REDUCING THE MORTALITY GAP IN PEOPLE WITH SEVERE MENTAL DISORDERS: THE ROLE OF LIFESTYLE PSYCHOSOCIAL INTERVENTIONS

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REDUCING THE MORTALITY GAP IN PEOPLE WITH SEVERE MENTAL DISORDERS: THE ROLE OF LIFESTYLE PSYCHOSOCIAL INTERVENTIONS

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Patients with severe mental disorders (SMD), including major depression, bipolar disorder, schizophrenia and related spectrum disorders, have a reduced life expectancy of 10-25 year compared with the general population. This life expectancy gap is mainly due to the co-occurrence of many physical diseases, such as hypertension, coronary heart disease, stroke, chronic obstructive pulmonary disease, tuberculosis, hepatitis and HIV. Factors contributing to the reduced life expectancy can be grouped into three main categories: a) factors related to the patient; b) factors related to clinicians; and c) factors related to the health system. As regards the first group, patients with SMD often adopt unhealthy lifestyle behaviors, including heavy smoking, reduced physical activity, sedentary behaviors, poor diet and alcohol or drug abuse, and are reluctant to seek for physical care with GPs and other medical specialists.

Increasing the levels of physical activity, improving the dietary patterns, and reducing the smoking habits of people with severe mental disorders represent a global health challenge and a public health priority. Until now, attempts made to reduce this mortality gap have acted at three different levels: health system level, physician level, and patient level. The third-level interventions include electronic alerts through smartphones and web-based platforms, intensive case management, promotion of healthy habits, complex psychosocial interventions. Several population-based studies have showed that lifestyle behaviors are amenable to change through the adoption of specific psychosocial interventions. However, most clinical guidelines, although emphasizing the importance of health monitoring and regular check-ups for patients with severe mental illnesses, do not make specific recommendations on the provision of lifestyle interventions. These lifestyle-oriented interventions, consisting of behavioral, educational, and psychological components, have been conducted mainly in research settings, and have shown a good impact on patients' physical health. Despite this, their feasibility in routine settings has not been tested yet. It seems to be clinically and ethically relevant to develop, validate and carry out interventions to improve the lifestyle's behaviors of patients with severe mental disorders, to reduce the presence of comorbidities and to improve their life expectancy. In this Research Topic we will summarize the available knowledge of the efficacy and effectiveness of psychosocial interventions aimed at improving healthy lifestyle behaviors and promoting the physical health of patients with severe mental disorders.

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EDITORIAL
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Editorial: Reducing the Mortality Gap in People With Severe Mental Disorders: The Role of Lifestyle Psychosocial Interventions

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Keywords: excess mortality, comorbidity, severe mental disorders, psychosocial interventions, healthy behaviors

Editorial on the Research Topic

Reducing the Mortality Gap in People With Severe Mental Disorders: The Role of Lifestyle Psychosocial Interventions

Compared to other non-communicable diseases, severe mental disorders (SMDs)—namely major depression, bipolar disorders, schizophrenia, and related spectrum disorders—are associated with a larger morbidity, poorer health outcomes, and higher mortality rates (1, 2). People suffering from SMD die on average 10 to 20 years earlier than the general population (3–4), and this gap tends to increase over time (5). Only a minority of premature deaths are attributable to unnatural causes, such as suicide, homicides, or accidents (6), while the vast majority of deaths is due to physical health problems, such as cardiovascular, respiratory or infectious diseases, diabetes mellitus, and cancers. This is why the excess mortality in people with SMD has been defined as a "public health scandal" (4).

Excess mortality and morbidity in SMD can be explained by intertwined components, including patients' individual factors (e.g., severity of symptoms, impulsivity, emotional dysregulation, deficits in cognitive and social skills), lifestyle behaviors (e.g., smoking, poor diet, sedentary behavior, alcohol and drug abuse), social disadvantages of people with SMDs (i.e., stigma, discriminating policies, unemployment, homelessness, limited family, social, and community resources), and healthcare disparities (e.g., poor quality of service provision, limited access to health information, reduced prescriptions for physical checkups, professionals' negative attitudes towards people with mental disorders) (7).

In the recent years, it became clear that the management of physical illnesses in people with SMD is challenging, and it is likely to become even more problematic in the years to come (8) due to several factors, including: 1) the extension of life expectancy of all members of the population, due to medical advancements, improvements in hygiene and food supply, and the consequent increase in the probability of developing physical disorders, particularly the noncommunicable ones (such as, cancer, diabetes, cardiovascular illness) (9); 2) the over-division and over-specialization of medical disciplines and the fragmentation of medical knowledge (10), which has also occurred within the field of psychiatry, with the consequence that in some cases psychiatrists deal only with specific age groups (children, adolescents, elderly) or specific diseases (e.g., only with patients with bipolar or eating disorders) or stages in disease-development (e.g., early intervention specialists) or treatment procedures; and 3) the increasing gap in knowledge within disciplines due to refinement

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and extension of training (e.g., between nurse assistants, nurses, specialized nurses, and PhD nurses) and the continuing lack of awareness of the need to prepare health workers during their training to deal with comorbidity.

In order to address this topic, the World Health Organization, within the Global Action Plan for the Prevention and Control of non-communicable diseases, has provided a set of actions to be undertaken by national health systems, including control of risk factors, scaling up management in primary health care, and development of national policies (11).

As awareness of this problem rises, it becomes clear that a single directed approach would not be enough, as excess mortality cannot be attributable to a single factor; therefore, a multilevel approach, in which the different stakeholders involved in health care provision establish workforces for the long-term management of physical and mental health conditions, is recommended (12). The different stakeholders would include policy makers, psychiatrists, other medical specialists, users, and carers of people with mental disorders (13).

Interventions aimed at reducing risk factors and improving physical health of people with SMDs may act at different levels, including: 1) the community and policy-making levels, through the development of national policies for the promotion of healthy lifestyle behaviors and the development of comprehensive health-care packages; 2) the health-system organizational level, through the improvement of screening programs for physical conditions, the promotion of care coordination strategies, and the development of guidelines for an integrated delivery of mental and physical health care; and 3) the individual clinical level, through the promotion of early management and treatment of physical conditions in patients with SMDs, the development, and the implementation of lifestyle behavioral psychosocial interventions addressing weight loss, tobacco smoking, healthy diet, physical exercise, and risky sexual behaviors (7).

In the Research Topic "Reducing the Mortality Gap in People With Severe Mental Disorders: The Role of Lifestyle Psychosocial Interventions," we have addressed the individual clinical level. In particular, the aim of our research topic was to summarize the current knowledge on the efficacy and effectiveness of psychosocial interventions aimed at improving lifestyle behaviors and at promoting physical health in patients with SMDs. Recently, several interventions targeting lifestyle behaviors have been developed, and many of them have proven to be effective both in randomized controlled trials and in routine clinical practice, although their dissemination on a large scale has not been satisfying so far (14). Other concerns are related to the following: a) The geographical distribution of available findings. In fact, national data about mortality of people with SMDs and about the efficacy of interventions to promote healthy habits in low- and middle-income countries are very scarce, particularly in those countries where mortality rates for infectious diseases and the reduced availability of healthcare resources could be responsible of an even greater morbidity and mortality of people with SMDs (15); b) the duration and intensity of psychosocial treatments, with the need of cost-effectiveness analysis; and c) the identification of effective delivery packages in routine care. In fact, these interventions can be delivered either individually or in group settings, with little evidence supporting differential efficacy profiles among the different formats.

Our research topic includes seven original research papers, three brief research reports, three perspective papers, one opinion paper, and four review papers. In particular, the 18 papers have focused on two main areas: a) the clinical characterization of patients with SMDs at risk of developing physical illnesses; and b) the different psychosocial strategies for the management of physical comorbidities in patients with SMDs.

As regards the clinical characterization of patients with SMD at risk of developing physical health problems, Ventriglio et al. have investigated the effect of oral vs. long-acting injectable antipsychotics on the onset of metabolic syndrome; Cuomo et al. have explored the possible relationship between smoking habits and vitamin D deficiency, while Bartoli et al. in their review have pointed out that the presence of depressive symptoms in patients with stroke is associated with higher mortality rates compared to those non-affected by post-stroke depression. The relationship between the presence of medical unexplained physical symptoms and the occurrence of mental disorders has been explored by Poloni et al. in a sample of 5,039 patients. Finally, the relationship between lifestyle behaviors, mental health, and suicide risk has been deepened by Berardelli et al. in their narrative review.

As regards the role of psychosocial interventions in the management of physical comorbidities in patients with SMDs, the papers by Dalcin et al. and Herbsleb et al. have dealt with the reduction of cardiovascular risk factors, while Elkholy et al. and Burns et al. have promoted interventions to reduce tobacco smoking in these patients. Interventions to promote physical exercise (Schmitt et al.; Belvederi Murri et al.; Korman et al.) and weight loss (McGinty et al.) have been described and their efficacy has been tested. Many psychosocial approaches have been developed to deal with more than one lifestyle behavior (e.g., Sampogna et al.; Taylor et al.; Kuzman et al.; Berardelli et al.; Barber and Thornicroft), while the role of carers and family members in promoting patients' healthy behaviors has been highlighted in the paper by Onwumere et al.

Taken together, all papers included in this Research Topic provide new insights on the topic of comorbidity between mental and physical disorders, highlighting that several efforts have already been made in this direction, but much work still remains to be done. In the years to come, research should focus on the identification of protective factors that could reduce morbidity and mortality of people with SMDs, on the identification of comorbid substance abuse, on the investigation of cost-effectiveness of psychosocial interventions, and on the identification of the characteristics of the interventions that can positively impact on patients' behaviors.

AUTHOR CONTRIBUTIONS

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

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CLINICAL STUDY PROTOCOL
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A Randomized Controlled Trial on the Efficacy of a Psychosocial Behavioral Intervention to Improve the Lifestyle of Patients With Severe Mental Disorders: Study Protocol

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Patients with severe mental disorders die on average 20 years prior to the general population. This mortality gap is mainly due to the higher prevalence of physical diseases and the adoption of unhealthy lifestyle behaviors.The LIFESTYLE trial aims to evaluate the efficacy of a new psychosocial group intervention (including psychoeducational, motivational, and problem-solving techniques) focused on healthy lifestyle behavior compared to a brief educational group intervention in a community sample of patients with severe mental disorders. The trial is a national-funded, multicentric, randomized controlled trial with blinded outcome assessments, which is carried out in six outpatient units of the Universities of Campania "Luigi Vanvitelli" in Naples, Bari, Genova, L'Aquila, Pisa, and Rome—Tor Vergata. All patients are assessed at the following time points: baseline (T0); 2 months post-randomization (T1); 4 months post-randomization (T2); 6 months post-randomization (T3); 12 months post-randomization (T4); and 24 months post-randomization (T5). T1 and T2 assessments include only anthropometric tests. The BMI, a reliable and feasible anthropometric parameter, has been selected as primary outcome. In particular, the mean value of BMI at 6 months from baseline (T3) will be evaluated through a Generalized Estimated Equation model. The work hypothesis is that the LIFESTYLE psychosocial group intervention will be more effective than the brief educational group intervention in reducing the BMI. We expect a mean difference between the two groups of at least one point (and standard deviation of two points) at BMI. Secondary outcomes are: the improvement in dietary patterns, in smoking habits, in sleeping habits, physical activity, personal and social functioning, severity of physical comorbidities, and adherence to medications. The expected sample size consists of 420 patients (70 patients for each of the six participating centers), and they are allocated with a 1:1 ratio randomization, stratified according to center, age,

gender, and educational level. Heavy smoking, sedentary behavior, and unhealthy diet pattern are very frequent and are associated with a reduced life expectancy and higher levels of physical comorbidities in people with severe mental disorders. New interventions are needed and we hope that the LIFESTYLE protocol will help to fill this gap.

Trial registration number: 2015C7374S.

Keywords: mortality gap, mental disorders, lifestyle, diet, physical activity

INTRODUCTION

In the last decade, the need to improve physical health in patients with severe mental disorders, namely schizophrenia, major depression, and bipolar disorders (1), has been repeatedly highlighted by several international scientific bodies and reported in several guidelines (2–6). Nevertheless, physical health of people with several mental disorders is often neglected by the patients themselves, as well as by their caregivers and mental health professionals (1).

Patients with severe mental disorders die on average 20 years prior to the general population (7). In patients with severe mental disorders, cardiovascular diseases, and other physical diseases contribute significantly to the reduced life expectancy, even if more than other "unnatural" causes, such as accidents or suicide (8–10). Among the relevant and modifiable factors for explaining the high cardiovascular morbidity and mortality of patients with severe mental disorders two factors have been repeatedly recognized: the poor access to prevention and screening programmes and the adoption of unhealthy lifestyle behaviors (11). It is unacceptable that life expectancy, which is substantially grown in developed countries in the general population, remains so short in people with schizophrenia and other severe mental disorders (12, 13).

Recently, it has been reported that receiving a diagnosis of schizophrenia is associated with at least 13–15 years of potential life lost; therefore, there is the need to develop and implement individual-based and/or community-level interventions in order to reduce this excess mortality in people with severe mental disorders (1, 14).

Interventions could improve global health and well-being in people with severe mental illness by modifying their unhealthy lifestyle behaviors. According to a recent review, people with mental disorders are more sedentary than the general population (matched for gender and age) and are significantly less physically active. Moreover, at least 50% of people with severe mental illness do not meet the general recommendation of performing at least 150 min of moderate physical activity per week (1). Moreover, patients with severe mental disorders have unhealthy diet pattern, with a low intake in fruit and fiber and a high intake of junk food (15, 16). Compared with the general population, people with mental disorders have a higher probability of being heavy smokers (i.e., more than two packs/day) (17–19).

Increasing the levels of physical activity, improving dietary patterns, and reducing smoking habits of people with severe mental disorder may represent a global health challenge and a public health priority.

On these premises, several psychosocial interventions—including behavioral, educational, and psychological components—have been developed worldwide for addressing these needs (20–25). In particular, some interventions have been specifically focused on improving dietary patterns [e.g., (24)] or smoking habits [e.g., (26)] or on physical inactivity, unhealthy dietary habits, and smoking [e.g., (22, 23)]. These lifestyle psychosocial interventions—that are different in format, setting, duration, and involved professionals—have been found to be effective in improving patients' physical health.

However, several aspects have been identified as critical for the provision of lifestyle interventions in the clinical routine care. The optimal duration of the intervention; the involvement of a multidisciplinary team: the evaluation of cost/effectiveness ratio: the feasibility of the intervention in the real word practice are some of the most crucial ones. Recently, Speyer et al. (22, 23) found that the CHANGE trial was not superior to treatment as usual in reducing cardiovascular risk in patients with schizophrenia spectrum disorders and abdominal obesity, but more data are needed for patients with other severe mental disorders.

Moreover, there is the need to understand if these interventions actually reduce the mortality gap, and they should be evaluated in routine care, in large samples and in the long term (25). In order to assess the efficacy and the feasibility of these lifestyle interventions, an easy, reliable, and affordable anthropometric parameter, as the Body Mass Index (BMI) should be selected (15, 16, 24). Under these premises, a multicentric collaborative study, coordinated by the Department of Psychiatry of the University of Campania "Luigi Vanvitelli in Naples, Italy" and funded by the Italian Ministry of Education, Universities and Research, has been proposed for evaluating the efficacy and effectiveness of new psychosocial group interventions targeted on lifestyle in a real-world sample of patients with severe mental disorders, in terms of reduction of BMI.

AIMS

The LIFESTYLE trial aims to evaluate the efficacy of a new psychosocial group intervention focused on healthy lifestyle behaviors compared to a psychoeducational brief group intervention in a community sample of patients with severe

mental disorders on several variables including BMI, comorbidity index, smoking habits, and dietary patterns.

The secondary aims of the trial are: (1) to identify predictive factors associated with poor response to the interventions; (2) to define the role of mediators and moderators for the efficacy of the interventions; (3) to describe differences according to diagnostic groups in terms of improvement of lifestyle behaviors; (4) to evaluate the long-term effects of the interventions and their cost-effectiveness; (5) to develop guidelines for improving healthy lifestyle in people with severe mental disorders in the clinical routine care.

METHODS

Design

The LIFESTYLE trial is a national-funded, multicentric, randomized controlled trial with blinded outcome assessments. The project has been funded by a grant of the Italian Ministry of Education, Universities and Research within the framework of the "Progetti di Rilevante Interesse Nazionale (PRIN) — year 2015". It is a multicentric study involving the outpatient units of the University of Campania "Luigi Vanvitelli" in Naples, University of Bari, University of Genova, University of L'Aquila, University of Pisa, and University of Rome—Tor Vergata. The University of Campania "Luigi Vanvitelli" in Naples is the coordinating center, which has originally conceived the study's idea and design.

This is a randomized head-to-head comparison trial with two parallel arms for evaluating the efficacy and effectiveness of psychosocial group interventions in improving lifestyle behaviors in patients with severe mental disorders. The two interventions have been developed by the research staff and are both focused on the improvement of lifestyle behaviors.

Patients' Recruitment

Patients are being recruited in six outpatient units from the universities of Naples, Bari, Genova, L'Aquila, Pisa, and Rome—Tor Vergata.

Eligible patients are identified by their clinicians and referred to the LIFESTYLE research staff by phone, email, or in-person contact. After the patients have been contacted, a meeting is arranged at the outpatient clinic with the referring clinician and the LIFESTYLE staff. Verbal and written information about the project are provided. If the patient accepts to participate to the study, an informed consent form is signed and an appointment for baseline assessment is made. Once the informed consent is collected, the patient is formally enrolled in the study's protocol. Before starting the baseline assessment, the LIFESTYLE staff member contacts the statistician working at the Coordinating Center for obtaining the randomization code for patients' group allocation. The randomization procedure is stratified according to center, age, gender, and educational level with a 1:1 ratio. The treating psychiatrist will continue to provide the usual treatment to patients.

Patients' Inclusion Criteria

Patients have to fulfil the following inclusion criteria:

- Age between 18 and 65 years.
- Diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, other psychotic disorders, major depressive disorder, or bipolar disorder according to the DSM-5 and confirmed by the Structured Clinical Interview for DSM-5 (SCID-5) (27).
- Ability to provide written informed consent.
- BMI $\geq$ 25.

Patients' Exclusion Criteria

Patients are excluded from the study if they meet one of the following exclusion criteria:

- Inability to perform moderate physical activity (i.e., walking at least 150 min per week, or 75 min of vigorous activity twice a week, according to the guidelines of the Italian Ministry of Health).
- Pregnancy or breast-feeding.
- Intellectual disability or severe cognitive impairment.
- Worsening of clinical status or hospital admission in the previous 3 months.

Blinding

Researchers and statisticians involved in patients' assessments are blinded to patient's allocation. Patients and health professionals providing the interventions are not blinded to patient allocation.

INTERVENTIONS

Arm I: Lifestyle Psychosocial Group Intervention

The theoretical background of the new psychosocial group intervention includes techniques derived from classic psychoeducation (28), motivational intervention (29–31), and cognitive-behavioral therapy (32).

The intervention has been developed following the guidelines on the management of physical health in people with mental disorders produced by the World Health Organization (33, 34), the European Association for the Study of Diabetes (35), the European Society of Cardiology (36), and the European Psychiatric Association (37).

The adopted methodology included the following phases: (1) analysis of the scientific literature; (2) evaluation of available handbooks and manuals on other psychosocial interventions targeting lifestyle behaviors; (3) focus groups with expert researchers and clinicians, and with users and carers, in order to identify the most relevant needs to be included in the intervention; (4) development of *ad-hoc* manuals by the research group with a detailed description of each session of the intervention. Manuals have been developed in order to ensure treatment fidelity among the different centers. Leaflets and other written materials are given to patients, whenever relevant.

The intervention lasts 5 months and it is administered to groups of 5–10 patients every 7–10 days. The sessions cover the following topics: (1) healthy diet; (2) physical activity; (3) smoking habits; (4) medication adherence; (5) risky behaviors; (6) promotion of circadian rhythms. Each module includes the

following components: (a) information on the risks of the specific unhealthy lifestyle and benefits in adopting healthy lifestyle; (b) teaching of practical strategies to change unhealthy behaviors; (c) identification of personal life goals for each participant, motivation to change, and problem-solving strategies. Sessions have been developed in order to stimulate discussion, work-groups and interaction among participants. At the end of each meeting, a 20-min session of moderate physical activity is scheduled (**Table 1**). The core feature of this intervention is the inclusion of the motivational component. During each session, group participants are supported by mental health professional in identifying a personal healthy lifestyle goal. After goal-definition, professionals help participant to define the motivations for lifestyle changing and teach problem-solving strategies for sustaining the behavioral change.

Arm II: Brief Educational Group Intervention

The brief educational group intervention, which includes elements from the psychoeducational approach and from problem-solving techniques, consists of 5 weekly sessions and it is administered to groups of 5–10 patients. The following topics are covered: (1) healthy lifestyle; (2) early detection of clinical relapses; (3) effects of pharmacological treatment and management of side effects; (4) stress management techniques; (5) problem-solving techniques.

Manuals have been developed in order to ensure treatment fidelity among the different centers. Leaflets and other written materials are given to patients, whenever relevant. During the sessions, interaction among participants is supported using role-plays and work-groups (**Table 2**).

TRAINING OF MENTAL HEALTH PROFESSIONALS

For each participating center, three mental health professionals (at least one being a psychiatrist) participated to a 5-day training course for the provision of the two interventions, held in Naples in June 2017. Supervision meetings are organized during the study period as well as regular phone and e-mail supervisions.

ETHICAL ISSUES

This study is being conducted in accordance with globally accepted standards of good practice, in agreement with the Declaration of Helsinki and with local regulations.

The study investigators ensure that all mental health professionals involved in the study are qualified and informed about the protocol, interventions, and trial-related duties. The coordinating center has a list of all qualified mental health professionals involved in the study.

A formal ethical approval for conducting the trial has been obtained by the Coordinating Center's Ethics Committee, which approved the whole study protocol on January 2017 (approval number: prot. 64).

ASSESSMENT TIME AND INSTRUMENTS

Researchers participating to the study are blinded to patient allocation. All patients are assessed at the following time points: baseline (T0); 2 months post-randomization (T1); 4 months post-randomization (T2); 6 months post-randomization (T3); 12 months post-randomization (T4); and 24 months post-randomization (T5). T1 and T2 assessments include only anthropometric tests. All data will be collected through a paper and pencil interviewing and the expected time for filling in all assessment tools is about 60/90 min. During the completion of the assessment battery, whether patients feel distressed or exhausted, the assessment can be stopped and another appointment will be scheduled in the next 2/3 days with the researcher.

The following questionnaires and schedules will be used during the study (**Table 3**):

- The Food Frequency Questionnaire—short version (38) is a 18-item questionnaire on the frequency of consumption of a variety of foods corresponding to one's usual diet. In order to compile the questionnaire, the Scotti-Bassani Atlas is used for selecting quantity of food.
- The International Physical Activity Questionnaire (IPAQ)—short form (39) is a 18-item questionnaire exploring physical activity in terms of time spent in walking, in moderate-intensity and vigorous-intensity activities.
- The Fagerström Test for Nicotine Dependence (FTND) (40) is a 6-item questionnaire assessing the intensity of physical addiction to nicotine in terms of number of cigarette smoked per day, compulsion to use, and nicotine addiction.
- The Pittsburgh Sleep Quality Index (PSQI) (41) is 19-item questionnaire assessing sleep quality over a 1-month time interval.
- The Leeds Dependence Questionnaire (LDQ) (42) is a 10-item questionnaire designed to measure dependence for a variety of substances.
- The Morisky Medication Adherence Scale (MMAS) (43) is a 4-item questionnaire for evaluating adherence to pharmacological treatments.
- The Cumulative Illness Rating Scale (CIRS) (44) is a 14-item questionnaire including a comprehensive assessment of physical comorbidities.
- The Manchester Short Assessment of Quality of Life (45) is a 17-item questionnaire assessing quality of life focusing on satisfaction with life as a whole and with life domains.
- The Recovery Style Questionnaire (RSQ) (46) is a 39-item self-report questionnaire 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.
- The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)—brief version, which includes the MATRICS Consensus Trail Making Test—part A, Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency-Animal Naming (47, 48).

TABLE 1 | Programme of LIFESTYLE psychosocial group intervention.

Starting session: Introduction of the intervention, aims, purposes, presentation of participants, and definition of personal healthy lifestyle goals
Module 1: Diet, information on health food, principles, and benefits of healthy eating
Module 2: Physical activity, how to increase routine physical activity
Module 3: Smoking habits, information on the dangers of smoking, craving, difficulties for quitting smoking and consequences of long-term abuse of nicotine.
Module 4: Medication adherence, strategies for improving adherence, medical consequences of non-adherence
Module 5: Risky behaviors, sexually transmitted disorders, substance, and alcohol abuse
Module 6: Promotion of regular circadian rhythm, problems related to irregular daily activities
At the end of each meeting, a 20-min session of moderate physical activity (i.e., walking) is implemented with participants
Information and leaflets are provided to participants during each session. Positive changes are highlighted, potential strategies for change are discussed at each module. The core feature of the intervention is the inclusion of the motivational component. During each session, group participants are supported by mental health professionals in identifying a personal healthy lifestyle goal. After goal-definition, professionals help participant to define the motivations for lifestyle changing and teach problem-solving strategies for sustaining the behavioral change

TABLE 2 | Programme of LIFESTYLE educational brief group intervention.

Starting session: Introduction of the intervention, aims, purposes, and presentation of participants
Module 1: Healthy lifestyle (e.g., healthy diet, physical activity, smoking habits, promotion of circadian rhythm)
Module 2: Early detection of psychiatric relapses
Module 3: Pharmacological treatment and management of side effects
Module 4: Stress management techniques
Module 5: Problem-solving techniques
Information and leaflets are provided to participants during each session. Positive changes are highlighted, potential strategies for change are discussed at each module. The main aim is to provide patients with the principles of healthy living (i.e., eating fruit and vegetable, drinking water, doing moderate physical activities, not abusing of alcohol, quit smoking, etc.)

- Internalized Stigma of Mental Illness (ISMI), a 29-item questionnaire for evaluating the experience of stigma and internalized self-rejection (49). Each item is rated on a 4-level Likert scale, where higher scores indicate greater levels of internalized stigma.
- Questionnaire on lifestyle behaviors, a 24-items questionnaire, developed by the Italian National Institute of Health, which evaluates dietary patterns (e.g., food eaten at breakfast or lunch time), smoking habits (e.g., numbers of cigarettes smoked per day; attempts to quit smoking), and physical activity (e.g., time spent in walking per day) (50).
- The Questionnaire on sexual health, it is a 13-item *ad-hoc* questionnaire developed by the research team, which evaluates sexual behaviors and attitudes.
- The Pattern of Care Schedule (PCS)—modified version (51), a 40-item questionnaire on pharmacological and non-pharmacological treatments as well as on health care access made by the patient. It is compiled by the researcher in collaboration with the patient. If information is inadequate, or if the researcher is not sure about patients' reliability, other sources (e.g., treating physician, relatives, etc.) can be consulted. During the study period, the treating clinician will continue to provide the usual treatment to patient, and—if necessary—to change or adjust the pharmacological regimen.
- The anthropometric schedule is compiled by the researcher for collecting information on weight, height, BMI, waist circumference, blood pressure, resting heart rate, HDL, LDL, and overall level of cholesterol, blood glucose, triglycerides, and blood insulin. Moreover, the homeostatic model assessment (HOMA) index will be calculated for quantifying insulin resistance and beta-cell functioning as well as the Framingham Risk Score, for evaluating cardiovascular risk.

