.06)**	Sex, age, history of medical and psychiatric disorders

(Continued)

TABLE 1 | Continued

Study	Country	Study design	Time period	Diagnosis	Sample size	Mean/median age (years) Male gender	Risk (95% CI)	Covariates in adjusted risk
Wang et al. (53)	U.S.	Retrospective case-control study	Up to July 29 2020	Depressive disorder (code 3548900) (including MDD) (SNOMED-CT) Controls = patients without a psychiatric disorder	1,460 patients with a recent (past year, but prior to COVID-19) diagnosis of depression	N/A	**Unadjusted OR: 1.56 (1.28–1.91)**	Age, sex, ethnicity, and medical comorbidities (cancers, CVDs, type 2 DM, obesity, CKD, COPD, asthma, and SUDs)

BD, bipolar disorder; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; DM, diabetes mellitus; HP, hypertension; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD, International Classification of Diseases; MDD, major depressive disorder; N/A, not available; OR, odds ratio; RR, risk ratio; SMI, severe mental illness; SNOMED-CT, systematized nomenclature of medicine-clinical terms; SUDs, substance use disorders. Bold values indicate statistical significance between groups.

†A secondary analysis was limited to patients with recently documented psychiatric diagnoses of interest recorded in an encounter between January 1, 2019, and March 3, 2020 (recent diagnoses).

DISCUSSION

Our systematic review shows that, after full adjustment for relevant confounders, the extent of the variation in COVID-19-related mortality rates between studies including people with schizophrenia spectrum disorders was large. COVID-19-related mortality risk was found to be 2- to 4-fold increased for patients with schizophrenia spectrum disorders, compared with controls. There are several reasons for this variation:

(1) studies showing higher adjusted mortality estimates included rather small samples of patients (47), and/or presented mortality data with large confidence intervals (33, 45, 47), indicating a low level of precision of the estimated mortality outcome(s),
(2) while some studies were strictly limited to patients with SZ (44), others included disorders covering more or less the whole spectrum of SZ-like disorders (42, 43, 45). In addition, there is (besides the lack of information about psychopharmacological treatments and psychiatric treatment settings of patients) a lack of specific information about the severity and the status (first-episode vs. chronic) of the disease. These elements are important to consider since different forms of the disorder may have different risks of COVID-19-related mortality, and
(3) the comparison group sometimes included non-SMI patients and at other times patients without a psychiatric disorder.

Although results are more stable for studies on MDD (COVID-19-related mortality risk in these patients seems to be 1.5- to 2-fold increased, compared with controls), these studies also in most cases did not include specific information on the mood state or disease severity of the patients. While some studies were strictly limited to patients with MDD (33, 51), others (42, 43) also included mild or moderate forms of the disease.

Finally, several studies (45, 49, 50, 52) involved a mixed population and did not make a distinction between the three main categories of SMIs. Studies on BD patients clearly are lacking.

Recently, several systematic reviews and meta-analyses (36, 37, 39, 40), showed that pre-existing mental disorders were associated with an increased COVID-19-related mortality risk, compared to controls, even after adjustment for age, sex, and other confounders. In the meta-analysis of Fond et al. (37), patients with SMI (schizophrenia spectrum disorders and/or BD) were found to have the highest risk of COVID-19-related mortality (adjusted OR = 1.67; 95% CI: 1.02–2.73). Vai et al. (36) also observed that the most robust associations were found for psychotic disorders (adjusted OR = 1.68; 95% CI: 1.29–2.18) and mood disorders (adjusted OR = 1.43; 95% CI: 1.15–1.79), after adjustment for age, sex, and other confounders, with a statistically significant difference ($p = 0.0047$) identified between adjusted estimates for SMI patients (adjusted OR = 1.55; 95% CI: 1.30–1.85) and patients with non-SMI psychiatric disorders (adjusted OR = 1.09; 95% CI: 0.92–1.29). A very recently published cohort study confirmed the previously published evidence (54). These results thus show that patients with SMI have a statistically significantly higher risk of death than patients with

non-SMI disorders. Moreover, analyses stratified by the number of redeemed psychotropic medications indicated that COVID-19-related mortality risk increases with higher psychotropic medication use (42). All these results therefore suggest an association between mental illness severity and COVID-19-related mortality risk.

A retrospective cohort study in patients with mood disorders has found that COVID-19-related mortality risk in these patients seems to be particularly elevated 2 weeks after admission, while there seems to be little difference in mortality risk with controls during early hospitalization (51). However, the meta-analysis of Vai et al. (36) found no evidence of increased in-hospital mortality in patients with psychiatric disorders vs. those without. Moreover, COVID-19-related mortality risk was significantly higher among psychiatric patients who were not admitted to the hospital than among hospitalized patients.

Factors Underlying the Association Between SMI and COVID-19-Related Mortality

Several demographic factors and somatic comorbidities have been identified that contribute to the higher observed mortality estimates associated with COVID-19 infection in people with SMI (42–44, 49, 50, 53, 55, 56) and without SMI (57–63). These include older age (≥65–70 years old), male gender, low socioeconomic status (SES) and educational level, and physical diseases (cardiovascular disease, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, diabetes). These identified factors may have a more profound impact on people with a SMI.

Firstly, as in the general population, particularly older individuals (≥60 years) with SMI are vulnerable to COVID-19. However, there seems to be an excess mortality due to COVID-19 among patients of this age group. Deaths due to COVID-19 were found to be 4 times higher for those with SMI, compared to individuals without SMI within the same age group [people with SMI: 0.01% (40–59 years), 0.12% (60–69 years), 0.46% (70–79 years), vs. individuals without SMI: 0.01% (40–59 years), 0.03% (60–69 years), 0.11% (70–79 years)] (55). Fond et al. (48) found that patients with SZ between 65 and 80 years had a higher risk of death [7.69% (<55 years) and 30.29% (≥65 <80 years)], compared to individuals without a SMI of the same age [4.04% (<55 years) and 22.4% (≥65 <80 years)] [Adj. OR (95% CI): 1.62 (1.27–2.06, $p = 0.0002$)]. These results can be linked to the accelerated biological aging hypothesis, one of the major causes of the higher premature mortality rates that are observed in people with SMI (64, 65). This means that aging of both body and brain, and, in particular for COVID-19, the senescence of immune cells (66), might be more rapid in these people. One study found that molecular brain age (i.e., biological age of the brain) was 2–6 years higher than the chronological age in individuals with SZ, and 4.7–7.5 years higher in subjects with BD. No increase in brain aging was noted in subjects with MDD (67).

The impact of SES, which has been found to be associated with health care access (68), on the risk of COVID-19-related mortality remains to be elucidated, particularly in individuals with SMI (55). Due to the complexity of SES and its metrics (such as the Townsend Deprivation Index or the Distressed Communities Index), it stays unclear which individual components are associated with COVID-19-related mortality. While the impact of certain socioeconomic aspects (e.g., lower education and race) on COVID-19-related mortality has been shown (69, 70), other components (such as poverty and unemployment) were found to be protective against COVID-19-related mortality (69). Moreover, these measurements remain indirect indices of health care access and are assessed only once at baseline. Therefore, misclassification due to the absence of repeated measurements might exist (33). The same applies to the impact of the type of care/facility on the treatment outcomes for persons with SMI with COVID-19, particularly during the first wave of the COVID-19 pandemic. At the beginning of this pandemic, in the U.S. (71) and in Europe (72) many inpatient psychiatric facilities created psychiatric COVID-19-positive units (PCU). When tested positive, psychiatric patients were transferred to these units, where they were treated medically for their COVID-19 illness by internists and medical nurse practitioners. Only if patients showed signs of respiratory distress, such as shortness of breath or chest pain, they were transferred to a medical emergency room for further evaluation (71). The organization of PCU, however, varied considerably across countries and over time (72). Therefore, it remains unknown what the effect is of the type of care/facility on COVID-19-related mortality figures in these persons.

Secondly, a higher somatic comorbidity burden in patients with SMI, compared to non-psychiatric patients, may also partly explain the increased COVID-19-related mortality risk. However, with the exception of cardiovascular diseases, results for other somatic comorbidities are sometimes inconsistent. In SMI and non-psychiatric populations hypertension, diabetes, and chronic obstructive pulmonary disease have been found to correlate with an increased risk of fatality in most (43, 49, 73–75), but not all studies (55, 76). Nevertheless, it is well-recognized that individuals with these comorbidities are at an increased risk for a severe course of COVID-19 (77). In addition, somatic comorbidities seem in general to be an important driver of the observed increased COVID-19-related infection and mortality estimates in patients with SMI (33, 43, 49, 53). The reasons why certain somatic comorbidities are associated with more severe COVID-19 illness in people with SMI are not yet fully understood (78).

Although results are inconsistent, the use of psychotropic medications may be another important risk factor. A recent meta-analysis (36) showed that, after adjustment for age, sex, and other confounders, COVID-19-related mortality was associated with exposure to antipsychotics (initiated before contracting COVID-19) (adjusted OR = 2.43, 95% CI: 1.81–3.25), but not to antidepressants (adjusted OR = 1.18, 95% CI: 0.93–1.50). However, a very recently published retrospective cohort study did not observe an association between antipsychotic use and COVID-19-related mortality (79). An important obstacle in finding an answer to the question whether there exists an association between the use of psychotropic medications and

COVID-19-related mortality is that specific data on the use of psychotropic medication and psychiatric status (acute phase vs. stabilization phase) across studies is lacking.

Some antipsychotic medications (particularly clozapine) seem to increase susceptibility to pneumonia and pneumonia-related mortality risk in individuals with SMI due to sedation, impaired swallowing and hypersalivation (80–82). Clozapine can also suppress immune function (78). In animal models, short- to intermediate-term exposure to clinically relevant levels of risperidone has been shown to induce inflammatory and adaptive immune process dysregulation, possibly affecting susceptibility to respiratory infections, including COVID-19 (83). Nevertheless, some studies found a protective effect for COVID-19 infection in patients treated with antipsychotics (84, 85). Based on preclinical findings, the antipsychotics chlorpromazine and haloperidol have been suggested to offer protection against SARS-CoV-2, possibly through their interactions with sigma-1 receptors, inducing anti-inflammatory effects by inhibiting cytokine production (86–90). However, initial observational clinical studies did not confirm that these agents offer protection against COVID-19 infection or COVID-19-related mortality (84, 91). However, the results of these studies have to be interpreted with caution, because of possible confounding factors. Moreover, it is important to make a distinction between acute and long-term treatment effects of antipsychotic treatment.

Valproate, a mood stabilizer, also may be associated with an increased risk of respiratory infections (92). By contrast, lithium, another mood stabilizer, seems to be associated with a decreased risk of respiratory infections and demonstrated potential antiviral properties at a preclinical level (92, 93). Lithium has even been proposed as a candidate treatment for COVID-19. It can suppress NOD-like receptor family pyrin domain containing-3 (NLRP3) inflammasome activity (which is implicated in the release of pro-inflammatory cytokines during the cytokine storm), inhibits cell death (resulting in a decrease in lung parenchymal damage), and is characterized by immune-regulatory mechanisms (preventing the harmful effects of immune hyperactivation) (94). However, its antiviral properties, as well as its safety as a potential antiviral agent (due to its narrow therapeutic index and high risk of toxicity), remain to be confirmed in clinical settings (93, 95).

More promising is the association that has been observed between FIASMA (Functional Inhibitors of Acid SphingoMyelinAse) treatments, including certain SSRI and non-SSRI antidepressants such as fluvoxamine and amitriptyline, and a reduction in clinical deterioration and mortality risk in patients with COVID-19. Acid sphingomyelinase (ASM) is an important lipid-metabolizing enzyme catalyzing the hydrolysis of sphingomyelin into ceramide and phosphorylcholine (91, 96). SARS-CoV-2 probably activates this ASM-ceramide system, facilitating viral entry and infection of human nasal epithelial cells by clustering ACE-2 receptors (97, 98). Functional Inhibitors of Acid SphingoMyelinAse antidepressants are thought to impair SARS-CoV-2 entry into epithelial cells by functional inhibition of the ASM-ceramide system (99). Several retrospective (100–102) and prospective (103) observational studies, as well as a small double-blind randomized trial (104) showed that taking a FIASMA treatment was associated with a lower risk of clinical deterioration or death in both non-psychiatric and psychiatric patients with COVID-19. The anti-inflammatory properties of certain antidepressants, probably due to their high affinity for sigma-1 receptors (105), may have additional value in managing COVID-19. Nevertheless, more large-scale double-blind controlled randomized clinical trials of these medications in patients with COVID-19 are needed (99, 106, 107).

Polypharmacy has been found to be associated with a higher risk of developing COVID-19 (108). Psychotropic polypharmacy is quite common in patients with SMI (12). According to a Swedish study, 25% of patients dispensed antipsychotic drugs receive a combination of two or more antipsychotic drugs. These patients also did more often take anxiolytics and sedatives than those prescribed antipsychotic monotherapy (109). Psychotropic polypharmacy, particularly during the treatment of elderly people with SMI, seems to be associated with greater adverse effects on most physical diseases, compared to monotherapy (4), as it carries the risk of adverse drug reactions. As the possible contribution of antipsychotic polypharmacy to the general excess mortality in people with SMI remains unclear (110, 111), further meta-analyses are needed analyzing mortality outcomes based on specific antipsychotic combinations rather than pooling data irrespective (111). The risks of adverse drug reactions due to psychotropic polypharmacy may be higher among certain regions in the world. Because of these aspects, the impact of psychotropic polypharmacy on COVID-19-related mortality therefore remains unknown.

Benzodiazepines (BZDs) and BZD-related medications (BZDRs) may also be of concern. A Swedish study in patients with SZ (112) showed that high exposure to BZDs is associated with an up to 70% higher mortality risk, compared with no users of BZDs. This is an important observation, knowing that the use of these medications by patients with SMI probably is even more common in other developed countries as the U.S (112). Although the risk of respiratory impairment associated with BZD use in the general population remains debated, in several studies current or recent exposure to certain BZDs or BZDRs has been found to be associated with an increased pneumonia risk (113), particularly in critically ill patients in intensive care units (114) or elderly (115, 116), whose immune system is vulnerable. BZDs and BZDRs, taken by 30–60% of individuals with SZ or BD (55), illnesses already characterized by a systemic pro-inflammatory state (see further), therefore may increase the risk for COVID-19-related mortality in these persons.

Finally, clinically relevant drug interactions between psychotropic medications and antiviral COVID-19 therapies may exist. The co-administration of protease inhibitors (blocking the protease enzyme that the virus needs to replicate), with certain antipsychotics (e.g., haloperidol and quetiapine), the mood stabilizer carbamazepine, or the BZDs midazolam or triazolam should be avoided because of increased toxicity and possible life-threatening events (117, 118).

Results of the studies included in our review indicate that COVID-19-related mortality risk, even after adjustment for all above mentioned factors, remains high in these patients (see **Table 1**). This indicates that SMI-related issues (i.e., immunological disturbances) may further increase the risk of

COVID-19-related mortality. In one of the included studies [i.c., (43)] the high risk of mortality associated with schizophrenia spectrum disorders ranked second behind age in strength of an association among all known demographic and medical risk factors examined.

Research has shown that disease-related immune dysregulation may provide some explanation for the higher susceptibility of people with SMI for severe clinical outcomes of COVID-19 (42, 83, 119, 120). Hyperactivation of the immune system, leading to excess release of pro-inflammatory cytokines (hypercytokinemia) or a "cytokine storm" (cytokine release syndrome), seems to play a major role in the process of disease aggravation in patients with COVID-19 infection (121–127). Circulating levels of inflammatory biomarkers, including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP), are often excessively elevated during severe SARS-CoV-2 infection. This disproportionate release of cytokines beyond that of a controlled immune response has been associated with poor outcomes and an increased risk of mortality (22, 122, 124, 126, 128, 129). As SMIs already are often characterized by a systemic pro-inflammatory state or overproduction of pro-inflammatory cytokines, which may persist even after patients' symptoms have improved (32, 33), the systemic hyperinflammation triggered by SARS-CoV-2 infection may be more pronounced in these individuals, leading to excess tissue damage, multi-organ failure, and death. A reduction in lymphocyte natural killer cell activity (a common finding in severe COVID-19) in some patients with SMI may further explain why COVID-19-related mortality rates are higher in these individuals (119, 120, 130–132). However, these hypotheses remain to be tested more rigorously.

Particularly in older patients, perturbations in gut microbiome composition, which seem to be related to elevated concentrations of inflammatory cytokines, may exacerbate COVID-19-related severity (133). This observation may be important knowing that people with SMI present with various alterations of the gut microbiome (134).

Prevention Strategies and Possible Therapeutic Options

Given the strong association between COVID-19-related mortality and SMI, it is paramount that COVID-19 vaccination and equitable access to COVID-19 vaccines for people with SMI should be a matter of priority (135–137). This should be even more obvious knowing that the management of physical diseases (including comorbid conditions causing more severe COVID-19 illness) in people with SMI is already suboptimal, due to non-medical factors such as stigmatization and disparities in physical health care (10, 11, 13). It is therefore astonishing to note that some governments within and outside the European Union (e.g., India) are still doubting whether these individuals should be prioritized for COVID-19 vaccination (135).

However, only granting priority access to people with SMI in national vaccination strategies will not be sufficient, as a significant COVID-19 vaccination gap seems to exist between these individuals and the general population, despite having been granted early universal or priority access to SARS-CoV-2 vaccination (138–140). Targeted interventions to maximize vaccination uptake among these patients will be needed (139, 140). There are ways mental health professionals and agencies can address barriers to COVID-19 vaccination, based on the Increasing Vaccination Model (IVM). Identifying and addressing internal conflicts (by using motivational interviewing), social network interventions (making clinician recommendations build on interpersonal trust), and direct behavior change interventions (including reminders and primes, automatic appointments, and presumptive healthcare professional communication) can be helpful in this regard (141). Developing an intentional vaccine delivery strategy in conjunction with experts, utilizing multiple communication channels, and expanding vaccine delivery outside of the hospital to reach patients can be another strategy (142). Finally, the involvement of peers, family, or volunteers to support people with SMI in making healthcare choices may also be helpful. These types of actions can pay off. Our research group has shown that vaccine willingness among patients with psychiatric disorders in our university psychiatric hospital with a targeted prevention program was just as high as in the general population: 93% or 1,070 of 1,151 patients who were offered COVID-19 vaccination accepted this vaccination (143). Other studies confirmed that vaccination willingness among these patients is at least almost as high as in the general population (144, 145).

Several therapeutic options for this vulnerable population may exist to reduce the increased mortality rate: the use of medications that target specific inflammatory markers, the use of a cytokine filter targeting multiple different cytokines at a larger scale, natural killer cell-based immunotherapies, and the use of nicotine, nicotinic receptor agonists, or positive modulators of these receptors (activation of these receptors, particularly α7 nAChR, can suppress production of pro-inflammatory cytokines as these receptors are abundantly expressed in a variety of immune cells) (122, 127, 130, 131). Early prediction of a cytokine storm is made possible by several biochemical and hematological markers (128). In addition to reducing pathogen exposure, individual immunity in this vulnerable population can be enhanced by promoting a healthy lifestyle, regular exercise, balanced nutrition, and quality sleep (125). However, more research on these therapeutic options is urgently needed.

Patients with SMI often have lower vitamin D levels (146). Several meta-analyses (147, 148) and publications (146, 149–153) suggest that vitamin D supplementation may be potentially effective in preventing COVID-19 infection and mitigating the clinical course of the disease. Study results, however, remain difficult to interpret due to possible confounding factors (149, 154).

STRENGTHS AND LIMITATIONS

Our review has particular strengths. Compared to other available systematic reviews, we developed a more comprehensive search strategy for the retrieval of reports of controlled trials. With the exception of Ceban et al. (38), our review is the only one that also

included the Embase database to obtain a more comprehensive coverage of the existing US and EU literature. Finally, a thorough and critical discussion of this issue is presented in this paper.

Nevertheless, our systematic and critical review has its limitations that are inherent to the nature of the available evidence, and in that respect comparable to the previously published reviews. An important limitation is that all included studies are observational and mostly retrospective, and therefore causal relationships cannot be inferred. Most of the included studies in our systematic review were carried out during the first wave of the COVID-19 pandemic, which lasted from February/March until May/June 2020. During this period, in most countries testing was largely restricted to individuals exhibiting symptoms or to certain risk groups, due to a limited PCR-testing capacity at that time. This biased deployment of testing can distort true estimates of COVID-19-related mortality rate in people with SMI. Most of the studies on mood disorders involved mixed populations and did not make a distinction as to whether an individual with a mood disorder had MDD or BD. The two largest studies on COVID-19-related mortality risk in patients with BD to date (42, 155) only included around 500 patients. This is an important limitation given the possible differential impact of COVID-19-related mortality risk across SMIs. Therefore, more studies are needed that present separate data for patients with BD and MDD to gain a better estimate of true COVID-19-related mortality risks associated with these groups of people with SMI. Control groups also varied across studies: some control groups excluded patients with psychiatric disorders, while others included non-SMI disorders. Finally, most studies did not provide detailed patient sociodemographic characteristics (i.c., mean/median age, gender), or other detailed information on clinical/psychiatric variables (such as severity and status of the disease), and smoking histories. Future studies therefore should further explore these issues to better understand which specific patients are at an increased risk of COVID-19-related mortality.

CONCLUSION

Even without taking COVID-19 into account, people with SMI already have a two to three times higher mortality rate than the general population, largely attributable to somatic comorbidities. Our review has shown that individuals with SMI, particularly patients with schizophrenia spectrum disorders, are at significantly higher risk of COVID-19-related mortality, not only due to higher somatic comorbidity rates and the possible use of psychotropic medication, but also to unknown factors at the moment that will have to be explored in future research. Severe mental illness therefore should be identified as a separate, independent risk factor for a more severe clinical course when infected with COVID-19 and targeted as a high-risk population. Consequently, targeted interventions to maximize vaccination uptake among these people should be prioritized in health policy worldwide.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

JD: search and analysis. 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.2021.798554/full#supplementary-material

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Barriers to Somatic Health Care for Persons With Severe Mental Illness in Belgium: A Qualitative Study of Patients' and Healthcare Professionals' Perspectives

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Background: A huge and still growing mortality gap between people with severe mental illness (SMI) and the general population exists. Physical illnesses, mainly cardiovascular diseases, substantially contribute to the high mortality rates in patients with SMI. Disparities in somatic health care access, utilisation, and provision contribute to these poor physical health outcomes.

Methods: A qualitative study, using semi-structured interviews, was set up to explore SMI patients' and healthcare professionals' perspectives on somatic health care in different psychiatric settings of the three Belgian regions (Flanders, Brussels, Wallonia). Interviews were digitally recorded and transcribed prior to qualitative inductive thematic analysis, using Nvivo software. The COnsolidated criteria for REporting Qualitative research (COREQ) were used for reporting methods and findings.

Results: Collaboration and information flows between psychiatric healthcare professionals, non-psychiatric healthcare professionals, and persons with SMI were troublesome. This seemed to be mainly due to stigma and prejudice and challenging communication and data transfer. Lack of sufficient training and experience to identify and treat somatic health problems in people with SMI (for psychiatrists and psychiatric nurses) and lack of psychiatric knowledge and feeling or sensitivity for psychiatric patients (for non-psychiatric healthcare professionals) further complicated adequate somatic health care. Finally, optimal somatic follow-up of patients with SMI was hampered by organisational problems (unavailability of equipment, unadapted infrastructure, understaffing, hospital pharmacy issues, and insufficient health promotion/lifestyle interventions), patient-related issues (unawareness of physical problems, non-adherence, need for accompaniment) and financial barriers.

Conclusion: There is an urgent need for integrated somatic and mental healthcare systems and a cultural change. Psychiatrists and primary care providers continue to consider the mental and physical health of their patients as mutually exclusive responsibilities due to a lack of sufficient training and experience, poor or absent liaison links, time constraints and organisational and financial barriers. Modifying these aspects will improve the quality of somatic health care for these vulnerable patients.

Keywords: physical health, severe mental illness (SMI), health disparities, qualitative research, health care, barriers

BACKGROUND

People with severe mental illness (SMI), usually defined as a psychiatric illness that causes serious functional impairment (i.e., schizophrenia, bipolar disorder, or major depressive disorder), have a two to three times higher mortality rate than the general population (1, 2). This increased mortality rate is observed in both high- and low-income countries (1). Somatic comorbidities, mainly cardiovascular diseases, contribute significantly to this excess mortality (3, 4), even in young adults with SMI (5).

Non-medical factors, including an unhealthy lifestyle (high-fat diet, smoking, substance use, lack of physical exercise), and the use of psychotropic medication (particularly antipsychotics) are important risk factors for somatic complications and disorders (2, 6–8). Disparities in somatic health care access, utilisation, and provision may be another cause of the excess mortality due to somatic comorbidities in this vulnerable population. Research has shown that people with SMI often receive fewer physical health screenings and interventions, compared to the general population, even in developed countries (1, 2, 9, 10). Despite clear directions and numerous recommendations over the last decade to improve the quality of somatic health care for people with SMI (1, 10–13), little to no progress has been made. Moreover, it even seems that the mortality gap between people with SMI and the general population is widening (14).

Several patient and illness-, treatment-, healthcare provider-, as well as healthcare system-related factors act as barriers to the recognition and management of somatic comorbidities in patients with SMI (2). A US study (15) showed that lack of awareness of somatic problems, poverty, financial barriers and stigma were primary barriers to oral health care for adult community mental health outpatients with SMI. Cognitive dysfunctions, lack of adherence, lack of integration services, and lack of access to somatic health care have been identified as barriers to appropriate lung cancer (16) and cardiovascular (17, 18) health care among people with SMI. The excess risk of mortality in patients with SMI due to disparities in somatic health, and associated high healthcare costs, make this group of patients an important public health issue that should be addressed (19).