The following semi-structured interviews will be used during the study:

- The Brief Psychiatric Rating Scale (BPRS) (52) is a semi-structured 24-item interview on psychopathological status. The items are grouped in four subscales: positive symptoms, negative symptoms, depressive-anxiety symptoms, and manic-hostility symptoms.
- The Personal and Social Performance Scale (53) is a 100-point single-item rating scale, subdivided into 10 equal intervals. The ratings are based mainly on the assessment of patient's functioning in four main areas: (1) socially useful activities; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behaviors.
- The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making DSM-5 diagnoses. It is administered by a trained mental health professional that is familiar with the DSM-5 classification and diagnostic criteria.

The inter-rater reliability among researchers participating in the study was tested through Cohen's Kappa coefficient during

TABLE 3 | Assessment tools and time-points of the evaluation.

Assessment tool	Domains covered	Assessments' timepoints					
		T0 (baseline)	T1 (2 months)	T2 (4 months)	T3 (6 months)	T4 (12 months)	T5 (24 months)
Pattern of Care Schedule (PCS)—modified version	A 40-item questionnaire on pharmacological and non-pharmacological treatments as well as on health care access made by the patient. It is compiled by the researcher in collaboration with the patient. If information is inadequate, or if the researcher is not sure about patients' reliability, other sources (e.g., treating physician, relatives, etc.) can be consulted	x			x	x	x
Socio-demographic schedule	Information were collected: age, gender, marital status, level of education, working condition, economic status, number of family members, illness duration, time in charge at the mental health centre (months), number of (voluntary and involuntary) hospitalizations, suicide attempts (numbers)	x					
Anthropometric schedule	It is compiled by the researcher for collecting information on weight, height, BMI, waist circumference, blood pressure, resting heart rate, HDL, LDL and overall level of cholesterol, blood glucose, triglycerides and blood insulin. Moreover, the homeostatic model assessment (HOMA) index will be calculated for quantifying insulin resistance and beta-cell function as well as the Framingham Risk Score, for evaluating cardiovascular risk	x	x	x	x	x	x
Structured Clinical Interview for DSM-5 (SCID-5)	It is a semi-structured interview guide for making DSM-5 diagnoses. It is administered by a trained mental health professional that is familiar with the DSM-5 classification and diagnostic criteria	x					
Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery—brief version	It includes the MATRICS Consensus Trail Making Test—part A, Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency-Animal Naming (45, 46)	x			x	x	x
Brief Psychiatric Rating Scale (BPRS)	It is a semi-structured 24-item interview on psychopathological status. The items are grouped in four subscales: positive symptoms, negative symptoms, depressive-anxiety symptoms, and manic-hostility symptoms	x			x	x	x
Cumulative Illness Rating Scale (CIRS)	It is a 14-item questionnaire including a comprehensive assessment of physical comorbidities	x			x	x	x
Fagerström Test for Nicotine Dependence (FTND)	It is a 6-item questionnaire assessing the intensity of physical addiction to nicotine in terms of number of cigarette smoked per day, compulsion to use, and nicotine addiction	x			x	x	x
Food Frequency Questionnaire—short version	It is a 18-item questionnaire on the frequency consumption of a variety of foods corresponding to one's usual diet. In order to compile the questionnaire, the Scotti-Bassani Atlas is used for selecting quantity of food	x			x	x	x
Internalized Stigma of Mental Illness Inventory	It is a 29-items questionnaire for evaluating the subjective experience of stigma	x			x	x	x
International Physical Activity Questionnaire (IPAQ)—short form	It is a 18-item questionnaire exploring physical activity in terms of time spent in walking, in moderate-intensity and vigorous-intensity activities	x			x	x	x
Questionnaire on sexual health	It is an ad-hoc questionnaire developed by the research team, which evaluates sexual behaviours and attitudes	x			x	x	x
Leeds Dependence Questionnaire (LDQ)	It is a 10-item questionnaire designed to measure dependence for a variety of substances	x			x	x	x
Manchester Short Assessment of Quality of Life	It is a 17-item questionnaire assessing quality of life focusing on satisfaction with life as a whole and with life domains	x			x	x	x

(Continued)

TABLE 3 | Continued

Assessment tool	Domains covered	Assessments' timepoints					
		T0 (baseline)	T1 (2 months)	T2 (4 months)	T3 (6 months)	T4 (12 months)	T5 (24 months)
Morisky Medication Adherence Scale (MMAS)	It is a 4-item questionnaire for evaluating adherence to pharmacological treatments	×			×	×	×
Personal and Social Performance Scale	It is a 100-point single-item rating scale, subdivided into 10 equal intervals. The ratings are based mainly on the assessment of patient's functioning in four main areas: (1) socially useful activities; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behaviours	×			×	×	×
Pittsburgh Sleep Quality Index (PSQI)	It is 19-items questionnaire assessing sleep quality over a 1-month time interval	×			×	×	×
Questionnaire in lifestyle behaviours	It consists of 24 items, which evaluates dietary patterns (e.g., food eaten at breakfast or lunch time), smoking habits (e.g., numbers of cigarettes smoked per day; attempts to quit smoking), physical activity (e.g., time spent in walking per day)	×			×	×	×
The Recovery Style Questionnaire (RSQ)	It is a 39-item self-report questionnaire exploring six styles of adaptation to severe mental illness and recovery: sealing over, tends toward sealing over, mixed picture in which sealing over predominates, mixed picture in which integration predominates, tends towards integration, and integration	×			×	×	×
ECG evaluation		×					

the training course on the assessment instruments (54). Case-vignettes, videos and role-play have been used in order to ensure fidelity. The Cohen's kappa values were found to be satisfactory for PSP with a value of 0.918 and for the BPRS with a value from 0.835 to 0.972. For the SCID-5, 100% agreement rate was found.

ANTICIPATED RESULTS

Primary Outcome

BMI has been selected as primary outcome since it is a reliable and feasible anthropometric parameter, and it has already been considered in previous studies on lifestyle interventions (15, 16, 24). The primary outcome is the change of the BMI at 6 months post-randomization (T3). We expect a mean difference between the two groups of at least one point (and standard deviation of 2 points) at BMI. The work hypothesis is that the LIFESTYLE psychosocial group intervention will be more effective than the brief educational group intervention in reducing the BMI.

Secondary Outcome

The secondary outcomes include an improvement in dietary patterns (i.e., a reduction in fat food and increase in consumption of fruits and vegetables), smoking habits (i.e., a reduction in the number of cigarettes smoked per day), sleeping habits (i.e., regular number of hours slept per night), physical activity (i.e., increasing in time spent walking per day), personal and social functioning (i.e., level of functioning and time dedicated to meeting friends), severity of physical comorbidities (i.e., reduction at the CIRS global score), and adherence to medications (i.e., reduction in changes in pharmacological doses and regimen).

Exploratory Outcomes

Exploratory outcomes include anthropometric measures, such as waist circumference measured between the iliac crest and lowest rib, blood pressure measured on the right upper arm after 10 min of rest in a sitting position, resting heart rate after 10 min of rest, HDL, LDL cholesterol, blood glucose, triglycerides, blood insulin, HOMA index, and Framingham score.

Moreover, the severity of psychiatric symptomatology (as evaluated at the BPRS) and the levels of cognitive dysfunctions (as evaluated at the brief-MATRICS) were considered exploratory outcomes.

BASELINE ASSESSMENTS

At baseline the following socio-demographic information were collected: age, gender, marital status, level of education, working condition, economic status, number of family members, illness duration, time in charge at the mental health center (months), number of (voluntary and involuntary) hospitalizations, suicide attempts (numbers). Moreover, ECG evaluation was mandatory in order to check the eligibility to perform moderate physical activity.

STATISTICAL ANALYSES

Sample Size and Power Calculation

A power analysis has been implemented in order to define the sample size needed to detect a significant BMI reduction (primary study's outcome) between the two groups. In particular, it has been estimated a sample size needed to observe a mean difference between the two groups of at least one point at the BMI (kg/m^2) (with standard deviation of 2), with power set at 90% and a significant two-tailed alpha level of 0.05, based on previous studies on the same topic [e.g., (21, 23)].

Taking into account the multicenter design of the study, sample size has been adjusted for the Intercluster Correlation Coefficient (ICC), set at 0.030, and for the coefficient of variation of cluster sizes (COV), set at 0.400 (55). Therefore, the sample size consists of 348 patients (29 patients per arm in each center). Each center is expected to recruit 58 patients, rounded to 60. Moreover, previous trials evaluating the efficacy of interventions focused on physical activities and diet reported a drop-out rate of 15%; thus, the sample size has been rounded to 35 patients per arm for each center. Therefore, the expected sample size consists of 420 patients (70 patients for each participating center). This sample size has been considered feasible by all participating centers (**Figure 1**).

Data Analysis

Statistical analyses will be conducted according to the "Intention To Treat" principle. Missing data will be handled using the Last Observation Carried Forward (LOCF). All patients who signed informed consent form as well as those who undergo the initial assessment will be included. Descriptive statistics will be calculated for the dependant and confounding variables for both groups. The homogeneity of the two groups for these variables at baseline will be checked. In all cases, a bilateral alpha of 0.05 is considered an error and confidence intervals are calculated at 95%.

The analytic plan includes:

1) The implementation of a generalized estimated equation model (GEE). The GEE provides an estimation of the longitudinal impact of the interventions on primary and secondary outcomes, controlling for confounders, such as physical comorbidities, severity of psychiatric symptoms, level of social functioning, quality of life, self-esteem, recovery style, support from social network. A generalized estimating equation model will be employed using the following outcomes variables: the BMI, the severity index of the Cumulative Illness Rating Scale, the abdominal circumference: plasma levels of glucose, insulin, triglycerides, and cholesterol levels (total, LDL, and HDL); systolic and diastolic blood pressure, and cigarettes smoked per day.
2) The development of a Structural Equation Model (SEM) in order to identify possible mediators and moderators of the efficacy of the interventions, controlling for several confounders such as age, gender, severity of symptoms, BMI, etc. In particular, the variable "duration of the intervention" will be tested as one of the most relevant mediator or moderator for the efficacy of the interventions.
3) The implementation of multivariable logistic regression models, in order to identify predictors of positive response for changing unhealthy behaviors. In particular, as regards the primary outcome, this will be transformed in binary variable (yes vs. no) using the reduction of at least 1 point at the BMI as threshold. The impact of possible predictors (e.g., having an healthy diet; walking at least 30min per day; quitting smoking) as well as confounders (such as age, gender, level of education, diagnosis, duration of the illness, type of pharmacological treatment received) will be tested in a logistic regression model.
4) A subgroups analysis, according to the different diagnostic groups, in order to identify different profiles of efficacy of the interventions. The hypothesis is that patients suffering from affective disorders (both major depression and bipolar disorders) will report a higher improvement in the reduction of BMI and in changing their unhealthy lifestyle behaviors compared to patients with schizophrenia.

All data will be collected and analyzed by a statistician, who will be blinded during the trial. Data will be stored in hard copy by each center in a safe place. They will be placed on an online dataset, and will be accessible to each unit. For each patient, only the recognition ID will be reported in the dataset. For safety reasons and to ensure patients' privacy, the dataset will be protected by a password. Each center will have its own password, and will be responsible for data entry. A statistician from the coordinating center will manage data collection and will provide assistance to researchers in case of difficulties in using the software. It will be possible to export data in compatible formats with common calculation software (e.g., Microsoft Access and Excel) and in specific software (e.g., SPSS, STATA) for statistical analyses.

STEPWISE PROCEDURE

From month 1 to 6, the following phases have been carried out: (1) development of the work plan for data collection in each participating center; (2) training course for mental health professionals on the interventions; (3) training course for researchers on assessment tools. From month 7 to 12, patients' recruitment has been implemented. From month 7 to 18, interventions are being provided to participating patients. From month 7 to 30, patients' follow-up assessments are being made. From month 31 to 36, statistical analyses will be performed as well as findings will be disseminated through papers and participation in conferences. The stepwise procedure is summarized in **Figure 2**.

DISCUSSION

Unhealthy and unbalanced diet, physical inactivity, smoking, and excessive alcohol or substance use are very common in people with severe mental disorders (12, 56–60). All these factors contribute to the excess mortality found in those people compared to the general population. It is an ethical and a

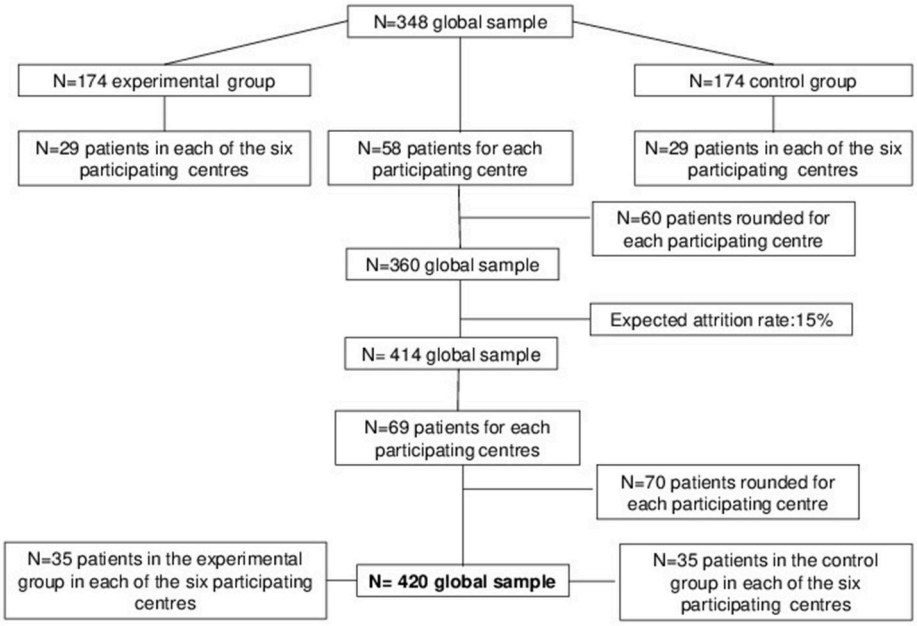

FIGURE 1 | Power analysis and sample size.

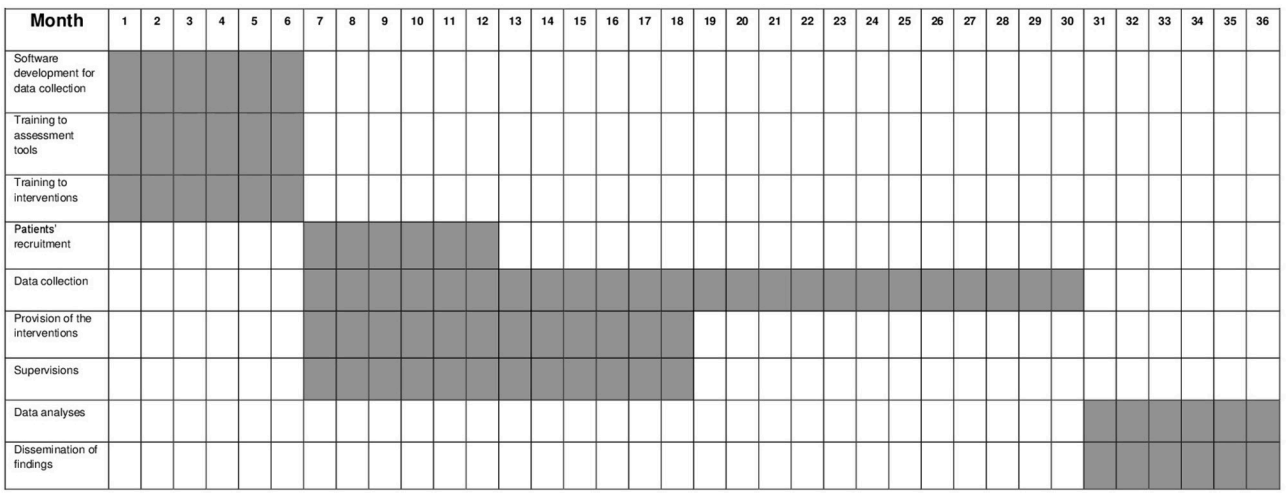

FIGURE 2 | Stepwise procedure.

clinical priority to develop and implement effective strategies for modifying and eliminating those risk factors (61, 62).

One possible strategy is the provision of psychosocial integrated interventions specifically tailored on the physical needs of patients with severe mental disorders (63). In fact, as recently pointed out by De Rosa et al. (25), although several psychosocial interventions have been developed on different aspects of unhealthy lifestyle behaviors, their feasibility has not been evaluated in routine care.

The research protocol presented herein proposes an innovative approach to manage unhealthy lifestyle behaviors in patients with severe mental disorders and to promote a pattern of change. In particular, the main novelties of the LIFESTYLE psychosocial group intervention are: (1) the integration of classic psychoeducational with motivational and cognitive-behavioral therapy techniques; (2) the adoption of a comprehensive approach, addressing not only unhealthy diet and overweight, but focusing on all aspects of unhealthy lifestyles; (3) the provision of the intervention to a mixed diagnostic group of patients; (4) the inclusion of the recommendations and/or guidelines on the management of physical health in people with mental disorders produced by the World Health Organization

(33, 34), the European Association for Study of Diabetes (35), the European Society of Cardiology (36) and the European Psychiatric Association (37).

The inclusion of the motivational interview is one of the major strengths of the LIFESTYLE intervention. Several studies (64–66) have proven that increasing motivation is a successful strategy in the whole medicine for supporting medication adherence (67) or weight loss (68). During the first session of the LIFESTYLE psychosocial group intervention, each participant is required to identify a personal lifestyle goal that should be realistic and achievable in a relatively short period of time. Patients are empowered to determine their lifestyle goals and the intervention can contribute to their specific recovery goals.

Moreover, it is well known that patients with severe mental disorders are at high risk of developing physical diseases and receiving late diagnoses due to the underestimation of somatic comorbidity. Through the psychoeducational approach, we will provide patients with information on main physical complaints and on how to detect them. In particular, through focus groups with the participation of expert clinicians and/or users and carers, we have developed written materials (such as leaflets and brief manuals) targeted to the physical needs of people with severe mental disorders that will be distributed to participants whenever necessary (69–71).

The LIFESTYLE trial adopted a comprehensive approach focusing on all aspects of unhealthy behaviors, since the increased morbidity and mortality of patients with severe mental disorders is due to the interaction of several risk factors. In particular, dietary pattern and sedentary behaviors are easier to change and therefore will be addressed in the first two sessions of the LIFESTYLE intervention, when patients' drop-out risk is higher. Another important topic is the reduction of smoking, which is frequent in patients with severe mental disorders (72–74). The reduction in smoking habit is not the primary outcome of the study, and for this reason we did not propose to patients specific pharmacological (e.g., nicotine patches, nicotine gum, bupropion, or nortriptyline) or non-pharmacological strategies (e.g., cognitive-behavioral therapy group targeted on substance abuse) for supporting smoking cessations, as already done in previous studies (26). Nevertheless, we expect a reduction in the number of cigarettes smoked per day, as a consequence of the global lifestyle improvement. Also, patients with severe mental disorders frequently have risky sexual behaviors, which are often due to the presence of cognitive deficits and manic symptoms, and represent the cause of many sexual transmitted diseases. Moreover, the sexual health of patients with severe mental disorders is often neglected by clinicians who do not routinely ask to patients about their sexual life (75, 76). The circadian rhythms are frequently altered due to polarity switch of mood in affective disorders or to the non-adherence to psychotropic medications. Therefore, in our intervention a specific session dealing with those aspects has been included, since these aspects must be taken into account for achieving a global improvement in lifestyle.

Non-adherence to medications is responsible for a variety of clinical and social problems, such as relapses, hospitalization, reduction in quality of life and in personal functioning [(77, 78)]; thus, improving medication compliance represents another important challenge addressed during the intervention. Since the LIFESTYLE intervention is patient-centered and motivational-led (78), it has been developed to fulfil the unmet needs of patients with severe mental illness, including the improvement of treatment adherence.

As regard our primary outcome measure, the BMI has been selected since it is a reliable and feasible anthropometric parameter to be analyzed. Of course, there are many factors which can have an impact on BMI changes, such as the pharmacological treatment (e.g., in the case of patients receive second generation antipsychotics) or other physical comorbidities (such as, endocrine diseases). We will be able to control for these possible confounders through multivariable statistical approach. Moreover, patients are required to identify a personal lifestyle goal to be achieved, and—by definition—such goal can be different for each participant, e.g., days spent in physical activities; drinking at least 2 l of water per day; reducing the number of cigarettes smoked per day; etc. and not easily measurable. In the experimental intervention, it has been included a brief session of moderate physical active at the end of each meeting, therefore we test the hypothesis that BMI can be reduced, even if the personal goal selected by the patient is related to smoking pattern or to other aspects of the lifestyle. As observed by Speyer et al. (22, 23), adopting an heterogeneous intervention, when every patient can choose the personal goal to be reached, can be the right choice for changing a complex phenomenon as lifestyle. The prevalence of unhealthy lifestyle behaviors is a transdiagnostic phenomenon and we decided not to tailor the intervention to a specific group of patients in order to involve the highest number of patients as possible. As recently pointed out (25) when the patient population is selected on the basis of the diagnoses, there are no data proving the higher efficacy of the lifestyle intervention.

In this study, we aim to evaluate the cost-effectiveness of the interventions, since only Verhaeghe et al. (79) found that the intervention is cost-effective only in men with a significant BMI reduction. For improving the dissemination of psychosocial interventions targeted on healthy lifestyle behaviors, it is necessary to prove that these interventions are cost-saving. In order to improve feasibility of the interventions in the clinical routine care, we decided not to include dieticians or physical trainers, since the involvement of health professionals different from psychiatrists or psychologists could hamper the dissemination of the interventions in the routine practice. Of course, this hypothesis should be further tested in multicentric studies involving different European countries, since it could be that workload and multidisciplinary staffs include different health professional according to the organization of the National health care. At least in Italy, the inclusion of specific health professionals such as dieticians and physical trainers is not the routine for the mental health care. A critical element in our research protocol is the attrition rate from the two intervention groups. As already pointed out in other studies on lifestyle psychosocial interventions, such as the CHANGE (22, 23) and CAPICOR (21) trials, the attrition rate ranges from 5 to 40% and we expect an attrition rate of at least 15%. Nevertheless, in order to guarantee attendance, patients will

continue to be in contact with their referring clinicians during the provision of the intervention, and will receive phone or e-mail reminders for each session of the intervention. Moreover, the active involvement of patients as "experts" could further motivate them to attend the sessions during the intervention. This project represents the first multicentric randomized head-to-head comparison trial for evaluating the efficacy of psychosocial interventions targeting unhealthy lifestyle in people with severe mental disorders in Italy. In particular, we aim to test the efficacy of two different interventions targeting lifestyle behaviors. In particular, considering that one of the main critical issue is related to the optimal duration of the interventions, this aspect will be evaluated in our trial since we will test the impact of the "duration of the intervention", as one of the possible mediator or moderator of the efficacy of the interventions.

The trial has some limitations, which must be acknowledged. A first limitation is the selection bias of patients accepting to participate to the LIFESTYLE trial. In fact, it could be that only highly motivated patients accept to take part to the study and will continue to attend all scheduled sessions. Another possible limitation is the use of manuals for clinicians carrying out the intervention. While this methodological choice was made in order to increase external validity and reliability of the interventions, it may have limited the generalizability of the intervention to other patients. Moreover, the two interventions are different in terms of frequency of contact with the mental health professionals. This aspect will be considered as a potential confounder for the effectiveness of the intervention. Finally, another possible limitation of the study is the global duration of the intervention. In fact, Naslund et al. (80) recently highlighted that lifestyle interventions of ≥12-months duration appear to be more effective compared to those lasting ≤6-months. Moreover, other studies have found a modest or small effect for short-term interventions, suggesting that longer interventions should be studied. On the other hand, long approaches are associated with a higher drop-out rate of patients who may have difficulties in attending structured long-term approaches (81–84). Therefore, we will explore the efficacy and the effectiveness of a medium-term intervention with multiple follow-up assessments.

CONCLUSIONS

In people with severe mental disorders, unhealthy lifestyle is very frequent and is associated with poor outcomes. Therefore, there is the need to develop and test the efficacy of new interventions for changing unhealthy behaviors. We hope that the study protocol presented herein will help to fill this gap and improve physical health of patients with severe mental disorders.

ADDED VALUE OF THIS STUDY

To our knowledge, this is the first multicentric randomized head-to-head comparison trial of behavioral change intervention targeting unhealthy lifestyle in people with severe mental disorders in Italy.

The main novelty of our approach is the integration of classic psychoeducation with motivational and cognitive-behavioral therapy techniques. Both interventions have been developed following the recommendations and guidelines on the management of physical health in people with mental disorders produced by the World Health Organization (33, 34), the European Association for Study of Diabetes (35), the European Society of Cardiology (36), and the European Psychiatric Association (37). Moreover, our interventions did not target only one aspect of unhealthy lifestyle behaviors, but aim to promote a global change in lifestyle behaviors, which should become more oriented to the healthy living approach. We believe that pursuing such aim should be more useful, feasible and acceptable in patients with severe mental disorders, rather than the achievement of changing just one among all unhealthy behaviors. Creating and disseminating the culture of "living healthy" should be useful to guarantee a long-term change in patients' behaviors and for reducing significantly the mortality gap with the general population.

LIFESTYLE WORKING GROUP

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ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethical Committee of the University of Campania Luigi Vanvitelli. The protocol was approved by the Ethical Committee of the University of Campania Luigi Vanvitelli. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

GS, AF, ML, and MM designed the study and wrote the protocol. AF, VDV, ML, CDR, CM, GB, VG, MS, and GS organized the training and supervisions for mental health professionals, and coordinated the activities with participating mental health centers. GS, ML, LS, and BP managed the literature searches and analyses. MB, MA, FP, LDO, and GDL coordinated the study in their center. The working group includes: GB, CDR, VG, CM, and MS (Department of Psychiatry, University of Campania Luigi Vanvitelli, Naples); AF, LL, and FV (University of Bari Aldo Moro); MBM, PC, and DZ (University of Genova);

FL, SP, and DS (University of L'Aquila); CC, ED, and MTA (University of Pisa); EB, CN and AS (University of Rome Tor Vergata). All working group participants contributed to the development of the training materials and participated to the training course for the interventions and for the assessment tools.

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Evaluating the Feasibility of a Pilot Exercise Intervention Implemented Within a Residential Rehabilitation Unit for People With Severe Mental Illness: GO HEART: (Group Occupational Health Exercise and Rehabilitation Treatment)

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Purpose: People with severe mental illness are sedentary, have high cardio-metabolic risks and significantly reduced life expectancy. Despite considerable data regarding positive physical and mental health outcomes following exercise interventions, implementation and evaluation of real-world programs is lacking. The primary aim of this study was to assess the feasibility of an exercise intervention implemented by exercise physiology (EP) students within a residential rehabilitation unit for residents with severe mental illness, together with assessment of a range of secondary physical and mental health outcomes pre- and post- the intervention.

Design: Single arm, prospective pilot study evaluating outcomes pre- and post- a 10 week intervention.

Method: Inactive people with severe mental illness participated in a mixed aerobic and resistance exercise intervention, three times per week for 10 weeks. Data was obtained from a sample of 16 residents with severe mental illness; primary diagnosis schizophrenia ($n = 12$). Primary outcomes were feasibility as assessed using recruitment, retention and participation rates, as well as reasons for withdrawal and amount of exercise achieved. Secondary outcomes included: functional exercise capacity was measured by the 6-min walk test; metabolic data obtained from anthropometric measurements; blood pressure; fasting cholesterol and blood sugar levels; and physical activity levels and mental health as assessed by self- administered questionnaires measured before and after the intervention.

Results: Broad level acceptance of the program: high recruitment (81%), retention (77%), and participation (78%) rates were observed. Promising improvements in functional exercise capacity, volume of exercise, and negative symptoms was demonstrated in those who completed.

Conclusions: Exercise interventions delivered by EP students in a residential rehabilitation setting for people with SMI are feasible; group setting, supervision and choice for engagement are important considerations. Evaluation of longitudinal, multi site studies, with the addition of dietary interventions within residential rehabilitation units are warranted. Addressing cost feasibility and cost effectiveness of such programs is recommended.

The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) number, Unique Identifier: ACTRN 12618000478213, http://www.anzctr.org.au Universal trial number (UTN) – U1111-1211-4009.

Keywords: severe mental illness, exercise, rehabilitation, pilot study, exercise physiology, mental health

INTRODUCTION

People living with severe mental illness (SMI) die approximately 15 years earlier than the general population (1), due in part to their increased risk of preventable conditions such as cardiovascular disease (CVD) (2). Modifiable lifestyle risk factors such as low exercise participation, smoking, and poor dietary habits are major contributors to these poor health outcomes, together with the cardio-metabolic burden of antipsychotic medications (3–8). In view of this, there is an urgent need to address modifiable risk factors that contribute to the mortality gap, such as physical inactivity and low cardio-respiratory fitness by developing effective strategies to improve the poor physical health of people with SMI (9, 10).

Individuals with SMI engage in lower amounts of exercise and have lower cardiorespiratory fitness (CRF) compared with the general population (11–13). Exercise protects against chronic disease, and can improve CRF which is inversely related to all-cause mortality (14). An increasing body of evidence also demonstrates a wide range of mental health benefits of exercise for people with SMI, including improved mood, cognition, quality of life, and reduced positive and negative symptoms of schizophrenia. (15–18).

Widespread implementation of exercise interventions within a mental health setting has been limited by a number of factors (19, 20). A prioritization of mental health interventions over physical health interventions by services has limited funds and spending on implementing physical health interventions, such as exercise. Also, mental health professionals often lack the confidence to design and deliver exercise interventions. Furthermore, there has been a lack of evaluation and dissemination of the results of successful real-world exercise interventions within mental health settings to guide other mental health clinicians wishing to develop exercise programs (20–22).

Mental health rehabilitation services support people with more chronic and enduring symptoms than general outpatient services, offer higher support and focus on functional improvements. In Australia, the Community Care Unit (CCU) is a voluntary residential rehabilitation unit for people with SMI, (predominantly living with chronic schizophrenia) in which a focus on holistic recovery is incorporated into the model of service (23) and hence may be an ideal setting for an exercise intervention implementation (24).

Few exercise studies have been conducted within residential rehabilitation services. One study reported difficulties with recruitment and retention ($n = 14$; 36% dropout), but reduced negative symptoms for participants who completed the personal trainer led exercise program (25). Another study conducted in a secure setting reported high adherence ($n = 8$; 0% dropout) to an off-site gym-based aerobic exercise program delivered by an exercise physiologist (EP), but no changes in CRF or endurance (26). A qualitative study ($n = 6$) of participant experiences in a CCU-based exercise intervention delivered by EP's reported that individualization and group dynamics were important aspects of the program (27). To date, studies in these settings have all relied on employed exercise staff to deliver the interventions, which may affect long term feasibility.

The aim of this pilot study was to evaluate a novel model for the provision of exercise interventions within a real-world residential rehabilitation setting. To address the barriers of resource limitations, this model involved senior exercise physiology (EP) students from a university degree program at no direct cost to the service. EP students were mentored in a multidisciplinary mental health team to implement and evaluate a 10-week exercise intervention for people with SMI living in a CCU in Queensland.

METHODS

Study Setting and Participants

The study was approved by the Metro South Human Research Ethics Committee (HREC 16/QPAH/042). All subjects provided written informed consent in accordance with the Declaration of Helsinki. Participants were recruited to the single-arm prospective cohort open pilot study from the Coorparoo CCU, a residential rehabilitation unit of the Metro South Addiction and Health Service in Brisbane, Australia. The CCU has capacity for 20 residents with diagnoses of SMI who are admitted for psychosocial rehabilitation. Most residents admitted to the CCU have diagnoses of either schizophrenia, schizoaffective or bipolar disorder as assessed by the CCU Consultant Psychiatrist, using the Diagnostic Statistic Manual of

Mental Disorders, Fifth Edition (DSM- 5). Recruitment occurred over a 3-week period prior to the intervention. Inclusion criteria for the study were; (i) current resident at the Coorparoo CCU, (ii) aged 18–65 years, and (iii) able to provide informed consent. Residents were excluded if they; (i) presented with absolute medical contraindication to exercise as determined by a general practitioner, (ii) were considered high risk for aggression or suicide. (As standard clinical practice, all patients of the mental health service are classified as low, medium, or high risk for aggression and suicide by an experienced mental health clinician or consultant psychiatrist, using a standardized risk screening tool) (28), (iii) were considered to have an acutely unstable mental state by the treating psychiatrist; (residents were considered stable if they had not attended the Emergency Department for mental health assessment or been hospitalized in the past 6 months) (iv) were pregnant, or (v) were engaging in an regular exercise or physical activity program outside of the CCU at the time of recruitment. Fourth year EP students assessed potential participants for risks to exercise using the Adult Pre-exercise Screening System (APSS). The APSS provides an evidence-based system for identifying and managing health risks for exercise and it is used to identify people who may have medical conditions, which put them at a higher risk of an adverse event during exercise. The APSS has 3 stages- stages 1 and 2 are self assessed and stage 3 is completed by a fitness professional to identify and stratify risks to exercise, including whether a recommendation of further medical assessment before exercise program is undertaken (29). In this study, participants with identified risks were reviewed by their general practitioner to determine suitability before inclusion. See Supplementary Image 1.

Intervention

Drawing on earlier research in this population, implementation of this exercise intervention addressed four main considerations (a) assessment of risk level, (b) assessment of cardiorespiratory fitness status, (c) achievement of an achievable intensity level, and (d) strategies to improve motivation and adherence (30).

Intervention duration was 10 weeks and session frequency was three times per week to maximize improvements in fitness (11). The intervention offered engagement in a total volume of moderate intensity exercise that was greater than 90 min per week, above which has been shown to be associated with improvements in mental health outcomes (17). Exercise sessions consisted of a 45-min group circuit in the shared courtyard of the CCU, which comprised a 5-min warm up, and 10-min cool down. The equipment used for the circuit included a recumbent bike, a treadmill, boxing pads and gloves, therabands, step and dumbbells. The circuit stations varied each week and included a mixture of aerobic and resistance exercises. Stations were designed such that they could be modified (regressed/progressed) to suit individual participant capacity and preference. The Borg Category Ratio 10 scale (31) was used to assess rate of perceived exertion (RPE) and to guide intensity of exercise prescription. Initial prescription was aimed at intensity achievable for participants with low initial CRF but progressed to reach moderate intensity by week 3 (11). EP students aimed to maintain an RPE at 2–3 for the first 2 weeks, then increased to a minimum RPE of 4/10 by week 3 and further increased as per individual participant's capacity. Following warm-up, participants rotated through 10–15 stations. The circuit began at intervals of 30 s of exercise interspersed with 30 s of complete rest and progressed to 60 s interval as the participants' functional capacity increased.

Fourth year EP students led the exercise circuit with supervision from an EP Clinical supervisor as part of a practicum placement from their university undergraduate degree program.

This intervention included several evidence based motivational strategies to increase participants' adherence to the program (30);

1. EP students and mental health staff gave validation and encouragement to participants throughout the intervention
2. EP students helped participants set realistic goals, and addressed individual preferences for exercise engagement
3. EP students and the consultant psychiatrist collaborated to identify and problem-solve barriers to participation and liaised regularly with mental health staff in team meetings to enlist their support with this.

Mental health residential rehabilitation staff were prepared for the intervention prior to study onset by provision of information regarding the protocol for the exercise intervention, and information regarding the potential physical and mental health benefits of exercise to people with SMI in emails and discussion in team meetings prior to the intervention beginning.

EP students were provided with an orientation to the facility, education about common mental disorders for residents, aims of the study and their role in delivery of the intervention. They also attended weekly supervision sessions with the consultant psychiatrist to learn more about mental health conditions and strategies to engage people with SMI.

Primary Outcomes

The primary outcome of the current study was feasibility, which was assessed using recruitment, retention and participation rates, reasons for withdrawal and amount of exercise achieved. *Recruitment* was calculated by the proportion of participants recruited to the study from all eligible CCU residents during the 3-week recruitment phase prior to the study onset. *Retention* was calculated by the proportion of those recruited that completed all pre- and post-measures. *Participation* was the proportion of total sessions in the study attended by participants. *Reasons for non-attendance* and *withdrawal* were recorded in the participant's log book together with adverse events.

Secondary Outcomes

Secondary outcomes included indicators of physical and mental health, exercise participation, and exercise motivations.

Functional exercise capacity was estimated by the 6-min walk test (6MWT). The 6MWT measures the distance in meters that an individual can walk in a 6-min period on a flat surface. It is a submaximal test that has been shown to be a reliable measure of exercise capacity in people with SMI (32, 33). In the current

study, 6MWT was carried out by trained EP students, utilizing the ATS guidelines (34) at baseline and week 10.

Physical activity and *sedentary behavior* was assessed using the Simple Physical Activity Questionnaire (SIMPAQ). The SIMPAQ is a 5-item interviewer-administered, self-report clinical tool to assess physical activity and sedentary behavior in the previous week in populations at risk of engaging in high levels of sedentary behavior, such as those with mental illness (35).

At baseline and week 10, *psychotic symptoms* were rated on the Brief Psychiatric Rating Scale (BPRS) through the use of a semi-structured interview guide and an anchored scoring version of the BPRS-A (36, 37). *Negative symptoms* were assessed via the Scale for the Assessment of Negative Symptoms (SANS) (38) using the Interview guide for Assessment of Negative symptoms (IG-SANS) (39).

Quality of life was assessed at baseline and at week 10 using the AQol-8D, a reliable and valid instrument, which is particularly suitable when psychosocial elements of health are of importance (40).

The Behavioral Exercise Regulations Questionnaire (BREQ-2) was used to measure *participants' motivations toward exercise* (41). Items on "identified regulation" (finding personal value in reasons for being active) and "intrinsic regulation" (personal enjoyment/liking of exercise) were combined to create a single domain "autonomous regulation," (defined as the combined mean of intrinsic and identified regulation) as per a previous validation study of the BREQ 2 in patients with SMI (42).

Metabolic parameters including fasting lipids, fasting glucose, waist circumference, and blood pressure, resting heart rate, as well as body mass index (BMI) were collected pre-, and post- the 10-week intervention.

Statistical Analyses

Statistical analyses were conducted using SPSS 24 (SPSS 2016). Feasibility measures were summarized with percentages. Normality probability plots and the Shapiro-Wilk statistic were used to check for normality and appropriate nonparametric statistics were applied to outcomes that were not parametric. Normally distributed pre and post outcome measures were tested using a paired *t*-test with significance level of $\alpha = 0.05$. Mean differences and associated 95% confident intervals (CI) were calculated and Cohen's d statistic was calculated. Non-parametric data was analyzed using medians, interquartile range and Wilcoxon signed rank tests.

RESULTS

Baseline Characteristics of Participants

Baseline characteristics of the study population are shown in **Table 1.** The mean age of participants was 31 (SD 7.9) of which 3 (30%) were female. The predominant diagnosis was schizophrenia or schizoaffective disorder (90%) (12). The average duration of illness was 10 years (SD 7.3). Half the cohort were taking clozapine, and greater than 80% were either on olanzapine or clozapine, the two most metabolically unfavorable antipsychotics with the highest risk of weight gain (7). More than half of the sample (54%) were current smokers. Of note, even though 23% of participants were screened as having increased risk of adverse event during exercise at baseline, all were cleared to participate in the study after an assessment by a general practitioner.

TABLE 1 | Baseline characteristics.

	Total sample *N* = 13	Completers *N* = 10	Withdrawals *N* = 3
Demographic			
Female; *n* (%)	4 (30)	3 (30)	1 (33)
Male; *m* (%)	9 (70)	7 (70)	2 (67)
Age (years), mean (SD)	31 (7.9)	32 (8)	27.6 (8)
Duration of illness, years, mean (SD)	10 (7.3)	11.6 (7.3)	5.1 (5.9)
Psychiatric diagnosis	***n* (%)**	***n* (%)**	***n* (%)**
Schizophrenia/ schizoaffective	12 (92)	9 (90)	3(100)
Bipolar affective disorder	1 (8)	1 (10)	0
Comorbid substance abuse	4 (30)	3 (30)	1 (33)
Medications			
Any antipsychotic	12 (92)	10 (100)	2 (66)
Clozapine	7 (54)	7 (70)	0
Olanzapine	4 (30)	3 (30)	1 (33)
Physical condition			
Hypertension	1(7)	0 (0)	0 (0)
Diabetes Mellitus	0 (0)	0 (0)	0 (0)
Abnormal lipid profile	4 (30)	4(40)	0 (0)
Current smoker	7 (54)	6 (60)	1 (33)
Physical health problem identified on risk screen	3 (23)	3 (30)	0 (0)

Recruitment and Retention

Figure 1 provides a summary of the recruitment and retention process of the current study.

Of 16 eligible residents (81%), consented to participate in the study and completed baseline measures. One resident declined due to lack of interest and two resident's mental state destabilized and hence were not eligible. Ten participants (77%) completed the 10-week study. Of the three who dropped out, one was due to discharge from the service, another preferred to exercise at an external facility, while the third completed the program but was unavailable to complete post measures due to unexpected discharge. Of those who completed the program, mean number of sessions attended was 23.4 (SD 5.34) out of a possible 30, an average attendance rate of 78%.

There were no adverse events during the intervention. Analysis of log books revealed primary reasons for non-attendance were (1) a schedule clash with another appointment

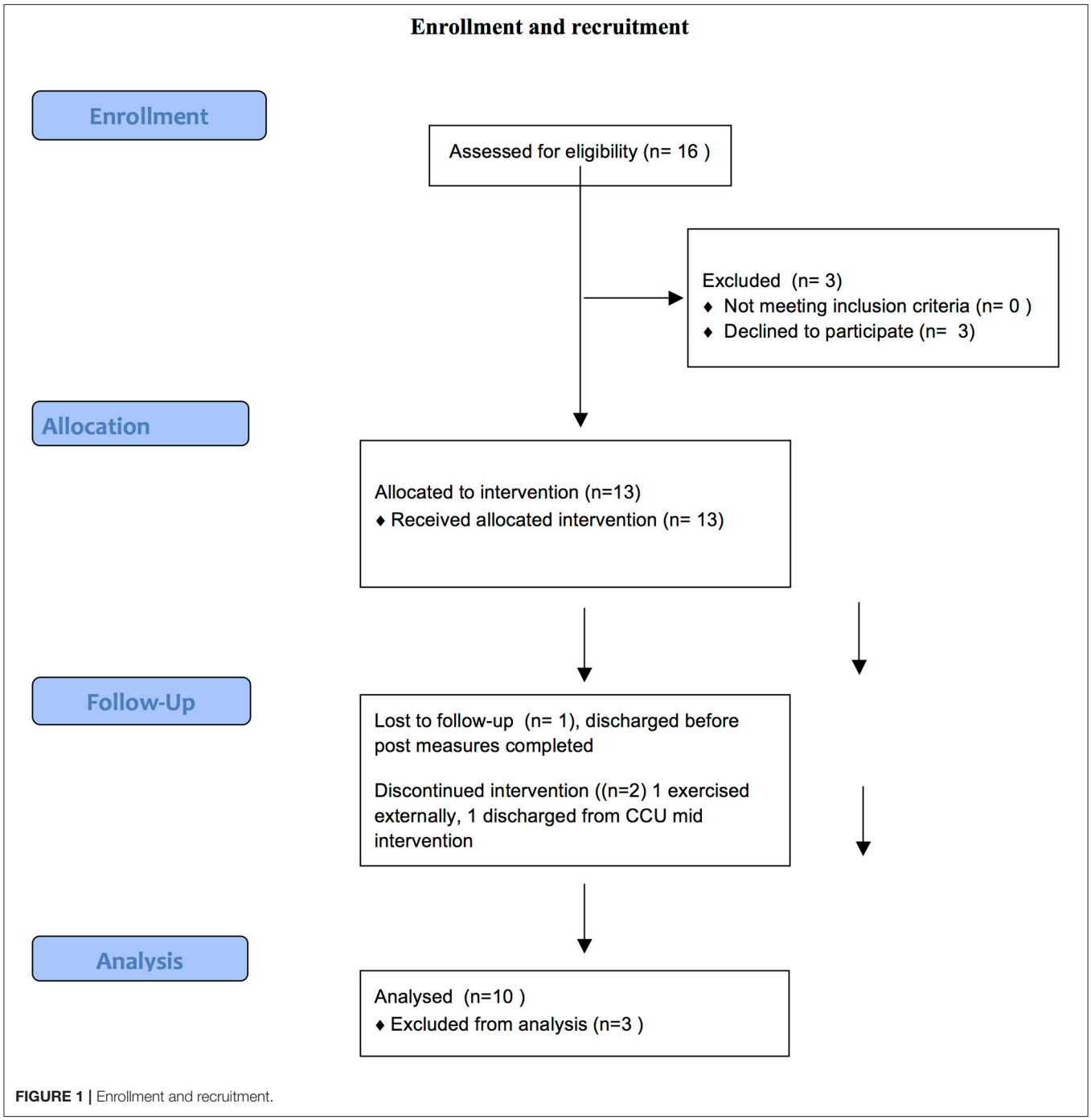

FIGURE 1 | Enrollment and recruitment.

(such as GP/ psychologist, blood tests), (2) morning sedation, and (3) feeling unmotivated to attend.

Pre- and Post-measures

Table 2 summarizes the changes in pre- and post-outcome measures after the 10-week exercise intervention. Baseline 6MWT distances for the sample were very low (452 m with SD of 65 m) reflecting reduced initial functional exercise capacity of the participants. Following 10 weeks, the distance achieved on the 6MWT increased significantly by a mean of 76.8 m (95% CI 54, 99), $p < 0.001$ with a large effect size (Cohen's $d = 0.7$). This represented a 16.8% increase on the 6MWT distance. 100% of participants increased their 6MWT distance post the exercise intervention and 80% of participants increased their 6MWT by greater than 50 m.

Reported volume of exercise engagement per week (minutes) also increased from pre-intervention (median = 60) to post-intervention (median = 130), $p = 0.019$, with

TABLE 2 | Pre- and post-measures.

(*N* = 10)	Baseline mean (SD)	Post mean (SD)	Mean difference (95% CI)	Test statistict (df) or z[b]	*P*-value
6MWT distance[1] (meters)	452 (65)	528 (85)	76.8 (54, 99)	7.78 (9)	<0.001*
[np]Self reported exercise in previous week (minutes/week)	60 (52.5)[a]	130 (15)[a]	–	−2.346[b]	0.019*
Self-reported sedentary behavior (hours/ day)	7.9 (4.5)	5.8 (2.5)	2.1 (−0.5, 4.7)	−1.82 (9)	0.101
[np]Fasting BSL[2]	5.1 (0.92)[a]	5.15 (0.72)[a]	–	−0.95[b]	$p > 0.30$
Fasting total cholesterol (mmol/L)	4.8 (0.57)	4.6 (0.64)	0.12 (−0.2, 0.44)	−0.83 (9)	$p > 0.30$
Body mass index (weight kg/height m[2)]	29.2 (4.9)	29.4 (4.6)	0.19 (−0.12, −0.9)	0.39 (9)	$p > 0.30$
Abdominal circumference (cm)	100.9 (11.6)	102.8 (12.7)	1.85 (−6.7, 3.01)	0.86 (9)	$p > 0.30$
Systolic blood pressure (mmHg)	134.1 (19.7)	127 (14.5)	7 (−5.8, 19.8)	−1.23 (9)	0.248
Diastolic blood pressure (mmHg)	85 (9.5)	79.3 (8.6)	5.7 (−0.7, 12)	−1.99 (9)	0.078
BPRS[3]	32.4 (8.3)	29 (6.1)	3.4 (0.03, 6.7)	−2.27 (9)	<0.049*
SANS[4]	45.2 (11.8)	30.7 (12.7)	14.5 (9.6, 6.8)	6.8 (9)	<0.001*
BREQ-2[5]					
[np]Amotivation	0.000 (0.81)[a]	0.000 (0.63)[a]	–	−0.135[b]	$p > 0.30$
[np]External regulation	1.12 (0.56)[a]	1.25 (1.13)[a]	–	−0.949[b]	$p > 0.30$
Introjected regulation	1.7 (1.25)	1.6 (1.08)	0.16 (−0.5, 0.84)	0.56 (9)	$p > 0.30$
Identified regulation	2.45 (1.16)	2.85 (0.94)	0.4 (−1.11, 0.31)	−1.2 (9)	0.235
Intrinsic regulation	2.75 (0.87)	2.5 (0.86)	0.23 (0.06, 0.3)	3.2 (9)	0.01*
Autonomous regulation	2.6 (0.8)	2.68 (0.82)	0.03 (−0.9, 0.83)	−0.097 (9)	$p > 0.30$

[1]*6MWT, 6 min walk distance;* [2]*BSL, Blood Sugar Level;* [3]*BPRS, Brief Psychiatric Rating Scale;* [4]*SANS, Scale for the Assessment of Negative Symptoms;* [5]*BREQ-2, Behavioral Exercise Regulations Questionnaire;***p < 0.05, significant; np, nonparametric outcomes.*

[a]*median (Interquartile range) for non-parametric outcomes.*

[b]*z statistic for Wilcoxon signed rank test for nonparametric outcomes.*

a large effect size ($r = 0.74$). 80% of participants increased their volume of exercise by 60 min or more, 20% reported a 30–60 min reduction compared to baseline. There were no changes in sedentary behavior, metabolic parameters or BMI following 10 weeks of exercise.

In terms of psychiatric symptom measures, both negative symptoms and overall symptoms showed significant reductions. The SANS score decreased by 14.5 (95%CI 9.6, 6.8) $p < 0.001$ with a large effect size (Cohen's $d = 0.8$). All of the participants showed a reduction on their SANS score, with 70% reducing by greater than 10 points, BPRS score decreased by 3.4 (95%CI 0.024, 6.7) $p < 0.01$ post intervention with a small effect size (Cohen's $d = 0.29$).

Participants' attitudes toward exercise as assessed by the BREQ-2 showed significant reduction in intrinsic regulation following the intervention (0.23, CI 0.06, 0.3) $p = 0.01$, with a small effect size (Cohen's $d = 0.2$). However, the change in external motivation domains (amotivation, external regulation and introjected regulation) and autonomous regulation was not significant.

There were no changes seen in the AQoL−8D in any domains or the weighted utility index following the exercise intervention (see Supplementary Table 1).

Additional Observations

This pilot revealed a number of important considerations for conducting exercise interventions in rehabilitation settings. Despite mental health staff being prepared for the exercise intervention prior to implementation, this was found to be insufficient to change the staff culture to allow the exercise intervention to be adequately prioritized from the outset. Initially staff scheduled other appointments or blood tests with participants during exercise session times, reporting that these were more important priorities for residents, which led to reduced participation in exercise. Frequently expressed initial concerns from staff were that if residents exercised they would be too tired to do other therapies. Mental health staff were provided with the opportunity to ask questions and have fears reassured.

Whilst students were given clear initial orientation to the rehabilitation unit and the study, EP students had little prior experience interacting with people with severe mental illness and as such were anxious how to engage them. Students

reported feeling uncertain about what to expect from patients and expressed fears about personal safety based on past media exposure. This reflected commonly held attitudes among the general community regarding SMI and the inflated perception of risk of violence (often portrayed in the media) that typically leads to stigma (43). During supervision, the researchers attempted to up skill EP students regarding the accurate evidence of the risk of violence for people with severe mental illness, the consequences of stigma, mental health literacy and the barriers to exercise engagement faced by people recovering from SMI. EP students were also encouraged to have un-structured individual contact with residents of the unit in addition to the exercise intervention (such as playing pool together or games) as this has been reported to be an important aspect of stigma reduction (44).

To improve participation, participants who reported morning sedation were offered a small group make-up session later in the day. Participants who regularly skipped sessions were asked what they would like to do in the program and then preferred elements of the circuit were increased, (i.e., boxing with the EP student) to individualize the program. In the final week of the intervention 3 participants reported loss of interest in some of the circuit elements, which was recorded in logbooks.

DISCUSSION

Feasibility

We found high recruitment (81%), retention (78%), and participation (78%) rates, suggesting feasibility of this exercise intervention for patients with SMI in a residential rehabilitation setting. Participation rates were comparable with those reported in two relevant meta-analyses of exercise interventions for people with SMI; (Vancampfort et al. 79–85%, Firth et al. 78.8%). They were also comparable to retention rates reported by the same meta-analyses; (Firth et al. 70–76%, Vancampfort et al. 78%) (17, 30).

For people with SMI, adherence to treatment recommendations is often poor, limiting the recovery of people with severe mental illness (45). Some antipsychotic trials report adherence can be as low as 50 %, with longer term medication adherence rates even lower, (e.g., CATIE trial, 36%) (46, 47). It is worth noting that in our brief pilot study, adherence rates were high and broadly comparable to brief psychological interventions for people with schizophrenia (84%), and depression (83%) (48, 49). This adds to the growing evidence that supports the feasibility of brief exercise interventions for people with SMI (17). However, to achieve a clinically meaning impact on physical health outcomes, engagement with exercise needs to be extended beyond a brief intervention. Future trials of exercise interventions that continue beyond 24 weeks, with follow up periods longer than one year are recommended for people with SMI.

Our recruitment rates (81%) were higher than those seen in Firth's (27.5%), however that study recruited from 4 sites, and hence their recruitment rates may be more generalizable than this single site pilot study (25–27).

Within a residential rehabilitation setting, our participation rates were comparable to Dodd et al's forensic residential rehabilitation study (73%). Firth et al. did not specifically report participation rates, however, did note low adherence as quantified by MET minutes of exercise. These studies differed in terms of flexibility of provision of the supervised exercise sessions, and this may have partially explained the differences in participation results. In our study, EP students were on practicum placement and had the flexibility to offer make-up sessions to participants who missed sessions or preferred a smaller group, hence offering options; Dodd et al. also reported this flexibility. In his residential rehabilitation study, Firth et al. also concluded that tailoring exercise programs to account for participant preference is an important engagement strategy. Given people with SMI frequently experience morning sedation and other medications side effects, offering choice of timing to increase engagement may be a useful strategy when planning exercise programs within residential rehabilitation.

A number of other factors may have contributed to our participation rates. First, the group setting may have allowed participants to encourage each other and provide support; which has been associated with reduced drop-outs in exercise interventions for people with SMI (17). Participants lived within the same residential facility, so exercising in a group may have enhanced social "connectedness," an important factor for autonomous motivation to engage in exercise for people with SMI (50, 51).

Second, in line with previous exercise intervention studies in this population, supervision from qualified exercise professionals may have improved adherence to the exercise intervention (17, 52). Given the complex barriers that people with SMI face, professional supervision and encouragement is vital when trying to engage this group in exercise; prior studies have shown that access to facilities alone has been unsuccessful in engaging people with SMI in exercise (53, 54).