Previous qualitative research (15, 20, 21) indicated that persons with SMI are largely dissatisfied with their somatic health care, due to significant barriers. However, most of this research has been performed in countries with differing healthcare systems from Belgium. The latter is important as Belgium, a country with a population of 11,639,146 (June 2021), has a complex political organisation. It is divided into three highly autonomous regions: Flanders (the Dutch-speaking region in the north), Wallonia (the French-speaking region in the south), and Brussels (the capital, which is officially bilingual). Finally, there is also a minority German-speaking community (in the east of Wallonia). Both federal and regional governments have responsibility for health care in Belgium. The Federal Public Service for Health, Food Chain Safety and the Environment oversees public health care. The regional Flemish, Walloon, and German-speaking communities all have their own administrative healthcare divisions.

AIM OF THE STUDY

The purpose of this study was to identify barriers to somatic health care in the Belgian context by exploring the perspectives on somatic health care of mental healthcare professionals and patients with an SMI in psychiatric settings of different Belgian regions. This study was part of a larger project aimed to examine the status of somatic health care of people with SMI and to understand why this care is sub-optimal in Belgium. Besides exploring the perspectives of patients and healthcare providers on this topic, other aspects (such as the prevalence of somatic problems in people with SMI, and the organisation and financing of somatic health care for people with SMI) have been examined in this project (22). The English version of the full report is accessible on the Belgian Health Care Knowledge Centre (KCE) website. The COnsolidated criteria for REporting Qualitative research (COREQ) were used for reporting methods and findings (see **Supplementary Material 1**).

METHODS

Design

The present study applied a qualitative research design. We conducted semi-structured individual face-to-face interviews and group interview sessions with healthcare professionals in several residential psychiatric settings. To explore the patients' perspectives on somatic health care in a psychiatric setting, we planned to conduct focus groups. After concertation with patients associations we thought patients would feel more comfortable in focus groups than during individual face-to-face interviews as they are used to discuss personal issues in groups (e.g., for therapy or in self-help groups). During all (individual and group) interviews, a set of predetermined questions was used to guide the interview. For multidisciplinary healthcare teams

and focus groups "case examples – patient scenarios" were used to facilitate the discussion. However, additional questions could be asked where appropriate.

Settings

For each region (Flanders, Wallonia, and Brussels) we identified four psychiatric settings: 1 psychiatric hospital (PH), 1 general hospital psychiatric ward (GHPW), 1 psychiatric nursing home (PNH) and 1 sheltered housing facility (SHF). Settings were identified through an address list of mental health care settings. We tried to find a balance between private/public, academic/non-academic, and Dutch/French-language settings.

Participants

Patient Inclusion Criteria

Patients were included if they had an SMI (defined in this study as having a diagnosis of schizophrenia or related conditions, bipolar disorder, or moderate to severe depression), for which they had been admitted to one of the four above mentioned psychiatric care facilities.

Patients had to be aged 18 years or older, Dutch or French-speaking, and previously stayed for at least once in the past 5 years in one of the above mentioned types of psychiatric settings. The relatively brief 5 year time period was chosen in order to allow patients to be still able to recall past events fully and accurately.

Recruitment Strategy

In January 2020, directors of psychiatric services were contacted personally by telephone. A formal invitation was sent by e-mail, if showing interest (only one director declined to take part in the study due to understaffing problems). Each setting in the sample was visited. During these visits we interviewed: a psychiatrist in an individual face-to-face interview, a somatic practitioner (general practitioner or specialist, if there was no general practitioner entitled to the setting) in an individual face-to-face interview, and the multidisciplinary team (psychiatric nurses, psychologists, educators) in a group interview.

Patients were recruited with the collaboration of patient organisations. They were invited by letter, e-mail, social media, newsletters, or when attending a meeting, and were asked to express their interest to participate in a focus group about their experience with the prevention, treatment, and/or follow-up of their somatic health problems during residential psychiatric care. For this communication, KCE provided a text which was adapted after discussion with and input of the patient organisations. Potential candidates were gathered by the patient organisations, ensuring that the inclusion criteria were met, and a list with the names of the candidates was transmitted to KCE researchers. Next, the KCE researchers contacted the potential participants directly by e-mail, sending the information about the project and the informed consent form (reviewed by one of the patient organisations to ensure readability). The patients were invited to read the information (information about KCE, aim of the study, inclusion criteria, practical information about the study, all necessary information for participation) and informed KCE researchers about their decision to participate or not. The informed consent form was signed before the start of the interview. A moderator read through the information sheet of the informed consent, gave explanations, and answered participants' questions. The moderator also asked permission to audio-record and transcribe the interview.

Ethical Approval

The qualitative study of the patients' perspectives was submitted and approved by the hospital-faculty ethical comity of the Erasme Hospital (Université Libre de Bruxelles – Belgian Advisory Committee on Bioethics study number CCB B406202042676).

Data Collection

Based on the literature and exploratory informal meetings with healthcare practitioners, three semi-structured interview guides were developed: one for physicians, one for the multidisciplinary team, and one for patients. Cases describing somatic health problems frequently occurring in the population of psychiatric patients (e.g., weight gain, diabetes) or common acute or chronic problems (a fall, a cough, chronic bronchitis) were used to facilitate the discussion within the multidisciplinary teams. These "case scenarios" were developed and discussed with a representative of one of the patient organisations before finalisation. Based on these scenarios, healthcare professionals were questioned about how somatic health was addressed and managed in their setting. The core topics of the interview guides were:

- What is the place of somatic care in the management of patients: from intake to discharge?
- How is the quality of the management of somatic chronic care perceived?
- What are barriers or challenges in somatic care for chronic and acute health problems, as well as prevention of health problems?
- What are examples of good practises?
- Do you have suggestions to improve somatic health care?
- How is the collaboration between healthcare professionals?

For patients, the same "case scenarios" as for the professionals, were used to structure the discussion if needed. All interviews were moderated in the respondents' native language by KCE researchers. A representative of the patient organisation was present during the interviews or, if not able to attend, contacted the patient after the interview to ensure he/she coped well with the interview and to build trust with the patient. Patients organisations also signed a confidentiality agreement.

Although interviews were originally planned in February, March, and April 2020, due to COVID-19 restrictions, several interviews were postponed to June-July 2020 (for healthcare professionals) and September-October 2020 (for patients). Three (out of 18) individual interviews with healthcare professionals (one with a French-speaking general practitioner and two with Flemish general practitioners) were performed remotely via the online Zoom application. In total, we met about 50 healthcare professionals from 10 different settings (due to the COVID-19 crisis we did not include healthcare professionals for all settings, see section on study limitations). This sample is described in

more detail in **Table 1**. For patients, all focus groups had to be carried out via the Zoom web application with a limit of five participants per session. For each focus group, one KCE moderator was foreseen, accompanied by one observer (a representative of a patient organisation) and one note-taker (KCE researcher). For each region we planned to have two focus groups, each consisting of 6–8 participants. So we intended to meet a minimum of 36 persons with an SMI. However, due to the COVID-19 crisis, the recruitment of participants was hampered. As only four Dutch-speaking patients and for Brussel only one patient finally agreed to participate, focus groups became individual interviews. For Wallonia, five patients were interviewed in one online focus group.

Data Analysis

Interviews were audio-recorded. After the interview, a transcript was made by an external firm. Next, the transcripts were coded by two KCE researchers (LK and WC) with NVIVO software. Data were analysed by thematic analysis. An inductive thematic analysis was performed by both researchers. Each researcher made a list of primary codes (WC for the Dutch interviews, LK for the French interviews) without clustering. In a second step, both Dutch and French codes were compared and clustered together, resulting in a hierarchical code tree. Findings were described based on these clusters of codes.

RESULTS

An overview of the themes emerging from the qualitative analysis is presented in **Figure 1**.

Healthcare Provider-Related Factors

Lack of Sufficient Training and Experience

Psychiatric Staff

Interviewed psychiatrists referred to their lack of training and experience in addressing somatic health care issues. They explained they were specialised in mental health care already early during their curriculum. Somatic health problems usually were less discussed during training and considered secondary to mental health. In the further course of their career, their knowledge about somatic health care and medical care skills tended to become passive knowledge. Because psychiatrists overemphasised mental health at the expense of somatic health care, they often felt uncomfortable when providing somatic medical care to patients with SMI and rather referred the patient to a general practitioner or specialist for their somatic problems.

> *"Whether it's simple hypothyroidism or... a simple lack of vitamins, I think we can handle that. But a patient with severe hypertension, for example, … is still something for an internist or a general practitioner… Our psychiatrists feel uncomfortable when confronted with somatic comorbidities… we have to recognise that we are specialists in psychiatry." (Psychiatrist-GHPW)*

The same applies to nurses. In PHs or GHPWs, nurses are "psychiatric nurses." During the interviews, psychiatric nurses mentioned they lost their competencies for a wide range of

TABLE 1 | Description of the healthcare provider participants.

	Flanders				Brussels				Wallonia			
Type of setting	**Psychiatric ward**	**Psychiatric hospital**	**Psychiatric nursing home**	**Sheltered housing facility**	**Psychiatric ward**	**Psychiatric hospital**	**Psychiatric nursing home**	**Sheltered housing facility**	**Psychiatric ward**	**Psychiatric hospital**	**Psychiatric nursing home**	**Sheltered housing facility**
Language	Dutch	Dutch	/	Dutch	French	French	Dutch	French	French	French	French	/
Psychiatrist	1	1	–	1	2	1 + 2**	1	1	1	1	–	–
Somatic Physician	1 emergency doctor	1 GP	–	1 GP	1 GP	1 GP + 1* GP	1 GP	/	1 GP	1 specialist	1 GP	–
Paramedical team	Team of nurses and psychologist	Team of nurses	/	Team of nurses and educators	/	Team of nurses and social workers	Team of nurses and educators	Multidisciplinary team	Team of nurses, psychologist, physiotherapist, educator	Multidisciplinary team	Multidisciplinary team	/

GP, general practitioner.
**via videoconference; **Psychiatrist in training.*

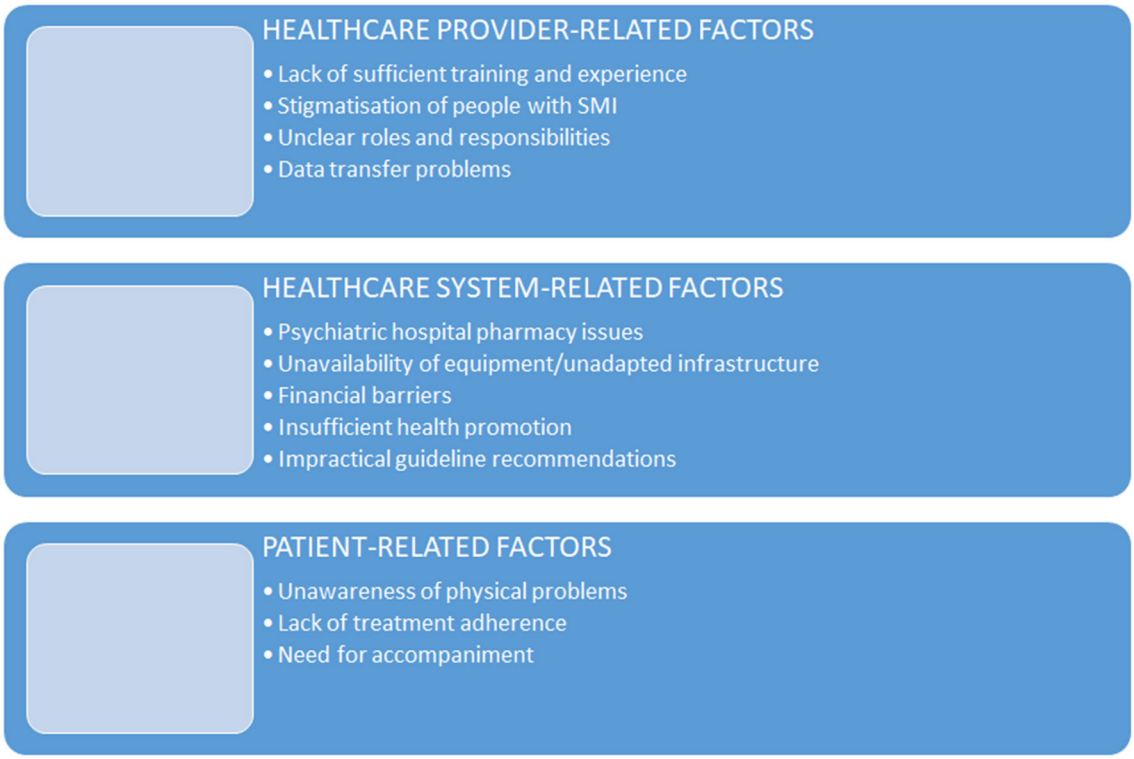

FIGURE 1 | Themes emerging from the qualitative analysis.

somatic healthcare tasks such as wound care, injections, or blood sampling. Because they are no longer or less experienced with these tasks, they are often tentative, unsure, or uncomfortable performing them.

Somatic Healthcare Providers

Interviewed participants mentioned that transfers to a somatic ward were not self-evident. They stated that staff at the somatic ward seemed very reluctant to take over the patient's care. If patients with SMI were treated at the emergency department, psychiatric staff complained of patients being referred back too soon to the psychiatric ward. Many of these patients did not receive a decent screening of somatic problems. Examinations, like an ECG, were not performed due to the young age of the patient, while the addictive behaviour justified it.

> *"If you kindly request an emergency physician in a general hospital to perform an electrocardiogram on a 30-year-old cocaine addict, and he tells you 'but he is not old enough to have a heart attack', while the patient already had two infarctions..."(Psychiatrist-GHPW)*

Uncomfortable feelings and lack of training and experience to cope with these patients were supposed to be the main reasons for this way of acting by the somatic staff.

Patients' Accounts

In general, psychiatric patients themselves experienced the limited somatic skills of healthcare providers as obsolete. They also felt that psychiatric healthcare professionals focus on mental health at the expense of somatic health care.

> *"Because my cough persisted for so long without any examination, . . . well after almost two months of coughing, I insisted that at least a doctor should be called to listen to my lungs at last" (Patient report)*

According to the patients' accounts, the provision of medical care varied substantially from setting to setting (PHs, GHPWs, PNHs, SHFs), within the same setting and among healthcare professionals. Patients also attributed differences in the management of medical care to the type of somatic health problem [priority was given to patients with an addiction or with a known somatic health problem at admission (e.g., diabetes)]. Medical care for unanticipated somatic health needs, however, was problematic. Patients mentioned they were well monitored for adverse drug reactions during the stay, with the exception of weight gain.

Stigmatisation of People With SMI

Somatic Healthcare Providers

The staff of psychiatric settings reported that dentists, general practitioners, or somatic specialists are less willing to treat residential psychiatric patients than those without such a

diagnosis. Psychiatric nurses mentioned that the waiting time could be several days before a specialist arrived. Even for staff within the GHPW, where the care of patients with somatic comorbidities should be easier to manage due to the easy access to any specialisation present within the general hospital, it was difficult to find a specialist willing to come to the GHPW to examine a patient.

According to psychiatric healthcare workers, patients with SMI are often perceived by somatic healthcare providers as non-hygienic, self-neglecting, difficult to understand, non-adherent, skipping appointments, manipulative, attention-seeking, pretending, or they "don't look sick" or "not that sick."

> *"These are patients who... how should I say it, they are not sexy, people tend to be condescending towards these patients, who not always have a neat appearance,.. they don't resemble most patients in a waiting room, or sometimes they are very weird. They talk to themselves, they have, I don't know, weird bags, messy hair. . . . , they cannot come on time, they come either two hours early or five hours too late, or they come another day. . . " (Psychiatrist-GHPW)*

Patients' Accounts

A major concern raised by patients was diagnostic misinterpretation or misattribution of signs and symptoms of somatic illness to the SMI, leading to under-diagnosis and mistreatment of the somatic condition, or delayed medical care. Indeed, patients often complained that their somatic health problems were not taken seriously by healthcare professionals. They mentioned that their symptoms were not fully explored or easily misattributed to stress or psychiatric illness. Sometimes healthcare staff even did not listen, ridiculed the patient, did not believe the patient, minimised or denied their problems. In addition, the way they expressed pain or discomfort was often not understood by the staff.

> *"Yes, you very often hear other patients on the psychiatric ward say 'I have something but the doctors don't believe me.' You hear that so often. Or, you go to a hospital and when they see in your medical file that you are admitted to a psychiatric ward, then suddenly they don't take you seriously."(Patient report)*

Patients also mentioned that some healthcare professionals, even psychiatrists, are patronising.

Unclear Roles and Responsibilities

Psychiatric nurses found it very difficult and time-consuming to find out who to consult in case of somatic health problems.

> *"The question is often 'Who does what?'. You have the main treating physician, in this case, the psychiatrist, but does the somatic specialist take over all somatic tasks? Or does he expect us to do certain things ourselves, such as prescribing and adjusting medication, somatic monitoring. . . "(Team-GHPW)*

Data Transfer Problems

Somatic Healthcare Providers

Healthcare providers stated that at the time of admission to the psychiatric setting the management of existing or chronic somatic problems was often delayed and complicated by the absence of information on the medical history of the patient.

Interviewees reported that data transfer problems occurred frequently and that there was always a risk of losing information.

> *"I think of a patient who was very feverish, . . . , I saw that she had been seen by a general practitioner two hours before, . . . the note was summarised as 'hyperthermia, suspected urinary tract infection' and that's all. So we don't know how much temperature, what was done during the physical examination, what was excluded, not excluded. Are there any instructions to follow if the temperature... So it's true . . . , it would help me a lot if there was more information." (Psychiatrist in training-PH)*

Patients' Accounts

Patients complained about healthcare providers not communicating about the timing of (follow-up) consultations, somatic diagnoses, the prescribed treatment including changes in medication schedule and possible side-effects, and who to contact in case of a somatic health problem during their stay.

Healthcare System-Related Factors

Psychiatric Hospital Pharmacy Issues

Some psychiatric patients with a chronic somatic disease (e.g., diabetes) did not receive the type or brand that was prescribed or which the patient is accustomed to, due to formulary restrictions (i.e., the medication was not available in the formulary or list of medications available for use at the hospital). However, the new medication of choice could be more expensive or less safe (e.g., due to medication compatibility issues during switching) than the restricted agent. A request for formulary addition from the general practitioner was not always granted. Moreover, when a new medicine was prescribed by a general practitioner or a specialist, it took a couple of days to get the prescribed medicine to the patient, because the prescription needed to be approved by the psychiatrist in charge and by the hospital pharmacy.

> *"Yes, indeed, if the psychiatrist is present, then you still have to see whether you can reach him to validate that prescription. Then the pharmacy still has to validate the prescription and then it's still possible that they have to order it (. . .) Yes, so sometimes two days pass before he gets his medication, while across the street in the village, there is a pharmacy and then they have it an hour later. And we need two days. . . "(Staff-PNH)*

Unavailability of Equipment/Unadapted Infrastructure

If somatic treatment following hospitalisation was necessary (e.g., perfusion), it was sometimes difficult to manage within the psychiatric setting due to the unavailability of equipment (e.g., infusion stand) or the lack of adaptive infrastructure (e.g., steps) preventing the patient from moving safely around the ward.

Financial Barriers

Often institutional financial constraints were put forward by patients and healthcare professionals as an explanation for inadequate somatic health care. This lack of resources leads to heavy workload as a result of understaffing, insufficient primary care providers (e.g., general practitioners) or non-psychiatric

specialists (e.g., dietitian, physiotherapist) in psychiatric settings, the critical shortage of medical equipment, inappropriate infrastructure to provide adequate somatic health care in psychiatric settings, and a nomenclature insufficient to fund appropriate somatic health care by the general practitioner. The current funding also seemed to be insufficient for the general practitioner or specialist to attend team meetings, or to work on electronic medical records.

"I am a self-employed person, paid on a flat-rate basis, the equivalent of seeing three psychiatric patients per day. In a nursing home, I would see 10 to 15 patients. So obviously, I don't do everything very well. (laughs) (...) In a nursing home, I would earn three to four times more."(General practitioner-PH)

Insufficient Health Promotion

Several lifestyle intervention and health promotion initiatives were mentioned by the interviewees, such as workshops on health related themes, smoking cessation interventions and the creation of smoke-free environments, interactive toothbrushing education, behavioural weight loss programs, the provision of sport equipment,… However, this seemed not to be a priority in psychiatric settings. Discouraging smoking and encouraging physical activities, for example, seemed to be very challenging due to a lack of time, limited space available for sport activities, specific patient characteristics, and barriers to finance sport facilities or competent technical staff to support sports initiatives or smoking cessation programs in psychiatric facilities. Moreover, patients of GHPWs complained they experience strong barriers to use sports facilities at the general hospital, particularly due to stigma. A domain that was reported to be very difficult to manage (also related to the side effects of the medication), was nutrition. The setting was not always able to supply dietetic food (e.g., in some places residents had to choose between different sugar-sweetened beverages during meals, because mineral water was not available).

Impractical Guideline Recommendations

Although recommendations certainly can be very helpful in the acute treatment, prevention and follow-up of somatic health problems, our study indicated that clinical somatic local guidance should be adapted to the specificities of psychiatric patients. Some guidelines were perceived as too general and therefore not applicable to very specific cases and contexts.

Patient-Related Factors

Unawareness of Physical Problems

Interviewed healthcare professionals mentioned that patients had difficulties expressing complaints and accepting that a consultation or examination is necessary. This has several consequences in terms of somatic healthcare provision: longer medical consultations or repetitive consultations for the same complaint. Unfortunately, healthcare professionals are often running out of time.

"(…) a real psychotic person doesn't know what's up or under and is busy with a lot of other things besides what he feels in his body. They often have no contact or less contact with their bodies. So before you realise that there's something wrong, that something is going on.… And then you still have to take him to the right consultation" (Staff-PNH)

Lack of Treatment Adherence

Interviewed healthcare professionals reported that once treatment is initiated, it is difficult to keep psychiatric patients adherent. Because of their illness, some patients also do not easily accept to be examined or have their parameters taken. According to healthcare providers this leads to a deterioration of somatic problems.

Need for Accompaniment

Psychiatric staff reported that psychiatric patients need to be accompanied to somatic health services (e.g., specialist, dentist, emergency service), particularly when the service is external to the psychiatric hospital or ward. Mentioned reasons for accompanying patients on visits to somatic healthcare professionals were: the patient is not calm enough to go alone, runaway risk, long waiting times (becoming a problem in noisy and crowded rooms), and the need to clarify somatic problems. However, accompanying patients weighs heavily on the workload of the healthcare teams, because it is very time-consuming.

Patients noted a less than optimal planning of somatic health care at the time of discharge, and that they were left to their own devices. They had to find a general practitioner outside the hospital, to manage their medication (as there was no supply from the hospital), and to make follow-up appointments for their somatic health care with the general practitioner or specialist.

DISCUSSION

Our qualitative study showed that healthcare provider-related factors (lack of sufficient training and experience, stigma, unclear roles and responsibilities, data transfer problems), healthcare system-related problems (hospital pharmacy issues, unavailability of equipment/unadapted infrastructure, financial barriers, insufficient health promotion, unadapted recommendations), and patient-related issues (unawareness of physical problems, non-adherence, need for accompaniment) complicates adequate somatic health care.

Emerging evidence shows that well-integrated care can improve the quality of health care and several patient outcomes (23–25). Therefore, healthcare professionals should take a holistic approach to health care for the benefit of the patient (26, 27), and all of the above mentioned barriers to somatic health care should be tackled with this basic idea in mind. For example, information sharing systems within and across different healthcare services, shared protocols between mental and somatic health services, and co-location of services can help solve problems regarding data transfer and unclear roles and responsibilities, and remove barriers to delivering integrated care (28). Being able to access information from single or multiple electronic individual medical records can be an important facilitator, as it allows healthcare professionals to identify and track individuals with an SMI needing somatic health services (28). This, however, requires an adequate IT infrastructure

and the tackling of medico-legal barriers. Shared protocols, setting out the responsibilities of mental health and somatic services in delivering somatic health care, is another important facilitator (14, 28). Clear agreements with physicians concerning the somatic health care of patients at the psychiatric ward could also reduce patients' waiting times and anxieties, and improve their medical follow-up.

Nevertheless, a successful ending of this mission requires a certain amount of flexibility and openness on the part of individual healthcare professionals. For example, our study showed that co-location of services does not necessarily lead to better somatic health care for people with SMI. Indeed, somatic and mental healthcare staff should also be willing to collaborate. According to Rodgers et al. (28) this emphasises that people rather than organisational systems or structures are primarily responsible for successful integration of care. In this regard, the concept of liaison services can be very important. Liaison services and care coordinators/navigators certainly can play a pivotal role in improving communication (28). It was noted during the interviews that a liaison person between the specialties (such as general practitioners with a special interest in psychiatry) improved communication and led to better somatic health care. One can also develop policies to promote the use of psychiatric-trained healthcare professionals, such as psychiatric nurses, on somatic wards (29), or vice versa.

Stigmatising attitudes towards people with SMI remain another important barrier to adequate somatic health care (28, 30). Our study showed that somatic healthcare professionals often are hesitant to handle people with SMI, due to prejudices and stigmatisation. Psychiatric staff (including general practitioners) reasoned this might be due to lack of training and experience, feelings of insecurity in dealing with people with SMI, the anticipation that people with SMI are non-adherent, the unkempt presentation of patients, the already heavy workload for somatic healthcare specialists and the complexity and/or the slow pace of working with people with SMI. People with SMI reported diagnostic misinterpretation and patronising attitudes.

Previous research indeed has shown that non-psychiatric healthcare providers often feel uncomfortable (e.g., feeling anxious) when working with psychiatric patients, due to a lack of essential communication skills, fear of being physically hurt, and stigmatisation and prejudices towards mental illness (29). These negative attitudes can compromise somatic healthcare professionals' ability to respond to medical symptoms and deliver qualitative somatic care (29). Interestingly, several studies (31–33) have demonstrated that even mental healthcare professionals have negative stereotypes and social distance desire towards people with SMI, particularly people with schizophrenia.