Third, final year EP students, whilst not fully accredited, generally have significant experience working as an exercise instructor in healthy populations prior to retention of their bachelor degree. In future programs, including a component of mental health training prior to being placed in a mental health service may be a strategy that could assist the EP students to assimilate more comfortably within the service (55). Exercise accreditation bodies are currently improving undergraduate course content to include more comprehensive education about mental illness. In addition, it was observed that EP students expressed attitudes reflecting the misperception of inflated risk of violence by people with SMI that can commonly lead to stigma. Prior stigma-reduction education programs for students have been successful (56). We found that education during supervision and encouraging direct personal contact with residents were important aspects of a student-led intervention to address stigma, and facilitate better integration of EP students into the mental health team.

Fourth, the exercise intervention occurred in the familiar courtyard of the CCU, with no transport or gym costs, hence limiting social and environmental barriers previously reported in the literature, including the anxiety that can be associated with accessing general community facilities (57, 58). For people with SMI living in residential rehabilitation units, who have

low exercise confidence and fitness, initial engagement in a familiar onsite location might be preferable preparation for later engagement in mainstream community exercise programs/gyms.

Finally, we found addressing the lack of priority given to physical health by mental health staff was necessary to improve staff engagement, and consequently participants' engagement in the intervention. Unhelpful staff attitudes about physical health has been reported as an important barrier to exercise engagement for people with SMI (57). We addressed this issue by inviting collaborative discussion between mental health staff, EP students and the consultant psychiatrist, to address fears, concerns and myths about people with SMI engaging in exercise interventions, and ensuring comprehensive dissemination of the available evidence about the benefits of physical activity in team meetings and via group email. This may be an important future implementation strategy in services where culture change is important (35, 59). Future implementations could investigate a parallel staff exercise intervention, which may improve staff attitudes toward the use of exercise for people with SMI (60).

Exercise Outcomes Within Mental Health Rehabilitation

Consistent with previous findings in SMI (32), our participants' baseline functional exercise capacities, as measured by the 6MWT, were low. However, there was a significant improvement in distance on the 6MWT following our intervention, (mean 70 m). Improvements of greater than 50 m have been shown to be representative of clinically significant change in other chronic disease populations with similarly low baseline 6MWT (61). Increasing functional fitness may have implications for everyday life for people with SMI, a particularly relevant finding in a residential rehabilitation setting in which independent functioning improvements are salient (62).

Our 6MWT improvements were higher than those reported in a secure residential rehabilitation setting, and an outpatient rehabilitation setting; the intensity of exercise in one study was lower than in ours, while the other had a higher mean age of participant (11, 24, 26). The lower baseline functional exercise capacity of our study participants may also have allowed for greater gains in function to be achieved and accounted for the larger change in distance on the 6MWT. Also, as we did not offer a practice test, the impact of learning effects affecting our result cannot be excluded.

We also observed a significant increase in the reported total volume of exercise per week, although participants still did not achieve widely accepted guidelines of 150 min per week of moderate intensity exercise (63). However, given our participants' low baseline exercise participation, the increase we found after a short intervention was promising. Achieving 150 min may be preferable as a long term or "aspirational" goal for people with SMI to prevent early disengagement (64). Whether the increase we found can be sustained or improved upon will require further longitudinal study.

Other Secondary Outcomes

Negative symptoms reduced significantly following the intervention. As this study was uncontrolled, this finding may have been due to other factors associated with the rehabilitation program and needs to be interpreted with caution. However prior meta-analyses of randomized controlled trials evaluating exercise interventions in people with SMI, and Firth et al's residential rehabilitation study revealed significant reductions in negative symptoms following exercise interventions (17, 25). Negative symptoms account for a substantial burden on independent functioning and can cause lifelong disability (65). Given the focus on functional improvement for people living in rehabilitation units, exercise interventions that have the potential to impact on negative symptoms may be a worthwhile inclusion in residential rehabilitation programs for people with SMI.

Of note, we found that intrinsic regulation ("I exercise because it's fun") showed a reduction following the exercise intervention. The EP students deliberately kept circuit elements similar during the 10-week period aiming to increase participants' competence and confidence in performing the circuit stations. This may have led to disinterest in some participants over time, which might provide an explanation. Given the importance of intrinsic motivation in sustaining regular exercise in people with SMI, creating effective exercise interventions that are considered fun/maintain interest over time is relevant and should be a major consideration (66). Consulting with participants to increase popular elements (such as boxing, as observed in this study) in future exercise interventions and offering a variety of physical activities, such as sports, may be worthwhile strategies for consideration. Consumer collaboration in the planning and delivery of exercise interventions, could be worthwhile strategies that would also align with recovery principles of rehabilitation services (20).

Consistent with prior studies of exercise interventions in people with SMI, we found no significant effect on BMI, abdominal circumference or other metabolic outcomes such as fasting blood sugars and lipids. Whilst the brief 10 week intervention may have been too short for change to be seen in metabolic outcomes, the literature reveals inconsistent effects of exercise on metabolic outcomes from exercise alone (11, 17). Whilst fitness improvements without weight loss following an exercise intervention can have a meaningful impact on cardio-metabolic risk reduction, (67), successful weight loss has been demonstrated in people with SMI in lifestyle interventions that included dietary components (24, 68, 69). Residential rehabilitation units typically focus on basic living skill acquisition such as cooking and shopping; as such these units may be an opportune setting to also evaluate dietary interventions that may target changes in metabolic outcomes and the nutrition of people with SMI.

Measures of quality of life have improved following exercise interventions for people with SMI (18). We did not find significant change following this 10 week intervention. Future trials with longer duration may clarify if quality of life measures may change following exercise interventions within residential rehabilitation units.

Limitations

The pilot study had several limitations. It was a small pilot study and due to the pragmatic nature of the study design, we did

not have any blinding process, or a control arm. It is possible that the improvement in functional exercise capacity may have occurred due to unknown external factors, although this is unlikely due to the long term sedentary nature of this population. The improvement in total psychotic and negative symptoms was more at risk of bias as these may have improved due to other aspects of their rehabilitation. Detailed assessment of mood pre and post the intervention and participant and staff acceptability questionnaires would be warranted to understand the broader acceptability of an exercise intervention implemented for people living in residential rehabilitation. Further, we used a measure of self-reported weekly exercise, rather than an objective measure such as accelerometry, thus risking potential inaccuracies and recall bias (70, 71). Of note, whilst the 6MWT has been used to estimate functional exercise capacity in SMI, the correlation between 6MWT and measured CRF in people with SMI has yet to be determined and the minimum clinically important distance has not yet been evaluated in people with SMI. These are both important potential areas of future investigation. Finally, our participants were young and had relatively few physical health co-morbidities, which limits the generalizability of these findings.

Conclusions

This pilot study revealed the feasibility of a, student-led collaboration in delivering an exercise intervention to a vulnerable, sedentary population of people with SMI, in an era of limited resources within public mental health services. Whilst cost-feasibility was not formally assessed, the intervention was low in cost as it involved EP students on practicum placement, and utilized existing exercise equipment and common space within the residential rehabilitation unit. Further, there was high recruitment, retention and participation rates, and no withdrawals due to injury or adverse events, reflecting feasibility within a residential rehabilitation setting. Elements of the program that may have contributed to feasibility included an on-site, supervised, group program, and offering personalized options for engagement. It may be relevant to other mental health residential rehabilitation units, such as Community Care Units.

Future Directions

Exercise interventions embedded within usual mental health care of a residential rehabilitation unit can be feasible, may lead to improvements in functional exercise capacity and reductions in negative symptoms.

Despite the limitations of pragmatic research, results from this pilot allowed exercise to be incorporated into core rehabilitation programs at three new CCU's, tripling EP student placement opportunities. Given the mortality gap and poor physical health of people with SMI, implementation and evaluation of exercise interventions embedded within MH services is an important next step toward translating evidence into practice.

Larger multi-site studies are warranted to further evaluate the feasibility of implementation of exercise interventions within residential rehabilitation units on a wider scale. The addition of dietary interventions in these settings may be important to have an impact on metabolic outcomes for people with SMI. In addition, studies with longer durations are needed to investigate the sustainability of lifestyle modification programs like this, the long-term benefits of exercise for individuals with SMI, together with the cost-feasibility and cost-effectiveness of such programs (72).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

NK, KN, DS, FD, KK, SR, and SheS contributed conception and design of the study. KN organized the data base. NK, DS, and SheS performed statistical methods. NK, DS, SheS, and ShuS wrote the first draft of the manuscript. NK, DS, ShuS, SheS, FD, SR, KK, and KN contributed to manuscript revision, read 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.2018.00343/full#supplementary-material

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MINI REVIEW
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Reducing the Mortality Gap in People With Severe Mental Disorders: The Role of Lifestyle Psychosocial Interventions

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This mini-review considers the mortality gap in persons with severe mental disorder (SMD) globally. Current estimates of 10–20 years of potential life lost may be too conservative, both in high (HIC) and low and middle-income countries (LMICs). There is an emerging consensus that natural causes account for the majority of deaths in persons with SMD in both resource settings. In HICs, cardiovascular causes predominate, and can be attributed to individual, health-system and societal level risk factors. Psychosocial lifestyle interventions target behavior specific risk factors for physical ill-health. There is good evidence for tailored weight-loss programmes, but mixed evidence for smoking cessation, substance misuse and risky sexual behavior. In terms of supporting persons with SMD, nurse-led services and the utilization of peer-support are showing promise. Future research efforts must focus on effective interventions and health system models for both high and low resource settings to address this startling health inequality.

Keywords: excess mortality, physical health, severe mental disorders, schizophrenia, bipolar disorder, depression, lifestyle psychosocial interventions, low-and-middle income countries

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This mini-review considers the evidence for the mortality disparity between persons with severe mental disorder (SMD) and the general population worldwide, where SMD is defined as schizophrenia and other psychotic disorders, bipolar disorder and severe depression. We will explore the causes of death in high income (HIC) and low and middle-income (LMIC) countries and review the multi-level risk factor model for mortality in SMD proposed by the World Health Organization (WHO) (1). Then, focusing on behavioral risk factors, we will discuss the emerging evidence base for lifestyle psychosocial interventions. Finally, we will consider different models of professional support systems for persons with SMD.

MORTALITY AS AN OUTCOME MEASURE

The WHO estimate that 10–20 years of potential life is lost in SMD (1). This wide estimate is derived from a number of meta-analyses containing data predominantly from HICs [e.g., (2)].

Concerningly, there is new evidence from HICs that the gap is increasing (3). What is the situation in LMICs? 10 years ago there was debate as to whether some outcomes, at least for schizophrenia, may in fact be better in developing countries (4, 5). This was based largely on three cross-national epidemiological studies sponsored by the WHO [IPSS (6), DOSMeD (7), ISOS (8)], which appeared to demonstrated higher rates of complete remission and better social functioning and mortality rates (expressed in standardized mortality ratios). However in a recent high quality Ethiopian study, the average potential years of life lost for persons with SMD was 28.4 years (9). This is in keeping with other cohorts in Madras (10) and Bali (11) which suggest mortality rates in LMICs may be in fact be worse.

CAUSES OF DEATH IN SEVERE MENTAL DISORDER

Our understanding of the causes of premature death in SMD has undergone radical change in recent decades. Historical data focusing on inpatient populations tended to over-estimate the rate of unnatural deaths in SMD (suicide, but also accidents and homicides). We now know that the mortality gap cannot be attributed to this alone. A retrospective study in Australia which linked data from mental and physical health services reported that the excess deaths were attributable to physical illnesses in over three-quarters of cases (3). This is in keeping with data from other HICs, where meta-analyses have identified cardiovascular diseases as the major cause of death in persons with SMD (12). The limited data from LMICs also suggest that the majority of deaths are due to natural illness (9–11). However, reflecting the pattern in the general population, infectious disease was the primary cause of death in an Ethiopian study (9).

Unnatural causes still account for about a quarter of deaths in persons with both in HICs and LMIC. This includes suicide, for which there is an increased risk amongst persons with SMD, especially within the first few years after contact with a psychiatric service (9, 13), but also accidental death (more common than suicide) and homicide (14, 15).

RISK FACTORS FOR EXCESS MORTALITY

The WHO have published a multilevel model for risk of excess mortality in persons with SMD (1). It considers individual factors (which can be disorder- or behavior-specific), health systems (such as financing) and social determinants of health (such as culture and societal values), highlighting the complexity of this problem.

Taking cardiovascular ill-health as an example, the contributing factors in persons with SMD may include disease-specific pathogenic mechanisms (see the emerging stress and inflammation theories), the metabolic side effects of antipsychotics [higher doses have been associated with higher risk of coronary heart disease and stroke (16)], behavioral factors [persons with SMD, when compared to general population controls, were less likely to be non-smokers or exercise to daily recommendations, and had poorer health outcomes (17)] and health system factors [persons with SMD are less likely to be referred for coronary revascularization procedures after a heart attack (18)] which are entwined with societal values.

Researchers in LMICs have called for further studies of the mechanisms underlying death from natural causes in persons with SMD (9). No doubt there will be identifiable risks at every level of the WHO model.

THE ROLE OF PSYCHOSOCIAL INTERVENTIONS IN REDUCING EXCESS MORTALITY

To reduce the mortality gap in persons with SMD, interventions are required at the individual to societal level. A full review of all of the current evidence is beyond the scope of this mini-review. We will focus on the psychosocial interventions aiming to tackle individual, behavior-specific risk factors.

Persons with SMD want to quit smoking (19), and there is some evidence of a modest benefit of smoking cessation counseling delivered by psychiatrists: number of cigarettes smoked in a typical week was significantly reduced after 12 months, however rates of abstinence determined by expired carbon monoxide was unchanged (20). There is better evidence for weight-loss programmes. Persons with SMD randomized to a tailored group weight management education and exercise sessions have achieved significant weight loss (21, 22) as well as reduced fasting glucose and medical hospitalizations after 6 months (22). Interventions aiming to reduce substance misuse and risky sexual behavior have had mixed results. One study demonstrated that an enhanced service delivered at the site of mental health treatment significantly improved testing and immunization for blood-borne infection, but despite risk reduction counseling (the psychosocial element) led to no change in risk behavior (23).

The evidence base for lifestyle psychosocial interventions in persons with SMD is mixed in both quality and results. We did not identify any studies in LMICs, where it is likely that interventions to reduce risk behavior for blood-borne infections would be highly relevant.

MODELS OF SUPPORT

In parallel with studies addressing specific risk behaviors, different models for supporting persons with SMD to achieve good physical health are being tested. There is evidence that nurse led services, both as care managers (prompting general and specialist services) and as practioners, can increase screening rates for cardiovascular risk factors (24, 25). Further studies will be required to determine if such enhanced services for persons with SMD result in reduced mortality. Another area of promise is peer-led intervention. In the United States, a chronic disease self-management program, adapted for persons with SMD and delivered by peers led

to improvements in self-rated physical and mental health scores (24). Importantly there was a clinically significant improvement in "patient activation" a measure of "individual's perceived ability to manage his or her illness and health behaviors."

CONCLUSIONS

In conclusion, persons with SMD are dying younger than the general population globally. There is an emerging consensus that the majority of excess mortality is due to poor physical health, with cardiovascular disease the major cause of death in HICs. Risk factor levels range from the individual (disorder and behavior specific) to the health system and social determinants. Studies have demonstrated that lifestyle psychosocial interventions have the potential to benefit persons with SMD, through tobacco-smoking cessation, increased activity and weight loss. Persons with SMD may require extra support to achieve healthy lifestyles, and both nurse-led and peer-led interventions have shown promise. However, the current evidence base for lifestyle psychosocial interventions is limited to HICs. With recent evidence demonstrating that the mortality gap may be even higher for persons with SMD in LMICs, this must become a focus for global health research.

AUTHOR CONTRIBUTIONS

SB drafted the manuscript under the supervision of GT, who revised the manuscript.

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BRIEF RESEARCH REPORT
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Effects of Long-Term Multimodal Psychosocial Treatment on Antipsychotic-Induced Metabolic Changes in Patients With First Episode Psychosis

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Background: Antipsychotic-induced weight gain and metabolic abnormalities are one of the major challenges in the treatment of psychosis, contributing to the morbidity, mortality and treatment non-adherence. Different approaches were used to counteract these side effects but showed only limited or short-term effects. This study aims to analyse the effects of a long-term multimodal treatment program for first episode psychosis on antipsychotic-induced metabolic changes.

Methods: We enrolled 71 patients with first episode psychosis treated at the Zagreb University Hospital Centre from 2016 until 2018. Participants were assigned to one of the two groups: day hospital program vs. treatment as usual (TAU). Outcomes were: body weight, blood glucose, lipids and cholesterol, psychopathology and global level of functioning during the 18-months follow-up.

Results: Although the TAU group gained more weight and had higher increase of blood glucose, while the day hospital group had a higher increase in total cholesterol at 18th month follow-up, after the adjustment for age, gender and baseline measures, the type of treatment was not significantly associated with any of the primary outcome measures. Patients' psychopathology measures significantly decreased and their functional level significantly increased at month 18th in both groups.

Conclusion: While both types of treatment were effective in reducing psychopathology and restoring the patients' level of functioning, both were relatively ineffective in counteracting antipsychotic-induced metabolic abnormalities and antipsychotic-induced weight gain.

Keywords: antipsychotics, schizophrenia, first episode psychosis, metabolic abnormalities, weight gain, psychosocial intervention, day hospital

INTRODUCTION

The second generation antipsychotics (SGA) are considered as the first line treatment for schizophrenia spectrum disorders. Unfortunately, most SGA are associated with a significant weight gain causing subsequent development of metabolic syndrome and increasing the risk of cardiovascular morbidity and mortality (1). In addition, significant weight gain may cause non-adherence to medication (2) and subsequently lead to relapses (3). Risk factors for antipsychotic-induced weight gain and metabolic abnormalities include polypharmacy (4), olanzapine or clozapine monotherapy (5), female gender, lower initial body mass index (6), positive treatment response (7) and family history of diabetes (8). The highest increase of weight gain is seen particularly during the first few months of treatment (9). Different strategies were used to counteract these side effects, such as changes of medication regimes (e.g., switch to antipsychotics with a lower propensity to cause weight gain, addition of drugs that may suppress appetite) (10, 11), psychoeducation (12) and exercise (13). However, in the clinical practice,antipsychotic-induced metabolic disturbances still remain one of the most important obstacles for effective treatment. During the last 20 years, multimodal programs for treatment of patients with first episode psychosis have been developed worldwide (14). These services usually incorporate a set of psychopharmacological and psychosocial approaches following individualized treatment plans. Patients with the first episode psychosis treated in our hospital are offered this kind of treatment through the day hospital setting. As this multimodalprogramme incorporatesstructured psychoeducation on healthy lifestyle and side effects of medication and unstructured exercise, we hypothesized that it may have advantage over treatment as usual (TAU) in counteracting antipsychotic-induced metabolic changes. Thus, we aimed to analyze the effects of the multimodal treatment of first episode psychosis on the antipsychotic-induced metabolic changes over an 18-months period. In addition, we explored the relationship of patients' psychopathology and functioning and the type of treatment.

METHODS

Participants and Protocol

This study was nested within the prospective cohort study: "Biomarkers in schizophrenia-integration of complementary methods in longitudinal follow up of first episode psychosis patients." The sample consisted of patients admitted to Zagreb University Hospital Centre (ZUHC), between 2016 and January 2018. Adult patients with the first psychotic episode pertaining to the schizophrenia spectrum diagnosed according to the research criteria of the International Classification of Disorders (ICD-10) (15) by the consensus of two experienced psychiatrists, were recruited to participate in the study. Exclusion criteria included the presence of somatic disorders/status, and use of medication and other substances with possible effects on metabolic features (diabetes, hypercholesterolemia, pregnancy or lactation, antidiabetic drugs, hypolipemics), and psychotic disorders due to organic causes. All patients treated at the ZUHC for first acute episode psychosis during the study period meeting those criteria were invited to participate in the study. After the patients reached the subacute phase of psychosis (usually in the first few weeks of antipsychotic treatment), they chose one of the two treatment groups according to their preference: day hospital treatment (which included a combination of pharmacological approach and psychosocial approaches (group psychotherapy, social skills training, metacognitive training, creative workshops, family therapy, and psychoeducation including topics on healthy lifestyle, antipsychotic-induced metabolic changes, diet encouragement and unstructured exercise in a closed group, three times a week, but decreasing in the number of weekly sessions over 12 months) or TAU (short outpatients visits usually once a month). The patients were followed-up for 18 months and assessed at baseline and month 18th for sociodemographic and clinical data, including data on lifestyle (smoking, drinking, drug use), metabolic parameters [blood glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides], weight, psychopathology with Positive and Negative Syndrome Scale, PANSS (16), quality of life using the World Health Organization Quality of Life Assessment, WHOQOL-BREF (17) and level of functioning using the Global Assessment of Functioning, GAF (18). Primary outcome of the study were metabolic side- effects assessed at 18-month. Secondary outcome included patients' psychopathology assessed at 18-month.

The study protocol was approved by the Ethics Committee of the ZUHC. The study was executed in accordance with World Medical Association Declaration of Helsinki 2013.

Statistical Analysis

Changes from the baseline values to values at the last assessment were presented with absolute and relative changes and their 95% confidence intervals. Differences in primary and secondary outcome measures between the two groups were analyzed using multivariable analysis of covariance (MANCOVA), adjusted for age, sex and baseline measurements (metabolic and BMI, and psychopathology). As the assumptions for MANCOVA we tested linearity of correlations between dependent and independent variables and multivariate normality by inspection of scatter plots, non-existence of univariate outliers and homogeneity of regression slopes, and the equality of error variances by Leven's test. The statistical significance was set at $p < 0.05$. Statistical data analysis was performed using the R Core Team (21).

RESULTS

We recruited 71 patients in the study and treated with day hospital treatment ($n = 21$) or TAU control group ($n = 50$). Sociodemographic and clinical characteristics at baseline are given in **Table 1**. The reasons for not choosing daily hospital over TAU were as follows: significant travel distance from hospital ($N = 25$), being employed or regular student with obligations several days per week and thus unable to attend the sessions

TABLE 1 | Baseline participants' characteristics.

	Day hospital ($n = 21$)		TAU ($n = 50$)	
Male gender	12	(57.1)	33	(66)
Age (years), median (IQR)	24	(21–25)	25	(22–33)
Being single	18	(85.7)	38	(76)
Years of education, mean (SD)	14	(3.2)	14	(4.3)
Employed	3	(14.3)	11	(22)
Age of first contact with psychiatry, median (IQR)	23	(19–25)	25	(20–31)
Number of cigarettes/day, mean (SD)	10	(11)	8	(12)
Occasional drug use	11	(54.2)	21	(42)
Occasional alcohol use	1	(4.7)	4	(8)
MAIN ANTIPSYCHOTIC				
amisulpirid or aripiprazole	5	(23.8)	5	(10)
fluphenazine or haloperidol	2	(9.5)	8	(14)
clozapine, olanzapine, quetiapine	8	(38.1)	21	(42)
risperidone, paliperidone	6	(28.6)	16	(34)
More than one antipsychotic	10	(47.6)	21	(42)
Mood stabilizers	3	(14.3)	12	(24)
Anxiolytics/hypnotics	6	(28.6)	17	(34)
Anticholinergics	5	(23.8)	11	(22)
Antidepressants	3	(14.3)	4	(8)

Data are presented as n (%), unless stated otherwise.
IQR, interquartile range; SD, standard deviation.

($N = 11$), being older than the majority of group participants and do not felt as fitting the group ($N = 5$) and preferring the individual over group treatment ($N = 10$).

During the study period, 12 patients from the TAU group (24%) were re-hospitalized due to relapses, all because of non-adherence to medication, and 3 patients from the day hospital group (14.2%). At the final assessment, patients in the day hospital group were treated with amisulpiride or aripiprazole ($n = 8$, 38.1%), clozapine/quetiapine /olanzapine ($n = 5$, 23.8%) or paliperidone/risperidone ($n = 4$, 19%), or stopped any antipsychotics ($n = 4$, 19%); a significant number of patients had at least one additional medication (another antipsychotic ($n = 7$, 33.3%), sedative/hypnotic ($n = 1$, 4.8%), mood stabilizer ($n = 3$, 14.3%), antidepressant ($n = 6$, 28.6%), 3 anticholinergic ($n = 2$, 9.5%)); patients in the TAU were treated with amisulpiride or aripiprazole ($n = 15$, 30%), haloperidol/fluphenazine ($n = 3$, 6%), clozapine/quetiapine/olanzapine ($n = 13$, 26%) or paliperidone/risperidone ($n = 15$, 30%), or stopped any antipsychotics ($n = 4$, 8%); a significant number of patients had at least one additional medication (another antipsychotic ($n = 20$, 40%), sedative/hypnotic ($n = 6$, 12%), mood stabilizer ($n = 10$, 20%), antidepressant ($n = 9$, 18%), 3 anticholinergic ($n = 7$, 14%)).

Metabolic Outcomes Over the Longitudinal Follow-Up

Changes of the metabolic features and BMI, as well as changes in symptoms over the 18-months longitudinal follow-up are given in **Table 2**. The associations of type of treatment (day hospital vs. TAU) and primary outcomes at 18-month data were analyzed using MANCOVA, with age, gender and baseline metabolic features and baseline BMI as covariates. The associations of type of treatment and psychopathology at 18-month data were analyzed using MANCOVA, with age, gender and baseline PANSS-positive, PANSS-negative, PANSS-general as covariates. The type of treatment: day hospital vs. TAU, was not significantly associated with any of the primary or secondary outcome measures, after the adjustments, as follows BMI [$F_{(1, 38)} = 0.00$; $p = 0.959$; $\eta^2 = 0.00$], triglycerides [$F_{(1, 38)} = 0.64$; $p = 0.429$, $\eta^2 = 0.017$], cholesterol [$F_{(1, 38)} = 2.29$; $p = 0.138$, $\eta^2 = 0.057$], LDL cholesterol [$F_{(1, 38)} = 2.72$; $p = 0.107$; $\eta^2 = 0.067$], HDL cholesterol [$F_{(1, 38)} = 0.00$; $p = 0.975$; $\eta^2 = 0.00$], glucose in blood [$F_{(1, 38)} = 0.46$; $p = 0.504$; $\eta^2 = 0.012$]; PANSS-positive [$F_{(1, 63)} = 2.17$; $p = 0.146$; $\eta^2 = 0.03$]; PANSS-negative [$F_{(1, 63)} = 0.03$; $p = 0.86$; $\eta^2 = 0.00$]; PANSS-general [$F_{(1, 63)} = 0.57$; $p = 0.454$; $\eta^2 = 0.00$] (**Table 2**).

DISCUSSION

We have assessed the effects of a multimodal psychosocial intervention on the antipsychotic-induced weight gain and metabolic changes in a moderate sample of first episode psychosis over a longer period. Overall, we did not confirm the hypothesis that a general multimodal program is more effective in counteracting weight gain or antipsychotic-induced metabolic abnormalities compared to TAU in patients with first episode psychosis over a longer follow-up period. In fact, both approaches seem to be rather effective for restoring patients' level of functioning, but less effective to counteract antipsychotic-induced weight gain and metabolic abnormalities, as the increase in body mass index and metabolic changes are significant over 18-months.

Unfortunately, this is in line with other studies which found that different interventions (lifestyle, psychoeducation, exercise) are of limited effectiveness when it comes to antipsychotic-induced weight gain or metabolic changes over a longer time period (e.g., 18-months of antipsychotic-treatment) (19, 20). This is also in line with the results of our previous study performed at the ZUHC, where we found no effects of the PsyLOG m-health intervention compared to TAUin preventing antipsychotic-induced weight gain and metabolic changes over 6 months follow-up (22). However, it is also possible that patients with first episode of psychosis are far more vulnerable group compared to patients with multiple episodes of psychosis when it comes to antipsychotic-induced weight gain. In fact, these patients usually have several risk

TABLE 2 | Changes of the primary and secondary outcomes according to the treatment group during the 18 months follow up.