Stigmatisation (and somatic care) may be further complicated by patient-related barriers such as cognitive and communication deficits and reduced pain sensitivity. Studies have shown that particularly people with schizophrenia are characterised by a reduced pain sensitivity (partly due to the analgesic properties of antipsychotic medications, partly to hypoalgesia as a potential endophenotype of schizophrenia spectrum disorders) and a decreased ability to communicate pain (due to the cognitive deficits). As people with SMI have high rates of somatic health conditions that are often associated with clinical pain (e.g., diabetes), these painful somatic conditions may often go unreported and lead to delays in the identification and treatment. This contributes to an increased risk of somatic comorbidity and mortality (13, 34, 35).

Some of the above-proposed initiatives can be implemented earlier than others. Effective communication between providers, shared protocols, and the empowerment of individuals to coordinate care needs of people with SMI may be realised rather quickly. The accomplishment of cultural changes and educational innovations to overcome the lack of training in the screening, assessment, and management of somatic health aspects amongst psychiatrists and psychiatric nurses, and vice versa, to reduce negative attitudes towards people with SMI on the part of somatic healthcare professionals by providing them "a guide in the handling of patients with SMI," and enhance their knowledge about the health risks associated with psychotropic medications, need more time (14).

Clinical experts, consulted for our report (22) repeatedly declared that the integration of primary care providers (in most cases a general practitioner) in psychiatric settings is vital to improving the somatic health care of patients with SMI. Olson et al. (36) showed that the lack of a primary care provider on an inpatient psychiatric ward was associated with increased suffering and poorer overall health in patients with SMI. Despite this, there is a shortage of primary care providers in Belgian psychiatric settings. There are manifold reasons for this: a restricted nomenclature, resulting in general practitioners and somatic specialists being hesitant to provide somatic health care to people with SMI, heavy workload, information-sharing difficulties (not being able to access information from medical records), and difficulties in dealing with the complexity of working with people with SMI. Physicians in our study had a feeling of ambivalence when taking up the somatic health care of these patients. They expressed concern regarding their lack of medical knowledge, limited training, and communication skills in treating mental illness, leading to a lack of confidence and diagnostic misinterpretation.

We also learned from our study that adequate somatic health care is hampered by organisational and logistical issues, such as limited on-site equipment, psychiatric staff time constraints, heavy workload of somatic healthcare professionals, and hospital pharmacy issues.

Healthcare providers in psychiatric settings stated that people with SMI and somatic comorbidities make heavy demands on their available time. They considered the organisation of consultations with somatic specialists not only as challenging but also as time-consuming. Staff members have to arrange the logistics for transport to the external ward or hospital and have to accompany the patient, for example, to ensure he is well-understood by somatic specialists and that follow-up is arranged. These measures, of course, require sufficient staffing. These problems have been confirmed in other studies (37, 38).

Another logistic problem cited by healthcare providers concerned the hospital pharmacy issues. Although formulary restrictions are implemented to reduce drug costs and ensure the appropriate use of pharmaceutical products, they can have negative effects on patient outcomes (particularly medication adherence, clinical outcomes, and treatment satisfaction) and enhance total medical costs by increasing health care resource utilisation (physician visits and hospitalizations) (39, 40).

An important aspect of a holistic approach to health care is to pay attention to the patients' autonomy and self-care behaviours. For example, medication adherence, which in all sections of our full report was identified as a patient- and illness-related barrier (22), has been shown to improve by applying collaborative, patient-centred communications skills (41), even in patients with SMI (42). However, the benefits of achieving patient-centred care for medication adherence through techniques such as motivational interviewing and shared decision making in people with SMI are minimal and less conclusive than in general medicine (43–45). Nevertheless, the success of these techniques may be improved if the relationship between patient and therapist is trusting and the technique is adapted to the patient's process and values (46).

Finally, healthcare professionals should focus not only on the screening and acute management of physical health aspects in people with an SMI, but also on the prevention and follow-up of patient's somatic health problems (47). Research (10, 48, 49) has shown that the integration of team members trained in a non-psychiatric discipline (e.g., nutrition, physiotherapy), and the involvement of peers, family, or volunteers to support people with SMI in making lifestyle behaviour changes or healthcare choices, improves their somatic health care. Lifestyle behaviour interventions, such as smoking cessation interventions, behavioural weight loss programmes, and psychoeducation (combined with behavioural interventions) are effective for persons with an SMI. Peer-led programmes for self-management of comorbid general medical conditions are effective for improving the health status of patients with an SMI (e.g., physical health-related quality of life, medication adherence) and the utilisation of healthcare services by these patients (50, 51). An ongoing randomised controlled trial is investigating the feasibility of a novel intervention involving training volunteers to be 'Health Champions' to support people with SMI using mental health services to manage and improve their physical health (52). Follow-up after discharge from psychiatric hospital is another necessity. After residential psychiatric care, general practitioners should be actively implicated by psychiatrists in providing post-discharge care of patients.

LIMITATIONS OF THE STUDY

Due to the COVID-19 crisis, we were not able to recruit as many participants as planned. Consequently, we did not reach data sufficiency. Moreover, we were obliged to "meet" the participants online. This way of data gathering may have resulted in a selection bias: patients had to feel comfortable with the use of information technology and the "distant" communication imposed by the video conference. It is therefore probable that we met patients with a higher socioeconomic status than would have been the case if we had been able to recruit people for an "in person" face-to-face interview. From the researchers' point of view, it is more difficult to create an atmosphere of trust and empathy in an online interview. Patients were also recruited through patients' associations. The associations might represent a specific type of patient, being involved in and aware of "self-care." On the other hand, one could also argue that given the inclusion of patients probably having a better somatic health status, our results may be rather conservative, having missed the most poignant storeys. All this means that our findings are not generalisable to all psychiatric settings and are in fact hypotheses that necessitate further research to come to firm conclusions. In addition, as a general observation we would like to emphasise the large variation we found in patients' accounts. Apart from individual differences, also organisational settings largely diverged. However, due to the small number of participants, we could not do specific subgroup analyses. In other words we could not differentiate between GHPWs, PHs, PNHs, and SHFs. We were forced to draw up general conclusions, without specifying the setting. In addition, during the interviews most attention was paid to what went wrong, leaving positive accounts largely unaddressed. However, this does not mean positive experiences are non-existent.

CONCLUSION

There is an urgent need for integrated somatic and mental healthcare systems and a cultural change. However, integrated care for people with SMI and somatic comorbidities is still a long way from becoming a reality. Psychiatrists and primary care providers continue to consider the mental and physical health of their patients as mutually exclusive responsibilities. Lack of sufficient training and experience, poor or absent liaison links, time constraints and organisational and financial barriers, limit the ability of most healthcare professionals to focus beyond their specialty. Modifying these aspects will improve the quality of somatic health care for these vulnerable patients. However, above all, a certain amount of flexibility and openness, as well as a willingness to communicate on the part of individual healthcare professionals is a prerequisite for successful management of somatic health care barriers.

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 Ethical Committee of the Erasme Hospital (Université Libre de Bruxelles – Belgian

Advisory Committee on Bioethics Study Number CCB B406202042676). The patients/participants provided their written informed consent to participate in this study.

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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.798530/full#supplementary-material

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CASE REPORT
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Case Series: Managing Severe Mental Illness in Disaster Situation: the Croatian Experience After 2020 Earthquake

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On the 29th of December 2020, amidst the COVID-19 pandemic, Petrinja in the Croatian Sisak-Moslavina County experienced a strong earthquake, resulting in a severe disruption in mental health service delivery. Specialized care community mental health teams were introduced days within the event with the aim to bridge the gap in psychiatric care that was severely disturbed in the region affected by the earthquake. Through a case series of patients with SMI, we describe how care was quickly deployed and delivered after a natural disaster and during a pandemic resulting in their functional recovery. Community mental health teams have the potential to provide feasible, comprehensive, and accessible mental health services, and their continued implementation in the post-disaster period in Croatia could be beneficial for care management of people with severe mental illness.

Keywords: severe mental illness, crisis, community mental health team, earthquake, CMHT

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INTRODUCTION

An earthquake of 6.4 moment magnitude (Mw) hit Petrinja in Croatian Sisak-Moslavina County on 29th of December 2020, which resulted in severe structural damage in the region and seven death causalities (1). It was also the second earthquake of that magnitude in Croatia that year; in March 2020, a 5.4 Mw earthquake hit the city of Zagreb, the capital of Croatia, but it did not affect Sisak-Moslavina County substantially (2). During the period when Petrinja earthquake hit, Croatia was facing a second lockdown to curb the number of COVID-19 cases. The health system and health personnel were overloaded with cases of COVID-19 nationwide (3).

Prior research shows that after exposure to severe trauma, such as an earthquake, the general population is at higher risk of developing psychiatric problems, especially post-traumatic stress disorder (PTSD), depression, and anxiety symptoms (4, 5). A significantly higher number of people show depressive and psychotic symptoms for months, even years after an earthquake has occurred (6–8). Furthermore, acute stress after these catastrophic events seldom increases the acute development of stress related disorders, such as peptic ulcer, hypertension, asthmatic attack, and ulcerative colitis (9–11). People with existing mental health issues, particularly severe

mental illness (SMI), are even more susceptible to the adverse impacts of stressful events and to developing concomitant symptoms and mental health issues (12). People with SMI may also not have sufficient coping mechanisms or social resources to cope with these stressors or traumatic events (13). Also, due to a significant number of comorbidities and a shorter lifespan than general population (14, 15), people with SMI may be prone to the worsening of somatic conditions. Early intervention after trauma reduces acute stress and prevents psychological disturbances and, consequently, stress related somatic symptoms, including cardiovascular, gastric, pulmonary, etc. (16).

The majority of studies that focused on interventions in humanitarian crises have been conducted in low- and middle-income countries (17–19). In high-income countries, earthquakes in Kobe, L'Aquila, and Tohoku were the most investigated (20). Humanitarian research is often conducted in partnership with humanitarian organizations that are responding to the crisis (21). One of those organizations set standards to be applied in humanitarian response[1], emphasizing the need for accessible health services to people with psychosocial disabilities[2]. Natural disasters are and will continue to represent a great challenge in addressing mental health issues globally (22, 23). Implementation of mental health policies that focus on prevention and improving crisis response in care delivery are important to support populations affected by natural disasters (24). Since the COVID-19 pandemic, several studies have described how double disasters (i.e., natural disasters coupled with the COVID-19 pandemic) affect the mental health of whole communities (25–30).

The scientific and clinical community have advocated for the development and implementation of community-based services for people with mental illness (23). Community mental health teams (CMHT) providing specialized community-based mental health care are one example of a service delivery model that can support care outcomes for people with mental illness, and many countries have integrated these teams as a part their overall mental health service infrastructure. CMHT can support people with mental illness in achieving their recovery goals in and around their community and provide appropriate specialized care in the event of a crisis to prevent unnecessary psychiatric-related hospitalization (31, 32).

This paper will present a case series study that consist of five case studies reporting on the deployment of CMHT in affected regions up to 7 months after the 2020 Petrinja earthquake to provide insights on the method and care delivered to manage the mental health of people with SMI. The cases will demonstrate the possibility of CMHTs to early detect, monitor, and manage SMI in disaster situations.

[1]Sphere Association. About (2018). Available online at: https://spherestandards.org/about/ (accessed December 1, 2021).

[2]Sphere Association. The Sphere Handbook Humanitarian Charter and Minimum Standards in Humanitarian Response (2018). Available online at: https://handbook.spherestandards.org/en (accessed December 1, 2021).

CASE DESCRIPTIONS

Prior to the earthquake in 2020, mental health care in the Sisak-Moslavina County was provided by both the Dr. Ivan Barbot neuropsychiatric hospital and the Dr. Ivo Pedišić general hospital serving a population of ∼160,000 inhabitants. After the earthquake, the psychiatric department within the "Dr. Ivo Pedišić" general hospital was repurposed for non-psychiatric use. The earthquake and COVID-19 pandemic resulted in only emergency services being maintained (33, 34). Emergency medical service (EMS) staff is usually not sufficiently trained in mental health care (35). Public transportation within the County was reduced and, in some places, stopped entirely, many private cars were damaged. As a result, regular psychiatric outpatient care in the County was hardly accessible for the majority of the population. Croatia has several years of experience in the implementation of CMHTs, partially through a European Commission project LaRge-scalE implementation of COmmunity based mental health care for people with seVere and Enduring mental ill health in EuRopE (RECOVER-E) (31) which focuses on the development, implementation, and evaluation of CMHTs for SMI in five sites in five Central and Eastern European countries. Following the joint initiative of the Croatian Psychiatric Association (CPA), RECOVER-E project experts from Croatia and the Dr. Ivan Barbot hospital, the Ministry of Health endorsed the establishment and deployment of CMHTs on January 3rd, 2021 for Sisak-Moslavina County. The Croatian Institute of Public Health provided the support to CMHTs from May 2021 until August 2021 when all previously existing psychiatric services have returned in function and the need for CMHTs diminished. CMHTs were funded by the Croatian Health Insurance Fund within the compulsory health insurance package. The structure of CMHT members was adopted from RECOVER-E project and adjusted to reflect local needs and opportunities (31). Members of the CMHT included at least one psychiatrist, psychiatry resident, psychiatric nurse, psychologist, and in some instances a child and adolescent psychiatrist. CMHTs included local mental health professionals from Dr. Ivan Barbot hospital and professional volunteers from the CPA. CMHTs provided on-site crisis resolution, psychological interventions, psychopharmacological home treatment, remote consultations, and a range of flexible interventions depending on specific needs such as liaising with the local general hospitals in case of emergent somatic comorbidity, liaising with general practitioners (GP) where medication prescription was needed, and liaising with other rescue teams in case of severe home damage related to the earthquake. The teams were situated in three major centers of the County, Petrinja, Sisak, and Glina, where temporary psychiatric ambulances separate from EMS were established. The information about implementation was shared through the local and national media, and informative brochures with contacts for CMHTs were distributed to first responder organizations, local civil defense, non-governmental organizations (NGO), and community health centers. The intervention was available to those who expressed the need for psychiatric care and to those who were detected in need by the community. A flexible team structure enabled all age groups to be treated. The patients would

be followed by the CMHT until returning to their previous level of functioning or declining further visits. The rate of declining was not investigated; however, there were obviously no contraindications since the team did not oppose the any discontinuation. From January 4th 2021 to August 1st 2021, CMHTs provided altogether 758 interventions to the people in Sisak-Moslavina County. Most interventions were provided to people suffering from stress related disorders (81%), and 9.3% for people with SMI. Of all interventions, 3.6% were provided for non-psychiatric reasons, such as gastritis, hypertension, and arrythmias. Other interventions (6.1%) included support for people with dementia, alcohol related disorders, insomnia, intellectual disabilities, behavioral and emotional disorders in childhood, and personality disorders. Five cases of patients demonstrate the role of CMHT in early detection, monitoring, and management of SMI.

Case 1

Seven days after the earthquake, a local NGO informed the CMHT about a patient in a possible acute mental health crisis in a remote, hard to reach community. The team managed to visit the patient within 2 days. A 57-year-old female appeared unwilling to participate in the intersection with the CMHT, appeared tense, depressed, and frightened. She was living with her son who described those symptoms have been present for more than a month. He informed their GP about her condition, but due to the disruption in healthcare services, they did not receive follow-up support or care. During the conversation, she would occasionally stare at one point on the celling but denied having any hallucinations. She confirmed that she was having difficulty sleeping and experienced anxiety. She accepted treatment support for the sleep troubles and anxiety and agreed to then have her mental health status re-assessed by the CMHT. The team prescribed her olanzapine 5 mg/daily. Three days after the first visit, her son contacted the team saying the patient refused to eat and drink. The CMHT requested the Croatian mountain rescue service to transport the CMHT to the patient, since the terrain was inaccessible for an EMS vehicle. Upon arrival, the patient refused to talk, and the son confirmed she muttered what seemed to resemble suicidal ideation. The team assessed this as a high-risk situation and took the patient and informed EMS about the arrival of the patient at the Dr. Ivan Barbot psychiatric hospital for inpatient admission. She was later diagnosed with unspecified psychosis and discharged after 3 weeks of hospitalization in an improved condition, however with negative symptoms still mildly present. By the end of July 2021, she continued to receive routine outpatient care at the Dr. Ivan Barbot psychiatric hospital.

Case 2

Following a telephone call 2 weeks after the earthquake, the CMHT visited a patient in a dislocated municipality. The patient was already receiving mental health care for unspecified psychosis and complex PTSD since 2005 but was not able to visit a psychiatrist due to the lack of public transportation after the earthquake. He shared the household with one of his parents, was unemployed, and received social allowances as his only source of income. He was prescribed diazepam by a GP in doses from 30 to 60 mg per day as needed. However, the patient complained that diazepam was not helping anymore: he had parasuicidal thoughts and could not sleep for longer than an hour every night. He did not want to be admitted to the hospital but was willing to take medications. The team administrated olanzapine 5 mg and started immediately providing short supportive psychotherapy session. After the initial 45-min session, the patient reported slight improvement, did not report any suicidal thoughts and intentions, and he made a suicide prevention contract with the team. For coping with depressive symptoms, the patient was prescribed with fluvoxamine 100 mg/daily and olanzapine 10 mg/daily. He and his parent were provided with all necessary mental health service contacts. CMHT visited next week and provided the second supportive psychotherapy session. The patient described vanishing of all suicidal thoughts and achieving a good sleep routine. The team contacted his GP for further prescription of medication and performed weekly telephone sessions with the patient. During the last visit in June 2021, the patient reported being stable. He found few new activities, was taking care of abandoned animals, and started to engage into physical activity. By that time, public transport returned to operation, and he continued his ongoing care with his treating psychiatrist.

Case 3

Approximately 2 weeks after the earthquake, the team was informed about a 44-year-old unemployed patient near Glina that was in psychiatric treatment since 2017 due to schizoaffective disorder and generalized anxiety disorder. His last psychiatric appointment was 6 months before the earthquake, when the psychiatrist continued with mirtazapine 30 mg/daily, paroxetine 20/daily, and pregabalin 450 mg/daily, and switched him from olanzapine 20 mg/daily to risperidone 4 mg/daily due to drowsiness. A few months before the earthquake, he was engaged in neurological treatment for restless leg syndrome and prescribed with ropinirole 8 mg/daily and diazepam 30 mg/daily. However, since the COVID-19 restrictions came into force and health services were disrupted after the earthquake, he was not able to stay in regular neurological outpatient visits. During the teams' first visit, the patient was anxious, seemed traumatized, had trouble sleeping, and prominent restless leg syndrome symptoms. He reported that he had severe limitations in functioning and felt unsafe in his home, despite the building being categorized safe to remain in by civil engineers employed by the municipality. The team re-prescribed olanzapine (10 mg/daily) and advised him to discontinue mirtazapine as a second antidepressant due to expected olanzapine induced drowsiness. The team provided supportive psychotherapy together with psychological debriefing. In the following week, the team gradually reduced doses of diazepam (to 20 mg/daily) and continued to provide supportive psychotherapy. The patient was followed until May 2021 in which anxiety and sleeping disturbances were reduced. He became more active and became a municipal maintenance worker. His restless leg syndrome improved, and the team gave him directions on continuing his neurological outpatient visits.

Case 4

In the middle of January 2021, the CMHT was consulted to see a mistrustful 59-year-old woman in Petrinja diagnosed with schizophrenia and multiple somatic comorbidities. The team was contacted by her daughter reporting the patient being suspicious and refusing to take her long-acting injectable antipsychotic that she had last received a few weeks before the earthquake. There was also a lack of information about when the next injection would be received, as there was no communication with her treating psychiatrist. The patient refused to be seen by an EMS team but agreed to meet with members of the CMHT in Petrinja's community health center. During the visit, the patient confided to the team members about her paranoid beliefs. She reported that household members were attempting to poison her, and that she does not like to take long-acting injectable antipsychotics as she felt she no longer had schizophrenia. She also complained about pelvic discomfort and vaginal bleeding. Because of the high risk of further illness progression due to medication non-adherence and the lack of support system, all possibly resulting in deterioration of psychic and somatic health, the team indicated a further diagnostic evaluation and treatment, so the patient was transferred to Dr. Ivan Barbot hospital. During the 1-month in hospital stay, she was seen by a psychiatrist, internal medicine specialist, and a gynecologist, and diagnosed with residual schizophrenia, bacterial pneumonia, and cervical polyps. She was prescribed with haloperidol 7 mg/daily, promazine 25 mg/daily, and biperiden 2 mg/daily upon which her psychotic symptoms diminished. She was successfully treated for pneumonia and after discharge continued the gynecological monitoring in an outpatient clinic. Until the beginning of August 2021, she continued to experience stability in her psychiatric state.

Case 5

After the earthquake, all beneficiaries from Counties' retirement homes were temporarily relocated to a hospice in the town of Topusko. In July 2021, 6 months after the earthquake, during the CMHT regular round of home visits, the team was notified about a beneficiary with previously diagnosed schizophrenia that started being hostile toward the hospice workers. The 47-year-old patient articulated that her body is not hers, and her sense of touch is unusual. During the placement in the Topusko hospice, she was treated for pulmonary tuberculosis, asthma, and COVID-19 infection with the introduction of quadruple antituberculosis therapy. She received regular mental health treatment, including 75 mg clozapine and 1.5 mg alprazolam daily. CMHT provided her with psychosocial support in the form of counseling and increased clozapine dose for 12.5 mg daily. One week after the initial visit, CMHT noticed an additional deterioration of her mental state in the form of paranoia toward other beneficiaries. Given the new circumstances, and despite the increased clozapine dosage, the possibility of antitubercular therapy-induced psychosis was considered. Therefore, CMHT transferred her to Dr. Ivan Barbot hospital where eventually the diagnosis of iatrogenic genesis of psychotic exacerbation was confirmed. Upon achieving the remission of psychotic symptoms, she was displaced to the Special Hospital for Pulmonary Diseases and Tuberculosis where she continued treatment for pulmonary tuberculosis.

DISCUSSION

This case series presents diverging experiences of mental health issues during the pandemic and in the aftermath of the 2020 earthquake. All cases demonstrate the importance of early detection of symptoms or changes in functioning and regular contact with patients to inform changes in mental health status or in circumstances.

We believe introducing CMHTs as a standard post-disaster mental health intervention could have several benefits. First, they improve access to psychiatric services which is often disrupted in disaster situation, such as in our experience. It is well-known that low levels of accessibility of mental health services increase the inequality in the provision of adequate care for people with SMI (36). The mental health services in general became less accessible during the pandemic in the majority of countries (33, 34). It was also noted that SMI patients had a higher level of morbidity and mortality due to COVID-19, and one of the explanations lies in the inadequate accessibility and provision of mental health services for SMI patients (37). Novel approaches to delivery of care during the pandemic have helped offset the psychiatric risks to SMI patients, and it is presumable that those approaches may be applicable to other disaster scenarios (12). The CMHT may represent the only accessible service in the event of an acute mental health crisis or given measures imposed during the COVID-19 pandemic.

Second, CMHTs can provide fast response to prevent further escalation of an acute mental health crisis. Early detection of symptoms has a positive impact on the outcome and recovery of the disease (38). Our CMHT was able to visit the patient in case number 1 within 48 h and used other available facilities in order to relieve the burden on EMS services. Implementation of mental health outreach teams immediately after severe earthquakes showed significant mental health benefits in Armenia, China, and Japan (39–43). After the 1988 Armenian earthquake, a psychiatric outreach program with trauma/grief-focused brief psychotherapy to adolescents was implemented, which was associated with a reduction of risk of developing PTSD and prevented the exacerbation of depressive symptoms (40, 41). In 2008, Sichuan earthquake psychological rescue services were quickly deployed as well as hotlines for psychological support have been implemented for people near the disaster areas, and also for general public (42). Brief mental health intervention provided demonstrated that overall patient-level results were extremely satisfactory, with marked improvements of functionality and/or symptom intensity seen in the affected population (43). After the 2011 Tohoku earthquake and tsunami, psychiatric mobile teams were immediately dispatched to work in collaboration with local mental health professionals (39). The teams supported them in continuing pre-disaster psychiatric services, providing on-site treatment of acute stress

and psychoeducation at communal shelters (39). For adequate post-disaster service, planning, preparation, and management are essential (44). Timely interventions can be observed in countries with predetermined guidelines for post-disaster period (25, 39, 42). Croatia has several recommendations for psychosocial support in disaster situations (45, 46). However, the precise establishment and provision of outreach psychiatric care in crisis situation is not defined (45, 46).

Finally, the flexibility in formation of CMHTs makes them efficient in detecting a wide range of clinical situations. In these cases, the connection of CMHTs with GPs, EMS, and hospital allowed the resolution of highly complex somatic conditions, like detecting iatrogenic psychosis. Unfortunately, CMHTs are not commonly seen in South Eastern European countries, but there are several initiatives and pilot programs that aim to develop and sustain community-based mental health services, including CMHTs (31, 47, 48). They are intended mostly for patients with SMI as an enforcement for rehospitalization prevention and overall admission reduction. CMHT can be adjusted across different clinical groups, such as for persons with first episode psychosis, those with intellectual disabilities, forensic patients, etc., and the members can be formed of different specialists (e.g., some teams include employment specialists, police officers, or social workers) (49–51).

This paper as a case series report has several limitations. The primary limitation is lack of a comparison group (52). However, this limitation is inherent to case studies. The benefits of receiving outreach community psychiatric care for patients with SMI have been emphasized (31, 32), and we believe we provided SMI patients with above-standard care especially in the situation where standard care is not available at all. CMHTs after 2020 Petrinja earthquake were conducted on the back of numerous highly devoted professional volunteers. Those professionals do not necessary reflect the overall mental health workforce in Croatia. Selection bias might also be present, since only patients who agreed to receiving treatment by the CMHT were included in this particular case series. However, we believe this case series provides valuable information about the management of patients with SMI in double disaster using CMHTs and will lead to more extensive research in the field of outreach post-disaster services.