	Baseline		At 18th month		Absolute changes (95% CI)		Relative changes (%) (95% CI)	
	Day hospital ($n = 21$)	TAU ($n = 50$)	Day hospital ($n = 21$)	TAU ($n = 50$)	Day hospital ($n = 21$)	TAU ($n = 50$)	Day hospital ($n = 21$)	TAU ($n = 50$)
PRIMARY OUTCOME								
BMI (kg/m^2)	23 (3.0)	24 (3.6)	24 (3.7)	25 (4.2)	0.91 (−0.02 to 2.16)	2.14 (1.13 to 3.31)	4 (0 to 9)	9 (5 to 14)
Triglycerides (mmol/l)	1.3 (0.69)	1.3 (0.62)	1.7 (2.24)	1.4 (0.82)	0.66 (−0.33 to 2.41)	0.17 (−0.14 to 0.43)	98 (−18 to 331)	21 (−3 to 43)
Total cholesterol (mmol/l)	4.3 (0.56)	4.7 (0.99)	4.9 (0.94)	4.7 (0.92)	0.49 (0.06 to 1.02)	0.05 (−.41 to 0.46)	11 (1 to 23)	4 (−5 to 14)
HDL cholesterol (mmol/l)	1.3 (0.33)	1.5 (0.39)	1.4 (0.41)	1.4 (0.45)	0.07 (−0.03 to 0.18)	−0.03 (−0.14 to 0.07)	6 (−2 to 15)	−1 (−8 to 6)
LDL cholesterol (mmol/l)	2.4 (0.49)	2.6 (0.91)	3.0 (0.94)	2.7 (0.84)	0.40 (−0.04 to 0.91)	0.03 (−0.33 to 0.39)	14 (−21 to 36)	9 (−5 to 23)
Blood glucose (mmol/l)	5.4 (2.77)	4.9 (0.61)	4.9 (0.81)	5.4 (1.13)	−0.92 (−3.53 to 0.61)	0.65 (0.21 to 1.16)	−2 (−21 to 14)	14 (5 to 24)
SECONDARY OUTCOMES								
PANSS-positive	25 (8.5)	25 (8.9)	9 (3.99)	11 (7.2)	−15.3 (−21 to −9.57)	−15.4 (−19.4 to −11.1)	−58 (−71 to−42)	−55 (−67 to −43)
PANSS-negative	24 (7.2)	24 (7.6)	13 (4.86)	14 (6.6)	−10.5 (−12.7 to −7.8)	−11.5 (−14.2 to−8.6)	−46 (−54 to −35)	−45 (−54 to −35)
PANSS-general	50(11.3)	51 (10.5)	24 (7.6)	26 (10.3)	−25.2 (−31 to −19.1)	−28.9 (−33 to −24.3)	−53 (−61 to −44)	−56 (−61 to −49)
GAF, median (IQR)	20 (15 to 35)	23 (15 to 30)	85 (80 to 90)	85 (63.8 to 91.2)	58.2 (46.7 to 68.9)	57.4 (52 to 62.6)	314 (189 to448)	283 (216 to 359)

Data are presented as mean (standard deviation) if not stated otherwise.
CI, confidence interval; IQR, interquartile range.

factors for significant antipsychotic-induced weight gain such as lower initial body weight, better treatment response and first treatment with antipsychotics. Furthermore, while being correlated to a certain extent, some of these antipsychotic-induced metabolic abnormalities, such as diabetes, often occur independently of weight gain, and thus can be counteracted only by close monitoring (23).

We did not analyze the effect of medication thoroughly. As most of the patients were treated with polypharmacy at different stages of treatment it is difficult to assess the effect of medication on weight gain and metabolic changes in this study. Although the majority of guidelines suggest monotherapy in the treatment of psychosis, polypharmacy is widespread in psychiatric practice worldwide (4), including the region where this study was performed (24). Thus, it is probably not sufficient to recommend monotherapy as the main strategy to counteract antipsychotic-induced weight gain and metabolic abnormalities as it is fair to assume that clinicians probably decide to use polypharmacy to treat complex clinical symptoms. The relatively high levels of functioning and significant decrease of the severity of psychopathology in these patients after 18-months of treatment suggest that effectiveness of treatment in terms of functioning is the main goal of treatment, while antipsychotic-induced weight gain or metabolic changes are regarded as a less important at best. However, acknowledging the effect of metabolic abnormalities on morbidity, more focused strategies to counteract these side effects are needed. While several interventions involving exercise proved to be efficient over a shorter period, this effect is lost over a longer period (19, 20). As the negative effects of metabolic abnormalities became apparent over time, it is crucial to sustain the effects of these interventions, possibly with a combination with psychosocial or behavioral interventions focused on sustaining motivation to exercise or regular supervision of exercise over a longer period (25). Therefore, finding a suitable program that could help sustaining the motivation for the continuation of exercises over a longer period still remains a treatment challenge.

LIMITATIONS OF THE STUDY

First, we did not use a randomized controlled design to assign the patients to the assessment groups, but we used a naturalistic design. While randomized control design is considered as standard for assessing the efficacy of an intervention, naturalistic design may mirror the real-life situation better. Furthermore, it could be argued that since the patients were choosing themselves one the two treatment options (day hospital or TAU) there may be systematic difference between them in aspects not measured in the study, e.g., motivation, adherence, etc. which may influence metabolic outcomes. Finally, we cannot exclude the effects of other factors not included in the study, such as personality styles,

eating habits and levels of activity during the studied period on metabolic outcomes.

AUTHOR CONTRIBUTIONS

MRK designed and performed the study, analyzed the data, and wrote the first draft of the study. DBK designed and performed the study, critically analyzed the data, and wrote the first draft of the study. IK and PM designed the study, analyzed the data and gave critical comments, and revised the first draft of the study. ZM, AKM, SKM, PB, DBK, and ZV performed the study and gave critical comments and revised the first draft of the study. ZB analyzed the data and gave critical comments and revised the first draft of the study.

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Longitudinal Associations of Modifiable Lifestyle Factors With Positive Depression-Screen Over 2.5-Years in an International Cohort of People Living With Multiple Sclerosis

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Background: Depression is common and has a significant impact on quality of life for many people with multiple sclerosis (MS). A preventive management approach via modification of lifestyle risk factors holds potential benefits. We examined the relationship between modifiable lifestyle factors and depression risk and the change in depression over 2.5 years.

Methods: Sample recruited using online platforms. 2,224 (88.9%) at baseline and 1,309 (93.4%) at 2.5 years follow up completed the necessary survey data. Depression risk was measured by the Patient Health Questionnaire-2 (PHQ-2) at baseline and Patient Health Questionniare-9 (PHQ-9) at 2.5-years follow-up. Multivariable regression models assessed the relationships between lifestyle factors and depression risk, adjusted for sex, age, fatigue, disability, antidepressant medication use, and baseline depression score, as appropriate.

Results: The prevalence of depression risk at 2.5-years follow-up in this cohort was 14.5% using the PHQ-2 and 21.7% using the PHQ-9. Moderate alcohol intake, being a non-smoker, diet quality, no meat or dairy intake, vitamin D supplementation, omega 3 supplement use, regular exercise, and meditation at baseline were associated with lower frequencies of positive depression-screen 2.5 years later. Moderate alcohol intake was associated with greater likelihood of becoming depression-free and a lower likelihood of becoming depressed at 2.5-years follow-up. Meditating at least once a week was associated with a decreased frequency of losing depression risk, against our expectation. After adjusting for potential confounders, smoking, diet, physical activity, and vitamin D and omega-3 supplementation were not associated with a change in risk for depression.

Conclusion: In a large prospective cohort study of people with MS and depression, in line with the emerging treatment paradigm of early intervention, these results suggest a role for some lifestyle factors in depression risk. Further studies should endeavor to explore the impact of positive lifestyle change and improving depression in people living with MS.

Keywords: Multiple sclerosis, epidemiology, depression, lifestyle, longitudinal, cohort study (or longitudinal study)

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, demyelinating, inflammatory disease of the central nervous system. Symptoms are diverse and can include sensory, motor and visual deficits, bowel and bladder dysfunction, cognitive impairment and fatigue. Neuropsychiatric symptoms are also common, with an episode of depression occurring for 50% of people with MS during their lifetime (1); the annual prevalence of depression has been estimated as 20% (2), increasing to 25% among people in the 18–45 years old age range (3).

In addition to its negative impacts on overall quality of life, depression is associated with suicide, a significant cause of mortality for people with MS (4). People with MS have both a higher suicide rate (5) and all-cause mortality rate compared to the general population (4), with up to 35% of people with MS reporting suicidal ideation during their lifetime (6). Suicidal ideation is strongly associated with depression and can be present even if depressive symptoms are mild (6). However, a greater severity of depression shows an even stronger association with suicidal thoughts (7). Suicidal ideation is associated with both actual and perceived disability, with depression a mediating factor in this relationship. Depression is therefore a modifiable factor, potentially via both prevention and treatment, to reduce the risk of suicide and improve mortality outcomes for people with MS (6).

The evidence base for treatment of depression for people with MS is limited. Pharmacological and psychological treatment are the mainstay in management: prescription of antidepressant medication for people with MS is widespread and there is a clear need to establish the evidence base behind this practice (8). The most recent Cochrane review of pharmacological treatment reported a trend toward efficacy for two antidepressant medications, but cautioned about the significant methodological problems of the research, high rates of adverse effects, and issues regarding loss to follow-up which may affect generalizability (9). A more recent review of clinical trials recommended antidepressant medication choice be based on the medication side effect profile and tailored for the individual, as the side effects of antidepressant medications can worsen common symptoms of MS, such as fatigue, sexual dysfunction, and bowel/bladder dysfunction (10). Most non-pharmacological research investigating the management of depression in MS has focused on psychological interventions, particularly cognitive behavioral therapy (11). A recent meta-analysis of cognitive behavioral therapy showed a moderate effect on depression in the short term for people with MS (11). Exercise therapy for depression is increasingly common and effective in the general population (12), and has also shown promise for people with MS (13). Mindfulness-based interventions for people with MS have also been shown to improve depression and quality of life at 6 months follow-up (14).

The challenge of treating depression extends to the general population where pharmacological and psychological interventions are also first-line treatments, yet have limited impact, only reducing the burden of depression by 10–30% (15). An emerging paradigm which provides a nexus between prevention, health promotion and clinical treatment of depression, is modification of known lifestyle risk factors for depression (16, 17). In the general population, prospective studies in teenagers and adults showed that modification of lifestyle factors, including diet, exercise, weight and smoking, improved and prevented depression (18, 19).

As part of the wider Health Outcomes and Lifestyle In a Sample of people with Multiple Sclerosis (HOLISM) Study, we previously described the results from our baseline cross-sectional study of 2,466 participants with MS (20), finding 19.3% screened positive for depression using the Patient Health Questionnaire-2 (21). We demonstrated strong and clinically meaningful associations between modifiable lifestyle risk factors and depression prevalence. In our current study, we investigated whether modifiable lifestyle factors were associated with screening positive for depression 2.5 years after our baseline study and the predictors of change in depression screen during follow-up.

METHODS

Participants and Recruitment

The methodology for the HOLISM study has previously been documented in detail at both baseline and 2.5-years follow-up (22, 23). Briefly, participants were recruited via online platforms that engaged people with MS. Participants used SurveyMonkey® to complete the survey and to provide informed consent. Participants were eligible if they reported having been diagnosed with MS by a medical doctor and were over 18 years old. Ethics approval was granted by St Vincent's Hospital Melbourne HREC initially, and the Health Sciences Human Ethics Subcommittee at the University of Melbourne (Ethics ID: 1545102).

Data Collection and Tools Used

Many of the same measures used at baseline were employed at follow-up to allow longitudinal analysis. A range of sociodemographic, behavioral/environmental, and

clinical parameters were queried by participant-completed questionnaires (22). Particular elements queried are described below.

Sociodemographic and Biometric Data

Data were collected on sex, age, height, weight, country of birth and residence, marital status, education level, employment and socioeconomic status among others.

Dietary Habits

We used a modified version of the Diet Habits Questionnaire (DHQ) (24) as previously described (22, 23). A higher score indicated a healthier diet and data were grouped into quartiles of their total score.

Vitamin D Supplementation

Participants were asked if they took a vitamin D supplement, the amount taken, frequency and duration of supplementation (22).

Omega-3 Supplementation

We assessed both the type and dose of omega-3 supplementation used by participants (22).

Exercise

We used the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (25), which assesses the frequency and duration of moderate and vigorous physical activity over the preceding 7 days. Data were categorized as low, moderate or high activity level according to the IPAQ guidelines.

Meditation

We assessed how often participants meditated on average per week and for how long each time (22).

Alcohol

We asked participants the frequency and volume of alcohol consumed, providing participants information of what a standard drink was. Data was then re-calculated in grams of alcohol to derive variables of low, moderate and high alcohol intake (26).

Smoking

Participants smoking behavior was queried and these then classified as being a never smoker, ex-smoker or current smoker.

Depression

At 2.5-years follow-up, we used the Patient Health Questionnaire-9 (PHQ-9) to assess depression risk (27). The PHQ-9 is a nine-question instrument that is widely used and has been validated in MS research (28). The PHQ-2 was used at baseline and includes two items of the PHQ-9, allowing calculation of PHQ-2 and PHQ-9 scores at follow-up review, and thus change in PHQ-2 between reviews. We used the PHQ-9 at follow-up due to its superior psychometric assessment to substantiate findings from baseline.

Participants were asked the frequency of the specific symptom in the past 2 weeks, with answers including "Not at all," "Several days," "More than half the days," and "Nearly every day." At least one of the asterixed two symptoms must be present for diagnosis of a Major Depressive Episode (29) and these items are included in the PHQ-2.

1) Little interest or pleasure in doing things*
2) Feeling down, depressed or hopeless*
3) Trouble falling asleep or staying asleep, or sleeping too much
4) Feeling tired or having little energy
5) Poor appetite or overeating
6) Feeling bad about yourself–or that you are a failure or having let yourself or your family down
7) Trouble concentrating on things, such as reading the newspaper or watching television
8) Moving or speaking so slowly that other people could have noticed; or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
9) Thoughts that you would be better off dead or hurting yourself in some way.

The PHQ-2 score ranges from 0 to 6 with scores >2 indicating a positive depression screen. The PHQ-9 score ranges 0–27, with scores >9 indicating positive depression-screen. Additionally, the PHQ-9 can be subdivided into grades of severity: 5–9 indicating minimal depression, 10–14 indicating mild depression, 15–19 indicating moderate depression, and 20–27 indicating severe depression. Moderate and severe depression were combined due to cell-size constraints ($n = 37$ with severe depression).

Clinical Measures

Disability was assessed using the Patient-Determined Disease Steps (PDDS) scale (30), from which the disease-duration adjusted Patient-derived Multiple Sclerosis Severity Score (P-MSSS) was calculated (31). Fatigue was assessed using the Fatigue Severity Scale (FSS) (32). Immunomodulatory medication use, including interferon-beta-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide, and natalizumab, as well as prescription antidepressant and anxiolytic medication use were queried at each review.

Data Analysis

Log-binomial regression models were used to evaluate associations of sociodemographic and lifestyle factors with positive depression-screen at follow-up, estimating a prevalence ratio. Log-multinomial regression models (33) were used to evaluate predictors of severity of PHQ-9 positive depression-screen. Multivariable models at 2.5-years follow-up were adjusted for contemporaneous P-MSSS, age, fatigue, and antidepressant medication use, these covariates were selected based on review of the literature for relevant characteristics and on material impact on models.

Log-binomial regression were used to evaluate sociodemographic and lifestyle factors associated with change in PHQ-2-defined depression-screen between baseline and 2.5-years follow-up. We estimated a risk ratio for baseline predictors and a prevalence ratio where change in determinants was evaluated against change in depression-screen state. In

these data analyses, those who changed from positive to negative depression-screen were compared to those who screened positive for depression at both timepoints, while those who changed from negative to positive depression-screen were compared to those who screened negative for depression at both timepoints. Multivariable models for predictors of change in depression-screen were adjusted for P-MSSS, age, fatigue, antidepressant medication use, and baseline continuous PHQ-2 score, these covariates were selected based on review of the literature for relevant characteristics and on material impact on models.

All multivariable models were done using complete-case analysis, that is they were constrained to those who had data on all the model covariates.

STATA/SE 15.0 (StataCorp, College Park, TX, USA) was used to analyse the data as previously described.

RESULTS

At baseline review, 2,466 participants with MS initiated the questionnaire, of whom 2,224 (88.9%) completed the PHQ-2 instrument. At 2.5-years follow-up review, 1,401 participants with MS initiated the questionnaire, of whom 1,309 (93.4%) completed the PHQ-2 instrument and 1,264 (90.2%) completed the PHQ-9 instrument. The prevalence of depression at 2.5-years review differed between the PHQ-2 and PHQ-9, the PHQ-2 estimating a prevalence of 14.5%, while the PHQ-9 estimated a prevalence of 21.7%.

As described elsewhere (22, 23, 26) the cohort was largely female at both timepoints, of mean age in the mid-40s, and, while the mean BMI was in the overweight range, the cohort consistently engaged in healthy behaviors, including >90% non-smoking, over half engaging in regular physical activity, and large proportions reporting vitamin D and omega-3 supplement use. Alcohol consumption was common, only around 20% reporting not drinking alcohol at either timepoint, though of those using alcohol, the majority drank low/moderate amounts. Diet quality scores were good, with average scores of 81 at both timepoints, particularly driven by high sub-scores in not having snacks and takeaway, lower fat consumption, and healthier food choices (data not shown). Other cohort characteristics are shown in **Table 1**.

Determinants of Depression at 2.5-Years Follow-Up

Current smokers were significantly more likely to have scores indicative of prevalent depression risk, both PHQ-2 and PHQ-9 (**Table 2**). Alcohol, on the other hand, showed a significant inverse association with depression risk, showing evidence of a dose-dependent association, particularly PHQ-9. Examining alcohol load found this association was solely driven by low/moderate consumption, with high alcohol consumption not significantly associated with depression risk (data not shown).

Higher diet quality scores also showed a dose-dependent association with lower frequencies of depression, though adjustment attenuated these associations. Those reporting consuming meat and dairy had higher frequencies of depression

TABLE 1 | Cohort characteristics at baseline and 2.5-yr follow-up, and characteristics of those retained at 2.5-years review vs. those lost to follow-up.

	Baseline (n = 2,466)	Baseline, completed 2.5-years (n = 1,401)	2.5-years (n = 1,401)
PHQ-2 SCORE > 2			
No depression risk	1,799 (80.9%)	1,139 (86.3%)	1,119 (85.5%)
Depression risk	425 (19.1%)	181 (13.7%)	190 (14.5%)‡
(Missing)	(242 (9.8%))	(81 (5.8%))	(92 (6.6%))‡
PHQ-9 SCORE			
0–4: normal			607 (48.0%)
5–9: minimal depression symptoms			383 (30.3%)
10–14: major depression, mild			144 (11.4%)
15–19: major depression, moderate			93 (7.4%)
≥20: major depression, severe			37 (2.9%)
(Missing)			(137 (9.8%))
PHQ-9 SCORE > 9			
No depression risk			990 (78.3%)
Depression risk			274 (21.7%)
(Missing)			(137 (9.8%))
REGION OF RESIDENCE			
Australasia	835 (34.0%)	560 (40.1%)	564 (40.3%)
Europe	648 (26.4%)	380 (27.2%)	378 (27.0%)
North America	913 (37.1%)	426 (30.5%)	430 (30.7%)‡
Other	63 (2.6%)	30 (2.2%)	29 (2.1%)
(Missing)	(7 (0.3%))	(5 (0.4%))	(0 (0%))
SEX			
Male	415 (17.6%)	241 (17.3%)	241 (17.3%)
Female	1,937 (82.4%)	1,150 (82.7%)	1,150 (82.7%)
(Missing)	(114 (4.6%))	(10 (0.7%))	(10 (0.7%))‡
SMOKE TOBACCO?			
Never	1,099 (48.0%)	707 (52.7%)	701 (52.7%)
Ex-smoker	908 (39.7%)	520 (38.8%)	527 (39.6%)
Current smoker	281 (12.3%)	114 (8.5%)	102 (7.7%)‡
(Missing)	(178 (7.2%))	(60 (4.3%))	(71 (5.1%))
ALCOHOL INTAKE			
Non-drinker	415 (18.2%)	215 (16.1%)	263 (20.7%)
<Once per week	897 (39.3%)	500 (37.3%)	411 (32.4%)†b
1–3 days per week	567 (24.8%)	362 (27.0%)	347 (27.3%)a
4–7 days per week	406 (17.8%)	265 (19.8%)	249 (19.6%)a
(Missing)	(181 (7.3%))	(59 (4.2%))	(131 (9.4%))a
ALCOHOL LOAD, STANDARD DRINKS PER DAY[c]			
Low	882 (41.3%)	461 (36.2%)	102 (9.5%)
Moderate	970 (45.4%)	631 (49.6%)	812 (75.8%)‡b
High	286 (13.4%)	180 (14.2%)	157 (14.7%)‡b
(Missing)	(328 (13.3%))	(129 (9.2%))	(330 (23.6%))‡b
PHYSICAL ACTIVITY			
Low activity	752 (36.2%)	423 (34.0%)	396 (31.8%)
Moderate activity	839 (40.4%)	533 (42.8%)	582 (46.7%)†

(Continued)

TABLE 1 | Continued

	Baseline (n = 2,466)	Baseline, completed 2.5-years (n = 1,401)	2.5-years (n = 1,401)
High activity	485 (23.4%)	290 (23.3%)	269 (21.6%)
(Missing)	(390 (15.8%))	(155 (11.1%))	(154 (11.0%))†
DIET–CONSUMES MEAT?			
No	761 (33.2%)	532 (39.6%)	513 (38.5%)
Yes	1,533 (66.8%)	813 (60.5%)	820 (61.5%)†
(Missing)	(172 (7.0%))	(56 (4.0%))	(68 (4.9%))†
DIET–CONSUMES DAIRY?			
No	862 (37.9%)	580 (43.4%)	564 (42.4%)
Yes	1,415 (62.1%)	756 (56.6%)	765 (57.6%)†
(Missing)	(189 (7.7%))	(65 (4.6%))	(72 (5.1%))‡
TAKING A VITAMIN D SUPPLEMENT?			
No	601 (24.4%)	271 (19.3%)	271 (19.3%)
Yes	1,865 (75.6%)	1,130 (80.7%)	1,130 (80.7%)‡
TAKING AN OMEGA-3 SUPPLEMENT?			
No	998 (40.5%)	469 (33.5%)	542 (38.7%)
Yes	1,468 (59.5%)	932 (66.5%)	859 (61.3%)[a]
TYPE OF MS AT COMPLETION OF SURVEY			
Benign	100 (4.1%)	64 (4.6%)	85 (6.2%)† [a]
RRMS	1,491 (61.6%)	875 (63.3%)	810 (59.2%)
SPMS	275 (11.4%)	144 (10.4%)	199 (14.6%)† [a]
PPMS	175 (7.2%)	100 (7.2%)	111 (8.1%)
PRMS	48 (2.0%)	18 (1.3%)	23 (1.7%)
Unsure/other	330 (13.6%)	181 (13.1%)	140 (10.2%)†
(Missing)	(47 (1.9%))	(19 (1.4%))	(33 (2.4%))[a]
TAKING ANY OF THE 11 SPECIFIED IMMUNOMODULATORY MEDICATIONS?			
No	1,321 (53.6%)	747 (53.3%)	812 (58.0%)
Yes	1,145 (46.4%)	654 (46.7%)	589 (42.0%)† [a]
TAKING PRESCRIPTION ANTIDEPRESSANT MEDICATION?			
No	1,964 (79.6%)	1,158 (82.7%)	1,149 (82.0%)
Yes	502 (20.4%)	243 (17.3%)	252 (18.0%)
TAKING PRESCRIPTION ANXIOLYTIC MEDICATION?			
No	2,211 (89.7%)	1,282 (91.5%)	1,285 (91.7%)
Yes	255 (10.3%)	119 (8.5%)	116 (8.3%)†
MEDITATES AT LEAST WEEKLY?			
No	1,566 (69.8%)	893 (67.2%)	850 (65.0%)
Yes	677 (30.2%)	436 (32.8%)	457 (35.0%)†
(Missing)	(223 (9.0%))	(72 (5.1%))	(94 (6.7%))
	Mean (SD; range)		
Age	45.7 (10.5; 17.5–79.0)	45.9 (10.5; 17.9–79.0)	48.4‡[b] (10.5; 19.3–81.5)
BMI	25.8 (6.5; 14.6–71.0)	25.2 (5.9; 15.4–57.7)	25.4 (6.0; 14.4–64.1)
	Median (interquartile range)		
PHQ-2	0 (0–1)	1 (0–2)	0‡ (0–1)
PHQ-9			0 (0–0)
IPAQ MET mins per week	1,092 (297–2,826)	1,200 (396–2,826)	1,200 (396–2,670)
DHQ total score	81 (71–89.5)	83 (73.5–91)	81[a] (71–90)
Disease duration since symptom onset, years	11.8 (6.2–20.4)	11.4 (5.4–20.2)	14.2‡[b] (8.1–23.2)
PDDS	2 (0–4)	1 (0–4)	1 (0–4)
P-MSSS	4.7 (2.6–7.4)	4.4 (2.4–7.3)	4.9[a] (2.6–7.3)
Fatigue Severity Score	44 (29–55)	42 (27–54)	42† (26–54)

(Continued)

TABLE 1 | Continued

Differences between categorical variables assessed by multinomial logistic regression. Differences between normally distributed continuous terms assessed by two-tailed t-test. Differences between non-normally distributed continuous terms assessed by Kruskal-Wallis rank test.

† $p < 0.05$ for differences between baseline and 2.5-years review.

‡ $p < 0.001$ for differences between baseline and 2.5-years review.

[a] $p < 0.05$ for differences between baseline and 2.5-years review for participants with 2.5-years follow-up data.

[b] $p < 0.001$ for differences between baseline and 2.5-years review for participants with 2.5-years follow-up data.

[c] Alcohol intake was categorized specific to sex, such that low alcohol intake was defined as <15 grams of alcohol per week, moderate was up to 30 grams alcohol per day for females and up to 45 grams alcohol per day for males, and heavy was over 30 grams alcohol per day for females and over 45 grams alcohol per day for males.

Note: some variables have missing values but where there were no missing values, this row is not shown for that variable.

BMI, body mass index; DHQ, Dietary Habits Questionnaire; IPAQ, International Physical Activity Questionnaire; PDDS, Patient-Determined Disease Steps Scale; PHQ, Patient Health Questionnaire; P-MSSS, Patient Determined Multiple Sclerosis Severity Score; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SCQ, Self-administered Comorbidity Questionnaire; SPMS, secondary progressive multiple sclerosis.

at follow-up, especially the PHQ-9, though adjustment attenuated all these associations. Both vitamin D and omega-3 supplementation were associated with lower frequencies of depression risk by both PHQ-2 and PHQ-9. However, while the associations of vitamin D supplementation persisted on adjustment, omega-3 associations were greatly attenuated.

Greater physical activity was associated with a significantly lower depression risk, robust to adjustment. Likewise, meditation was associated with significantly reduced prevalence of depression by both scores, though only that for PHQ-9 persisted on adjustment.