In sum, after a disaster, CMHTs have the potential to deliver feasible, comprehensive, and accessible mental health services in remote areas affected by a disaster or impacted more substantially due to public health measures in the place, for instance, in the event of the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. All patients in this case series gave informed consent for the publication.

AUTHOR CONTRIBUTIONS

SM, AI, IS, DP, HH, RM, LR, MK, AP, DŠ, and MRK participated in the project and in the study. SM, AI, IS, and DP participated in the writing of the first draft of the manuscript, gave critically relevant comments in the revised version of the manuscript study, and approved the final version of it. HH, RM, and LR gave critically relevant comments and approved the final version. MK, AP, LZ, and DŠ gave critically relevant comments, participated in the writing of the final revision of the manuscript, and approved the final version of it. MRK revised the first draft of the study, and gave critically relevant comments on the subsequent revisions of the manuscript, and approved the final version of it. 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.2021.795661/full#supplementary-material

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Scaling Evidence-Based Interventions to Improve the Cardiovascular Health of People With Serious Mental Illness

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People with serious mental illnesses (SMIs) experience excess mortality, driven in large part by high rates of cardiovascular disease (CVD), with all cardiovascular disease risk factors elevated. Interventions designed to improve the cardiovascular health of people with SMI have been shown to lead to clinically significant improvements in clinical trials; however, the uptake of these interventions into real-life clinical settings remains limited. Implementation strategies, which constitute the "how to" component of changing healthcare practice, are critical to supporting the scale-up of evidence-based interventions that can improve the cardiovascular health of people with SMI. And yet, implementation strategies are often poorly described and rarely justified theoretically in the literature, limiting the ability of researchers and practitioners to tease apart why, what, how, and when implementation strategies lead to improvement. In this Perspective, we describe the implementation strategies that the Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness is using to scale-up three evidenced-based interventions related to: (1) weight loss; (2) tobacco smoking cessation treatment; and (3) hypertension, dyslipidemia, and diabetes care for people with SMI. Building on concepts from the literature on complex health interventions, we focus on considerations related to the *core function* of an intervention (i.e., or basic purposes of the change process that the health intervention seeks to facilitate) vs. the *form* (i.e., implementation strategies or specific activities taken to carry out core functions that are customized to local contexts). By clearly delineating how implementation strategies are operationalized to support the interventions' core functions across these three studies, we aim to build and improve the future evidence base of how to adapt, implement, and evaluate interventions to improve the cardiovascular health of people with SMI.

Keywords: implementation strategies, scale-up, serious mental illness, cardiovascular health, evidence-based interventions, implementation

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of preventable death for people with serious mental illnesses (SMIs) (1), due in large part to elevated rates of CVD risk factors (obesity, hypertension, dyslipidemia, and diabetes mellitus) and risk behaviors (tobacco smoking, physical inactivity, and unhealthy diet) that are 1.5–3 times higher in people with SMI than in the overall population (2–5). These disproportionately high rates are driven by a number of factors. At the patient level, metabolic side effects of psychotropic medications (6, 7) and shared pathophysiology between certain CVD and SMI conditions (e.g., altered inflammatory processes) (8, 9) can directly affect cardiovascular health; whereas socioeconomic risks, lack of social support, and cognitive impairment can contribute to suboptimal health habits and impede productive engagement with the healthcare system (10, 11). At the level of care delivery, the poor integration between general medical and specialty mental healthcare likely contributes to significant disparities in the levels of guideline-concordant care delivered to patients with SMI (12, 13). Primary care physicians may lack the comfort or experience in treating people with SMI, mental health specialists may view physical healthcare as outside their purview, and importantly, delivery systems often do not support or reimburse coordination efforts.

Fortunately, there are evidence-based interventions that can help improve the cardiovascular health of people with SMI. A growing number of behavioral interventions tailored to people with SMI have been shown in clinical trials to facilitate weight loss and tobacco smoking cessation (14–16). However, translating the improvements demonstrated in trials has been limited in real-life clinical settings, leading to the well-documented research-to-practice gap that undermines the uptake of many clinical interventions (17). In part, this is because *implementation*—or the process of gaining targeted organizational members' skillful, consistent, and committed use of a practice (18)—is often fraught with challenges, with roughly two-thirds of implementation efforts failing to achieve the intended result (19), and almost half having no effect on outcomes of interest (20). Implementation barriers are numerous and varied, including factors at the provider-level (e.g., providers' lack of self-efficacy to perform an evidence-based practice), organizational-level (e.g., lack of fit between the intervention and current workflows), and system-level (e.g., lack of policies and financing mechanisms that would support sustainable change).

To enhance the uptake of interventions, many translational projects employ *implementation strategies*, which refer to methods or techniques used to improve adoption, implementation, and sustainment of interventions (21). Implementation strategies constitute the "how to" component of changing healthcare practice (21) and range from discrete, relatively "light touch" strategies (e.g., reminder systems for clinicians) to more intensive multi-component strategies that may target multiple levels (e.g., organizational-level, provider-level, and consumer-level). The wide variation in implementation strategies is useful for addressing the diverse array of barriers that may affect implementation outcomes and long-term adoption. However, the tremendous variation, both in terms of the strategies themselves and the ways in which the strategies are described, have led some to characterize the literature on implementation as a 'Tower of Babel" (22). Although several taxonomies have been developed to organize the types of strategies available (23, 24), implementation strategies are often poorly described in the literature and rarely justified theoretically. Given this lack of precision, implementation scholars are increasingly calling upon the research community to more clearly delineate how implementation strategies are operationalized (21, 25). With more robust specifications of who enacts the strategies and for what purpose, researchers and practitioners will be better able to tease apart why, what, how, and when implementation strategies actually lead to improvement.

In this paper, we describe the implementation strategies being leveraged by the Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness, a research-practice translation center funded by the National Institute of Mental Health (NIMH) that aims to reduce premature mortality among people with SMI (26). The Center's goals are to develop and test implementation strategies to support the scale-up of three evidenced-based interventions related to: (1) weight loss; (2) tobacco smoking cessation treatment; and (3) hypertension, dyslipidemia, and diabetes care for people with SMI. Building on concepts from the literature on complex health interventions, we first consider the *core functions*, or basic purposes of the change process that the health intervention seeks to facilitate. We next describe the *forms*, or implementation strategies used to carry out the core functions, using Proctor et al.'s recommendations for specifying and reporting implementation strategies (21). By delineating how the selected implementation strategies have been operationalized to support the interventions' core functions across these three studies, we aim to inform and improve future efforts to adapt, implement, and evaluate interventions to improve the cardiovascular health of people with SMI.

Evidence-Based Interventions to Improve Cardiovascular Health

The Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness aims to develop and test multi-component implementation strategies to support the scale-up of three evidence-based interventions to reduce cardiovascular risk in SMI. The first project, named ACHIEVE-Dissemination (or ACHIEVE-D for short), is a 6-month evidence-based behavioral weight loss program tailored to adults with SMI that is being delivered in Psychiatric Rehabilitation Programs throughout Maryland. The intervention was adapted from the ACHIEVE randomized-controlled trial (RCT) (15, 27), in which participants who received the intervention (i.e., group and individual weight management sessions and group exercise classes primarily delivered by trained interventionists) experienced clinically significant weight loss (7 lbs. at 18 months). To promote scale-up of the intervention so that it could be implemented by mental health program staff, we adapted the ACHIEVE program using the Enhanced Replicating Effective Programs

(REP) Framework (28) to increase the acceptability and feasibility of the ACHIEVE-D curriculum in community settings.

The second project, IMPACT, is a 12-month intervention to support the uptake of evidence-based tobacco smoking cessation treatment (14, 29) in community mental health clinics in Maryland. The overarching premise is that clinics should implement the following evidence-based practices: (1) screening for tobacco use in all patients, (2) assessment of willingness to quit for those who smoke, (3) behavioral counseling for those interested in cutting down or quitting smoking, and (4) pharmacotherapy for those interested in cutting down or quitting smoking. The IMPACT intervention is designed for community mental health organization leaders and providers (e.g., therapists including licensed social workers, counselors, and psychologists; and physician, nurse practitioner, and physician assistant prescribers) to deliver the program to patients who attend community mental health clinics and currently smoke tobacco. To increase mental health providers' uptake of the intervention, we are using Gurses et al.'s interdisciplinary framework of clinicians' compliance with evidence-based guidelines (30) to guide our assessment of baseline characteristics of the clinics, providers, and evidence-based practice as well as relevant mechanisms of change (i.e., providers' knowledge and self-efficacy) to be targeted by implementation efforts.

The third project, RHYTHM, is a 12-month care coordination intervention that aims to equip mental health providers with the ability to coordinate guideline-concordant care for hypertension, dyslipidemia, and diabetes mellitus among people with SMI in the context of Psychiatric Rehabilitation Programs implementing behavioral health homes in Maryland (31–33). Guided by the Translating Evidence into Practice (TRIP) model for large-scale knowledge translation into community settings (34), the study team conducted a comprehensive review of clinical guidelines and scholarly literature to create a bundle of evidence-based care processes for hypertension, dyslipidemia, and diabetes tailored for people with SMI. The bundle includes two overarching components: (1) clinical care processes (e.g., annual dilated eye exam for patients with diabetes), and (2) care coordination and management processes (e.g., using a brief form to facilitate communication between a primary care provider and behavioral health home team at the time of a routinely scheduled visit). These evidence-based practices will be implemented using an adapted version of the Comprehensive Unit Safety Program (CUSP) strategy, which seeks to foster a team-based quality improvement culture and reduce preventable harm (31).

Form vs. Function

These three evidence-based interventions to improve cardiovascular health for people with SMI can be thought of as *complex health interventions* in which (1) the intervention's multiple components interact in a summative and synergistic fashion; (2) individuals delivering and receiving the intervention exhibit a highly complex set of behaviors; (3) changes are required at multiple levels (e.g., organizational, workforce, or patient); (4) outcomes are numerous and variable; and (5) there is some flexibility in how the intervention is implemented (35). Within the literature on complex health interventions, there is a useful distinction between the *core functions* of an intervention, which speaks to the basic purposes of the change process that the health intervention seeks to facilitate; and its *forms*, which speaks to specific strategies or activities that may be customized to local context and that are needed to carry out the core functions (36). With regards to an intervention's core functions, it is important to note that the "basic purposes of the change process" applies to both the clinical/therapeutic/administrative changes associated with improving health outcomes for patients (e.g., reducing consumption of sugar-sweetened beverages in people with SMI) as well as the implementation-related changes associated with putting the clinical or behavioral intervention into practice (e.g., training providers to increase their knowledge of an intervention). In this Perspective, we focus on the core functions of the implementation-related changes and how these map on to the specific forms, or implementation strategies, designed to facilitate these changes.

Core Functions of the Interventions

All three of the Center's projects share certain *core functions* related to putting the clinical interventions into practice (**Table 1**). For example, a core function that supports the delivery of guideline-concordant care across all three projects is to create written processes and defined standards including manuals for delivering care. Moreover, since all of the interventions are being implemented by mental health program staff—not research staff—another core function is to educate clinicians and staff to be able to deliver the interventions' components with fidelity and to use skills in motivational interviewing (i.e., an evidence-based and patient-centered communication method) to more effectively engage with clients in conversations around the targeted behaviors. To complement this educational component, a third core function is to provide opportunities to practice the motivational interviewing techniques that mental health program staff are introduced to through training. All of the projects also aim to facilitate a supportive implementation climate at the organizational-level in which mental health program staff perceive that the adoption, implementation, and use of an innovation is expected, rewarded, and supported by the organization (37).

Several of the core functions are also specific to the design of a particular intervention. In ACHIEVE-D, for example, mental health program staff serve as "coaches" to deliver weight management and exercise sessions. Consequently, a core function specific to this intervention that will be tested in the "enhanced condition" of the project is to provide tailored feedback to coaches on their delivery of these sessions. In IMPACT, in which therapists and prescribers are responsible for delivering smoking cessation treatment, a core function is to provide clinical consultation and support related to behavioral counseling for smoking cessation and prescription of pharmacotherapy. Lastly, for RHYTHM, which seeks to improve care coordination processes, one of this project's core functions is to foster a team-based quality improvement culture where providers work together to identify a patient-centered problem and then address barriers to receipt of evidence-based care for that problem.

TABLE 1 | Overview of the interventions' core functions and forms.

Intervention	Core Functions	Forms (implementation strategies)
All ALACRITY center projects	Create written processes, defined standards, and manuals for delivering guideline-concordant care	Protocol
	Educate clinicians and staff to deliver the intervention	Training
	Provide opportunity to practice motivational interviewing skills when discussing the targeted behavior	Avatar practice modules
	Facilitate a supportive implementation climate for change	Organizational strategy meetings, adapted comprehensive unit safety program (CUSP)
Setting-specific		
ACHIEVE-D: 6-month tailored behavioral weight loss intervention delivered by psychiatric rehabilitation program (PRP) staff	Provide tailored feedback to staff on their delivery of the intervention (in the enhanced arm)	Performance coaching
IMPACT: 12-month evidence-based tobacco smoking cessation treatment delivered by community mental health clinic prescribers and therapists	Provide clinical consultation and support	Coaching
		Expert consultation
RHYTHM: 12-month care coordination intervention for hypertension, dyslipidemia, and diabetes mellitus delivered by behavioral health home providers and PRP staff	Foster a team-based quality improvement culture	Adapted comprehensive unit safety program (CUSP)

Specifying Implementation Strategies

Whereas the core functions help to clarify the basic purposes of the change process, the corresponding forms—or implementation strategies—illustrate the specific activities that are needed to carry out the core functions and that can be customized to a local context.

In order to describe how implementation strategies have been operationalized with enough detail to enable measurement and reproducibility, Proctor et al. (21) recommends that researchers specify the: (1) actor(s), (2) action(s), (3) action target(s), (4) temporality, (5) dose, (6) implementation outcomes affected, and (7) theoretical, empirical, or pragmatic justification. The *actor* is defined as the stakeholder who actually delivers the implementation strategy, which for all three Center projects includes faculty and intervention experts from the Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness. The *actions* indicate the actions, steps or processes, and sequences of behavior (e.g., provide clinical supervision), whereas *action targets* refer to conceptual targets they attempt to impact (e.g., knowledge about the evidence-based practice). *Temporality* refers to the stage or phase when the strategy is used, *dose* refers to the dosage or intensity of the strategy, and *implementation outcomes* typically refer to Proctor et al.'s (38) taxonomy of implementation outcomes (acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability). Last, the *justification* includes the rationale for why a strategy is being used.

For the Center's three interventions, the core functions of the changes process that are shared across projects also have corresponding implementation strategies in common, although the strategies vary in terms of how they are being operationalized (**Table 2**). For example, in order to support the core function of educating clinicians and staff to deliver the intervention, all of the projects include synchronous training that is delivered virtually in real-time as an implementation strategy. However, the dose of the training ranges from 2 h (for prescribers in IMPACT) to 15 h (for coaches in ACHIEVE-D), reflecting both the amount of content that needs to be covered as well as the feasibility of conducting the targeted actions.

To meet the needs of the core functions of the change process that are intervention-specific, the Center is also employing an array of implementation strategies that are particular to each project. For example, to enable a culture of quality improvement at participating sites, the RHYTHM project is leveraging an adapted Comprehensive Unit Safety Program (CUSP) implementation strategy comprised of provider training (which is a discrete strategy common across projects) that is combined with expert facilitation and implementation of a five-step quality improvement process (which are strategies specific to RHYTHM). The CUSP strategy is designed to foster a team-based quality improvement culture, in which clinicians and staff are first trained on the science of quality improvement, and then work in CUSP teams to create a process at their organization for continuously identifying and addressing barriers to evidence-based care. By training providers and putting standard processes to implement evidence-based care in place, the CUSP implementation strategy is designed to improve the organization's culture as well as providers' self-efficacy to deliver guideline-concordant care.

DISCUSSION

Improving the cardiovascular health of people with SMI is a lynchpin to reducing premature mortality in this

TABLE 2 | Specification of implementation strategies.

	Implementation strategy	Action	Action targets	Temporality	Dose	Outcome
All ALACRITY center projects						
	Treatment protocol	Provide a manual for delivering the evidence-based practices	Knowledge and self-efficacy of coaches/peer leaders (ACHIEVE-D), therapists/prescribers (IMPACT), and clinic staff (RHYTHM) to deliver the intervention	Ongoing	As needed	Adoption, fidelity
	Synchronous online training	Present information needed to implement all intervention components including brief training on motivational interviewing (MI); provide opportunity to practice skills	Knowledge, self-efficacy, and skills of coaches/peer leaders (ACHIEVE-D), therapists/prescribers (IMPACT), and clinic staff (RHYTHM) to deliver the intervention	Pre-implementation	ACHIEVE-D: (15 h) IMPACT: (4 h)/for therapists; (2 h)/for prescribers RHYTHM: (12 h)	Adoption, fidelity
	Avatar practice modules	Provide opportunity to practice motivational interviewing techniques for targeted behaviors	Self-efficacy of coaches (ACHIEVE-D), therapists/prescribers (IMPACT), and clinic staff (RHYTHM) in using motivational interviewing techniques	Monthly	ACHIEVE-D: (20 min) IMPACT: (15 min) RHYTHM: (15 min)	Penetration amongst clients, fidelity to the MI method
Setting specific						
ACHIEVE-D	Performance coaching (for the enhanced arm of the project)	Provide tailored feedback to coaches regarding their delivery of video-taped group sessions	Coaches' ability to deliver group sessions with fidelity to the curriculum; motivational interviewing skill development	Monthly	1 h	Penetration amongst clients, fidelity to the intervention
	Asynchronous online training	Review key concepts and discussion points prior to delivering the module; complete learning activity and quiz for each online training module	Coaches and peer leaders' knowledge, self-efficacy, and skills to deliver upcoming group sessions	Monthly	20 min	Penetration amongst clients Fidelity to the intervention
	Organizational strategy meetings	Provide data feedback on client attendance at group sessions; identify barriers at the individual and organizational levels; support group problem-solving; support learning within teams	Implementation climate and leadership engagement at the organizational level	Monthly	30 min	Adoption, Penetration amongst clients, fidelity to the intervention
IMPACT	Asynchronous online training	Present introductory information on core components of IMPACT	Therapists and prescribers' knowledge of the intervention	Pre-implementation	Once (1 h)	Adoption
	Coaching calls	Provide clinical consultation and support for behavioral counseling or pharmacotherapy	Therapists and prescribers' knowledge, skills, and access to expertise	Monthly	(30 min)/therapists (15 min)/prescribers	Fidelity to the intervention
	Expert consultation	Provide support for behavioral counseling or pharmacotherapy	Prescribers and therapists' knowledge and skills, and access to expertise	Ongoing	As needed	Fidelity to the intervention
	Organizational strategy meetings	Provide data feedback on delivery of core components; identify barriers at the organizational level; support group problem-solving	Implementation climate and leadership engagement at the organizational level	Monthly	30 min	Adoption, Penetration amongst clients, Fidelity to the intervention
RHYTHM	Adapted comprehen-sive unit safety program (CUSP)	Identify barriers, plan strategies to remove barriers, study and refine strategy; support learning within teams; support team members	Clinic staff members' knowledge, self-efficacy, skills, and access to internal expertise; remove barriers; promote supportive organizational climate for RHYTHM	Monthly	2–3 h	Acceptability, Adoption, Feasibility, Fidelity to the intervention, Penetration amongst clients

Actors: *All actions performed by faculty and intervention experts from the Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness.*

Theoretical justification: *ACHIEVE-D: Enhanced Replicating Effective Programs (REP) Model; IMPACT: Gurses et al.'s interdisciplinary framework of clinicians' compliance with evidence-based guidelines; RHYTHM: Translating Evidence into Practice (TRIP) model.*

population. To effectively scale-up interventions that have demonstrated significant improvements in CVD risks and risk behaviors in clinical trial settings, it is imperative to use implementation strategies that speak to both the core functions of the intervention's change processes *and* the localized implementation context. In this Perspective, we describe how the Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness is operationalizing implementation strategies to support the core functions of three evidence-based interventions related to weight loss (ACHIEVE-D); tobacco smoking cessation treatment (IMPACT); and hypertension, dyslipidemia, and diabetes mellitus care (RHYTHM) for people with SMI which, in total, address all cardiovascular risk factors. By clearly specifying how the implementation strategies have been operationalized, our goal is to contribute to the evidence base of why, how, and when implementation strategies can lead to supporting successful uptake of interventions, and ultimately, improved patient outcomes.

Moving forward, it will be important to consider how implementation strategies are being adapted to increase their acceptability and feasibility in real-life clinical settings, including modifications to improve their fit with local populations, settings, and contexts. The need to account for such adaptations is particularly salient amidst the backdrop of the COVID-19 pandemic, in which the turbulence of the external environment has prompted the need for significant modifications. For example, for all three of the Center's projects, training for mental health program staff was originally designed to be delivered in-person. With the onset of the pandemic, and ensuing restrictions related to in-person gatherings, the Center's faculty and intervention experts had to quickly pivot to reformat the training for the virtual environment. In order to systematically capture these adaptations, the Center plans to use the FRAME-IS model (39), a comprehensive framework for documenting modifications to implementation strategies, in an effort to specify implementation strategies not just in their intended form, but also in the ways in which they have evolved to respond to localized needs. Moreover, as the effectiveness of implementation strategies will likely vary (40), we plan to measure the fidelity with which the strategies are enacted so that we can better ascertain whether the strategies' effectiveness (or relative lack thereof) can be attributed to the strategy itself or to other contextual factors.

The ALACRITY Center projects are pilot in scope, and are designed to provide a foundation to inform future scale-up of evidence-based interventions to decrease cardiovascular risk in persons with SMI. Future work should incorporate hybrid implemementation effectiveness trials testing how these strategies can support intervention implementation on a larger scale. In addition, the implementation strategies used in the Center's current projects are largely focused on supporting change at the provider- or patient-level. In order to achieve widespread scale-up, an important next step will be to consider how to integrate these strategies with system-level and policy strategies at multiple levels (e.g., governmental, payer, system, and organizational). For example, it will be critical to consider what reimbursement mechanisms or other funding streams would be most appropriate and feasible to incentivize uptake of the evidence-based interventions in community settings. The ALACRITY Center's planned future work will include this policy and system-level focus with the goal to accelerate nationwide scale-up of evidence-based interventions addressing cardiovascular risk, and ultimately, reduce premature mortality in people with SMI.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

CY, EEM, SG, AD, FD, KG, GJ, DT, KM, and GD contributed to the conception and design of the study. CY, EEM, SG, EM, and GD drafted the manuscript and all authors assisted with critically reviewing and revising the manuscript for important intellectual content. EEM and GD were responsible for obtaining funding for the study. All authors contributed to the article and approved the submitted version.

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Concept of the Munich/Augsburg Consortium Precision in Mental Health for the German Center of Mental Health

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The Federal Ministry of Education and Research (BMBF) issued a call for a new nationwide research network on mental disorders, the German Center of Mental Health (DZPG). The Munich/Augsburg consortium was selected to participate as one of six partner sites with its concept "Precision in Mental Health (PriMe): Understanding, predicting, and preventing chronicity." PriMe bundles interdisciplinary research from the Ludwig-Maximilians-University (LMU), Technical University of Munich (TUM), University of Augsburg (UniA), Helmholtz Center Munich (HMGU), and Max Planck Institute of Psychiatry (MPIP) and has a focus on schizophrenia (SZ), bipolar disorder (BPD), and major depressive disorder (MDD). PriMe takes a longitudinal perspective on these three disorders from the at-risk stage to the first-episode, relapsing, and chronic stages. These disorders pose a major health burden because in up to 50% of patients they cause untreatable residual symptoms, which lead to early social and vocational

disability, comorbidities, and excess mortality. PriMe aims at reducing mortality on different levels, e.g., reducing death by psychiatric and somatic comorbidities, and will approach this goal by addressing interdisciplinary and cross-sector approaches across the lifespan. PriMe aims to add a precision medicine framework to the DZPG that will propel deeper understanding, more accurate prediction, and personalized prevention to prevent disease chronicity and mortality across mental illnesses. This framework is structured along the translational chain and will be used by PriMe to innovate the preventive and therapeutic management of SZ, BPD, and MDD from rural to urban areas and from patients in early disease stages to patients with long-term disease courses. Research will build on platforms that include one on model systems, one on the identification and validation of predictive markers, one on the development of novel multimodal treatments, one on the regulation and strengthening of the uptake and dissemination of personalized treatments, and finally one on testing of the clinical effectiveness, utility, and scalability of such personalized treatments. In accordance with the translational chain, PriMe's expertise includes the ability to integrate understanding of bio-behavioral processes based on innovative models, to translate this knowledge into clinical practice and to promote user participation in mental health research and care.

Keywords: precision medicine, mortality, schizophrenia, depression, bipolar disorder, comorbidities

INTRODUCTION

Every year, approximately one third of adults in Germany and Europe meet the diagnostic criteria for a mental illness. Furthermore, 50% of adult mental health problems start before or during adolescence (1). Schizophrenia (SZ), bipolar disorder (BPD), and major depressive disorder (MDD) represent 12% of these illnesses [or 16% if clinical high-risk (CHR) states are included] and rank among the 10 most disabling diseases worldwide (2). Furthermore, in 2017 in Germany alone the costs of these diseases were €3.1 billion for SZ, €5.8 billion for BPD, and €8.7 billion for MDD (3). This burden results from chronic and/or relapsing syndromes that affect ∼50% of patients, i.e., 6% of the adult population, and include a wide spectrum of impairments, such as cognitive and negative symptoms (e.g., avolition, social withdrawal); affective symptoms, with depressive, dysphoric or elevated mood; persistent psychotic experiences (e.g., suspiciousness, persecutory ideas, and auditory hallucinations); and lasting psychosocial and vocational deficits (4, 5). Overall, there is a need for a deeper understanding, more accurate prediction, and personalized prevention of disease chronicity across these disorders and mental illnesses more broadly.