Determinants of PHQ-9 Grade of Depression at 2.5-Years Follow-Up

Many of the factors associated with overall depression risk (PHQ-9 > 9) in **Table 2** were also associated with the gradations of depression severity (**Table 3**). The positive associations of current

smoking with depression risk were much stronger for major depression. There was an inverse association between alcohol and overall depression risk, only evident for major depression, while no associations were seen for minimal depression symptoms. As with overall depression risk, however, while both moderate and high alcohol intake were inversely associated with major depression risk, there was no benefit of high alcohol intake with depression (data not shown).

Higher diet quality was associated with a significantly reduced risk of depression, most strongly with major depression. Likewise, for meat and dairy consumption, the positive associations were much stronger with severe depression. Vitamin D and omega-3 supplementation both showed strong and significant inverse associations with major depression risk.

The association of physical activity with depression was only evident for major depression, showing no associations with minimal depression symptoms. For major depression, however, those engaging in more physical activity had markedly lower frequencies of major depression, over 50%. Meditation, on the other hand, while strongly associated with PHQ-9 overall, showed no material dose-dependency, only being significantly associated with mild major depression.

Baseline and Trajectory Determinants of Change in PHQ-2 Depression Between Baseline and 2.5-Years Follow-Up

A change in PHQ-2 depression was evaluated as a change in state between baseline and 2.5-years follow-up, such that participants could go from having not screened positive for depression at baseline to positive screen at follow-up ("becoming depressed"), screening positive for depression at baseline and losing this at follow-up ("losing depression"), or having no change, this including screening positive for depression or not at both timepoints (**Table 4**). For trajectory analysis, then, gaining depression risk was compared against those without depression risk at both time points, while losing depression risk was compared against those with depression risk at both time points.

While there was some indication that smoking had a prospective association with subsequently becoming depressed, these associations were essentially abrogated on adjustment. Alcohol consumption, on the other hand, was associated with greater risk of losing depression and lower risk of becoming depressed, much more robust to adjustment. As seen with cross-sectional depression, there was no association of high alcohol consumption with change in depression state, suggesting these associations are particular to moderate alcohol intake. Higher diet quality showed a prospective association with reduced risk of becoming depressed, fairly robust to adjustment. Meat and dairy consumption were inconsistently associated with change in depression, with some indication that consumption was associated with becoming depressed, but these associations largely attenuated on adjustment. Vitamin D supplementation showed a strong association with a reduced risk of becoming depressed, robust to adjustment. Omega-3 supplementation was not associated with either becoming depressed or losing depression.

Overall physical activity was not associated with change in depression state. Of interest, those who reported meditating at least weekly at baseline had a significantly reduced risk of losing depression, robust to adjustment, though there was no association of meditation with risk of gaining depression.

DISCUSSION

Depression is common (1), poorly treated, under-diagnosed (34) and has been reported to exert the greatest influence on quality of life for people with MS, irrespective of disability level (35). In the general population, depression typically has a strong genetic basis and has episodes with full or partial recovery (29). However, for people with MS, depression is persistent (8) and genetic determinants are not the primary drivers (1). Instead, for people with MS depression is likely due to the psychological adjustment to the illness, as well as underlying physiological processes driving the disease. While it is well-established that the underlying processes of MS are multifactorial, including neurodegeneration, autoimmunity and inflammation; depression has more recently been recognized as having an inflammatory component mediated by modifiable lifestyle factors (16, 36). Lifestyle factors, combined with the stress of diagnosis and adjustment to illness, may cause overactivation of the hypothalamus-pituitary-adrenal axis, increasing cortisol and systemic inflammation (16). Identification of risk factors for MS and depression and their link via the common pathway of inflammation opens the critical avenue for preventive and therapeutic interventions (20, 36) potentially leading to improved morbidity and mortality outcomes.

In the current study, we have completed a comprehensive investigation of modifiable lifestyle factors associated with screening positive for depression, and the predictors of change in depression state over 2.5 years of follow-up. Moderate alcohol use was associated with lower depression risk, particularly severe depression at 2.5-years follow-up, which is consistent with our baseline findings (20). These results are also in keeping with the literature, where moderate alcohol intake has been associated with better mental health-related quality of life in MS (26). In the general population, moderate alcohol intake has been associated with lower rates of depression in primary care settings (37). Beyond the association of alcohol use and depression, we found that moderate alcohol intake was associated with greater risk of losing depression and lower risk of becoming depressed. These data are supported by findings in the general population that moderate alcohol intake is associated with lower incidence of becoming depressed (38). Moderate alcohol intake results in significant reduction of proinflammatory cytokines (39), reducing inflammation, suggesting a mechanism of preventing and potentially treating depression. Heavy alcohol use or alcohol dependence, on the other hand, is harmful for general health and increases the prevalence of depression in both the general population and MS (37, 38, 40). Our HOLISM findings are consistent with this literature, finding no beneficial association of heavy alcohol intake and depression trajectory, nor with mental or physical health benefits (20, 26).

TABLE 2 | Predictors of depression risk at 2.5-years follow-up.

	PHQ-2			PHQ-9		
	n/N with PHQ-2 > 2 (%)	**Univariable**	**Adjusted**	**N with PHQ-9 > 9 (%)**	**Univariable**	**Adjusted**
SMOKE TOBACCO?						
Never	84/695 (12.1%)	1.00 [Reference]	1.00 [Reference]	121/677 (17.9%)	1.00 [Reference]	1.00 [Reference]
Ex-smoker	78/513 (15.2%)	1.26 (0.95, 1.68)	1.20 (0.91, 1.58)	107/491 (21.8%)	1.22 (0.97, 1.54)	1.13 (0.90, 1.41)
Current smoker	28/99 (28.35)	**2.34 (1.61, 3.40)**	**1.63 (1.12, 2.37)**	46/94 (48.9%)	**2.74 (2.11, 3.56)**	**1.96 (1.51, 2.55)**
Trend:		***p < 0.001***	***p = 0.016***		***p < 0.001***	***p < 0.001***
ALCOHOL INTAKE						
Non-drinker	45/256 (17.6%)	1.00 [Reference]	1.00 [Reference]	69/246 (28.1%)	1.00 [Reference]	1.00 [Reference]
<Once per week	69/405 (17.0%)	0.97 (0.69, 1.36)	1.04 (0.74, 1.45)	98/387 (25.3%)	0.90 (0.69, 1.18)	0.89 (0.69, 1.15)
1–3 days per week	41/342 (12.0%)	0.68 (0.46, 1.01)	0.82 (0.55, 1.20)	59/333 (17.7%)	**0.63 (0.47, 0.86)**	**0.74 (0.55, 0.99)**
4–7 days per week	27/245 (11.0%)	**0.63 (0.40, 0.98)**	0.83 (0.54, 1.27)	39/240 (16.3%)	**0.58 (0.41, 0.82)**	0.74 (0.53, 1.03)
(Missing)		***p = 0.007***	*p = 0.18*		***p < 0.001***	***p = 0.030***
ALCOHOL LOAD[a]						
Low	21/102 (20.6%)	1.00 [Reference]	1.00 [Reference]	29/97 (29.9%)	1.00 [Reference]	1.00 [Reference]
Moderate	109/799 (13.6%)	0.66 (0.44, 1.01)	0.80 (0.53, 1.23)	151/775 (19.5%)	**0.65 (0.47, 0.91)**	0.77 (0.56, 1.06)
High	21/156 (13.5%)	0.65 (0.38, 1.14)	0.84 (0.48, 1.45)	34/154 (22.1%)	0.74 (0.48, 1.13)	0.97 (0.65, 1.45)
Trend:		*p = 0.19*	*p = 0.52*		*p = 0.32*	*p = 0.98*
DHQ TOTAL SCORE						
32–70	74/336 (22.0%)	1.00 [Reference]	1.00 [Reference]	111/323 (34.4%)	1.00 [Reference]	1.00 [Reference]
>70–80	51/320 (15.9%)	**0.72 (0.52, 1.00)**	0.80 (0.58, 1.11)	83/309 (26.9%)	**0.78 (0.62, 0.99)**	0.87 (0.69, 1.10)
>80–89	46/349 (13.2%)	**0.60 (0.43, 0.84)**	0.82 (0.59, 1.14)	58/335 (17.3%)	**0.50 (0.38, 0.67)**	**0.67 (0.51, 0.88)**
>89–100	19/303 (6.3%)	**0.29 (0.18, 0.46)**	**0.50 (0.31, 0.80)**	22/296 (7.4%)	**0.22 (0.14, 0.33)**	**0.36 (0.24, 0.55)**
Trend:		***p < 0.001***	***p = 0.005***		***p < 0.001***	***p < 0.001***
CONSUMES MEAT?						
No	53/505 (10.5%)	1.00 [Reference]	1.00 [Reference]	70/490 (14.3%)	1.00 [Reference]	1.00 [Reference]
Yes	137/803 (17.1%)	**1.63 (1.21, 2.19)**	1.22 (0.92, 1.63)	204/773 (26.4%)	**1.85 (1.44, 2.37)**	**1.41 (1.11, 1.78)**
		p = 0.001	*p = 0.17*		***p < 0.001***	***p = 0.004***
CONSUMES DAIRY?						
No	58/551 (10.5%)	1.00 [Reference]	1.00 [Reference]	71/534 (13.3%)	1.00 [Reference]	1.00 [Reference]
Yes	131/753 (17.4%)	**1.65 (1.24, 2.21)**	1.27 (0.96, 1.69)	203/725 (28.0%)	**2.11 (1.65, 2.69)**	**1.60 (1.26, 2.02)**
		p = 0.001	*p = 0.10*		***p < 0.001***	***p < 0.001***
TAKING A VITAMIN D SUPPLEMENT?						
No	49/192 (25.5%)	1.00 [Reference]	1.00 [Reference]	63/186 (33.9%)	1.00 [Reference]	1.00 [Reference]
Yes	141/1,117 (12.6%)	**0.50 (0.37, 0.66)**	**0.61 (0.46, 0.81)**	211/1,078 (19.6%)	**0.58 (0.46, 0.73)**	**0.70 (0.56, 0.87)**
		p < 0.001	***p = 0.001***		***p < 0.001***	***p = 0.002***
TALKING AN OMEGA-3 SUPPLEMENT?						
No	87/464 (18.8%)	1.00 [Reference]	1.00 [Reference]	128/450 (28.4%)	1.00 [Reference]	1.00 [Reference]
Yes	103/845 (12.2%)	**0.65 (0.50, 0.85)**	0.87 (0.67, 1.12)	146/814 (17.9%)	**0.63 (0.51, 0.78)**	**0.80 (0.66, 0.98)**
		p = 0.001	*p = 0.28*		***p < 0.001***	***p = 0.031***
PHYSICAL ACTIVITY, BY IPAQ						
Low activity	86/391 (22.0%)	1.00 [Reference]	1.00 [Reference]	122/377 (32.4%)	1.00 [Reference]	1.00 [Reference]
Moderate activity	69/577 (12.0%)	**0.54 (0.41, 0.73)**	0.75 (0.55, 1.01)	97/556 (17.5%)	**0.54 (0.43, 0.68)**	**0.74 (0.59, 0.93)**
High activity	16/268 (6.0%)	**0.27 (0.16, 0.45)**	**0.49 (0.30, 0.82)**	30/261 (11.5%)	**0.36 (0.25, 0.51)**	**0.60 (0.42, 0.87)**
Trend:		***p < 0.001***	***p = 0.003***		***p < 0.001***	***p = 0.002***
MEDITATES AT LEAST WEEKLY?						
No	133/839 (15.9%)	1.00 [Reference]	1.00 [Reference]	198/817 (24.2%)	1.00 [Reference]	1.00 [Reference]
Yes	50/454 (11.0%)	**0.70 (0.51, 0.94)**	0.75 (0.56, 1.00)	70/432 (16.2%)	**0.67 (0.52, 0.86)**	**0.73 (0.58, 0.92)**
		p = 0.019	*p = 0.052*		***p = 0.001***	***p = 0.008***

Analyses by log-binomial regression, estimating a prevalence ratio (PR) (95% CI). Adjusted models adjusted for age, P-MSSS, FSS, and use of antidepressant medication. Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are p-values.

[a] *Alcohol intake was categorized specific to sex, such that low alcohol intake was defined as <15 grams of alcohol per week, moderate was up to 30 grams alcohol per day for females and up to 45 grams alcohol per day for males, and heavy was over 30 grams alcohol per day for females and over 45 grams alcohol per day for males.*

BMI, body mass index; DHQ, Dietary Habits Questionnaire; FSS, Fatigue Severity Scale; IPAQ, International Physical Activity Questionnaire; PHQ, Patient Health Questionnaire; P-MSSS, Patient Determined Multiple Sclerosis Severity Score.

TABLE 3 | Predictors of depression risk level vs. no depression risk at 2.5-years follow-up, as measured by PHQ-9.

	N with PHQ9 = 0–4 (Normal) (%)	N with PHQ9 = 5–9 (Minimal) (%)	N with PHQ9 = 10–14 (Major, moderate/severe) (%)	N with PHQ9 = ≥15 (Major, moderate/severe) (%)	aPR Minimal depression symptoms vs. no depression risk	aPR Major depression, mild vs. no depression risk	aPR Major depression, moderate/severe vs. no depression risk
SMOKE TOBACCO?							
Never	358 (52.9%)	198 (29.3%)	67 (9.9%)	54 (8.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Ex-smoker	228 (46.4%)	156 (31.8%)	54 (11.0%)	53 (10.8%)	1.06 (0.91, 1.23)	1.04 (0.77, 1.41)	1.33 (0.99, 1.79)
Current smoker	21 (22.3%)	27 (28.7%)	23 (24.5%)	23 (24.5%)	**1.34 (1.02, 1.75)**	**2.17 (1.50, 3.15)**	**1.99 (1.45, 2.74)**
Trend:					*p = 0.071*	***p = 0.002***	***p < 0.001***
ALCOHOL INTAKE							
Non-drinker	107 (43.5%)	70 (28.5%)	32 (13.0%)	37 (15.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
<Once per week	170 (43.9%)	119 (30.8%)	53 (13.7%)	45 (11.6%)	1.03 (0.84, 1.26)	0.98 (0.69, 1.40)	0.78 (0.57, 1.06)
1–3 days per week	174 (52.3%)	100 (30.0%)	32 (9.6%)	27 (8.1%)	0.97 (0.78, 1.20)	0.74 (0.49, 1.11)	**0.63 (0.42, 0.94)**
4–7 days per week	130 (54.2%)	71 (29.6%)	24 (10.0%)	15 (6.3%)	0.97 (0.78, 1.22)	0.80 (0.53, 1.22)	0.68 (0.41, 1.11)
Trend:					*p = 0.67*	*p = 0.13*	***p = 0.030***
ALCOHOL LOAD[a]							
Low	41 (42.3%)	27 (27.8%)	11 (11.3%)	18 (18.6%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderate	388 (50.1%)	236 (30.5%)	82 (10.6%)	69 (8.9%)	1.00 (0.76, 1.31)	0.88 (0.52, 1.48)	**0.62 (0.43, 0.89)**
High	74 (48.1%)	46 (29.9%)	23 (14.9%)	11 (7.1%)	1.09 (0.79, 1.51)	1.29 (0.73, 2.29)	0.75 (0.41, 1.38)
Trend:					*p = 0.48*	*p = 0.14*	*p = 0.18*
DHQ TOTAL SCORE							
32–70	104 (32.3%)	107 (33.2%)	52 (16.2%)	59 (18.3%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
>70–80	129 (41.8%)	97 (31.4%)	45 (14.6%)	38 (12.3%)	0.88 (0.73, 1.07	0.81 (0.60, 1.11)	0.79 (0.58, 1.09)
>80–89	178 (53.1%)	99 (29.6%)	34 (10.2%)	24 (7.2%)	**0.77 (0.63, 0.93)**	**0.67 (0.47, 0.96)**	**0.60 (0.42, 0.87)**
>89–100	195 (65.9%)	79 (26.7%)	13 (4.4%)	9 (3.0%)	**0.70 (0.57, 0.87)**	**0.33 (0.19, 0.58)**	**0.33 (0.17, 0.62)**
Trend:					***p < 0.001***	***p < 0.001***	***p < 0.001***
CONSUMES MEAT?							
No	290 (59.2%)	130 (26.5%)	42 (8.6%)	28 (5.7%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	317 (41.0%)	252 (32.6%)	102 (13.2%)	102 (13.2%)	**1.28 (1.09, 1.49)**	**1.41 (1.04, 1.90)**	**1.51 (1.07, 2.13)**
					p = 0.002	***p = 0.026***	***p = 0.020***
CONSUMES DAIRY?							
No	311 (58.2%)	152 (28.5%)	39 (7.3%)	32 (6.0%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	293 (40.4%)	229 (31.6%)	105 (14.5%)	98 (13.5%)	**1.21 (1.04, 1.40)**	**1.61 (1.18, 2.21)**	**1.49 (1.06, 2.10)**
					p = 0.012	***p = 0.003***	***p = 0.022***
TAKING A VITAMIN D SUPPLEMENT?							
No	66 (35.5%)	57 (30.7%)	28 (15.1%)	35 (18.8%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	541 (50.2%)	326 (30.25)	116 (10.8%)	95 (8.8%)	0.91 (0.76, 1.10)	0.73 (0.53, 1.00)	**0.61 (0.46, 0.79)**
					p = 0.35	*p = 0.050*	***p < 0.001***

(Continued)

TABLE 3 | Continued

	N with PHQ9 = 0–4 (Normal) (%)	N with PHQ9 = 5–9 (Minimal) (%)	N with PHQ9 = 10–14 (Major, moderate/severe) (%)	N with PHQ9 = ≥15 (Major, moderate/severe) (%)	aPR Minimal depression symptoms vs. no depression risk	aPR Major depression, mild vs. no depression risk	aPR Major depression, moderate/severe vs. no depression risk
TALKING AN OMEGA-3 SUPPLEMENT?							
No	177 (39.3%)	145 (32.2%)	69 (15.3%)	59 (13.1%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	430 (52.8%)	238 (29.2%)	75 (9.2%)	71 (8.7%)	0.91 (0.79, 1.05)	**0.75 (0.57, 0.99)**	0.84 (0.65, 1.09)
					p = 0.19	***p = 0.039***	*p = 0.18*
PHYSICAL ACTIVITY							
Low activity	127 (33.7%)	128 (34.0%)	64 (17.0%)	58 (15.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Moderate activity	294 (52.9%)	165 (29.7%)	53 (9.5%)	44 (7.9%)	0.93 (0.79, 1.10)	**0.72 (0.53, 0.98)**	0.72 (0.52, 1.00)
High activity	162 (62.1%)	69 (26.4%)	20 (7.7%)	10 (3.8%)	0.96 (0.77, 1.20)	0.69 (0.44, 1.10)	**0.48 (0.27, 0.86)**
Trend:					*p = 0.57*	***p = 0.035***	***p = 0.004***
MODERATE/HIGH PHYSICAL ACTIVITY?							
No	127 (33.7%)	128 (34.0%)	64 (17.0%)	58 (15.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	456 (55.8%)	234 (28.6%)	73 (8.9%)	54 (6.6%)	0.94 (0.80, 1.10)	**0.71 (0.53, 0.96)**	**0.67 (0.49, 0.91)**
					p = 0.44	***p = 0.024***	***p = 0.012***
MEDITATES AT LEAST WEEKLY?							
No	374 (45.8%)	245 (30.0%)	109 (13.3%)	89 (10.9%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	229 (53.0%)	133 (30.8%)	35 (8.1%)	35 (8.1%)	0.99 (0.85, 1.15)	**0.66 (0.48, 0.90)**	0.85 (0.63, 1.14)
					p = 0.86	***p = 0.008***	*p = 0.28*

Analyses by log-multinomial regression[29], estimating a prevalence ratio (PR) (95% CI). All models adjusted for age, P-MSSS, FSS, and use of antidepressant medication.

Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are p-values.

[a]Alcohol intake was categorized specific to sex, such that low alcohol intake was defined as <15 grams of alcohol per week, moderate was up to 30 grams alcohol per day for females and up to 45 grams alcohol per day for males, and heavy was over 30 grams alcohol per day for females and over 45 grams alcohol per day for males.

BMI, body mass index; DHQ, Dietary Habits Questionnaire; FSS, Fatigue Severity Scale; IPAQ, International Physical Activity Questionnaire; PHQ, Patient Health Questionnaire; P-MSSS, Patient Determined Multiple Sclerosis Severity Score.

TABLE 4 | Baseline demographic and lifestyle predictors of change in PHQ-2 depression state between baseline and 2.5-years follow-up.

	N with depression at both baseline and follow-up (row %)	N with depression at baseline, not at follow-up (row %)	RR loss of depression vs. always depressed	aRR loss of depression vs. always depressed	N with negative depression-screen at both baseline and follow-up (row %)	N with no depression at baseline but with depression at follow-up (row %)	RR gain of depression vs. never depressed	aRR gain of depression vs. never depressed
SMOKE TOBACCO?								
Never	23 (35.9%)	41 (64.1%)	1.00 [Reference]	1.00 [Reference]	546 (91.2%)	53 (8.9%)	1.00 [Reference]	1.00 [Reference]
Ex-smoker	33 (46.5%)	38 (53.5%)	0.84 (0.63, 1.11)	0.88 (0.66, 1.18)	363 (90.8%)	37 (9.3%)	1.04 0.70, 1.55)	1.11 (0.74, 1.66)
Current smoker	15 (50.0%)	15 (50.0%)	0.78 (0.52,1.16)	0.79 (0.53, 1.19)	61 (82.4%)	13 (17.6%)	**1.83 (1.04, 3.22)**	1.38 (0.72, 2.63)
Trend:			*p = 0.16*	*p = 0.21*			*p = 0.14*	*p = 0.36*
CURRENT SMOKER?								
No	56 (41.5%)	79 (58.5%)	1.00 [Reference]	1.00 [Reference]	909 (91.0%)	90 (9.0%)	1.00 [Reference]	1.00 [Reference]
Yes	15 (50.0%)	15 (50.0%)	0.85 (0.58, 1.25)	0.85 (0.58, 1.24)	61 (82.4%)	13 (17.6%)	**1.80 (1.05, 3.09)**	1.33 (0.71, 2.48)
			p = 0.41	*p = 0.39*			***p = 0.033***	*p = 0.38*
ALCOHOL INTAKE								
Non-drinker	21 (56.8%)	16 (43.2%)	1.00 [Reference]	1.00 [Reference]	137 (87.3%)	20 (12.7%)	1.00 [Reference]	1.00 [Reference]
<Once per week	28 (40.6%)	41 (59.4%)	1.33 (0.88, 202)	1.56 (0.97, 2.49)	353 (89.1%)	43 (10.9%)	0.82 (0.50, 1.33)	0.72 (0.44, 1.18)
1–3 days per week	10 (33.3%)	20 (66.7%)	1.50 (0.96, 2.35)	**1.71 (1.03, 2.84)**	278 (92.7%)	22 (7.3%)	**0.54 (0.31, 0.95)**	0.61 (0.35, 1.08)
4–7 days per week	12 (41.4%)	17 (58.6%)	1.32 (0.81, 2.13)	1.58 (0.92, 2.73)	203 (91.9%)	18 (8.1%)	0.61 (0.34, 1.10)	0.57 (0.31, 1.05)
Trend:			*p = 0.21*	*p = 0.073*			***p = 0.039***	*p = 0.083*
DRINKS ALCOHOL?								
No	21 (56.8%)	16 (43.2%)	1.00 [Reference]	1.00 [Reference]	137 (87.3%)	20 (12.7%)	1.00 [Reference]	1.00 [Reference]
Yes	50 (39.1%)	78 (60.9%)	1.37 (0.92, 2.03)	**1.60 (1.02, 2.51)**	834 (91.0%)	83 (9.1%)	0.68 (0.43, 1.06)	0.65 (0.41, 1.03)
			p = 0.12	***p = 0.041***			*p = 0.088*	*p = 0.065*
ALCOHOL LOAD[a]								
Low	37 (50.0%)	38 (50.0%)	1.00 [Reference]	1.00 [Reference]	304 (87.0%)	45 (13.0%)	1.00 [Reference]	1.00 [Reference]
Moderate	21 (32.3%)	44 (67.7%)	**1.33 (1.01, 1.75)**	**1.47 (1.10, 1.96)**	480 (92.1%)	41 (7.9%)	**0.60 (0.41, 0.88)**	0.70 (0.47, 1.05)
High	9 (47.4%)	10 (52.6%)	1.05 (0.65, 1.72)	1.12 (0.67, 1.86)	139 (92.7%)	11 (7.3%)	0.54 (0.30, 1.00)	0.54 (0.27, 1.06)
Trend:			*p = 0.28*	*p = 0.14*			***p = 0.010***	***p = 0.025***
HIGH ALCOHOL CONSUMPTION[a]?								
No	58 (42.1%)	82 (57.9%)	1.00 [Reference]	1.00 [Reference]	820 (89.9%)	92 (10.1%)	1.00 [Reference]	1.00 [Reference]
Yes	9 (47.4%)	10 (52.6%)	0.92 (0.58, 1.45)	0.91 (0.57, 1.46)	139 (92.7%)	11 (7.3%)	0.71 (0.39, 1.28)	0.64 (0.33, 1.22)
			p = 0.71	*p = 0.69*			*p = 0.25*	*p = 0.18*
DHQ TOTAL SCORE								
32–70	25 (43.9%)	32 (56.1%)	1.00 [Reference]	1.00 [Reference]	168 (85.3%)	29 (14.7%)	1.00 [Reference]	1.00 [Reference]
>70–80	20 (41.7%)	28 (58.3%)	0.99 (0.71, 1.39)	0.99 (0.71, 1.38)	206 (88.0%)	28 (12.0%)	0.86 (0.54, 1.38)	0.98 (0.59, 1.60)
>80–89	15 (36.6%)	26 (63.4%)	1.12 (0.81, 1.55)	1.04 (0.75, 1.45)	269 (91.8%)	24 (8.2%)	**0.61 (0.37, 0.99)**	0.79 (0.47, 1.31)
>89–100	11 (55.0%)	9 (45.0%)	0.77 (0.45, 1.30)	0.70 (0.41, 1.18)	332 (93.8%)	22 (6.2%)	**0.47 (0.28, 0.79)**	0.59 (0.34, 1.02)
Trend:			*p = 0.69*	*p = 0.44*			***p = 0.001***	***p = 0.041***

(Continued)

TABLE 4 | Continued

	N with depression at both baseline and follow-up (row %)	N with depression at baseline, not at follow-up (row %)	RR loss of depression vs. always depressed	aRR loss of depression vs. always depressed	N with negative depression-screen at both baseline and follow-up (row %)	N with no depression at baseline but with depression at follow-up (row %)	RR gain of depression vs. never depressed	aRR gain of depression vs. never depressed
CONSUMES MEAT?								
No	21 (51.2%)	20 (48.8%)	1.00 [Reference]	1.00 [Reference]	426 (92.0%)	37 (8.0%)	1.00 [Reference]	1.00 [Reference]
Yes	50 (40.0%)	75 (60.0%)	1.22 (0.87, 1.72)	1.45 (0.98, 2.16)	548 (89.3%)	66 (10.8%)	1.30 (0.89, 1.89)	1.07 (0.72, 1.59)
			p = 0.25	*p = 0.063*			*p = 0.18*	*p = 0.73*
CONSUMES DAIRY?								
No	20 (45.5%)	24 (54.6%)	1.00 [Reference]	1.00 [Reference]	466 (93.4%)	33 (6.6%)	1.00 [Reference]	1.00 [Reference]
Yes	51 (42.2%)	70 (57.9%)	1.10 (0.81, 1.50)	1.17 (0.84, 1.62)	503 (88.1%)	68 (11.9%)	**1.72 (1.16, 2.54)**	1.41 (0.94, 2.11)
			p = 0.54	*p = 0.36*			***p = 0.007***	*p = 0.096*
TALKING A VITAMIN D SUPPLEMENT?								
No	18 (46.2%)	21 (53.9%)	1.00 [Reference]	1.00 [Reference]	130 (84.4%)	24 (15.6%)	1.00 [Reference]	1.00 [Reference]
Yes	53 (41.7%)	74 (58.3%)	1.04 (0.75, 1.45)	1.03 (0.73, 1.45)	845 (91.5%)	79 (8.6%)	**0.60 (0.40, 0.91)**	**0.64 (0.42, 1.00)**
			p = 0.82	*p = 0.87*			***p = 0.015***	***p = 0.047***
TALKING AN OMEGA-3 SUPPLEMENT?								
No	38 (50.0%)	38 (50.0%)	1.00 [Reference]	1.00 [Reference]	267 (89.9%)	30 (10.1%)	1.00 [Reference]	1.00 [Reference]
Yes	33 (36.7%)	57 (63.3%)	1.23 (0.93, 1.62)	1.25 (0.94, 1.66)	708 (90.7%)	73 (9.4%)	0.96 (0.65, 1.42)	1.08 (0.71, 1.66)
			p = 0.15	*p = 0.13*			*p = 0.83*	*p = 0.72*
PHYSICAL ACTIVITY, BY IPAQ								
Low activity	37 (42.1%)	51 (58.0%)	1.00 [Reference]	1.00 [Reference]	273 (88.1%)	37 (11.9%)	1.00 [Reference]	1.00 [Reference]
Moderate activity	23 (46.0%)	27 (54.0%)	0.94 (0.69, 1.28)	0.89 (0.64, 1.23)	407 (91.5%)	38 (8.5%)	0.76 (0.50, 1.16)	1.13 (0.72, 1.78)
High activity	6 (30.0%)	14 (70.0%)	1.21 (0.88, 1.67)	1.11 (0.78, 1.59)	236 (92.9%)	18 (7.1%)	0.70 (0.41, 1.18)	1.04 (0.58, 1.88)
Trend:			*p = 0.51*	*p = 0.69*			*p = 0.15*	*p = 0.92*
MODERATE/HIGH PHYSICAL ACTIVITY?								
No	37 (42.1%)	51 (58.0%)	1.00 [Reference]	1.00 [Reference]	273 (88.2%)	37 (11.8%)	1.00 [Reference]	1.00 [Reference]
Yes	29 (41.4%)	41 (58.6%)	1.02 (0.78, 1.32)	0.95 (0.72, 1.27)	643 (91.5%)	56 (8.5%)	0.80 (0.55, 1.17)	1.18 (0.77, 1.81)
			p = 0.91	*p = 0.74*			*p = 0.24*	*p = 0.45*
MEDITATES AT LEAST WEEKLY?								
No	48 (37.5%)	80 (62.5%)	1.00 [Reference]	1.00 [Reference]	637 (90.2%)	69 (9.8%)	1.00 [Reference]	1.00 [Reference]
Yes	23 (60.5%)	15 (39.5%)	**0.60 (0.40, 0.92)**	**0.61 (0.40, 0.94)**	337 (90.8%)	34 (9.2%)	0.94 (0.63, 1.38)	0.90 (0.60, 1.35)
			p = 0.017	***p = 0.024***			*p = 0.73*	*p = 0.62*

Analyses by log-binomial regression, estimating a risk ratio (RR) (95% CI). Adjusted models adjusted for age, baseline P-MSSS, baseline FSS, and baseline use of antidepressant medication.

Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are p-values.

[a]*Alcohol intake was categorized specific to sex, such that low alcohol intake was defined as <15 grams of alcohol per week, moderate was up to 30 grams alcohol per day for females and up to 45 grams alcohol per day for males, and heavy was over 30 grams alcohol per day for females and over 45 grams alcohol per day for males.*

BMI, body mass index; DHQ, Dietary Habits Questionnaire; FSS, Fatigue Severity Scale; IPAQ, International Physical Activity Questionnaire; PHQ, Patient Health Questionnaire; P-MSSS, Patient Determined Multiple Sclerosis Severity Score.

Being a smoker was significantly predictive of positive depression screen and more severe depression at follow-up. This finding parallels the association between smoking and lower mental health-related quality of life, which we previously demonstrated in people with MS (26). After adjusting for potential confounders, we did not find an association between smoking and subsequent change in depression risk, however, while the clinical implications of smoking and depression require further research, the evidence base is clear that smoking is a major risk factor for the development and progression of MS and other comorbidities (41, 42). Smokers commonly have depression, and vice versa, people with depression are more likely to smoke, and smoking cessation interventions are more successful if management includes interventions for depression (43). Being or becoming a non-smoker clearly has multiple direct and indirect benefits for people with MS.

Intervention trials in the general population show that improving diet quality, increasing exercise, sunlight exposure (44), and supplementing with omega-3 and vitamin D are effective adjunctive treatments to antidepressant medication (45). Vitamin D and omega-3 supplementation was common in this sample, with roughly three-quarters taking vitamin D and two-thirds taking omega-3 supplements. This supplement use is becoming quite common among MS patients, given the abundance of research evidence suggesting a potential protective association on MS onset and progression. While not yet proven, and thus not recommended by medical practitioners as a treatment against MS, such supplementation is a relatively inexpensive and simple lifestyle modification for people to undertake, and one without material side effect, and consequently it is frequently seen in MS cohorts.

Observational studies in the general population and MS indicate that low vitamin D is a modifiable risk factor for depression (46, 47). Our data at baseline and 2.5-years follow-up found an association between supplementation with vitamin D and risk of positive depression screen, and as well as severity of depression.

A recent meta-analysis supports that omega-3 intake is associated with a lower risk of depression (48). In line with the literature in the general population, our data found an inverse association between omega-3 supplementation and both the risk of positive depression screen and severity of depression, though not with change in depression state. The literature on health benefits for people with MS is not consistent. While omega-3 supplementation has been associated with better health-related quality of life and reduced disability among people with MS (49), another study found no benefit for disability progression, quality of life, relapses, MRI lesions or fatigue (50). A recent pilot trial found no effect of omega-3 on depression in people with MS (51). However, omega-3 supplementation is safe and provides numerous health benefits across the life cycle and in other diseases, such as cancer and autoimmune conditions (52–54). Its effects are thought to be via immunomodulation, anti-inflammation, neuroprotection and neurotransmission (55). Reverse causality is possible, as people without depression are more likely to engage in more healthy behaviors. Nonetheless, our data and other studies support a possible link between supplementation of omega-3, and mental and physical health outcomes in people with MS (20, 49).

Healthy diet is critical for optimal neurological function (16), evidenced in our growing knowledge of the connection between the gut microbiome, neurotransmitters and mental health (56). While we found no association between diet quality and depression risk, there was a dose-response association between diet quality and depression severity. Dose-response relationships have been found between diet quality and depression in the general population (57) and better diet quality has been associated with improved mental health-related quality of life in people with MS (58). Dairy, but not meat intake, was associated with greater depression risk on PHQ-9 but not PHQ-2. In our study, the relationship between diet and depression risk may reflect reverse causality. The observed association of dairy intake and depression risk is less clear and is likely also to be affected by reverse causality. These results are partly in line with previous work, including work showing a vegan diet improved depression in the general population (59). A whole food plant-based diet has been recommended for people with MS and more widely for general health (60). It is important for clinicians to consider dietary advice as part of an effective management strategy for depression (61).

Low physical activity was strongly associated with an increased depression risk and depression severity. We did, however, not find an association between physical activity and change in depression risk. Our data reinforce findings that people with MS who exercise regularly have better quality of life and favorable depression scores (57, 62) consistent with findings in the general population (63). The relationship between physical activity and depression is likely bi-directional and we cannot quantify the degree of reverse causality that may be present in our data. However, the evidence base from clinical trials is strong enough for clinicians to inform people with MS of the benefit of regular physical activity (64). There is a synergistic benefit to be gained through regular exercise on mood and to reduce obesity and comorbid medical disorders for direct benefit in MS (16, 65, 66).

Meta-analysis of meditation and mindfulness-based stress reduction programs shows a benefit for depression across the general population and for people with other chronic illness (16, 67). For people with MS, mindfulness meditation holds potential to improve immune function and reduce inflammation (68). A recent randomized controlled trial of mindfulness-based interventions improved depression and quality of life, with gains maintained at long-term follow-up (14). In line with these studies, we have shown meditation is cross-sectionally associated with lower depression risk at 2.5-years follow-up, although our findings did not show meditation to be associated with depression trajectory during follow-up. This disparity may reflect the relative insensitivity of our assessment of meditation, as well as the inherent subjectivity of meditation. Thus, further longitudinal analyses, ideally with rigorous assessment of meditation behavior, are needed to assess the role of meditation in depression and MS.

A preventive medical approach to MS management, both pharmacological and otherwise, is in line with the broad shift toward early intervention in the disease course (69). At baseline (20) and here at 2.5-years follow-up, the HOLISM study has shown clinically and statistically significant associations between key modifiable lifestyle risk factors and depression, as well as better mental and physical health-related quality of life (20, 58). Moreover, in another study of people with MS who attended lifestyle modification workshops, we found showed improved mental health-related quality of life at 1, 3 and 5 years follow-up (70–72), also finding that those with greater adherence to lifestyle modification had better outcomes. More complete data revealed adherence to lifestyle changes and outcome improvements at 1 and 3 years follow-up, including stabilized disability, reduced relapse rates, and better physical health-related quality of life (72). These results are supported by work in other chronic illnesses, finding depression was reduced in people with diabetes and elevated coronary risk factors who underwent intensive lifestyle modification (73). Thus, there is potential for lifestyle factors like those assessed here to have positive effects on depression. If validated in other samples and supported by randomized controlled trials, such lifestyle modification could be an additional point of intervention to improve depression among people living with MS.

Strengths and Limitations

A major strength of our sample was the breadth of data and exposure gradient for lifestyle factors and sociodemographics. However, some subsets of data, such as severe depression remained small. It may be that such severely depressed people would not participate in this study and thus, our assessment of the frequency and determinants of severe depression may be affected. Our sample may be biased due to participants being recruited via online platforms, potentially recruiting a healthier and more actively engaged sample of people with MS at baseline and follow-up. In addition, there was appreciable attrition between baseline and follow-up reviews, with a retention rate of 56.8%. While there was some evidence that those retained in the study engaged in more healthy behaviors like not smoking, other behaviors like alcohol, physical activity and supplement use were not materially different between the original sample and those participating at follow-up, nor were clinical characteristics like disability or fatigue materially different. However, significantly more people with depression risk at baseline were lost to follow-up, suggesting that our estimates of depression prevalence at follow-up may underestimate the true prevalence, and that associations with depression state may be affected by this differential loss to follow-up.

Our data are self-reported so the potential for recall bias exists. Reverse causality cannot be excluded from some associations and may have contributed to some of our trajectory data. However, the biological plausibility, dose-response effect and results from existing literature supports a potential causal relationship between several lifestyle factors and depression risk. Our data have many strengths, we recruited and retained a large sample size, including people with all types of MS from geographically diverse backgrounds. Validated tools were used wherever possible and potential confounders were adjusted for. However, not all participants responded to every question and thus, there was some missing data. Accordingly, all multivariate models were complete-case analysis, restricted to those with data on all model parameters.

A large proportion of this cohort (42–46%) was taking immunomodulatory medications. This is fairly similar to frequencies reported in other MS cohorts. The associations of immunomodulatory medication use with depression state will be described in another paper. However, our evidence indicates that controlling for disability and fatigue is adequate to account for clinical variability and its association with depression in this sample.

Factors which might have impacted upon depression risk, and which would have been useful to account for, but which we did not have information, include addiction and drug use, membership in community and other organizations, and local environmental characteristics, particularly air/water and noise pollution. Addiction and drug use are obviously quite relevant, but we only queried tobacco and alcohol use. While it is possible for some covariance of illicit drug use with tobacco/alcohol, our failure to measure these exposures is a limitation. Membership in community and other social organizations could also impact upon depression, so data on this would have been a useful analysis, but one which we unfortunately cannot examine. Likewise, environmental and noise pollution would be of interest, both for overall quality of life and potentially for its impacts on physical activity and time outdoors. Future studies would be strengthened by measuring these parameters.

Another element of interest is socioeconomic status, since this can impact upon depression and modify the relationship of other factors with depression. However, we only measured this factor at follow-up, precluding a more definitive assessment of its prospective relationship, especially with change in depression state. Accordingly, we do not control for it here, though it is examined in another manuscript.

CONCLUSION

In a large prospective cohort study of people with MS and depression, we have found evidence that a variety of lifestyle factors are inversely associated with depression, though of these, only alcohol, diet and supplement use were independently associated with change in depression. These results, if confirmed, suggest that some healthy lifestyle behaviors may positively impact depression risk among people living with MS.

ETHICS STATEMENT

The Health Sciences Human Ethics Sub-Committee at the University of Melbourne provided ethical approval for the study (Ethics ID: 1545102). Participants were asked to read the participant information and to consent before entering the survey.

AVAILABILITY OF DATA AND MATERIAL

Data may not be shared due to the conditions approved by our institutional ethics committee, in that all data are stored as re-identifiable information at the University of Melbourne in the form of password-protected computer databases, and only the listed investigators have access to the data. All data have been reported on a group basis, summarizing the group findings rather than individual findings so personal information cannot be identified. Therefore, we can supply aggregate group data on request. Readers may contact George Jelinek or Tracey Weiland.

AUTHOR CONTRIBUTIONS

GJ, TW, KT, SS, CM, CB, and ADL are responsible for study concept; KT drafted and edited the manuscript; SS, CM, CB, and EO contributed to cohort management and cleaned and prepared the data for analysis. SS undertook data analyses. TW, GJ, SS, SN, ADL, CB, EK, and CM contributed to editing an earlier version of the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest Statement: GJ receives royalties for his books, Overcoming Multiple Sclerosis and Recovering from Multiple Sclerosis. GJ, SN, and KT have received remuneration for conducting lifestyle educational workshops for people with MS.

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Early Post-stroke Depression and Mortality: Meta-Analysis and Meta-Regression

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Background: Post-stroke depression (PSD) is a common and serious complication after stroke. In this systematic review and meta-analysis, we evaluated the association between early PSD and mortality, considering depressive symptoms occurring within the first 3 months after the neurological event.

Methods: This meta-analysis was conducted following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and based on studies indexed till May 2018 in PubMed and Web of Science databases. The relative risk (RR) for mortality in individuals with PSD, as compared with non-depressed ones, was estimated. Findings were pooled according to a random-effects model. Meta-regression and subgroup analyses were carried out.

Results: We included seven studies, accounting for 119,075 individuals, of whom 17,609 suffering from an early PSD. We found higher rates of mortality in subjects with PSD as compared with non-depressed ones (RR = 1.50; 95%CI: 1.28 to 1.75; $p < 0.001$). Heterogeneity across studies was moderate ($I^2 = 50.7\%$). Subgroup analysis showed a slightly higher effect of PSD on short-term mortality (RR = 1.70; $p < 0.001$), as compared with long-term one (RR = 1.35; $p = 0.01$). According to relevant meta-regression analyses, the estimate was influenced by sample proportion of men ($p = 0.043$).

Conclusions: Despite some limitations, our study shows the negative impact of early PSD on survival rates. Mechanisms underlying this association still need to be elucidated and several interpretations can be hypothesized. Future research should test if an early management of depression may increase life expectancy after stroke.

Keywords: stroke, depression, mortality, meta-analysis, meta-regression

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INTRODUCTION

Stroke is the second leading cause of death worldwide, accounting for 6.3 million deaths in 2015 (1), and a major public health issue associated with an increasing global burden of disease (2) and different physical (3) and neuropsychological consequences (4). Post-stroke depression (PSD) is a common and serious complication after stroke (5), occurring in about one third of subjects,

especially during the first stage after the acute event (6). The pathophysiology of PSD is probably multifactorial, deriving from a complex interaction between ischemia-induced neurobiological dysfunctions and psychological distress (7, 8). Although an early detection of PSD is a key issue in clinical practice, its identification remains challenging (9). This may be due to some neurological symptoms which could conceal primary mood abnormalities (5), as well as the lack of satisfactory diagnostic tools for case-finding (10). However, PSD represents one of the main factors limiting recovery and rehabilitation (9), predisposing to severe disability, functional and cognitive impairment, greater dependency in daily activities, and low treatment adherence (11, 12). In addition, several studies identified PSD as a potential risk factor for mortality (13–15). Consistently, a previous systematic review and meta-analysis (16), including 13 studies and 59,598 subjects, estimated a small, though significant, effect of PSD on mortality. However, findings were probably influenced by the methodological heterogeneity across studies. In particular, along with follow-up duration, high time variability for PSD assessment in different studies should be taken into account, considering that PSD frequency may change over time (5). Indeed, some studies evaluated early PSD (14), whereas other assessed depression up to several years after stroke (15). Since symptoms usually occur within the first 3 months after stroke (17), it seems important to evaluate the impact on survival of early PSD, including findings of recent studies published in this field (11, 18). We thus conducted a systematic review and meta-analysis, to investigate the association between early PSD and mortality, considering different factors that might potentially influence the estimated effect, including sample characteristics, assessment methods, follow-up duration, and quality.

METHODS

This systematic review and meta-analysis was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (19).

Search Strategy

We updated the strategy of our previous systematic review and meta-analysis (16), searching for articles indexed in PubMed and Web of Science electronic databases up to May 30th, 2018. No language restriction was set. We used the following terms for the PubMed search: "*(depression [Mesh] or depression [all fields]) and (Stroke [Mesh] or post-stroke [title/abstract] or post stroke [title/abstract]) and (Mortality [Mesh] or mortal* [title/abstract] or death* [title/abstract])*." We used a similar search phrase for Web of Science database: "*(depress* or mood* or affective*) and (stroke* or post-stroke or poststroke) and (mortal* or death*)*."

Eligibility Criteria

Studies which compared the survival rates in adults with and without PSD, respectively, were considered eligible. To be included, studies had to assess PSD within 3 months after an acute stroke. Both ischemic and hemorrhagic stroke were considered. We excluded articles providing continuous scores based on psychometric scales for depression, without dichotomization based on a cut-off value.

Data Extraction and Quality Assessment

Two authors (FB and CDB) independently completed the preliminary screening, based on titles and abstracts, in order to identify potentially eligible articles. The final inclusion decision was based on full text evaluation. We built a data extraction template, including key items for all eligible studies, i.e., year of publication, country, sample size, PSD and mortality assessment methods, follow up duration, rates of mortality in individuals with and without PSD, respectively.

In addition, we performed a quality evaluation of included studies, based on items derived from the Newcastle Ottawa Scale for non-randomized studies (20). We evaluated sample representativeness, recruitment source comparability between PSD and non-PSD groups, quality of methods to assess PSD and to retrieve information on cases of death, as well as the investigation of potential confounders.

Two authors (FB and CDB) independently extracted data and assessed quality for blind check of accuracy. Discordances were resolved by consensus with other co-authors.

Data Analysis

We conducted a meta-analysis estimating the relative risk (RR) for mortality in individuals with PSD as compared with those without. We carried out a *post-hoc* stratification of data, according to study follow-up duration. Findings were pooled according to the random-effects model and were summarized using a conventional forest plot. In addition, we carried out random-effects meta-regression analyses with Hartung-Knapp modification (21), exploring whether the estimated association between PSD and mortality might vary according to different study characteristics. These included continuous variables such as sample size, mean age, male gender proportion, and follow-up duration, as well as a categorical variable distinguishing methods to assess PSD (i.e., standardized clinical interviews, psychometric scales, or clinical records). We also carried out sensitivity analyses excluding studies with potential methodological issues based on considered quality items.

Statistical significance was set at $p < 0.05$. Consistency across studies was measured using the I^2 index, with standard values of 25, 50, and 75% taken to indicate low, moderate and high levels of heterogeneity, respectively (22). Analyses were performed using the Stata statistical software package (release 14).

RESULTS

Study Selection

Our search generated 439 and 1,821 records from PubMed and Web of Science databases, respectively. The preliminary evaluation based on titles and abstracts, identified 62 potentially eligible studies. Further screening of full texts allowed to exclude 55 articles. Seven studies met eligibility criteria and were included in our meta-analysis (11, 14, 18, 23–26). Details on study selection process are shown in **Figure 1**.

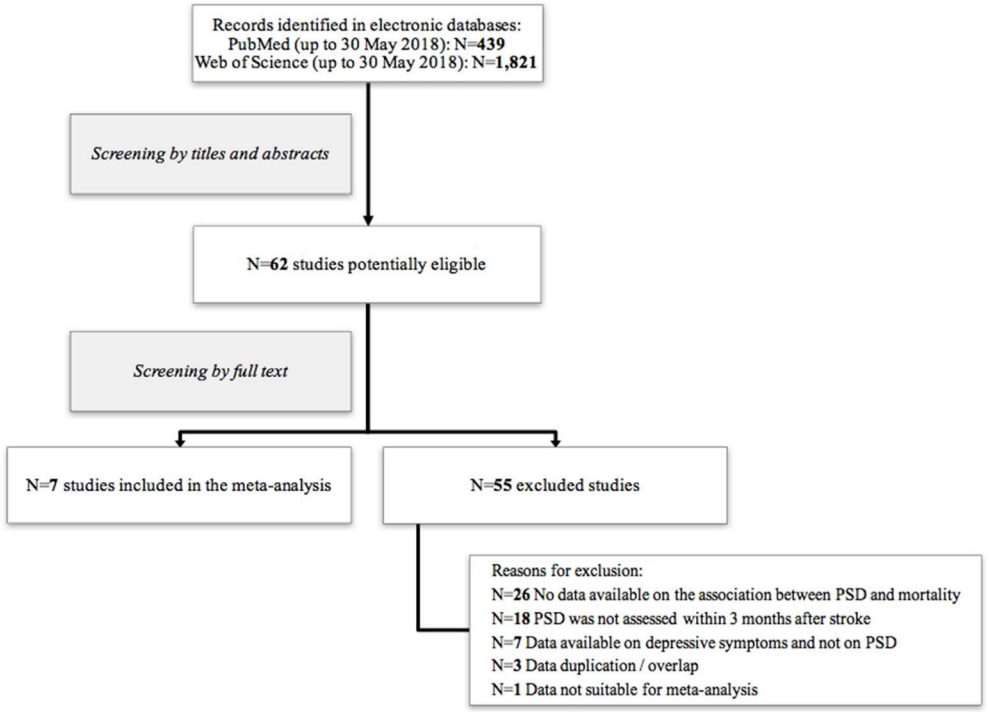

FIGURE 1 | Flow chart of included/excluded studies.

Study Characteristics and Quality Assessment

All included studies, published between 1993 (24, 25) and 2016 (18, 23), were written in English. Full characteristics are shown in **Table 1**. Most of studies could be considered sufficiently representative since they recruited subjects selected from specific catchment areas. However, one study (14) selected participants from a randomized-controlled trial on psychological treatments after stroke, who are likely to be different from the standard clinical population suffering from stroke. Moreover, all studies recruited both PSD and non-PSD individuals from the same setting, thus guaranteeing recruitment source comparability between cases and controls. In addition, all studies but one (23), deriving diagnosis from register-based information, tested PSD using clinical interviews or psychometric scales. One study (26) used only the first question of the Hamilton Depression Rating Scale, thus limiting its psychometric validity. In terms of mortality, adequate sources, such as death registries, were used in most of studies. In two studies (24, 25), information on mortality was unclear and probably not sufficiently valid, since the vital status of patients at follow-up could not be checked in a high proportion of cases (>10%). Finally, all studies but two (24, 25), which provided only unadjusted data, estimated the association between PSD and mortality after controlling for possible demographic and clinical confounders. Quality evaluation is summarized in **Table 2**.

Synthesis of Results

Seven studies (11, 14, 18, 23–26) based on 119,075 individuals (17,609 suffering from PSD and 101,466 non-depressed individuals) had data suitable to estimate the random-effect RR. We used unpublished information provided by the authors from four studies (11, 14, 23, 26). As a whole, 3,588 cases of death at follow-up were detected from PSD samples and 12,906 from comparison groups. Random-effects meta-analysis estimated higher rates of mortality in subjects suffering from PSD, as compared with non-depressed ones (RR = 1.50; 95%CI: 1.28 to 1.75; $p < 0.001$), with moderate heterogeneity across studies ($I^2 = 50.7\%$) (**Figure 2**). The subgroup analysis showed a slightly higher effect size in studies testing mortality within 2 years after stroke (RR = 1.70; $p < 0.001$), as compared with those based on a longer period of observation (RR = 1.35; $p = 0.01$) (**Figure 2**). However, a relevant meta-regression analysis showed no influence of follow-up duration on the estimated effect size (ß = −0.016; $p = 0.711$). Other meta-regression analyses, considering sample size, mean age, and PSD assessment methods, did not show any significant influence on effect size, apart from the proportion of recruited men (ß = 0.039; $p = 0.043$). In addition, sensitivity analyses based on quality issues confirmed the significant relationship between early PSD and lower life expectancy, with relative risk of mortality varying between 1.45 and 1.62 (**Table 2**).

TABLE 1 | Characteristics of included studies.

Study (reference)	City, Country	Participants			PSD assessment	Follow-up (yrs.)
		N	Mean age (yrs.)	Men (%)		
Ayerbe et al. (11)	London, UK	1,354	68.1	54.0	HADS	5
de Mello et al. (18)	São Paulo, Brazil	191	63	60.2	PHQ-9	1
House et al. (14)	Leeds and Bradford, UK	448*	70.7	53.8	PSE	2
Jørgensen et al. (23)	Denmark	116,569**	68.7**	53.8**	Clinical registries	2
Morris et al. (24)	Baltimore, USA	91	60.4	59.3	PSE	10
Morris et al. (25)	New South Wales, Australia	84	71.1	53.6	CIDI	1.25
Willey et al. (26)	New York, USA	340	68.8	43.5	Single item from HRSD	5

BDI-II, Beck Depression Inventory-Second Edition; CIDI, Composite International Diagnostic Interview; HADS, Hospital Anxiety and Depression Scale; HRSD, Hamilton Rating Scale for Depression; PHQ-9, Patient Health Questionnaire; PSE, Present State Examination.

**Data from 446 individuals were included in the meta-analysis, since data from two subjects were missing.*

***Data from the subsample of subjects survived and evaluated for depression within 3 months after stroke.*

TABLE 2 | Quality assessment and sensitivity analyses.