The six German Centers for Health Research (DZGs) carry out research on common diseases of particular importance for the health of the German population. The DZG were introduced to translate research findings more effectively into medical care and back ("From bench to bedside and back"). A new national research network on mental disorders, the German Center of Mental Health (DZPG), has now been established and is currently in a 6-month networking period to develop a coherent and complementary research program. In a review process, the Federal Ministry of Education and Research (BMBF) selected six partner sites of the DZPG, which include the universities of Berlin and Bochum, the Central Institute of Mental Health Mannheim/University of Heidelberg/University of Ulm, the universities of Jena/Halle/Magdeburg, and the universities of München/Augsburg, and Tübingen. The Munich/Augsburg site encompasses the Ludwig-Maximilian-University (LMU), Technical University of Munich (TUM), University of Augsburg (UniA), Helmholtz Center Munich (HMGU), and Max Planck Institute of Psychiatry (MPIP), which together form the research network "Precision in Mental Health (PriMe): Understanding, predicting, and preventing chronicity."

The Munich Metropolitan Area hosts an internationally acclaimed hub for mental health research with two excellence universities, the LMU and TUM; the UniA, with its newly established medical faculty; the HMGU; and the MPIP. This excellence builds on a long track record in bio-behavioral neuroscience, which originated in E Kraepelin's and A Alzheimer's seminal work on affective, psychotic, and neurodegenerative disorders and continues to thrive until today. Located in the Munich Metropolitan Area (26,000 km^2), the PriMe consortium covers a catchment population of more than 6.2 million people, with 90,000 annual admissions (5,000 for SZ, 2,000 for BPD, and 22,000 MDD). The consortium extends to collaborating institutions, including outpatient and primary care networks (**Figure 1**). With its urban and rural regions, this catchment area is ideally suited for translational research from preclinical innovation across the clinical trial stages to final implementation in primary and resident specialist care.

In the following, PriMe's scientific goals will be outlined by exemplifying some of the key contributions toward establishing a precision medicine framework for the Munich Metropolitan Area and the DZPG. To substantially improve patient outcomes, this framework will integrate better mechanistic understanding of pathogenesis and chronicity, individualized prediction, treatment and early intervention, as well as clinical implementation of disruptive therapeutic innovations across this value chain. In

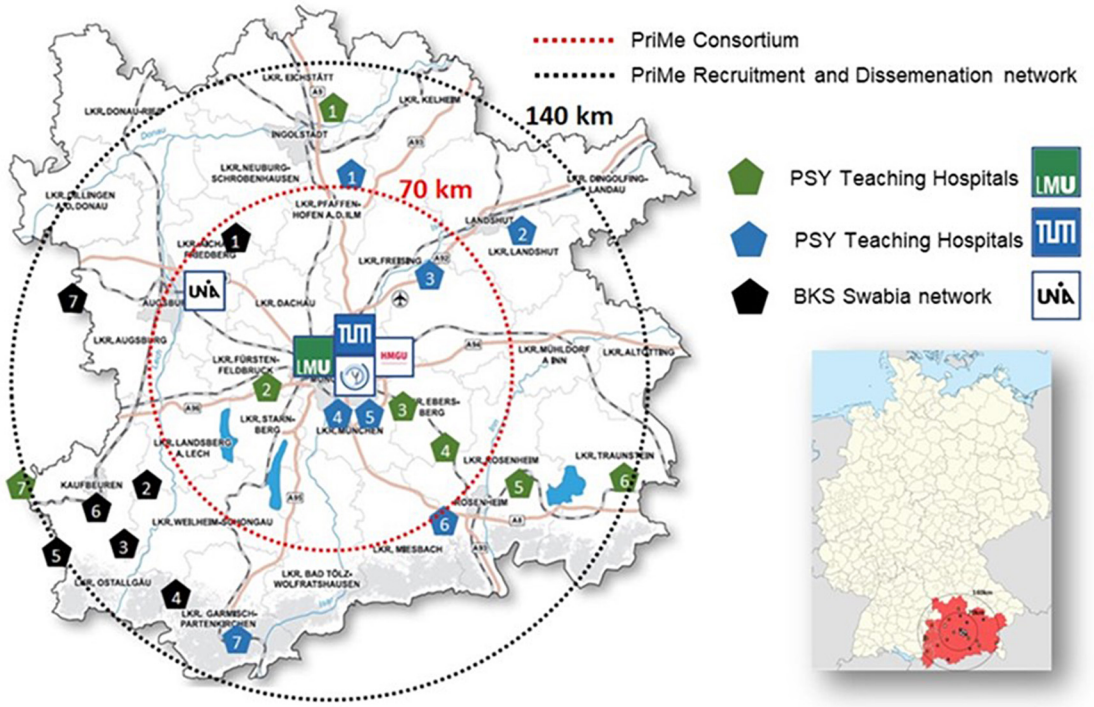

FIGURE 1 | Map of the PRiME's catchment area. PSY Teaching Hospitals LMU: 1. Klinikum Ingolstadt, 2. Hospital Fürstenfeldbruck, 3. Hospital München Ost, 4. Hospital Wasserburg, 5. Hospital Rosenheim, 6. Day Clinic Freilassing, 7. Hospital Memmingen. PSY Teaching Hospitals TUM: 1. Hospital Pfaffenhofen, 2. Hospital Landshut-Achdorf, 3. Hospital Freising, 4. Hospital Schwabing, 5. Hospital Bogenhausen, 6. Hospital Agatharied, 7. Hospital Garmisch-Partenkirchen. BKS Swabia network UniA: 1. Outpatient unit and day clinic Aichach, 2. Hospital Kaufbeuren, 3. Hospital Memmingen (allocated to two institutions), 4. Hospital Kempten, Day Clinic Lindau, 6. Hospital Obergünzburg, 7. Hospital Günzburg.

the subsequent chapters, we outline the specific need for early intervention and prevention in regards to SZ, BPD, as well as MDD and describe the novel scientific concept of the PriMe consortium including its preliminary work. Based on PriMe's precision medicine framework, we present its five-part thematic focus. Furthermore, we illustrate PriMe's infrastructure and its embedding in the German psychiatric research landscape. Moreover, we underline PriMe's efforts in facilitating patient participation as well mentoring services for early career scientists. In addition, we discuss five platforms which will be implemented as part of the DZPG. These platforms are structured around the themes "Multimodal Data and Model Humanized Systems," "Predictive Data Science," "Personalized and Innovative Therapies," Ethical, Societal, and Implementation Challenges" as well as "Clinical Trials and Evidence-Based Medicine." We conclude by providing an outlook on PriMe's activities contributing to an overarching program for the DZPG.

FOCUS OF PriMe ON EARLY INTERVENTION AND PREVENTION OF CHRONICITY AND MORTALITY

Importantly, the risk for chronicity-related functional deficits is not confined to the established stages of SZ, BPD, and MDD but encompasses earlier, subthreshold mental conditions, commonly referred to as CHR states (**Figure 2**). In SZ, the attenuated psychotic or basic symptoms that characterize these CHR states mark a more specific and imminent risk for psychosis, and early precursors can be traced back to adolescence and even earlier. Generally, such precursors represent critical windows for early detection, prevention, and intervention strategies. For the last 15 years, PriMe members have established and maintained research and clinical infrastructures for the early identification of vulnerable individuals in at-risk and first-episode stages of SZ, BPD, and MDD, and PriMe aims to use these infrastructures to develop biomarker-informed, disease-interceptive treatments.

Mortality is markedly increased in SZ, BPD, and MDD, resulting in a mean of more than 10 years lost because of earlier death (6). Higher mortality is likely caused by complex interactions of risk factors, including psychiatric and somatic comorbidities, lifestyle-related factors, suicide and secondary illness/treatment effects (7). Furthermore, interactions between psychiatric illnesses, such as posttraumatic stress disorder (PTSD) and anxiety disorders, functional somatic syndromes, substance abuse, sleep disorders, neurodevelopmental conditions (e.g., autism), and personality disorders, also contribute directly or indirectly to this excess mortality. Detecting and treating such comorbidities in early SZ, BPD, and MDD may avert disease progression and promote clinical and functional recovery.

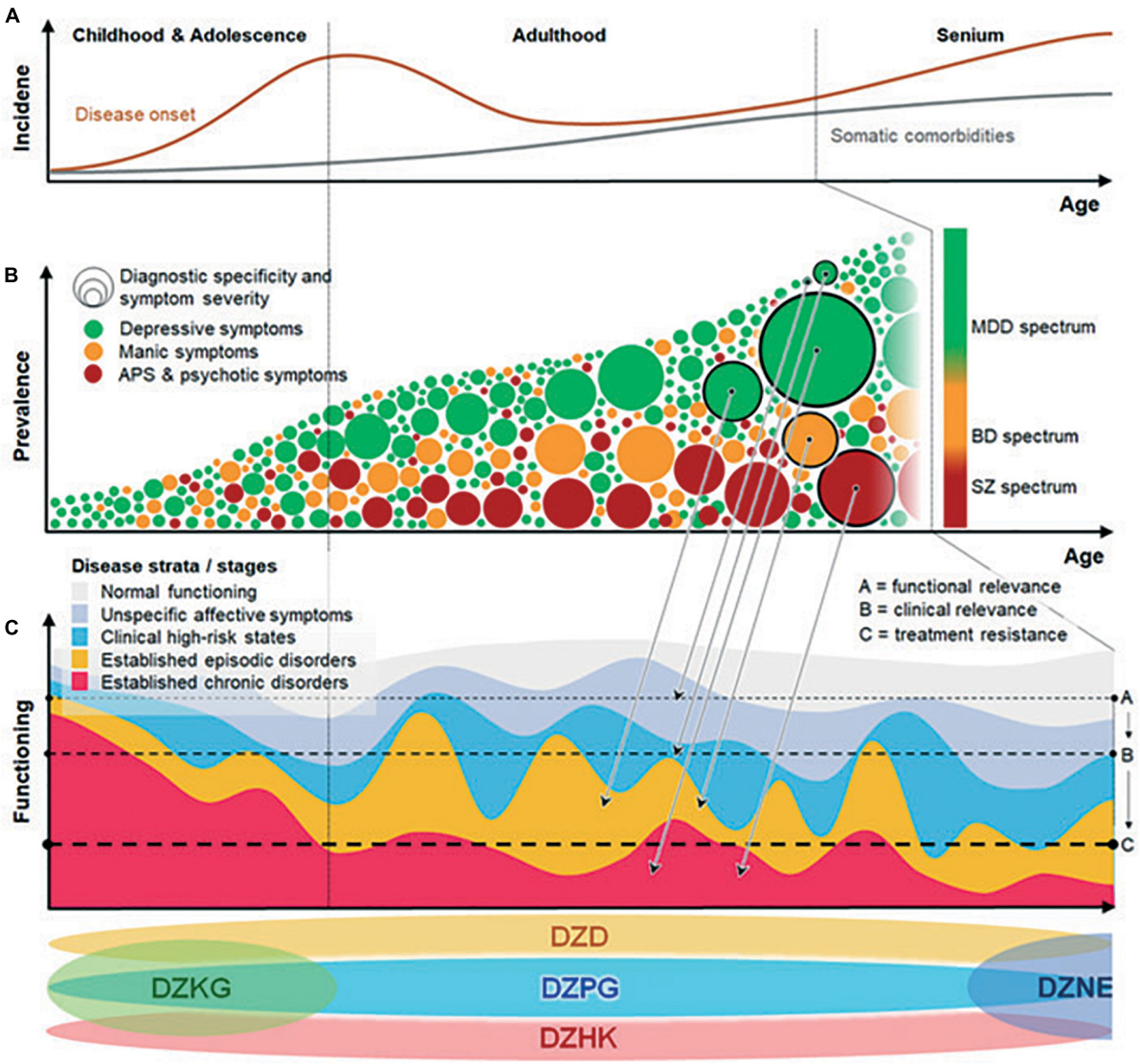

FIGURE 2 | Concept figure illustrating the dynamics of mental disorders from a life-span perspective: **(A)** Incidence increases between adolescence and adulthood and toward old age. **(B)** Disease phenotypes evolve from non-specific to specific/severe manifestations. Arrows from panels **(B)** to **(C)** indicate how specificity/severity of phenotypes relates to disease strata. Heterogeneity increases as progressive and non-progressive trajectories, ranging from highly disabling phenotypes to minor impairments, mix at the population level. **(C)** Increasing functional impairment with disease progression from unspecific, at-risk to established episodic or chronic disease strata. At the bottom of the figure the positioning of different German Centres of Health covering mental healthcare-relevant topics across the lifespan are depicted. BPD, bipolar disorder; CHR, clinical high risk; DZD, German Center for Diabetes Research; DZHK, German Center for Cardiovascular Research; DZKJ, German Center for Child and Adolescent Health; DZPG, German Center for Mental Health; MDD, major depressive disorder; and SZ, schizophrenia.

Somatic comorbidities are hallmarks of SZ, BPD, and MDD that strongly contribute to the excess mortality of these system-level disorders. These comorbidities include metabolic illnesses, such as type II diabetes (T2D) and cardiovascular disorders (CVDs), and are main drivers of reduced life expectancy (8). They share pathophysiological (including immunological) pathways with mental disorders: For example, patients with T2D have an increased risk for MDD, and depressive syndromes worsen outcome in patients with myocardial infarction or stroke. PriMe aims at understanding, modeling, and treating the common roots of mental and somatic illnesses with a particular focus on immunological mechanisms (**Figure 3**). Often the aspects of somatic comorbidities in SZ, BPD, and MDD, i.e., their poor coverage, especially in primary care settings, are neglected. Particularly patients with depression and comorbid somatic disorders are cared for by primary care physicians (P). Similarly, pediatricians/family physicians are the first contact point for youths with psychosomatic syndromes, that may point to an increased risk for mental illness. Therefore, PriMe has teamed up with local networks of PCPs, pediatricians, and youth mental health services. PriMe also seeks close collaboration with the German Center for Child

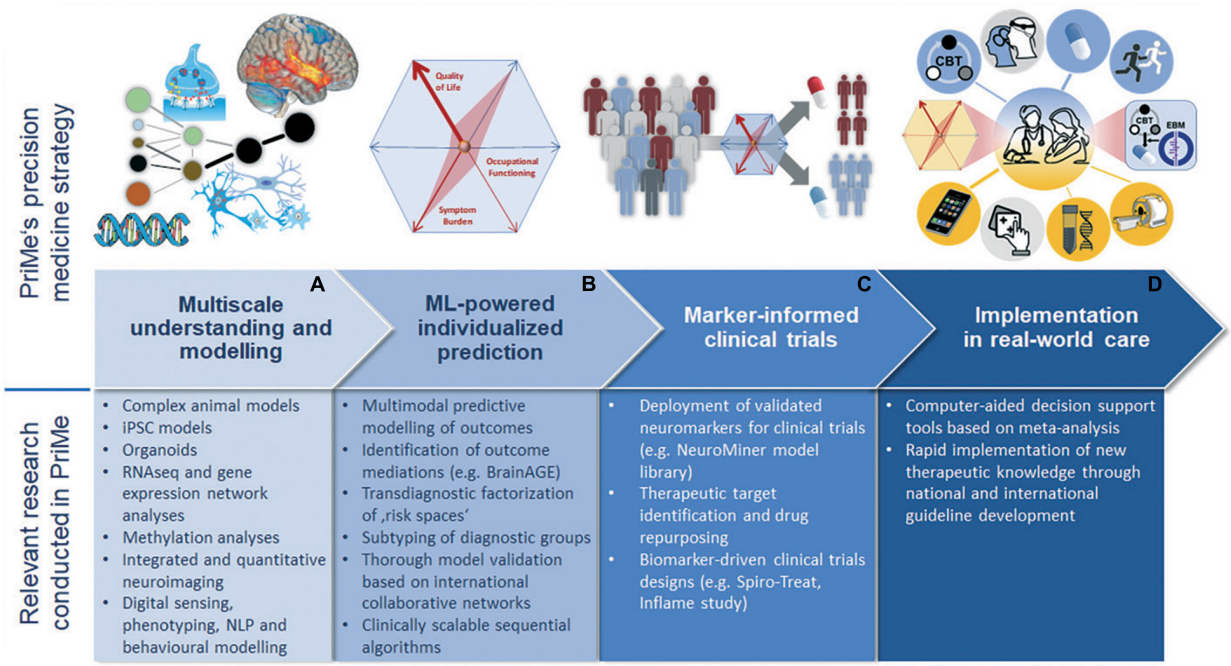

FIGURE 3 | Concept figure representing the translational chain from understanding over development of predictive tools to their translation into clinical practice through stratified clinical trials **(A–D)**. The upper part depicts the envisaged bench-to-bedside sequence, while the lower part lists relevant research activities at each translational step that are being pursued by PriMe. iPSC, induced pluripotent stem cells; ML, machine learning; MRI, magnetic resonance imaging; NLP, neurolinguistic programming; NTBS, non-invasive transcranial brain stimulation; and PriMe, Precision in Mental Health.

and Adolescent Health (DZKJ). At the other end of the life span, mental illness and somatic comorbidities represent risk factors for neurodegenerative diseases, which is why PriMe members collaborate closely with the local German Center for Neurodegenerative Diseases (DZNE) site. These networks will support the final step of the translational cascade, i.e., the implementation of easy-to-use clinical decision support tools in real-world care settings (**Figure 3**).

The seminal paper of the Lancet Commission (9) identified unhealthy diet and sedentary lifestyle as major risk factors for the physical illness burden of patients with SZ, BPD, and MDD. The Commission gives recommendations on how to influence this modifiable risk factor, e.g., including regular exercise in treatment plans. For the last 15 years, PriMe researchers have been working along the translational cascade (**Figure 3**) to better understand the neural effects of physical exercise (10) and to derive novel therapeutic interventions to improve patients' capacity for neural plasticity, reintegration of body and mind functions, and functional recovery (11, 12), (WO/2006/120030).

Suicide risk and long-term psychopharmacological treatment also impact mortality rates. Population-based studies demonstrated that mortality can be reduced by more than 50% by effective antipsychotic treatment, especially when administered as a long-acting injection. PriMe researchers have acquired substantial expertise (**Figure 3**) in meta-analyses (13) of side-effect profiles of psychopharmacological treatments from the literature, making this knowledge available through computer-aided decision support tools (see the section "Prediction: Translating Understanding Into Precision Medicine Tools"). Furthermore, they have been involved in large-scale studies comparing the effectiveness and side-effect profiles of oral antipsychotics vs. long-acting injectables (13).

Lastly, the SARS-CoV-2 pandemic is challenging societies and health care systems, as well as the mental well-being of large parts of the population. In this context, a challenge for psychiatry is defining its role within the medical system, e.g., how psychiatric services can treat the mentally ill while supporting somatic medicine. To adapt patient services, the five PriMe institutions quickly established the following research structures: (1) epidemiological research ("MentalHealthCOVID-19" living systematic review on the consequences of the COVID-19 pandemic on mental health); (2) clinical research (online intervention programs for people with and without mental illness); (3) care structure research (Germany-wide survey on psychiatric care structures by the German Association for Psychiatry, Psychotherapy and Psychosomatics [DGPPN]); (4) nationwide surveys at UniA focusing on health care workers; and (5) biological research in close cooperation with the virology departments, e.g., LMU's All Corona Care Study (ACC) on mental stress and resilience of health care workers (N = 8,000) and the involvement of LMU in the "EviPanUnimed" study within the BMBF-supported National research network of University Medicine on COVID-19 (NUM). TUM's "MentalHealthCOVID-19" project is a living systematic review of epidemiological studies on the mental health consequences

of the COVID-19 pandemic and related containment measures. The SARS-CoV-2–related research activities of PriMe members aim at collecting and analyzing multimodal data on the indirect effects of the pandemic in patients with SZ, BPD, and MDD and on the direct inflammatory effects that potentially interact with neurobiological risk factors for SZ, BPD, and MDD on a mid- to long-term basis.

NOVEL SCIENTIFIC CONCEPT AND PRELIMINARY WORK OF THE PriMe CONSORTIUM

PriMe aims to add a precision medicine framework to the DZPG that will propel deeper understanding, more accurate prediction, and personalized prevention of disease chronicity across mental illnesses. This framework will be structured into five methodological platforms that span the entire translational chain (**Figure 3**) and will be used by PriMe to innovate the management of SZ, BPD, and MDD from rural to urban areas and from patients in early disease stages to patients with long-term disease courses. PriMe's goal is to establish precision medicine in mental health as the key clinical paradigm, allowing the development and implementation of personalized, preventive interventions for patients with SZ, BPD, and MDD. In accordance with the translational chain (**Figure 3**), the expertise stems from the ability to integrate understanding of bio-behavioral processes based on innovative models and translate this knowledge into clinical practice *via* predictive tools, novel treatments, and implementation strategies that follow the principles of open science. This expertise will enable groundbreaking innovations and clinical translation based on deeply phenotyped, representative cohorts of patients with SZ, BPD, and MDD, in addition to healthy individuals.

Understanding and Identifying Genetic and Environmental Risk Factors for Unfavorable Disease Courses

Both genetic and environmental risk factors moderate the development of SZ, BPD, and MDD across diagnostic boundaries. PriMe partners have delivered important insights into genetic disease mechanisms *via* genome-wide association studies (GWASs) and large-scale sequencing approaches, taking leading roles in genomic consortia (ConLiGen, Restless Legs syndrome and Dystonia, the Psychiatric Genomics Consortium, and CLOZIN) and methods development. The first GWAS on lithium response, the identification of *MEIS1* as a major risk gene in restless leg syndrome, contributions to the pharmacogenetics of antidepressant response, and the genetic architecture of MDD (14) are only a few high-impact examples published by PriMe researchers. To improve mechanistic insights, these approaches have been extended to omics layers, from transcriptomics and epigenomics to metabolomics, with a focus on single-cell resolution. At the environmental level, early adverse life experiences constitute major risk factors for unfavorable courses of SZ, BPD, and MDD. PriMe members have been striving to understand how these experiences act upon risk genes *via* dysregulation of molecular, cellular, brain-based, systemic, and social network functions (gene × environment interactions) that lead to the biological embedding of psychological trauma and ultimately poor disease outcomes (**Figure 4**). PriMe partners described the first molecular mechanism of gene × childhood trauma interactions linked to FK506 binding protein 5 (FKBP5) (15). FKBP5 acts as an endogenous regulator of the stress-neuroendocrine system and plays an important role in neurons and immune cells and thus constitutes a risk factor in stress-related disorders. FKBP5 also provides a starting point for uncovering signatures of childhood adversity on molecular (mainly epigenetic), neuroanatomical, endocrine, psychophysiological, functional, and psychosocial levels. These findings stimulated pharmacological innovations and new research on trauma-focused interventions.

Trauma-Related Gene × Environment Interactions and Neuroimmune Mechanisms Moderate Neurodevelopment From the Womb to Early Adulthood

A better longitudinal understanding of exposure and bio-behavioral risk patterns in any given patient will personalize prevention and treatment strategies more precisely than current cross-sectional high-risk detection approaches. To this end, PriMe researchers have reported how (1) pre- and perinatal risk factors influence brain development so that their brain structural, functional, and neurocognitive impacts can be traced into adulthood (e.g., Developing Human Connectome Project, Bavarian Longitudinal Study of Prematurity); (2) epigenetic changes after exposure to prenatal adversity may contribute to the risk for psychiatric disorders; and (3) polygenic risk markers, in combination with measures of childhood trauma, predict depression and psychosis onset in adolescence and early adulthood (16).

Environmental risk factors may also act on molecular or brain pathology *via* known psychosocial, psychological, and neurocognitive mechanisms. PriMe has accumulated evidence that personality traits (low extraversion and high neuroticism and anxiety), impaired neurocognitive functions (low cognitive control and processing speed), dysfunctional coping styles (repetitive negative thinking, dysfunctional emotion regulation), interpersonal dysregulation (insecure or disorganized attachment, impaired coping with social exclusion), and psychosocial risk factors (low social support and socioeconomic status, parental psychopathology, and migration status) entail unfavorable disease outcomes (17).

An important mode of action of these factors on disease pathology and the course of SZ, BPD, and MDD is the activation of neuroimmune mechanisms within critical maturational windows. Prenatal immune activation, e.g., by maternal infection during pregnancy, acts synergistically with exposure to postnatal trauma to induce long-lasting neurochemical and behavioral disturbances. Microglia are innate immune cells that colonize the developing brain and sense pathological changes in the

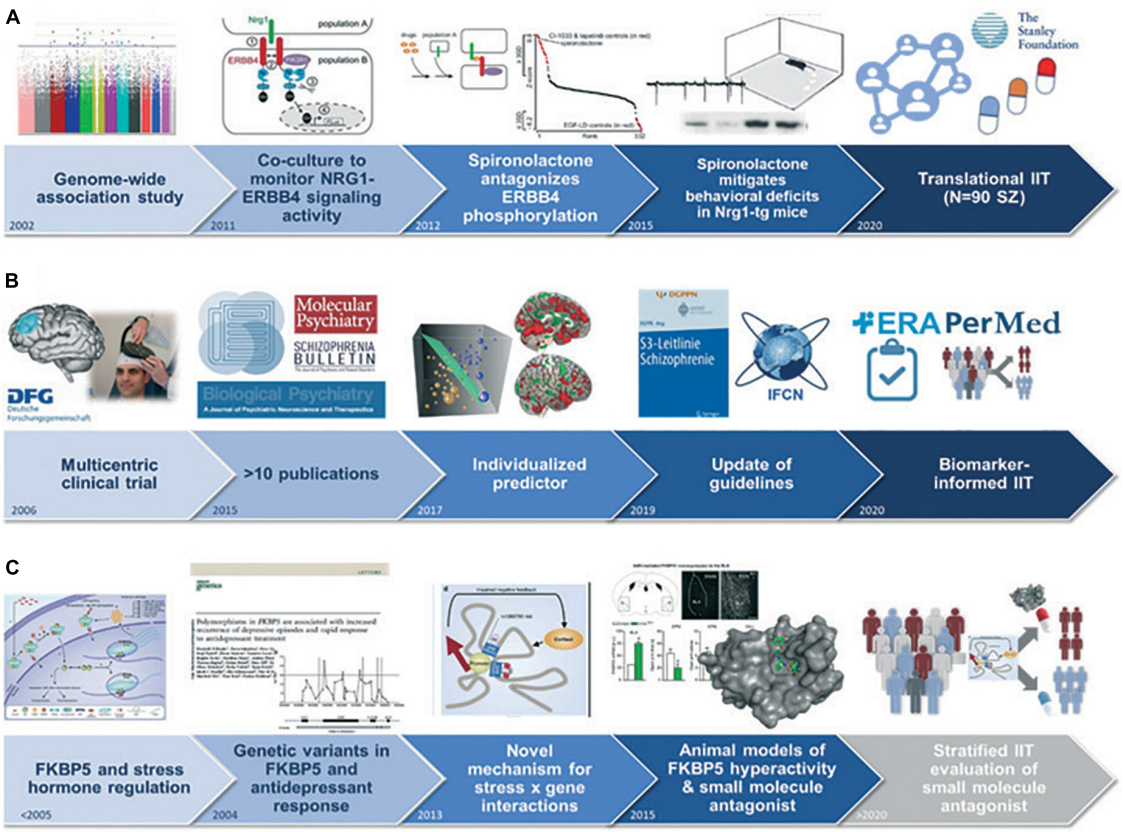

FIGURE 4 | Use cases exemplifying the potential of biomarkers and risk prediction models for clinical translation: **(A)** Development and clinical evaluation of spironolactone as treatment for cognitive deficits in patients with schizophrenia (42). **(B)** Development and validation of an individualized structural magnetic resonance imaging-based rTMS response predictor for the targeted treatment of negative symptoms in schizophrenia (43). **(C)** Identification of a molecular mechanism of difficult-to-treat depression leading to the development of a small-molecule antagonist of FKBP5-induced disinhibition in rodents, with planned clinical translation (44, 45). IIT, investigator-initiated trial.

central nervous system (CNS) (18). They are crucial for neural plasticity and the maintenance of brain homeostasis but can be primed for innate immune memory. Recently, PriMe members provided the first single-cell analysis of human microglia in health and MDD (German Research Foundation CRC/TRR167), revealing disease-associated states that may be exploited for therapeutic purposes (19). PriMe investigators have also contributed important new leads in the description of autoimmune mechanisms that underlie forms of psychosis that are responsive to immunomodulatory therapies.

Prediction: Translating Understanding Into Precision Medicine Tools

The ability to predict disease courses, treatment responses, and relapse patterns of any given patient is the pacemaker of personalized medicine. Individualized prediction depends on quantitative models that integrate mechanistic knowledge with clinical, psychological, psychosocial, environmental, and biological disease markers. These multi-modal analytical approaches rest on representative longitudinal patient cohorts that cover the cross-sectional and outcome-related heterogeneity of the target population and facilitate the prediction of short-term treatment responses to long-term disease outcomes. PriMe members have successfully established, coordinated, and analyzed such cohorts over the last 20 years, including the EU-funded PRONIA study (N = 1,976), which is currently powering the development of precision medicine tools for patients with early stage affective and psychotic disorders (20), and the PsyCourse study (N = 1,303), which aims to decompose the heterogeneity of psychotic and affective syndromes into distinct trajectories and patient subtypes (16). Furthermore, antidepressant treatment response was longitudinally characterized within the MARS study in 1,400 patients to develop depression-specific outcome predictors and disease course models (21). The BeCOME study (N > 350, recruitment ongoing) expands this concept to a transdiagnostic approach, which aims at identifying disease domains through multilevel deep phenotyping, thus contributing to a new and more precise taxonomy for affective syndromes.

High-quality longitudinal samples of patients covering the three target conditions are essential but not sufficient for developing tools that enable more precise mental health care strategies, and cutting-edge methods in predictive data science

are equally important. PriMe members are pioneers in psychiatric machine learning (ML) and have showed that clustering patients with established psychosis reveals disease subtypes with distinct disease courses and genetic underpinnings (17). They developed novel methods to efficiently combine diverse phenotypic and biological model predictions in individual patients and observed that such algorithms enable the clinically scalable prediction of poor outcomes in at-risk states for psychosis or recent-onset depression (20). Multi-site clinical trial data showed that it is equally possible to establish models for predicting response to non-invasive transcranial brain stimulation (NTBS) or antipsychotic treatments. These achievements were facilitated by the ML platform NeuroMiner,[1] which has been developed by PriMe partners since 2009 and provides clinician neuroscientists with openly accessible algorithms for robust model construction, validation, and knowledge sharing. PriMe has also spearheaded deep learning in large-scale population studies, e.g., ML-derived decision support based on neuroimaging (22). Pushing these modeling approaches closer to their clinical implementation, PriMe members have established an ML Model Library[2] that provides the research community with access to published models for external validation and experimental clinical use.

Furthermore, the in-depth analysis of multimodal, large-scale samples planned by PriMe (see the section "Innovative Therapies to Preempt Disease Progression and Chronicity") requires novel computational approaches beyond classical ML. These approaches involve deep learning that can integrate multiple layers of biological and phenotypic measurements, including high-frequency sensor-based assessments, to identify clinically useful predictive signatures. These technologies enable analysis of high-throughput data as generated by ecological momentary assessments (EMA), digital sensing, and natural language processing and thus hold great promise for novel diagnostic and therapeutic applications. PriMe members developed mobile sensing technology to continuously collect and analyze these novel information domains, including measures of mobility, smartphone interaction behavior, speech and verbal synchrony, facial expressions, eye tracking, and keyboard usage (23).

Furthermore, PriMe members aim to digitize and standardize the routine collection, integration, safe processing, and redistribution of clinical information to establish personalized, measurement-based care in psychiatry. All these efforts are supported by cutting-edge tools for federated and privacy-preserving ML and guided by ethical standards for medical innovation and health technologies. The Munich School for Data Science and the German Human Genome-Phenome Archive will contribute significant expertise in embedding ethical artificial intelligence (AI) approaches in the new technologies.

A critical link between animal models and individualized prediction approaches is established by means of psychiatric neuroimaging. PriMe members have initiated standardized imaging protocols across all their scanner facilities and participate as neuroimaging partners in a German-wide initiative to standardize neuroscience data for open science and data sharing (NFDI-Neuro). This includes expertise in the development of novel multimodal imaging techniques and their evaluation in neuropsychiatric patients, including the characterization of functional and structural brain network profiles in patients with SZ, BPD, and MDD. In a recent study, the effect of brain stimulation on these brain networks was optimized for application in individual patients, and biophysical modeling of excitatory and inhibitory neurotransmitter signaling revealed region-specific stimulation effects. Moreover, PriMe partners have developed methods for cutting-edge analysis of broadly available and cost-effective electroencephalogram (EEG) recordings for the standardized assessment of brain oscillations and synchrony in psychiatric disorders. PriMe members at TUM have also pioneered quantitative metabolic and functional imaging of the human brain that provides novel insights into the neuroenergetics and directional signaling of large-scale brain networks (24). This research has been further extended to incorporate the dynamics of neurotransmitter signaling in relation to classical brain network imaging. This technology has been used to describe trajectories of aberrant dopamine transmission and their impact on brain network activity in the course of psychotic disorders and characterized the dynamics of gamma aminobutyric acid/glutamate signaling in relation to brain connectivity in the healthy brain (25).

Innovative Therapies to Preempt Disease Progression and Chronicity

PriMe identification strategies aim at personalizing available interventions, developing novel treatments, and clinically combining both to prevent disease progression, recurrence, chronicity, and mortality. Thus, disease-relevant model systems and readouts with translational relevance need to be established, a process that is especially challenging for psychiatric disorders (**Figure 4**). Induced pluripotent stem cells (iPSCs) from individuals with SZ, BPD, and MDD have opened avenues to study human neurodevelopment, polygenic risk, and neuro-immune interactions. PriMe members have established and shared more than 100 iPSC lines from patients treated at LMU and MPIP. Research conducted with iPSC-derived neurons and glia, including microglia, and cerebral organoids as neurodevelopmental models (26) showed their translational potential for investigating molecular and cellular mechanisms of treatment response. PriMe also hosts the German Mouse Clinic (GMC), which includes an open-access phenotyping platform for the comprehensive characterization of mouse models of human diseases and for preclinical drug testing. PriMe has thus established pathways for forward and reverse translation to facilitate the development of innovative and targeted treatments.

In neuropsychopharmacology, PriMe has envisaged (1) hit-to-lead approaches, in collaboration with partners such as the Lead Discovery Center in Dortmund, and several hits emerging from human genetic and basic research findings are now being studied, including new targets for MDD (FKBP5, SLC6A15, Beclin1, and Erythropoietin variants); and (2) drug repurposing, where preclinical evidence from cellular and animal models puts the focus on the neuregulin-1 (NRG1)-ErbB4 pathway, which, as

[1] http://proniapredictors.eu/neurominer/index.html

[2] http://proniapredictors.eu/

a regulator of the excitatory/inhibitory disbalance in SZ, likely contributes to residual cognitive symptoms: In a large drug screen conducted by LMU, spironolactone emerged as a pathway modulator (27), leading to a pioneering and recently completed multicenter Investigator-Initiated Trial (**Figure 4**).

PriMe additionally focuses on brain circuits and networks as targets for NTBS. LMU researchers established and coordinate the German Center for Brain Stimulation (GCBS) Consortium within the BMBF-funded German Research Network for Mental Disorders, an internationally visible hub for translational research on NTBS (with >30 publications during the funding period) aimed at developing innovative NTBS-based treatment strategies for psychiatric disorders. Moreover, together with the GCBS, PriMe partners are conducting various translational studies (28) and randomized controlled trials (RCTs) for the treatment of SZ and MDD that are funded by the DFG, BMBF, and EU (ERA-NET NEURON and ERA PerMed). For the region of South Bavaria, neurostimulation centers at LMU and UniA collaborate with NTBS groups at the TUM and provide novel NTBS methods and protocols to patients with SZ and MDD with a fast translational track from discovery to clinical application.

PriMe further explores other novel treatments, such as exercise therapy (ET), and is performing the largest ongoing RCT on ET in SZ (BMBF-funded ESPRIT Consortium) (29). In the field of psychotherapy, PriMe partners, funded by the DFG, BMBF, EU, and Innovationsfond, develop novel mechanism-based therapeutic strategies, including (1) trauma-focused interventions for disorders related to early adversity, bodily distress, and cognitive bias; (2) transdiagnostic interventions for depression and anxiety disorders; (3) interpersonal therapies for persistent depressive disorder; (4) interventions tailored to vulnerable and underserved groups (e.g., refugees); (5) emotion regulation training for young patients with MDD; and (6) family based programs aimed at preventing adolescent depression in at-risk cohorts. PriMe has also conducted proof-of-concept psychotherapy studies targeting empirically established biobehavioral mechanisms and including pre-post neuroimaging for identifying neurobiological markers of change (KFO 256). In addition, PriMe members have tested novel treatments for the interactions of bodily symptoms (including pain) and depression in oncology and neurology (German Cancer Aid, BMBF IFB Dizziness). These studies integrate concepts of acute and long-term treatment, aim at potential stratifiers for future interventions and leverage the development of psychobiological markers. These strategies are also adaptive to acute societal needs: As thousands of refugees a day arrived in Munich in 2015, PriMe coordinated medical and psychological emergency care and, together with other centers, tested a stepped care approach in psychotherapeutic interventions for these vulnerable persons (MEHIRA) (30).

Implementation: From Synthesis of Current Knowledge to Guidelines and Knowledge Transfer

PriMe has internationally recognized expertise in the field of evidence-based mental health care, spearheaded by the schizophrenia guideline groups [Association of the Scientific Medical Societies in Germany (AWMF) evidence and consensus-based S3 guidelines, World Federation of Societies of Biological Psychiatry guidelines, and International College of Neuropsychopharmacology guidelines for SZ] and the Section on Evidence-Based Medicine (EBM) in Psychiatry and Psychotherapy. The section now leads the Cochrane Schizophrenia Group and excels in all types of systematic reviews (**Figure 4**). PriMe will set new standards in methodology and translate results into novel therapeutic decision support tools. Examples are "living" (MentalHealthCOVID-19) and crowdsourcing-based systematic reviews on the mental health consequences of the COVID-19 pandemic; the EVENT study, which translates meta-analytic data (31) into digital decision aids for patients and professionals; and the cooperative SISYPHOS project, which is developing the first living guideline in German mental health care for digital and individualized treatment decisions.

PriMe researchers greatly value the principles of reproducibility and open science. To this end, the biobanks of PriMe's institutions pertain to the highest quality standards for ascertaining clinical phenotyping and biological data on genetics, proteomics, neuroimaging, and neurophysiology. PriMe researchers follow the TUM Open Access Policy or are members of LMU's Open Science Center (OSC) and Open Science In Medicine (OSIM) initiative. These programs are led by LMU Psychology and supported by a DFG priority research program focusing on the reproducibility of scientific findings (32). Since 2019, they have been sharing raw data and scripts from published articles (33, 34) and providing data for large multi-site analyses (32). To encourage reproducible data science, PriMe members have also established a public-access library hosting all published NeuroMiner models and Neuromodulation and Multimodal NeuroImaging software (NAMNIs) (YZEpLGDMJM0),[3] a standardized software that facilitates replicability of results. Predictive, personalized, and technology-based medicine can come with ethical and societal challenges, e.g., algorithmic bias, impact on patient autonomy, social stigmatization, and loss of quality of life (35), and PriMe will address these issues with an interdisciplinary and flexible ethics approach which aims to recognize and address ethical and social issues as they emerge during innovation and translation.

INFRASTRUCTURE OF PriMe INCLUDING USER INVOLVEMENT AND YOUNG SCIENTISTS

PriMe's translational mindset evolved through an array of national and international research consortia, centers of excellence, several graduate schools, a clear commitment to all aspects of evidence-based psychiatry, and a broad array of implementation approaches. PriMe members broadened the scope of these approaches from the classical "bench-to-bedside" paradigm to concepts of forward and reverse translation and

[3]https://zenodo.org/record/4547552#

"bench-to-individualized guideline" strategies. These structures not only permit a seamless translation of novel preclinical approaches to clinical care but also enable a reverse, "guideline-to-bench" translation. PriMe fully supports translational research in the DZPG with infrastructures that cover the entire translational chain. These infrastructures include outstanding platforms for the identification of risk factors (multi-omics technologies), the production and analysis of predictive human cellular and humanized animal models, drug discovery, highly specialized imaging tools, centralized biobanks, comprehensive patient cohorts, and an extensive network of clinical trial centers led by the Munich Study Center (MSZ). PriMe's specific contributions to DZPG research hubs include the central biorepository and datasets of the German National Cohort study (NAKO Gesundheitsstudie), the open-access German Mouse Clinic (GMC), the outstanding neuroimmunology hub (e.g., SyNergy Excellence cluster), the Leibniz Supercomputing Center (LRZ), strong artificial intelligence (AI)ML analysis platforms, NTBS facilities, comprehensive clinical trial and patient-recruitment infrastructures, and excellence in EBM *via* a Cochrane Review Group. Built in 2001, the GMC was the first platform worldwide (36) for systematic phenotyping and has advanced to a well-established and unique center for state-of-the-art mouse phenotyping. The GMC is an open-access phenotyping platform characterizing mouse models for human diseases in multiple body systems and physiological pathways in a variety of therapeutic areas. Its collaboration with more than 170 groups has resulted in more than 200 highly cited publications on neurodevelopmental and disorder-related phenotypes, advances in modeling abnormal neurodegenerative and aging patterns [with the German Center for Neurodegenerative Diseases (DZNE)], and diabetes models (with the German Center for Diabetes Research [DZD]). Founded in 1962, the LRZ is the IT service provider for PriMe partners and serves as a hub for other research organizations in Bavaria. LRZ is located in the Munich Metropolitan Area and is one of the three national members of the Gauss Center for Supercomputing, the High-Performance Computing Center Stuttgart (HLRS), and the Jülich Supercomputing Center. Helmholtz AI has established a network of method specialists (AI consultants) for short- and mid-term collaborations. The Helmholtz AI computing resources are available for all collaborative projects on identifying biomarkers and patient groups at risk for chronicity. The TUM Institute for AI and Informatics in Medicine (AIIM@TUM) is leading DIFUTURE, one of the four consortia funded by the BMBF, during the development and networking phase of the Medical Informatics Initiative. Its infrastructure and AI expertise will support the advanced analysis of preclinical and clinical data in a secure, federated, and privacy-preserving manner.

NAKO (37) (since 2014, N = 20 500, ages: 19–69), KORA (since 1984, N = 18 000, ages: 25–74), and GINIplus and LISA (since 1995, N = 9,085; see the section "Prediction: Translating Understanding Into Precision Medicine Tools") are longitudinal cohort studies collecting information on mental health (e.g., depression, anxiety, PTSD, cognitive impairment, sleep disorders, subjective health, well-being), lifestyle (e.g., smoking, physical activity, alcohol, and body mass index), comorbidities (myocardial infarction, stroke, T2D, cancer), sociodemographics (socioeconomic status, household size), and bio-samples, multi-omics data, and whole-body MRI. Specifically, the GINIplus and LISA studies provide unique opportunities to investigate how early life events affect long-term mental health development. Both studies recruited multi-site birth cohorts comprising healthy, term-born infants from the general population and have been regularly following these cohorts (38). In close collaboration with PriMe members, age-appropriate mental health assessments have been integrated during the 10-year follow-up, which will enable PriMe and the DZPG to identify risk factors for disease progression, recurrence, and chronicity. The cooperation of PriMe partners in KORA, will allow disease course and outcome data on the available cohorts to be added.

Furthermore, PriMe has access to deeply phenotyped, longitudinal cohorts, enabling the study of risk factors of poor outcomes of CHR (PRONIA) and first-episode (PRONIA, BeCOME) and multi-episode disease stages (PsyCourse, BeCOME) in SZ, BPD, and MDD. PRONIA is a European sample of 1,400 patients with CHR states, first-episode depression, and psychosis that provides clinical, neuropsychological, imaging, proteomic, inflammatory, and genetic data. It is involved in the NIMH-funded HARMONY consortium, which aims at thoroughly validating predictors of disease outcome in CHR states of psychoses. PsyCourse includes 1,303 patients with multi-episode SZ and BPD, 800 of whom were followed up at four different times (17). BeCOME is a prospective, ongoing, transdiagnostic cohort focusing on affective and anxiety disorders. The goal is to characterize underlying multilevel biological trajectories of affective syndromes. BioMD-Y collects genetic and clinical data and comprehensive information on childhood trauma and other adverse life experiences in a longitudinal cohort of patients with adolescent depression (N = 420). PriMe institutions and the 32 teaching hospitals and integrated community hospitals in the Munich Metropolitan Area have implemented a powerful recruitment network to conduct large-scale clinical trials based on the aforementioned interventional approaches. This *trans*-sectorial recruitment approach is enhanced by a recruitment collaboration with an extended network of resident specialists (N = 270) and primary care physicians (N = 400) with 1.04 million patient contacts/year. Thus, PriMe covers all relevant sectors of the local health care system and integrates both urban and rural care environments.

Implementation of research involving service users is urgently needed. Specifically for PriMe, existing participative research approaches have been combined to form the "Munich working group for participatory research within the DZPG," which now involves people from most stakeholder groups (patient and caregiver representatives) in the greater Munich area and has already contributed to the current application. This working group will serve as an advisor for DZPG research projects with regard to participatory research. In addition, it will initiate user-led research projects. Hereby, the working group can build upon existing participatory collaborations, such as the EVENT project, which embeds meta-analytic knowledge on antipsychotic drugs effects in an app to stimulate shared decision-making between

patients and clinicians, or a recent study on the inclusion of caregivers in clinical decision-making (39).

Regarding implementation research, PriMe members have a long-standing track record in this field. Among many others, three projects (SISYPHUS, the MUNICH model, and RETURN) demonstrate the wide spectrum of efforts in this area: (1) The SISYPHOS project will test two strategies for implementing the German national schizophrenia guideline across 16 psychiatric hospitals. (2) The Munich Model is a disease management program that has been successfully implemented by TUM since 2006; it incorporates all evidence-based treatments and strategies related to relapse prevention in SZ and MDD, such as personal compliance profiles, psychoeducation, depot treatment, and others, and its success has been demonstrated (40). (3) The RETURN study focusses on how people with mental illness can best be supported when returning to their workplaces after being treated in a psychiatric hospital (41).

PriMe offers infrastructures for the training of medical students, nurses, psychologists, and medical specialists toward primary care, psychiatry and psychotherapy, and psychosomatic medicine and of clinician scientists. Examples is new master's course in psychotherapy at LMU Psychology in collaboration with LMU Psychiatry; the Medical Education Centers at LMU and TUM; the "Hausarzt 360" program, with its large network of teaching practices; and the new DFG-funded Graduate School "Predictors and outcomes in primary depression care" (POKAL). The PriMe initiative will offer internationally competitive education to early career researchers (ECRs) through structured graduate programs in neuroscience and psychiatric research. These programs, such as the International Max-Planck Research School Translational Psychiatry (IMPRS-TP) and the Else Kröner-Fresenius College "Translational Psychiatry," build on existing infrastructures for career development with an international perspective. Courses, seminars, lectures, Thesis Advisory Committees, and our internationally staffed research groups communicate in English. International Ph.D. students and postdocs serve as role models for ECRs with an international background. Attracting and developing young, high-potential scientists are important aspects of academic competition. Systematic mentoring is key in this respect and addressed by university programs.

DISCUSSION

A disease stage-sensitive prevention approach is needed to reduce the disabling manifestations of SZ, BPD, and MDD. As previously shown, prevention is most effective during active biobehavioral maturation phases, i.e., typically at the junction between adolescence and early adulthood (**Figure 2**). Detecting vulnerable individuals in these stages is challenging given the low temporal stability and low diagnostic specificity of symptom patterns (**Figure 2**). Hence, powerful yet broadly accessible diagnostic, prognostic, and therapeutic tools are needed to precisely identify and preventively treat persons at risk for poor disease courses. At this stage, preventive treatments should not only aim at reducing symptom burden but also strengthen the person's resilience against adverse outcomes and follow well-established concepts of primary prevention for children and adolescents. However, such preventive approaches will not completely avert clinical and functional deterioration in vulnerable populations. Therefore, new stage-sensitive therapies are needed for patients with established disorders to reduce symptoms, disability and comorbidities and activate recovery with risk-informed plasticity-enhancing interventions. IT-powered mental health networks distributed across the patient's local network of mental healthcare providers are indispensable for tailoring treatments to the patient's needs and covering the critical windows in a person's life in an ongoing and participatory fashion. Finally, similar concepts apply to the increased risk for neurodegenerative disorders, which are frequently preceded by affective syndromes during the transition to old age (**Figure 2**). PriMe will engage with the DZKJ and the DZNE to address these critical time windows synergistically.

In Germany, major roadblocks currently exist on the path to mental health care approach because the national health care system is primarily focused on the management of manifest and chronic conditions. This approach largely dismisses a trajectorial concept of mental disorders and wastes opportunities for earlier, more preventive and less burdensome interventions. A downstream effect is that mental health care services lack a unified digital backbone that would integrate and organize the multi-faceted health-related data produced by the streams of diagnostic and therapeutic processes. Building clinical networks on such an infrastructure (**Figure 5**) not only allows patients to be more effectively treated by the connected stakeholders of a local healthcare system but also expedites the development and transfer of tools and treatments to care according to a bidirectional process. By making data available that represent disease variability across all stages of SZ, BPD, and MDD, clinical networks would facilitate research into the mechanistic understanding, predictive modeling, and development of personalized therapeutics (**Figure 4**). At the end of this translational chain, clinical networks would quickly harness the results of well-powered clinical trials that test the effectiveness of personalized therapeutic strategies with measurable markers. Based on these concepts, PriMe's objectives in the DZPG areto develop, test and implement an early, preventive, stepped-care approach to the treatment of SZ-, BPD-, and MDD-spectrum disorders and their most prevalent comorbidities in the DZPG to continuously support all DZPG sites to do likewise for other mental disorders (e.g., addiction, anxiety disorders) by enabling multisite projects to develop strategies for any disease phenotype with the standardized toolkits of PriMe's 5 interconnected platforms (**Figure 5**) and by validating components of these strategies retrospectively in PriMe's existing large-scale cohorts and prospectively in PriMe's deeply characterizable and representative catchment population (**Figure 1**). Further information on these five platforms is provided below:

Platform I: Multimodal Data and Model Humanized Systems

This platform will focus on biobanking, neuroimmunology, stem cells, and multi-omics (**Figure 5**) and will be powered by the

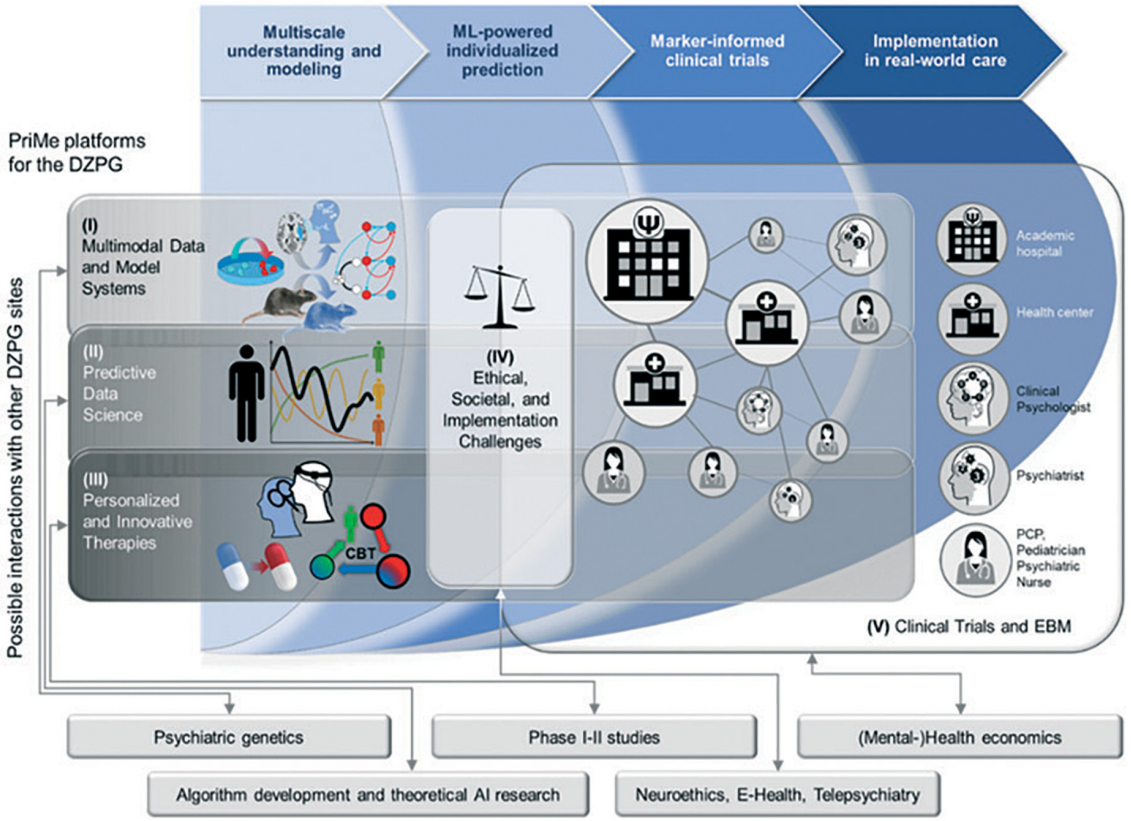

FIGURE 5 | Mapping between PRiME's translational chain and envisaged research platform in the new German Centre for Mental Health (DZPG). These platforms will be generic and thus accessible by all sites of the DZPG to facilitate the rapid translation of knowledge into therapies for all mental disorders. Boxes represent topics where PriMe could benefit from the expertise of other potential DZPG sites. AI, artificial intelligence; DZPG, German Center for Mental Health; EBM, evidence-based medicine; and ML, machine learning.

centrally managed, high-capacity biobanks of PriMe partners, providing harmonized recruitment and phenotyping standard operating procedures for all patient admissions to the mental health services of PriMe. This PriMe Biobank network will enable other sites to safely process, distribute and analyze biological specimens and patient-derived induced pluripotent stem cells (iPSCs) on demand across the DZPG. The Neuroimmunology hub and Munich Sequencing Alliance (see the section "Innovative Therapies to Preempt Disease Progression and Chronicity") will use this harmonized biomaterial repository to produce multi-omics data for complex analytical endeavors and clinical applications across the DZPG. Harmonized phenotyping and (single-cell) multi-omics approaches that can be further expanded nationally and internationally will be critical for obtaining the sample sizes necessary for detecting relationships between risk factors, symptoms, and diseases.

To facilitate forward and backward translation of pathophysiological knowledge between iPSCs, animals, and humans, cutting-edge multimodal imaging is planned (e.g., simultaneous dopamine-PET/functional MRI/EEG in humans complemented by sub-second multi-site dopamine imaging in behaving mice). MRI, PET, and EEG protocols and data acquisition at the research-dedicated PriMe imaging facilities will be harmonized and supported by a computational backbone to store, preprocess and distribute imaging data. This imaging repository will be integrated into the biobank to make brain descriptors of mental disorders readily available for downstream analyses.

Behavioral indicators of disease progression risk and chronicity will be assessed with innovative digital approaches (smartphone-based EMA, mobile sensing, natural language processing). These digital markers of normal and pathological behavior will be safely stored and processed in PriMe's extended biobank repository, thus enabling further modeling and predictive and therapeutic research in the DZPG. By using available blood and imaging-based markers and environmental and behavioral variables, PriMe will enable the DZPG to produce and harmonize cellular (iPSCs, organoids) and animal models reflecting the pathophysiology of unfavorable courses in mental disorders.

Platform II: Predictive Data Science

PriMe proposes an ML-based data analytics platform as a core transdiagnostic facility of the DZPG. The platform will bundle clinical domain knowledge and applied engineering to derive predictive models from representative datasets, enabling the early

identification of patients at risk of disease progression and the modeling of common comorbidities by using multi-view and transfer learning based on the KORA, NAKO, and GINIplus and LISA samples. The platform will be jointly run by (1) the new TUM Institute for AI and Informatics in Medicine, focusing on advanced neuroimaging and ML methods in collaboration with the new Neural Engineering for Mental Health network at TUM; (2) the HMGU Institute of Computational Biology, contributing multivariate genomic data analysis and deep-learning–based integration with clinical covariates; and (3) the LMU Section for Neurodiagnostic Applications in Psychiatry (SNAP), focusing on data fusion, disease subtype identification, and clinically scalable algorithms for outcome prediction. The outstanding expertise of this platform will support the DZPG in extracting, understanding, and utilizing predictive information from genetic to psychosocial data layers. Collaborations with other DZPG sites with expertise in computational learning theory and algorithm development could further strengthen the platform's capacity to model complex psychiatric disorders with ML.

The platform researchers will collaborate with DIFUTURE to build a digital ontology of quantitative psychiatric phenotypes, including clinically relevant measures of disease progression and chronicity in SZ, BPD, and MDD. This phenotypic ontology will lay out a "coordinate system" for the development of a DZPG Model Library that incorporates and disseminates predictive models along the translational chain. Thus, the Library will provide Platform V with well-validated models to facilitate marker-informed clinical trials. Furthermore, predictive signatures hosted in the Library will enable Platforms I and III to explore mechanistic underpinnings and novel modes of action by manipulating key elements of these signatures in appropriate cell and animal model systems and to test them in phase 1 and 2 clinical trials. Finally, adhering fully to open science principles, the Library will enable the DZPG to exchange models with external researchers and thus accelerate the development of reliable precision mental health tools.

The validation opportunities provided by the PriMe Model Library will be supported by our existing longitudinal datasets, which will be made accessible to DZPG-initiated neuromarker research. These datasets will allow to establish the prevalence, relevance, and validity of patient-derived predictive models in large-scale longitudinal cohorts of healthy people (see, e.g., KORA and NAKO studies in the section "Innovative Therapies to Preempt Disease Progression and Chronicity"). Furthermore, our cohorts of patients at different stages of SZ, BPD, and MDD recruited in previous projects (see "Innovative Therapies to Preempt Disease Progression and Chronicity") or prospectively generated in the DZPG framework (cf. Platform V) will provide researchers with opportunities for external validation and comparative neuroscience across the diagnostic entities covered by the DZPG.

Platform III: Personalized and Innovative Therapies

We propose to establish a platform in the DZPG for the development of immune- and neuromarker-informed personalized interventions combining existing, repurposed, or novel pharmacological compounds; psychotherapeutic interventions; NTBS; and further treatment modules (e.g., ET, immunomodulatory and neuroprotective therapies). For example, we will use our large-scale and rich databases of exercise interventions in patients with SZ and healthy marathon runners (total N of both >350) and our experience in conducting such trials to (a) enable a better understanding of how exercise induces brain plasticity (reverse translation, Platform I) and (b) facilitate new exercise trials in the DZPG (Platform V). Effective personalization requires transdisciplinary research to (1) better understand multi-level therapeutic mechanisms (Platform I), (2) measure the differential and additive efficacy of existing/repurposed interventions and novel modes of action (Platform I), (3) establish models that inform treatment choices based on the given patient's estimated response likelihoods and poor outcome risks (Platform II), (4) test novel marker-informed interventions in multi-site clinical trials, and (5) embed this knowledge into routine clinical evidence and care (Platform V). These marker-informed interventions are particularly promising for halting disease progression or even achieving complete recovery in early disease stages.

Psychotherapy plays a major role in primary mental health care and is recommended in current guidelines for SZ, BPD, and MDD. However, any given patient's access to specific psychotherapeutic methods varies considerably between urban and rural regions. In addition, psychotherapy often needs to be specifically combined with pharmacological interventions to fulfill the different requirements of acute and long-term treatment. As part of Platform III, PriMe researchers aim to individualize psychotherapy based on modules (e.g., trauma-focused, interpersonal, metacognitive, or behavioral activation-based), frequency, duration, and modalities (in person vs. videophone). To this end, predictive studies are needed to identify which patient benefits from which treatment, thus leading to algorithms that optimally sequence and combine psychological and pharmacological interventions.

The infrastructures of the GCBS and the Munich Center for Brain Stimulation will provide a platform for basic research (e.g., tDCS- or rTMS-functional MRI), translational studies (tDCS + cognitive training), IITs (sham-controlled rTMS/tDCS clinical trials), personalized IITs (MRI-guided rTMS/tDCS), and home-treatment applications (tDCS with digital remote monitoring) that uses all available NTBS methods. This long-standing expertise will serve the planned DZPG as a research, intervention, and implementation hub for all aspects of personalized NTBS, i.e., it will (a) develop predictors in proof-of-concept experiments and validate them in RCTs, (b) define and validate cross-disorder paradigms derived from model system findings (e.g., for the treatment of cognitive symptoms), and (c) provide findings from human to the preclinical platforms (reverse translation).

To further exploit the possibilities of physical exercise therapy to improve outcomes and foster recovery across various psychiatric conditions, we will use our large-scale and rich databases of exercise interventions in patients with SZ and healthy marathon runners (total *N* of both >350) and our

experience in conducting such trials to (a) enable a better understanding of how exercise induces brain plasticity (reverse translation Platform I) and (b) facilitate new exercise trials in the DZPG (Platform V).

Platform IV: Ethical, Societal, and Implementation Challenges

Analysis and evaluation of ethics and user involvement in personalized and health technology-based medicine in psychiatry and psychotherapy are core principles of PriMe. Ethically guided personalized profiling based on collating and analyzing a multitude of data from an individual patient implies major ethical challenges regarding health literacy, quality of life, stigmatization, data protection, and allocation of scarce healthcare resources. These challenges arising from the objectives of PriMe touch the ethical principles of autonomy, solidarity, beneficence, non-maleficence, and justice, which govern therapeutic interactions between healthcare professionals and patients and their relatives. The development and implementation of novel health technologies, particularly when these are based on data-driven approaches, require responsible innovation. PriMe will offer its expertise on embedded ethics of medical innovation and health technologies to the DZPG. The integration of ethical principles in the biobehavioral modeling of psychiatric phenotypes will benefit from other DZPG sites that have established track records in neuroethics and philosophy (**Figure 5**).

Involvement of patients, relatives, and researchers from non-medical disciplines is key for the translation and implementation of research into practice. The PriMe health services research group has pioneering expertise in forming patient advocacy groups. We will offer our expertise in this area to develop standardized procedures that ensure that patients and families are always heard and integrated in the DZPG. A key aspect of such user involvement lies in the development of diagnostic, prognostic, and therapeutic methods that optimally mitigate biases in clinical decision-making. To this end, PriMe will develop standards for implementing personalized profiling tools in in-person and virtual clinical practice. Adaptations of shared decision-making (SDM) for different precision care scenarios will be conceptualized with service users and providers and integrated with other DZPG sites' expertise in e-Health and telepsychiatry (**Figure 5**).

Platform V: Clinical Trials and Evidence-Based Medicine

Another focus of PriMe are IITs, which can be run in our large clinical recruitment network. This approach ensures that the concept of early translation of novel therapies into real-world clinical settings can be readily achieved. Along these lines, PriMe proposes establishing a DZPG Platform for phase II to IV IITs and joining similar efforts for earlier phases of therapeutics development (**Figure 5**).

Evidence-based medicine and research synthesis are additional strengths of the PriMe consortium, which also hosts the Cochrane Schizophrenia Group. PriMe will produce high-end meta-analyses and support other DZPG partners in this regard. Moreover, it will translate results of meta-analyses into smartphone-based support for SDM, as tested in the ongoing EVENT study. One well-established tool to implement new evidence-based treatments are guidelines. Because of the increasing density of scientific information and unfriendly analogous formats, guidelines are frequently outdated and not sufficiently adopted by clinicians. PriMe researchers are leading or participating in guideline development for SZ, BPD, and MDD and are currently implementing innovative online tools to make these accessible to users, including children and adolescents. PriMe plans to use living guidelines, which continuously integrate newly published studies, to broadly disseminate newest therapeutic evidence to practitioners and patients. In October 2020, SISYPHOS (see the section "Prediction: Translating Understanding Into Precision Medicine Tools"), a collaborative project of PriMe members, received funding to implement such a system for the new German S3 SZ guideline. This project will serve as a blueprint for the development of living German S3 guidelines for other diseases in the DZPG (i.e., interleaved collaboration with platform IV and SDM-guided implementation on Platform V) (**Figure 5**).

Finally, there is complementarity and collaboration with other German Centers for Health Research. The long-term outcome of mental disorders is determined by risk factors acting throughout the lifespan. Examples of early life risk factors that contribute to mental and somatic disorders in adulthood are infections during pregnancy; birth and delivery complications; vitamin deficiencies; and childhood trauma. Psychiatric and somatic comorbidities emerging during adulthood represent risk factors for chronic disease courses later in life. Both comorbidity clusters are preventable and share common immunological and metabolic mechanisms. PriMe hosts experts on microglia, the resident immune cells of the CNS that play central roles both in neurodevelopmental disorders and neurodegenerative diseases, providing a unique collaborative link with other DZPG centers and between PriMe and CHANCE, the Munich consortium of the DZKJ and the DZNE. Metabolic and inflammatory mechanisms also link PriMe with the health centers for diabetes research (DZD) and heart diseases and CVDs (DZHK).

Outlook

During the ongoing 6-month Concept Development Phase from September 2021 to February 2022, PriMe will collaborate with all relevant partners to formulate an overarching program and governance structure for the DZPG that involves PriMe and other DZPG sites. To this end, we plan to implement the following steps: Coordinated by the local board of directors, the consortium will establish a PriMe office to support all processes during the Concept Development Phase. A strategic survey of the unmet needs of the main disorders studied in the DZPG will be conducted. In parallel, we will implement a discussion forum for PriMe's strategic partners, including ECRs and clinician scientists, psychiatrists, psychologists, PCPs, basic researchers, and representatives of patient, caregiver, and advocacy groups. We have held an initial 2-day workshop to agree on the major tasks, milestones, and deliverables for the networking phase

and the governance structure and have established a scientific workgroup for each of the four elements of the translational chain (namely understanding and modeling, predictive markers, clinical trials, and implementation). For each of these groups, each DZPG site will delegate a basic scientist, a clinician, an ECR, and a member from a user organization. Each working group has named a spokesperson who is responsible for reporting the progress to the board of directors of the DZPG basis to ensure a continuous build-up of an overarching program resting on the translational chain. Strategic decisions will be achieved with respect to the PriMe site during biweekly meetings of the local board of directors and for the entire DZPG during monthly meetings of the coordinators and co-coordinators at each site. Results from the Concept Development Phase will be presented at the final symposium, and the results of each working group will be published, leading to an overarching program for the DZPG.

AUTHOR CONTRIBUTIONS

All authors prepared the manuscript.

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The Complex Interplay Between Physical Activity and Recovery Styles in Patients With Severe Mental Disorders in a Real-World Multicentric Study

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Compared with the general population, people with severe mental disorders have significantly worse physical health and a higher mortality rate, which is partially due to the adoption of unhealthy lifestyle behaviors, such as heavy smoking, use of alcohol or illicit drugs, unbalanced diet, and physical inactivity. These unhealthy behaviors may also play a significant role in the personal and functional recovery of patients with severe mental disorders, although this relationship has been rarely investigated in methodologically robust studies. In this paper, we aim to: a) describe the levels of physical activity and recovery style in a sample of patients with severe mental disorders; b) identify the clinical, social, and illness-related factors that predict the likelihood of patients performing physical activity. The global sample consists of 401 patients, with a main psychiatric diagnosis of bipolar disorder (43.4%, $N = 174$), psychosis spectrum disorder (29.7%; $N = 119$), or major depression (26.9%; $N = 118$). 29.4% ($N = 119$) of patients reported performing physical activity regularly, most frequently walking (52.1%, $N = 62$), going to the gym (21.8%, $N = 26$), and running (10.9%, $N = 13$). Only 15 patients (3.7%) performed at least 75 min of vigorous physical activity per week. 46.8% of patients adopted sealing over as a recovery style and 37.9% used a mixed style toward integration. Recovery style is influenced by gender ($p < 0.05$) and age ($p < 0.05$). The probability to practice regular physical activity is higher in patients with metabolic syndrome (Odds Ratio - OR: 2.1; Confidence Interval - CI 95%: 1.2–3.5; $p < 0.050$), and significantly lower in those with higher levels of anxiety/depressive symptoms (OR: 0.877; CI 95%: 0.771–0.998; $p < 0.01$). Globally, patients with severe mental disorders report low levels of physical activities, which are associated with poor recovery styles. Psychoeducational interventions aimed at increasing patients' motivation to adopt healthy lifestyle behaviors and modifying

recovery styles may improve the physical health of people with severe mental disorders thus reducing the mortality rates.

Keywords: lifestyle, physical activity, sedentary behaviors, mortality, severe mental disorders

BACKGROUND

Recovery is a "process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential". In patients with severe mental disorders, recovery should represent the final goal of personalized treatment plans for all clinicians (1–3). The recovery styles adopted by patients with severe mental disorders predict their personal and psychosocial functioning as well as their adherence to therapeutic plans. McGlashan et al. (4) described a continuum of recovery styles, from "sealing over", which is characterized by avoiding the illness experience and is associated with negative long-term outcomes (5), to "integration", characterized by incorporating the psychotic episode into own identity. The integration style is associated with better long-term outcomes, in terms of adherence to treatments and engagement in psychosocial interventions (6–8).

The full recovery of people with severe mental disorders is hampered by many clinical and socio-demographic factors, including patient's age, pre-morbid level of functioning, educational level, working condition, social network, cognitive schemas (9), severity and type of symptoms, duration of illness, level of insight (10), clinical staging, previous treatments, time to remission, patient's social network, family ties, environmental exposures, presence of physical comorbidities (11, 12). In particular, patients with severe mental disorders have very poor physical health, suffering from coronary heart diseases, diabetes, respiratory, renal, and infectious diseases (13–17). The higher presence of physical illnesses compared to the general population is due to several causes (18, 19), including the adoption of unhealthy lifestyle behaviors, such as heavy smoking (20–23), heavy alcohol drinking (24–26), use of illicit drugs (27, 28), unbalanced diet and low levels of physical activity (29).

Physical activity, which is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure", and physical exercise, defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" (30), have positive effects on both physical and mental health (31). In fact, people who perform regular physical activity have a reduced risk of all-cause mortality and cardiovascular mortality.

Interventions increasing the levels of physical activity improve body composition and cardiorespiratory fitness and reduce the cardiometabolic burden and psychiatric symptoms (32). They also improve patients' quality of life, cognition, personal functioning, life skills, and social networks (33–35). Moreover, by improving patients' self-confidence and motivation to change, physical activity is also associated with improvement in the recovery process.

The physical health of patients with severe mental disorders is too often devaluated (36–39). Clinicians worldwide tend to prioritize other (mental) health domains, with the consequence of not motivating enough their patients toward physical activity (40–42). The clinical, biological, and social correlates of physical activity in people with severe mental disorders have been investigated only in a few studies (43, 44). Moreover, studies exploring the relationship between physical activity and recovery styles are also lacking (45).

Appropriate interventions increasing the levels of physical activity of patients with severe mental disorders should be developed (46, 47). Several trials have been promoted with a specific focus on physical activity, including a motivational coaching in order to increase the participation in physical activity programmes of patients with severe mental disorders (48–50).

In this paper, we: (a) describe the levels of physical activity and the recovery styles in patients with severe mental disorders; (b) investigate the clinical, social, and illness-related factors that are associated with the levels of physical activity in patients with severe mental disorders.

METHODS

The present paper is based on data collected within the LIFESTYLE trial (51), a national, multicentric, randomized, controlled trial with blinded outcome assessments, coordinated by the University of Campania "Luigi Vanvitelli" in Naples and carried out in collaboration with Universities of Bari, Genova, L'Aquila, Pisa, and Rome-Tor Vergata.

Patients were included in the study if they met the following criteria: (1) age between 18 and 65 years; (2) diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, other psychotic disorder, major depressive disorder, or bipolar disorder according to the DSM-5 and confirmed by the Structured Clinical Interview for DSM-5 (SCID-5); (3) ability to provide written informed consent; (4) BMI $\geq$ 25; (5) in charge to the local mental health center at least for three months before recruitment.

The main outcome measure considered for this analysis is the level of physical activities. Physical activity has been evaluated with the International Physical Activity Questionnaire (IPAQ)—short form (52), which is a 18-item questionnaire exploring physical activity in terms of walking, moderate-intensity, and vigorous-intensity physical activities.

The 24-items Questionnaire on lifestyle behaviors, developed by the Italian National Institute of Health, has been used to explore patients' dietary patterns (e.g., food eaten at lunch or dinner), smoking habits (e.g., number of cigarettes smoked per day; attempts to quit smoking), and physical activity (e.g., time spent in walking per day) (53).

Recovery styles have been evaluated with the Recovery Style Questionnaire (RSQ) (54), a 39-item self-report assessment

instrument exploring six styles of adaptation to severe mental disorder and recovery: "sealing over", "tends toward sealing over", "mixed picture in which sealing over predominates", "mixed picture in which integration predominates", "tends toward integration", and "integration".

Other assessment tools include the Food Frequency Questionnaire - short version (55); the Fagerström Test for Nicotine Dependence (FTND) (56); the Pittsburgh Sleep Quality Index (PSQI) (57); the Leeds Dependence Questionnaire (LDQ) (58); the Morisky Medication Adherence Scale (MMAS) (59); the Cumulative Illness Rating Scale (CIRS) (60); the Manchester Short Assessment of Quality of Life (61); the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)—brief version (62, 63); the Internalized Stigma of Mental Illness (ISMI) (64); *ad-hoc* questionnaire on sexual health; the Pattern of Care Schedule (PCS)—modified version (51).

Information on weight, height, BMI, waist circumference, blood pressure, resting heart rate, HDL, LDL and overall levels of cholesterol, blood glucose, triglycerides, and blood insulin have been collected by the researcher with the Anthropometric schedule. The homeostatic model assessment (HOMA) index and the Framingham Risk Score have been calculated for quantifying insulin resistance and cardiovascular risk, respectively.

Patients' psychopathological status has been assessed with the 24-item Brief Psychiatric Rating Scale (BPRS) (65). Patients' social functioning has been explored through the Personal and Social Performance Scale (66), a 100-point single-item rating scale, subdivided into four main areas: (1) "socially useful activities"; (2) "personal and social relationships"; (3) "self-care"; and (4) "disturbing and aggressive behaviors".

This study was conducted in accordance with globally accepted standards of good practice, in agreement with the Declaration of Helsinki and with local regulations. The study protocol was formally approved by the Ethics Committee of the Coordinating Center in January 2017 (Approval Number: 64). All other methodological details of the LIFESTYLE study are reported in (51) and the trial registration number is the following: 2015C7374S.

Statistical Analyses

Descriptive statistics and frequency tables have been used to assess patients' socio-demographic and clinical characteristics. Chi-square with multiple comparisons and ANOVA with Bonferroni corrections have been adopted to detect differences in the levels of physical activities. Bivariate analyses have been performed in order to evaluate the association between the levels of physical activities, the recovery styles, and the severity of clinical symptoms.

Multivariate logistic regression models have been implemented to identify predictors of practicing physical activity. The models have been adjusted for several socio-demographic characteristics, including gender, age, presence of physical illness, being married, level of education, satisfaction with one's own life, adaptive and maladaptive coping strategies, duration of illness, and recovery styles. This statistical approach has been already adopted in previous published papers based on the LIFESTYLE trial (51, 67, 68) and the categorical variable "Center" was also entered in the regression model.

A multiple imputation approach has been used for managing missing data. The level of statistical significance was set at $p < 0.05$ and statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 26.0, and STATA, version 15.

RESULTS

Patients' Socio-Demographic and Clinical Characteristics

The final sample consists of 401 patients, mostly female (57.1%, $N = 229$) and with a mean age of 45.6 ($\pm$11.8) years. Patients are affected by bipolar disorder (43.4%, $N = 174$), psychosis spectrum disorder (29.7%; $N = 119$), or major depression (26.9%; $N = 118$); the duration of the illness is about 15.6 ($\pm$11.3) years.

Most patients present mild symptoms at the BPRS and have a discrete level of personal functioning (PSP value: 65.7 $\pm$ 15.1).

Most patients are either overweight (35.4%; $N = 142$; BMI ranging between 25–29.9) or obese (34.9%; $N = 140$), with a mean BMI of 32.2 ($\pm$5.5). 40.6% of patients are heavy smokers and 67.8% drink alcohol more than three times per week. 53.4% of patients ($N = 214$) suffer from the metabolic syndrome; in particular, 56.6% ($N = 227$) have systolic hypertension, 36.1% ($N = 143$) diastolic hypertension and 26.9% ($N = 108$) hyperglycaemia.

As regards diet habits, 31.0% of patients eat less than two portions of fruits per week and 37.6% less than two portions of vegetables per week. 43.5% of the sample drink about one liter of water per day, below the WHO recommended threshold of more than two liters/day (**Table 1**).

Recovery Styles and Levels of Physical Activity

The "sealing over" recovery style is adopted by 46.8% of patients ($N = 174$), a "mixed style" is used by 37.9% of patients ($N = 141$), and "integration" is used by 8.9% of patients ($N = 33$) only (**Figure 1**). Recovery styles vary according to gender ($p < 0.05$) and age ($p < 0.05$), while there are no differences according to the diagnostic category. Patients adopting "integration" have lower levels of anxiety/depressive and hostility symptoms compared to those using "sealing over" ($p < 0.030$ and $p < 0.050$, respectively) (**Table 2**).

Regular physical activity is performed by 29.4% ($N = 119$) of patients. The most frequent physical activities performed by patients are walking (52.1%, $N = 62$), going to the gym (21.8%, $N = 26$), running (10.9%, $N = 13$), playing football (7.6%, $N = 9$), cycling (9.2%, $N = 11$), and swimming (2.5%, $N = 3$). Physical activities' preferences are not influenced by body mass index, age, and duration of illness. Only playing football is preferred by male patients ($p < 0.001$).

Vigorous physical activity performed for at least 75 min per week is done by 15 patients (3.7%), while moderate physical activity by 21.7% of patients (**Table 3**).

TABLE 1 | Socio-demographic and clinical characteristics of the sample.

	Global sample (*N* = 401)		Practicing regular physical activity				
			Yes (*N* = 118)		No (*N* = 283)		*P*-value
Socio-demographic variables							
Gender, Female, % (*N*)	57.1 (229)		51.7 (51)		59.4 (168)		NS
Age group, % (*N*)							0.001
18–34 years	19.2 (77)		27.1 (32)		15.9 (45)		
Age 35–64	79.1 (317)		67.8 (80)		83.7 (237)		
Over 65	1.7 (7)		5.1 (6)		0.4 (1)		
Occupational status, employed, % (*n*)	46.1 (185)		44.9 (53)		46.6 (132)		NS
DSM-5 diagnosis, % (*N*)							NS
Psychosis spectrum disorder	29,7 (119)		37.3 (44)		26.5 (75)		
Bipolar disorder	43.4 (174)		39.0 (46)		45.2 (128)		
Depressive disorder	26.9 (108)		23.7 (28)		28.3 (80)		
Duration of the illness, years M (SD)	15.6 (11.3)		15.0 (11.2)		15.9 (11.4)		NS
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Clinical variables							
Brief psychiatric rating scale							
Global score	5.4	2.0	5.3	1.9	5.4	2.1	NS
Anxiety/depressive symptoms	8.8	3.1	8.0	3.2	9.1	3.1	0.003
Anergia	7.7	3.17	7.0	2.8	7.9	3.2	0.004
Hyperactivity symptoms	4.7	1.9	4.8	1.8	4.7	1.9	NS
Hostility symptoms	4.0	1.9	3.7	1.5	4.2	1.9	0.036
Personal functioning, global score	65.7	15.1	66.1	14.6	65.4	15.4	NS
Adherence to treatment	1.1	1.0	0.9	0.9	1.1	1.1	NS
Levels of internalized stigma	10.9	2.1	10.7	2.2	11.1	2.1	NS
Quality of life, global score	4.1	1.0	4.3	0.9	3.9	1.1	NS
MATRICS—Bacs scoring	36.9	50.3	34.7	13.9	37.9	58.9	NS
MATRICS—Category fluency	17.9	5.4	17.6	5.3	18.0	5.5	NS
MATRICS—Trial Making Test	52.4	28.6	52.7	24.0	52.3	29.9	NS
	%	***N***	**%**	***N***	**%**	***N***	
Typical antipsychotic	21.2%	(85)	21.2%	(25)	21.2%	(60)	NS
Atypical antipsychotic	59.6%	(239)	62.7%	(74)	58.3%	(165)	NS
Mood stabilizer	54.9%	(220)	56.2%	(159)	51.7%	(61)	NS
Benzodiazepines	46.6%	(187)	47.0%	(133)	45.8%	(54)	NS
Tricyclic antidepressant	5.7%	(23)	6.8%	(8)	5.3%	(15)	NS
Second generation antidepressant	46.4%	(186)	42.4%	(50)	48.1%	(136)	NS
Lifestyle behaviors	**%**	***N***	**%**	***N***	**%**	***N***	
Smoker, yes	40.6%	(163)	37.3%	(44)	42%	(119)	NS
Fruit intake, three or more times/week	69%	(249)	73.4 %	(80)	67.1%	(169)	NS
Vegetable intake, three or more times/week	62.4%	(227)	59.3%	(64)	63.7%	(163)	NS
Water consumption daily, at least two liters	39.5%	(158)	39%	(46)	39.7%	(112)	NS
Metabolic parameters	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Systolic blood pressure, mmHg	125.6	13.5	124.1	12.8	126.3	13.8	NS
Diastolic blood pressure, mmHg	80.7	8.9	79.8	7.5	81.1	9.5	NS

(Continued)

TABLE 1 | Continued

	Global sample (*N* = 401)		Practicing regular physical activity				
			Yes (*N* = 118)		No (*N* = 283)		*P*-value
Waist circumference, cm	109.3	14.0	106.6	13.6	110.4	14.1	0.015
Glycemia, mg/dl	95.4	27.0	94.2	22.9	95.9	28.6	NS
Insulinemia, microU/ml	17.4	18.3	15.1	11.5	18.3	20.5	NS
Triglycerides, mg/dL	171.2	129.7	177.7	152.6	168.5	119.0	NS
Total cholesterol, mg/dL	189.9	40.9	189.4	38.9	190.0	41.8	NS
Low density lipoproteine, mg/dL	119.2	34.9	118.2	32.4	119.6	36.0	NS
High density lipoproteine, mg/dL	46.0	14.6	44.9	12.1	46.5	15.6	NS
HOMA index	4.9	11.6	3.8	3.7	5.4	13.6	NS
Framingham risk score	9.8	4.5	9.4	5.1	9.9	4.2	NS
Framingham risk score- −10 Years	9.3	7.5	9.3	7.9	9.4	7.4	NS
Metabolic Syndrome	53.4%	(214)	45.8%	(54)	56.5%	(160)	0.049
BMI, M (SD)	32.5	5.5	31.3	4.9	33.0	5.7	0.004

NS, Not significant.

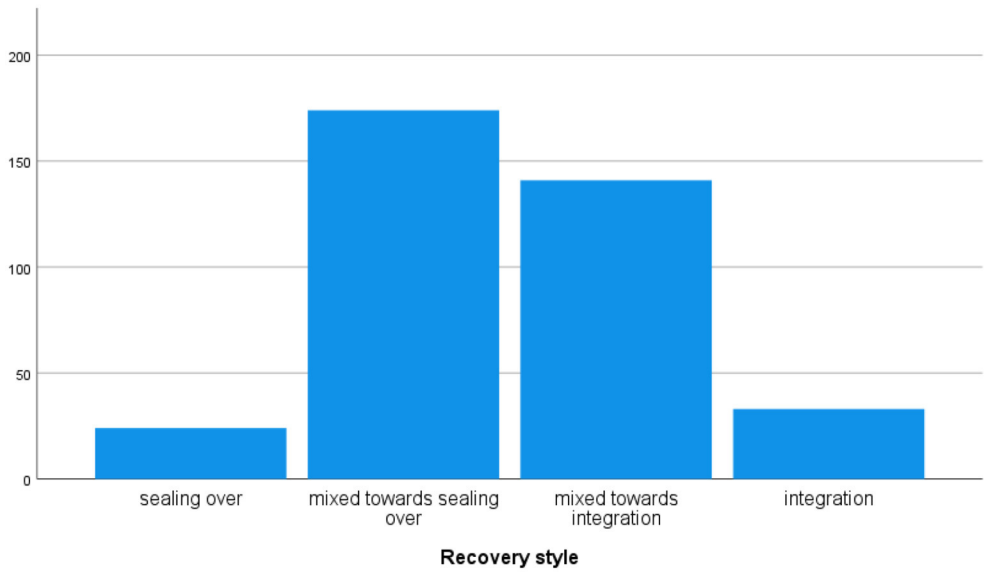

FIGURE 1 | Recovery style in the global sample.

Patients performing regular physical activities have lower levels of anergia (7.0 ± 3.2 vs. 8.1 ± 2.8, $p < 0.001$) and hostility (4.2 ± 1.9 vs. 3.7 ± 1.5, $p < 0.001$) at the BPRS compared with those not practicing physical activities; no other significant clinical differences exist in the other clinical domains between the two groups. Patients practicing physical activity report higher levels of perceived satisfaction with the quality of life compared with non-active patients (4.3 ± 0.9 vs. 3.9 ± 1.1, $p < 0.005$). There are no differences in the levels of personal functioning, internalized stigma, treatment adherence, and cognitive functioning. The levels of physical activity do not differ according to the condition of being smokers or being alcohol drinkers (**Table 1**). No differences were found between those patients practicing regular physical activities and those not practicing it in the recovery styles.

Multivariate Analyses

According to the multivariate logistic regression models, patients with metabolic syndrome have a higher probability to practice regular physical activity (OR: 2.1; CI 95%: 1.2–3.5; $p < 0.050$). Patients with higher levels of anxiety/depressive symptoms (OR: 0.877; CI 95%: 0.771–0.998; $p < 0.01$) have a significantly lower tendency to practice physical activity. The likelihood of practicing regular physical activity is not influenced by

TABLE 2 | Differences in recovery styles according to practicing regular physical activity and to symptoms' severity.

	Practicing regular physical activity				*P*-value
	Yes (*N* = 118)		No (*N* = 283)		
	%	*N*	%	*N*	
Sealing over	5.8	6	6.7	18	NS
Mixed toward sealing over	48.1	50	46.3	124	
Mixed toward integration	35.6	37	38.8	104	
Integration	10.6	11	8.2	22	
Missing		14		15	

		Mean	SD	*P*-value
BPRS Anxiety/Depressive symptoms	Sealing over[a]	9.8	2.7	0.030
	Mixed toward sealing over	9.1	3.2	
	Mixed toward integration	8.8	2.9	
	Integration[a]	7.6	2.8	
BPRS Anergia symptoms	Sealing over	8.2	3.3	0.365
	Mixed toward sealing over	7.8	3.2	
	Mixed toward integration	7.7	3.0	
	Integration	6.9	2.2	
BPRS Total symptoms	Sealing over	6.0	2.5	0.436
	Mixed toward sealing over	5.4	2.2	
	Mixed toward integration	5.3	1.8	
	Integration	5.5	2.2	
BPRS Hyperactivity symptoms	Sealing over	5.2	1.7	0.486
	Mixed toward sealing over	4.8	1.9	
	Mixed toward integration	4.7	1.7	
	Integration	4.5	1.7	
BPRS Hostility symptoms	Sealing over[b,c,d]	5.3	2.9	0.016
	Mixed toward sealing over [d]	4.0	1.9	
	Mixed toward integration[b]	4.0	1.8	
	Integration[c]	3.9	1.3	

Pairwise comparisons with Bonferroni corrections: [a]$p < 0.042$; [b]$p < 0.014$; [c]$p < 0.015$; [d]$p < 0.040$; NS, not significant.

TABLE 3 | Levels of physical activity evaluated at the IPAQ.

	Global sample (*N* = 401)	Practicing regular physical activity		*P*-value
		Yes (*N* = 118)	No (*N* = 283)	
Number of days practicing vigorous physical activity				0.001
None	87.3% (350)	72.9% (86)	83.9%(99)	
At least 1 day	12.7 % (51)	27.1%(32)	16.1%(19)	
Performed at least 75 min of vigorous physical activity per week, yes	3.7% (15)	7.6% (9)	2.1% (6)	0.017
Number of days practicing moderate physical activity				0.001
None	78.3% (314)	52.5% (62)	89.0% (252)	
At least 1 day	21.7% (87)	47.5% (56)	11% (31)	
Number of days walking at least 10 min/days				0.002
Seven/seven	35.4 % (142)	45.8% (54)	31.1% (88)	

other lifestyle variables, including diet, smoking, or drinking water, as well as other illness-related variables, such as duration of illness, pharmacological treatment, and recovery style (**Table 4**).

DISCUSSION

Recovery from severe mental illness is a complex and multifaceted process, which represents the ultimate goal of a

TABLE 4 | Predictors of practicing regular physical activity.

	B	S.E.	Sign.	OR	95% CI	
					Lower bound	Upper bound
Lifestyle-related factors						
Smoker	−0.302	0.293	0.302	0.739	0.417	1.312
Fruit intake	−0.181	0.463	0.697	0.835	0.337	2.068
Vegetables intake	−0.229	0.371	0.537	0.795	0.384	1.646
Water consumption daily	0.016	0.195	0.934	1.016	0.693	1.491
Metabolic Syndrome	0.718	0.279	**0.010**	**2.050**	**1.188**	**3.540**
Illness-related factors						
MANSA total score	−0.031	0.159	0.844	0.969	0.710	1.323
PSP total	0.002	0.011	0.891	1.002	0.980	1.024
BPRS hyperactivity	0.156	0.094	0.097	1.169	0.972	1.406
BPRS anxiety/depressive	−0.131	0.066	**0.046**	**0.877**	**0.771**	**0.998**
BPRS anergia	−0.078	0.066	0.241	0.925	0.812	1.054
BPRS hostility	−0.103	0.116	0.371	0.902	0.719	1.131
BPRS total	0.060	0.102	0.559	1.061	0.869	1.296
Atypical antipsychotic	−0.290	0.315	0.358	0.748	0.404	1.388
Typical antipsychotic	−0.330	0.361	0.361	0.719	0.355	1.458
Benzodiazepine	−0.232	0.288	0.420	0.793	0.451	1.393
Trycyclic antidepressant	−0.147	0.645	0.820	0.863	0.244	3.057
II gen. antidepressant	−0.220	0.317	0.487	0.802	0.431	1.492
Constant	3.630	2.305	0.115	37.717		

Regression model has been controlled for possible confounding factors including age, gender, duration of the illness, and center.
Significant values have been highlighted using bold characters.

treatment plan for patients affected by different mental disorders. The adoption of different recovery styles by patients influences their personal and psychosocial functioning, therapeutic adherence, and treatments' engagement.

In our sample, the majority of recruited patients use a "sealing over" recovery style, which is associated with a negative long-term outcome (4). In fact, "sealing over" patients have an insecure identity (7), report negative experiences in early attachment, have social difficulties, and are affected by predominant negative symptoms. On the contrary, people adopting an "integration" style (i.e., incorporating the psychotic episode into their identity), report more favorable long-term outcomes in terms of engagement with services and perceived quality of life (69–71). A recent study carried out in Italy found that the integration style is associated with a good functional outcome, through acceptance of the psychotic experience and the awareness of the need for support and care, while patients adopting sealing over were less likely to maintain their social role and to invest in interpersonal relationships, with a global poorer long-term outcome (6). Unfortunately, in our study, only a minority of patients adopt this recovery style.

The present study is focused on recovery styles and the association with the levels of physical activities. In fact, recovery styles influence treatment engagement and illness status (45), as also the propensity to perform physical activities. On the other hand, physical activity can promote recovery by improving patients' self-confidence, health status, and motivation to change. In our sample, patients reported low levels of physical activities and low levels of recovery (characterized by a prevalence of sealing over style), confirming the bidirectional relationship between recovery and physical activity. It would be interesting to explore the effects of a physical activity intervention on the levels of recovery styles of patients with severe mental disorders in a longitudinal study.

A significant obstacle to recovery in people with severe mental disorders is represented by the high rate of physical comorbidities and the reduced life expectancy compared with the general population (72–76). Several factors contribute to the higher mortality and morbidity in patient with severe mental disorders, such as the higher prevalence rate of metabolic syndrome compared to the general population (77, 78) and the adoption of unhealthy lifestyle behaviors (79). In fact, patients with severe mental disorders are frequently physically inactive, not fulfilling the WHO recommendations (80, 81). Our findings confirm the low levels of physical activity in patients with severe mental disorders (29), with only one patient out of three reporting to perform any type of physical activity. Moreover, when considering the type of physical activity, only 3.7% of patients performed at least 75 min of vigorous physical activity per week, which is the WHO recommended threshold for having a beneficial impact on physical health. It may be that people do not even know what is considered "regular physical activity" (82), suggesting the need to develop and carry out informative

interventions tailored to the general population and people with severe mental disorders. Within the LIFESTYLE project, our research team has developed a psychoeducational lifestyle group intervention for people with severe mental disorders (51), whose efficacy in the improvement of healthy lifestyle behaviors has been documented in a randomized controlled trial (67, 68).

The various socio-demographic variables considered did not influence the choice of any specific physical activity, differently from data collected in the general population (83). This finding confirms that it is not possible to simply translate the strategies developed for the general population to increase physical activities to people with severe mental disorders, but that more specific and targeted interventions are needed (84, 85).

In our regression models, lifestyle- and illness-related factors have been tested as possible predictors of practicing regular physical activity. The presence of the metabolic syndrome was the only lifestyle factor significantly predicting the likelihood of patients practicing physical activity, even after controlling for age, gender, duration of illness, and pharmacological treatments. Other lifestyle factors, such as diet or smoking, do not have any impact on the outcome. It may be that patients with severe mental disorders are reluctant to practice physical activities regularly and tend to do so only as a "last resort" when they are diagnosed with severe physical disturbances, such as hypertension or obesity, which are core elements of the metabolic syndrome. This finding suggests the need the improve regular physical check-up visits for patients with severe mental disorders, who are instead treated with reluctance by other physicians (86, 87). Studies including not only overweight patients may further confirm this hypothesis and explore the role of "trait" factors such as affective temperaments, personality traits, or cognitive styles on the propensity to practice regular physical activity in patients with severe mental disorders.

The following limitations of the study are hereby acknowledged. First, the inclusion of overweight patients only, which limits the generalizability of our findings to patients with different metabolic profiles. Second, the recruitment of a mixed sample of patients with severe mental disorders, which may have reduced the effect related to the diagnostic category. Third, the relatively low sample size, which does not allow us to draw firm conclusions about our findings.

In conclusion, our findings confirm that patients with severe mental disorders are sedentary and perform any type of physical activity only rarely. The recovery of patients with severe mental disorders is related to the adoption of healthy lifestyle behaviors (88–92).

Strategies aimed at increasing the levels of physical activity in patients with severe mental disorders may improve physical and mental outcomes and reduce the mortality rate. A possible way forward to improve practicing of physical activities in patients with severe mental disorders should include a specific motivational coaching on the role of exercise intervention and a personalized, patient-centered approach tailored to the needs of each individual patient.

DATA AVAILABILITY STATEMENT

Data published in this paper is available from the corresponding author upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee University of Campania L. Vanvitelli. The patients/participants provided their written informed consent to participate in this study.

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

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Effects of exercise on mortality rates of individuals with severe mental illness

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Persons with severe mental illness have a 10-to-20-year shorter life span than the general public. Excess morbidity and mortality in this patient population has been described as a major public health challenge worldwide. Despite robust extant literature on the role of exercise in reducing morbidity and mortality, especially from cardiovascular disease and diabetes (highly prevalent in this patient population), Very few clinical programs or clinical research projects currently exist to implement and study the effects of exercise on decreasing morbidity and mortality in this highly vulnerable patient population. Given the global lack of trained mental health providers, the need to integrate healthcare providers from different disciplines, such as nurses, physical therapists, occupational therapists, physician assistants, cannot be overstated. This mini-review will provide an historic perspective and current data supporting the need to establish exercise, and other Lifestyle Psychiatry interventions, as a key component of treatment for all patients with serious mental illness.

KEYWORDS

exercise, morbidity and mortality, serious mental illness, treatment, health monitoring

Introduction

The National Institute of Mental Health (NIMH) defines severe mental illness (SMI) as a "mental, behavioral, or emotional disorder resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities" (1). Examples of SMI include schizophrenia, bipolar disorder, and schizoaffective disorder. These conditions can be debilitating for individuals and often create poor quality of life, ultimately resulting in shorter life spans, especially when accounting for disability-adjusted life years (2). Individuals with SMI die 10 to 15 years earlier than the general population, on average (3). Compared to healthy controls, SMI patients have a 1.5–2.6 times greater risk of death (4, 5). Mortality in patients with SMI can be attributed to suicide and accidents, but these are not the most common causes of death (6, 7). Cardiovascular, respiratory, infectious disease, diabetes mellitus, and cancers are major contributors to the excess mortality seen in patients with SMI (8). Cardiovascular disease is easily the highest among these and only 25% of those who died with SMI are given a diagnosis for this (9).

One approach to treating SMI would be to implement lifestyle interventions that would not only improve psychiatric symptoms, but also address underlying physical health conditions. These conditions, often brought on by morbid obesity secondary to many of the psychopharmacological treatments for SMI, later result in decreased life expectancy (3). One of the proposed mechanisms to increase life expectancy and reduce mortality, as well as improve quality of life, is physical exercise (10).

Findings

As stated previously, the mortality rates are quite high in SMI patients and some studies even suggest that the mortality rate may be increasing (4). Exercise would be beneficial here as it improves mortality risk in most of the physical health conditions mentioned, particularly cardiovascular disease (11). There are additional reasons to consider exercise as a means of reducing mortality in SMI. For example, SMI patients tend to consume a poor diet compared to the general population that is high in saturated fat and low in fiber (12). SMI patients also live a more sedentary lifestyle compared to the general population and are more likely to be obese (13).

Antidepressant and antipsychotic medications are the mainstay of treatment options for SMI. However, obesity, hyperlipidemia, insulin resistance, and arrhythmias are well known side effects of these medications (14). Nonetheless, underdosing is not appropriate, as the psychiatric symptoms experienced in SMI are often debilitating. Exercise can be beneficial in this regard, as it can reduce the severity of psychiatric symptoms in a number of conditions. Most effects are seen in severe depression and anxiety (15). Improvement of SMI symptoms can be seen in insomnia, schizophrenia, dementia, delirium, and agitation (16–19). Medications are necessary as a baseline for treatment, but exercise can be a useful adjunct, not only for psychiatric disease but also for cardiovascular disease, as several studies have shown.

For example, a study was conducted on 51 overweight and obese individuals with SMI who underwent a 12-month multimodal weight control program. These individuals were all on a regimen of second-generation antipsychotic medications and divided into an intervention and control group. 31 out of the 51 individuals, called the intervention group, participated in a program that incorporated nutrition, exercise, and behavioral interventions. The remaining 20 individuals were in the control group and received antipsychotic treatment only. 20 out of the 31 subjects in the intervention group participated in the multimodal weight control program to its completion. Metrics used included body mass index, weight, hemoglobin A1c levels, blood pressure, and cholesterol levels. There were statistically significant improvements across all metrics in the intervention group, and those in the control group continued to gain weight. This research study suggests exercise can reduce disease burden and mortality (20).

Discussion

The role of exercise in maintaining physical and mental health is not new. Its origins can be traced back to Hippocrates. Over the centuries, regular exercise has been demonstrated to not only help maintain health but be an effective component of a comprehensive biopsychosocial treatment strategy for virtually all chronic diseases. In fact, regular exercise has been shown to impact positive health outcomes from a biological, psychological, and social perspective. Despite the robust extant clinical literature on the role of exercise in promoting health and well-being, and decreasing morbidity and mortality, it has been largely neglected in patients suffering from serious mental illness, despite the shortened lifespan in this patient population noted above.

A reasonable question to consider is why is this effective treatment so infrequently included in the comprehensive treatment of patients suffering from serious mental illness? A number of factors may explain this ongoing issue. First, regular exercise has not been part of the "culture" of treating this patient population (21). Until the late 1970's, patients with SMI were treated in state hospitals for months to years. During these extended hospitalizations, patients would get daily activity and smoking breaks to get outside, but exercise was rarely included. As hospitalization stays continued to decrease to days to weeks over the past 40 years, structured exercise was even less, often restricted to smoke breaks in a confined locked area. Discharge planning was focused largely on psychotropic medication management, stable housing, and outpatient social support (22). The ongoing stigma of mental illness has likely played a role in this. Patients suffering from SMI have been portrayed as potentially dangerous and a burden to society on the big and little screen (movies and TV) over the years, and funding for research and treatment has lacked far behind other "physical" illnesses, like cardiac, endocrine and oncologic diseases.

From a purely public health perspective, including regular exercise in the treatment of patients suffering from SMI would likely result in significant cost savings, not to mention the positive impact on overall health, well-being and ultimately decreased morbidity and mortality. A key factor to consider in prescribing an exercise program should be consideration of what the patient finds enjoyable and is safe and feasible given their living situation (23). The increased socialization group exercise can provide, may also be an integral component of a comprehensive biopsychosocial treatment plan.

Conclusion

The focus of this special issue of the journal was to examine strategies to decrease mortality in patients suffering from SMI. Although proper medication management and psychosocial intervention are important, the role of regular exercise cannot be overstated. The impact of Lifestyle Psychiatry interventions has been well documented to increase quality and quantity of life for all persons, especially those with chronic diseases (24). Exercise is a key component of Lifestyle interventions. We believe a thoughtful exercise plan should be included in every patient suffering from mental illness, especially those with SMI.

An exercise program has minimal side-effects, but should be monitored by a health professional, and is extremely cost-effective. Prospective outpatient, community-based clinical trials will help determine the most efficacious and effective interventions, from a personalized medical approach (25). Low tech, inexpensive treatments, like an exercise program, may have the greatest impact on increasing the lifespan in patients suffering with SMI. Let's have well controlled clinical data answer this question, never losing sight of the fact that it is one piece, albeit an important one of a larger treatment puzzle.

Although the role of regular exercise has been well documented to reduce mortality in persons with serious mental illness, the role of the psychiatrist has been largely neglected. As clinicians, psychiatrists providing care for those suffering from SMI must take an active role in "prescribing" and monitoring exercise as a critical component of comprehensive care of their patient. The extant literature does not emphasize the important role of engaging the patient to determine an exercise program that is logistically possible (access to equipment as needed), and most importantly something that is fun for the patient. Recent literature has reported the role wearable activity monitoring devices can play. Step tracking devices have been shown to increase walking distance daily through real time, non-judgmental feedback. Given the ever-growing clinical data on the value of exercise on physical and mental health for persons with SMI, we propose all psychiatry residency programs should include specific didactic and clinical instruction on how to incorporate personalized physical activity into the treatment plan for all patients with SMI, in the inpatient and outpatient setting.

Author contributions

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

Conflict of interest

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

Publisher's note

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