Study (reference)	Sample representativeness	Recruitment comparability	Depression assessment	Information on mortality	Control for confounders
Ayerbe et al. (11)	(+)	(+)	(+)	(+)	(+)
de Mello et al. (18)	(+)	(+)	(+)	(+)	(+)
House et al. (14)	(–)	(+)	(+)	(+)	(+)
Jørgensen et al. (23)	(+)	(+)	(–)	(+)	(+)
Morris et al. (24)	(+)	(+)	(+)	(–)	(–)
Morris et al. (25)	(+)	(+)	(+)	(–)	(–)
Willey et al. (26)	(+)	(+)	(–)	(+)	(+)
RR (95%CI) Sensitivity analyses	1.49 (1.25 to 1.78)	–	1.62 (1.27 to 2.05)	1.45 (1.21 to 1.74)	1.45 (1.21 to 1.74)

DISCUSSION

Summary and Interpretation of Findings

The current systematic review and meta-analysis, based on seven studies (11, 14, 18, 23–26), highlights the impact of early depression after stroke on survival rates. To our knowledge, this is the first meta-analysis estimating a higher risk of mortality in people suffering from PSD, considering depressive symptoms occurring in the early stage after the acute event. Subjects with early PSD had a risk of death about 1.5 higher as compared with non-depressed individuals, considering both short- and long-term mortality. Nevertheless, a comprehensive interpretation of these findings should take into account quality issues of included studies and a partial inconsistency of findings. Considering both internal and external validity (27, 28), we found that some studies included in this meta-analysis might have been influenced by the lack of representativeness (14) and control for confounders (24, 25), as well as by the potential low accuracy of PSD diagnosis (23) and mortality assessment at follow-up (24, 25). Nevertheless, quality-based sensitivity analyses seem consistent with the overall estimation.

In addition, our results should be interpreted considering the statistical heterogeneity, likely to be due to systematic differences in important methodological characteristics, such as target population, PSD definition, follow-up duration. The estimated excess of mortality in early PSD could not be explained by heterogeneity attributable to most of study characteristics, apart from gender. It should be considered that the strength of the relationship between PSD and mortality might be higher among men, although available data did not allow stratifying findings according to gender.

Even considering quality issues and heterogeneity, evidence from this meta-analysis is in line with findings of a previous systematic review and meta-analysis, showing an association between depression, assessed at any time after stroke, and mortality (16). Moreover, similar findings were reported in individuals with heart failure, in which depression was associated with higher risk of mortality (29). Our results are consistent with epidemiological evidence, showing the impact of depression on poor outcomes after acute vascular events (26).

Pathophysiological mechanisms which can explain the association between PSD and increased risk of mortality, remain to be clarified although several possible interpretations could be postulated. A first hypothesis may be related to depression effects on cardiovascular risk, possibly leading to recurrent cerebrovascular events and higher mortality. Indeed, individuals suffering from depressive disorders are more prone to unhealthy lifestyle behaviors, including higher rates of smoking, alcohol

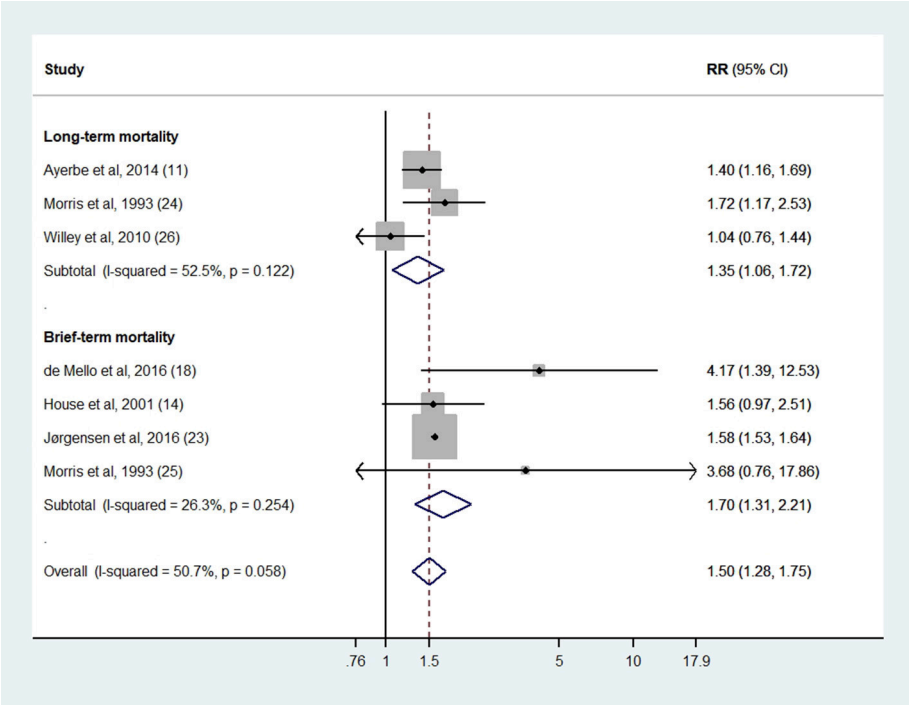

FIGURE 2 | Association between early post-stroke depression and mortality. Short-term mortality = 1 or 2 years after stroke; Long-term mortality = 5 or more years after stroke.

intake, physical inactivity, and poor dietary patterns (30, 31). Consistently, it should be considered that individuals with depression are generally less likely to be adherent and compliant to prescribed treatments and medications, being thus more vulnerable to poor clinical consequences (11, 32). Second, early depressive symptoms may occur more frequently in subjects with severe stroke-related consequences, such as disability, neurocognitive deficits, and functional impairment (33, 34). Thus, depression might be significantly related to stroke severity, that, in turn, might increase the risk of death. Third, evidence of pharmacological treatment for PSD have produced mixed results (35, 36) and benefits of selective serotonin reuptake inhibitors (SSRIs) have been questioned, considering the possible association with an even increased mortality (37). Consistently, even if antidepressants have shown to improve depressive symptoms and functional outcomes (38, 39), some studies estimated a higher likelihood of overall major bleeding and an increased risk of death in subjects treated with SSRIs (40). Thus, the excess of mortality in individuals with PSD might be partially explained by possible negative effects of a SSRI treatment on survival. Finally, mortality could be attributable also to non-natural causes of death. Stroke survivors show higher risk of death by suicide, especially if they suffer from current or lifetime mood disorder, recurrent stroke, and cognitive impairment (41). A recent systematic review and meta-analysis (42) including 10,400 stroke survivors, estimated that a clinically meaningful suicidal ideation may occur in about one out of eight individuals after the neurological event. Consistently, it has been reported that individuals suffering from stroke have rates of suicide attempts twice as high as the general population (43, 44).

Limitations

Although the current meta-analysis provided preliminary evidence on PSD effect on mortality, caution should be used in interpreting our findings, due to some limitations.

First, we could not systematically control for treatment-related factors, such as antidepressant medication as well as other interventions for depression prevention and management (5), which might influence the association between PSD and survival rates. This seems a key issue since previous studies highlighted a possible effect of antidepressants on mortality after stroke (40).

Second, it should be considered that there is not a gold standard for PSD diagnosis and that standardized scales, combining depressive and somatic items, are not currently available (10). Consistently, we found variability across studies in terms of assessment tools for depression, varying from clinical interviews such as PSE (14, 24) and CIDI (25), to psychometric scales (11, 18, 26). Diagnostic issues arise from specific features of stroke survivors, in which neurological symptoms and neurocognitive deficits could hide symptoms of independent mood disorders (5).

Finally, even if the number of subjects and cases included in this meta-analysis is adequate, only seven studies met inclusion criteria. Since <10 studies were included in our meta-analysis

(45), we could not assess risk of publication bias by using appropriate statistical approaches (46).

Clinical Implications

Findings of this meta-analysis indirectly support the need of a regular assessment of depressive symptoms in subjects with stroke. Early depression after stroke often remains underdiagnosed and untreated, due to the lack of a gold standard for PSD assessment as well as of diagnostic issues related to clinical characteristics of this special population (10, 17). For example, stroke-related neurological symptoms such as aprosodic speech, abulia, or flat affect may hinder the clinical evaluation of depressive symptoms, whereas aphasia may lead to an underestimation of PSD (5). Consistently, evidence on pharmacological treatment of depression after stroke is limited and little is known about possible long-term adverse effects (47). In addition, further research is needed to explore efficacy of non-pharmacological interventions and prevention strategies for PSD. Various psychosocial, behavioral, and rehabilitative interventions (48–50) have been tested and may be possibly effective in reducing depressive symptoms. Although important gaps in terms of the most effective treatment for PSD remain, a greater awareness on depression after stroke and its impact on survival among patients, families, and health professionals, could facilitate recognition, earlier treatment, and improved outcomes (51).

CONCLUSIONS

Despite some limitations, our systematic review and meta-analysis suggests the potential impact of early PSD in influencing mortality of stroke survivors. Although the underlying mechanisms of this relationship remain unknown, PSD seems to negatively influence both short- and long-term life expectancy. Further research is required to evaluate whether an early management of mood disorders in individuals with stroke may improve their outcomes and related mortality gap.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the intellectual content of the paper. FB and GC: conception and design; FB and CD: search and screening, data extraction, dataset management, and drafting of the manuscript; FB and CC: statistical analysis and interpretation of data; GC, MC, and CC: critical revision of the manuscript; GC and MC: supervision. All authors gave approval of the final version of the manuscript.

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REVIEW
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Lifestyle Interventions and Prevention of Suicide

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Over the past years, there has been a growing interest in the association between lifestyle psychosocial interventions, severe mental illness, and suicide risk. Patients with severe mental disorders have higher mortality rates, poor health states, and higher suicide risk compared to the general population. Lifestyle behaviors are amenable to change through the adoption of specific psychosocial interventions, and several approaches have been promoted. The current article provides a comprehensive review of the literature on lifestyle interventions, mental health, and suicide risk in the general population and in patients with psychiatric disorders. For this purpose, we investigated lifestyle behaviors and lifestyle interventions in three different age groups: adolescents, young adults, and the elderly. Several lifestyle behaviors including cigarette smoking, alcohol use, and sedentary lifestyle are associated with suicide risk in all age groups. In adolescents, growing attention has emerged on the association between suicide risk and internet addiction, cyberbullying and scholastic and family difficulties. In adults, psychiatric symptoms, substance and alcohol abuse, weight, and occupational difficulties seems to have a significant role in suicide risk. Finally, in the elderly, the presence of an organic disease and poor social support are associated with an increased risk of suicide attempt. Several factors may explain the association between lifestyle behaviors and suicide. First, many studies have reported that some lifestyle behaviors and its consequences (sedentary lifestyle, cigarette smoking underweight, obesity) are associated with cardiometabolic risk factors and with poor mental health. Second, several lifestyle behaviors may encourage social isolation, limiting the development of social networks, and remove individuals from social interactions; increasing their risk of mental health problems and suicide.

Keywords: suicide, suicide attempts, suicidal thoughts, lifestyle behavior, lifestyle intervention, suicide prevention

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INTRODUCTION

Several well-established psychosocial factors and lifestyle behaviors including life satisfaction, economic adversities, family environment, major life and occupational stressor(s), substance and alcohol abuse, medical conditions, cigarette smoking, being sedentary, underweight or obese, and diet are considered prominent factors in the development of severe mental disorders and suicide risk. Psychiatric patients, including patients affected by schizophrenia, bipolar disorder, schizoaffective disorder and depressive disorder, have higher mortality rates and higher suicide risk compared to the general population (1, 2). Increased mortality is probably also due, besides psychiatric impairment and psychotropic medication use, to unhealthy lifestyle behaviors including

poor diet, excessive smoking, alcohol use, and lack of exercise. These unhealthy lifestyle behaviors can increase the development of many physical diseases including overweight, obesity, metabolic syndrome, diabetes, cardiovascular disease, cerebrovascular disease, hepatitis, amongst other medical conditions (3, 4).

Suicide has been described as a multi-faceted construct in relation to psychiatric symptoms, medical conditions, and lifestyle risk factors (5–7). Moreover, lifestyle behaviors are involved in the pathogenesis of medical and severe psychiatric disorders such as depression and psychosis (8, 9), increasing the risk of suicide (10).

Recently, considerable attention has been paid to the concept of life satisfaction and well-being as psychosocial indicators of mental health (11). It has been hypothesized (12, 13) that life satisfaction and meaning in life can help people overcome adversity. Factors associated with optimal well-being and life satisfaction included prudent lifestyle behaviors such as healthy eating, adequate sleep, physical activity, avoiding tobacco, and limiting alcohol consumption (14). Few studies have revealed that suicide ideation is related to psychiatric symptomatology, lifestyle behavior, and lower life satisfaction (15, 16). Koivumaa-Honkanen et al. (17) in a study of 29,067 Finnish adults found that unhappiness was associated with an increased risk of suicide. This group also reported that unhappiness was associated with older age, male gender, sickness, living alone, smoking, heavy alcohol consumption, physical inactivity, and belonging to intermediate social class.

In the past few decades, a lot of progress has been made to identify public health strategies for the prevention of mental health and suicide. Although the approach to suicide has always involved clinical aspects, especially the assessment and the treatment of depression (18), it seems necessary to consider also risk factors that can be identified and modified through specific lifestyle interventions.

Based on data demonstrating how lifestyle behaviors may be involved in both the genesis of severe psychiatric disorders and in increasing suicide risk (19), we aimed to provide a narrative review synthetizing existing published literature on lifestyle interventions and suicide prevention in psychiatric patients behavior. Additionally, we provide a review of the literature on lifestyle interventions promoting mental health reducing suicide risk in the general population and in patients with psychiatric disorders.

Lifestyle behaviors and interventions may differ at different life stages of life. Given this, we reviewed lifestyle behaviors and interventions associated with suicide risk in three age group categories: adolescents and young people (age 16–30), young adults and adults (age 30–65), and older adults and elderly (age >65).

MATERIALS AND METHODS

We searched the relevant databases including MEDLINE, ISI Web of Knowledge – Web of Science Index, Cochrane Reviews Library and PsychoINFO for papers published from January 2000 to March 2018.

The following keywords were used: "lifestyle intervention," "life satisfaction", "diet," "physical activity," "nutrition," "cholesterol," "diabetes," "lifestyle behaviors," "cigarette smoke" matched with "suicide risk," "healthy population," "mental disorders," "schizophrenia," "psychotic disorders," "bipolar disorder," "depression," "adolescents," "adults," and "elderly." Inclusion criteria were: studies adopting psychosocial interventions for promoting changes in lifestyle behaviors, studies aiming to improve patients' physical status (evaluated in terms of body mass index – BMI, level of physical activity, smoking status, etc.) and studies that assess the association between lifestyle behaviors and psychiatric disorders and suicide risk. Only papers written in English were included. Studies included in this narrative review were those that examined suicide and lifestyle interventions in adolescence, young adults or adults and the elderly. Studies in which the age group investigated was not clearly defined were excluded from this review.

Randomized controlled trials, clinical controlled trials, pilot studies, cohort studies and reviews were considered eligible for the review process. In addition, the reference lists of all included studies and of relevant existing systematic reviews were checked for possible studies. Papers were screened by an independent researcher (IB) and assessed for eligibility by a senior expert (MP).

LIFESTYLE BEHAVIOR AND SUICIDE IN ADOLESCENTS AND YOUNG PEOPLE

Suicidal ideation and suicide attempt are relatively common in this phase of life; with completed suicide being the second most common cause of death in adolescents (20).

It has been described that 10–20% of adolescents suffer from a mental disorder (21). Adolescence is often associated with elevated levels of anxiety, stress, and adverse life events, which may lead to maladaptive feelings of hopelessness, personal failure, and suicidal ideation (22). While positive coping strategies, efficacious problem-solving skills, and general life satisfaction are considered protective for suicide (23). Common severe psychiatric disorders in adolescents include depression, anxiety disorders, behavioral problems (e.g., oppositional defiant disorder or conduct disorder), early psychosis, eating disorders (e.g., anorexia nervosa and bulimia nervosa) and addictive disorders (24), all risk factors for suicidal behavior in adolescents (25, 26).

Unhealthy lifestyle behaviors may impact mental health and suicidal behavior by influencing emotions and judgement. Studies have demonstrated that adolescents with first-episode psychosis have a high prevalence of tobacco, alcohol and cannabis use, selective dietary habits, lower physical activity, and lower level of activity during leisure time (27–30). Other studies have demonstrated a close relationship between cannabis use, hypomania, mania, and suicide risk in adolescents (31, 32). Furthermore, a relationship between weight, social relations, and

depressive symptoms has been described (33); stressing the link between lifestyle behavior, mental health and suicide risk.

High symptom of any personality disorder in adolescence have negative repercussions on functioning over the subsequent 10 to 20 years. For instance, elevated Borderline Personality Disorder (BPD) symptoms in adolescence have been shown to be an independent risk factor for substance-use disorders during early adulthood, alcohol consumption, psychopathology, health risk behaviors, and suicide risk (34–37). Prevention and early intervention for BPD are necessary not only for reduction on psychiatric symptoms but also for improving psychosocial functioning and decreasing substance abuse, which are known risk factors for suicide.

Im et al. (38) examined 370,568 students with the aim of recognizing risk factors for suicidal ideation in adolescents found that low sleep satisfaction, high stress, alcohol consumption, smoking, and sexual activity, were significant lifestyle factors associated with suicidal ideation. Lee et al. (39) in a sample of 860 adolescents confirmed the relationship between several lifestyle behaviors and suicide risk including sleep disturbance, internet game addiction, and interpersonal factors (e.g., family conflicts and peer problems). A recent systematic review of 17 studies recognized that, in adolescents, a diagnosis of binge eating disorder was predictive of suicidality, while a high body mass index (BMI) was not (40). Substance-use disorders, including alcohol use disorder, are considered one of the most important risk factors associated with suicide risk during adolescence (41, 42). Moreover, it has been reported that the more the number of substances abused the higher the suicide risk (43). Borges et al. (44) in a recent trial on 1,071 young Mexicans reported that the use of cannabis before age 15, high frequency of cannabis use and another recent substance-use disorder increased the risk of suicide. Park et al. (45) collected data from 68,043 adolescents with the purpose of investigating the undesirable effects of frequent use of caffeinated energy drinks. Their results indicated that energy drink consumption was associated with sleep dissatisfaction, severe stress, depressive mood, suicidal ideation, suicide plan, and suicide attempt. Similarly, Kim et al. (46) in a study of 121,106 Korean adolescents confirmed that severe stress, inadequate sleep, and low school performance were associated with more energy drink consumption and suicide attempts.

Evidence suggests that sedentary lifestyle may impact emotional and mental health in adolescents (47). A systematic review on this topic found a strong relationship between sedentarism, depressive symptomatology, psychological distress, and suicide ideation in adolescents (48). In this regard, Lester et al. (49) demonstrated that participation in sports reduced the incidence of suicidal ideation.

Internet use has a mixed effect on children and young people's well-being. On one hand, internet users may develop a social support that may be artificial. On the other hand, it exposes adolescents to cyberbullying and meeting strangers online (50). In recent years, there has been an increased interest in the relationship between internet use, cyber-bullying, and suicide (51). A recent systematic review of 51 articles investigated the relationship between internet use and self-harm/suicidal behavior. This review demonstrated that internet addiction and elevated levels of internet use, were associated with a higher suicide risk (52). John et al. (53) highlighted that compared to non-victims of cyberbullying, victims of cyberbullying had a greater risk of both self-harm and suicidal behaviors. Rodelli et al. (54) evaluated the associations between physical activity, sport participation, healthy diet, higher sleep duration and lower levels of smoking and lower levels of alcohol use, and suicidal ideation when faced to cyberbullying. Results showed that cyberbullying victimization was associated with higher suicidal ideation while increased physical activity, sleeping longer, healthy diet and lower levels of smoking were associated with lower suicidal ideation. Moreover, a systematic review on the role of web technologies, mobile solutions, social networks, and machine learning in the prevention of suicide risk highlighted that many of these methods can help prevent suicide (55).

The potential role of family relationships (conflict, negative relationship with parents, other) as a risk factor for suicide was evaluated in 36,757 French adolescents (56). Results from this study demonstrated that negative relationships with parents and parental discord was significantly associated with suicide risk and/or depression in adolescents regardless of gender. The role of family interventions in the prevention of mental illness, substance abuse, and suicide ideation and attempts have been evaluated (57). The author suggested that family interventions could be useful in the prevention of suicidal ideation and behavior in both adolescents and parents.

LIFESTYLE BEHAVIOR AND SUICIDE IN YOUNG ADULTS AND ADULTS

In adults, the relationship between lifestyle behavior, severe psychiatric symptoms, and suicide risk is well documented (58, 59). Recent literature has demonstrated that behavioral lifestyle interventions help patients with serious mental illnesses lose weight and reduce cigarette smoking. Behavioral lifestyle interventions also helped patients achieve changes in fasting glucose levels in patients taking antipsychotic medications (60); simultaneously reducing the possibility of developing medical conditions; indirectly reducing the risk of suicide.

Studies have demonstrated that adult psychiatric inpatients who had attempted suicide presented higher levels of sedentarism and higher tobacco use compared to psychiatric patients who did not attempt suicide (61, 62).

Research reporting on the relationship between suicide, obesity, total serum cholesterol, and dietary patterns is controversial (63). Research examining the relationship between lipid profile and suicide attempts have shown that compared to non-attempters, suicide attempters had lower cholesterol levels (64, 65). More recently, a case control study of a Mexican population found a positive association between lower cholesterol levels and suicide attempt (66). Although the mechanism behind hypocholesterolemia and suicide has not been elucidated, it has been hypothesized that altered cholesterol at synaptic lipid rafts cause a decrease in serotonin transmission, neurotransmitter implicated in the pathophysiology of suicide

(67, 68). A recent systematic review and meta-analysis of 11 studies evaluating lipid profile in suicide attempters and non-attempters in people with bipolar disorder failed to clarify the relationship between LDL-cholesterol, triglycerides and suicide in these patients. Shrivastava et al. (69) in a naturalistic cross-sectional cohort study of 60 patients with early psychosis, found that low levels of cholesterol were present only in the group of patients with severe suicidality. Similarly, Messaoud et al. (70) found a positive association between low plasma cholesterol level and suicidal behavior in patients with major depressive disorder.

Studies on the associations between depression, suicidal behavior, glucose levels or insulin resistance are scarce. Higher glucose levels have been associated with dysthymia (71) and higher HbA1c concentrations have been associated with psychotic depression (72). Koponen et al. (73) in 448 patients aged 35 years old found that patients with depression and suicidal behavior had higher blood glucose concentrations at baseline and at 2 h in the oral glucose tolerance test (OGTT).

Although dietary habits have been linked to depression, only few studies have examined the association between dietary patterns and suicide risk (74, 75). Li et al. (75) found that a dietary pattern comprise of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and fish was associated with a decreased risk of suicide. Mukamal et al. (74) reviewed retrospectively the dietary information of 6,803 adults describing the differences in eating habits between suicide attempters and non-attempters. Results indicated that male attempters presented low consumption of vegetables and female attempters presented insufficient fruit consumption. It was further observed that female attempters ate significantly less fish and sea food compared to female non-attempters. Finally, results showed that fruits, vegetables, and meat were significantly under-consumed in those individuals with a history of suicide attempt.

The relationship between body mass index (BMI) and suicide risk in adult seems controversial. A study by Perera et al. (63) supported the hypothesis of an inverse association between BMI and completed suicide, where underweight was associated with an increased risk of completed suicide while obesity and overweight were associated with a decreased risk of suicide in comparison to people of normal weight. Contrarily, Branco et al. (76) stressed that obesity was associated with a higher prevalence of suicide risk, especially in women. Kim et al. (77) on 6,022 nationally representative sample of Korean adults aged 18 to 74 found that being underweight was associated with higher suicide risk and obesity was associated only with risk of suicide ideation but not with suicide attempt. In the same study, underweight individuals were more likely to report severe level of perceived stress (OR, 1.7; 95% Cl, 1.26–2.17) and life dissatisfaction (OR, 1.3; 95% Cl, 1.07–1.68) compared to obese individuals.

A strong relationship exists between well-being and physical activity, sports activities and level of fitness (78, 79). Physical activity and sports activities are considered protective lifestyle behaviuors against stress, depression and other unhealthy behaviors linked to medical illness. In particular, sport activities improve coronary functioning and reduce obesity prevalence (61, 80). Physical activity could be effective in reducing mental health disorders and suicidal behaviors through biological and psychosocial mechanisms; for example, releasing endorphins, increasing serotonin and norepinephrine synthesis, increasing the sense of mastery, self-esteem and social interaction (81). Vancampfort et al. (82) in a recent metanalysis showed that in adults, low physical activity was associated with higher suicide risk. Adams et al. (83) demonstrated that vigorous/moderate physical activity was associated with a positive perceived health and modestly associated with psychiatric symptoms and suicidal ideation reduction; confirming the link between physical activity and well-being.

In patients with schizophrenia, the evidence suggests that increasing physical exercise promotes wellbeing, and improves mental health in these patients (84). Dietary habits and levels of physical activity were evaluated in 428 people with schizophrenia spectrum disorders and increased waist circumference demonstrating that in these patients the intake of fiber, vegetables, fruit, and fish were insufficient and these patients also had low levels of physical activity. Furthermore, negative symptoms were associated with poor diet and less physical activity (85).

The positive relationship between smoking and suicide risk in adult patients with psychotic disorders has been evaluated in a systematic-review and a meta-analysis of observational studies on this topic (86). The same authors, in a randomized study, investigated the effect of smoking reduction on suicidality on 255 patients with a psychotic disorder. This author found that smoking reduction, besides the positive effects on physical health, had a protective effect on suicidal ideation in people with psychosis (87). Bhatt et al. (88) characterized and identified risk factors for suicide attempt in patients with psychiatric disorders. Findings from this study indicated no significant differences on demographic characteristics between psychiatric inpatients who attempted suicide and psychiatric inpatients who did not attempt suicide. The only risk factors for suicide in psychiatric patients found in this study were the presence of impulsivity and borderline personality symptoms. Howard et al. (89) in a recent population-based cohort study on 12,888 subjects (6,456 men, 6,432 women) investigated the relationship between chronic disease conditions, smoking habits, alcohol consumption, depressive symptoms, personality type, and other psychological parameters and suicide found that male sex, obesity, smoking, and living alone were associated with depression and with risk of suicide.

Several studies have focused on the role of occupation and work stressors on suicide risk. Research on this topic has shown that work characteristics and personal resources are linked to depression and suicide attempts (90). A study on 2,855 employees demonstrated that job autonomy, task variety, work-family conflict, family-work conflict, and job dissatisfaction contributed to suicide attempts (89). Furthermore, Kerr et al. (91) showed that poor interpersonal relationships, unemployment, debt and financial difficulties contribute to an increased risk of suicide in the general population. A recent study of 2,027 employed patients in primary care setting examined the association between workplace and suicidal ideation (92). Suicidality was significantly associated with work intensity in men and with work-related emotional demands in women.

Alcohol and substance abuse can worsen psychological well-being and contribute to suicide risk (93). Consumption of alcohol immediately prior to suicide is common (94, 95), with an estimated 37% of deaths from suicide having positive blood alcohol concentrations on toxicology screening indicating acute alcohol consumption before death (96). Bowden et al. (97) in a large cohort study of 2,803,457 residents of Wales, UK, highlighted the relationship between emergency alcohol-related hospital admission and the increased risk of suicide. A recent systematic review of 108 studies explored the associations between substance use and suicide risk in low- and middle-income countries (98) demonstrated an association between alcohol use, intoxication and pathological use of alcohol, tobacco, cannabis, illicit drugs and non-medical use of prescription drugs and suicide risk. Furthermore, Choi et al. (99) examined blood alcohol concentration (BAC) among suicide decedents aged 50 years or older. This study showed that alcohol problems prior to suicide, relationship problems and death/suicide of family/friends were associated with greater odds of having a positive BAC. This study also found that alcohol intoxication was linked to more violent means of suicide.

LIFESTYLE BEHAVIOR AND SUICIDE IN OLDER ADULTS

Over 20% of adults aged 60 and over suffer from a psychiatric or neurological disorder. In the elderly, severe mental disorders present differently than in younger adults. The most common mental and neurological disorders in this age group are depression and dementia. However, anxiety disorders, schizophrenia and psychotic disorders, and substance use problems are also prevalent (100). A body of literature supports the association between late-life suicide ideation and various risk factors including depression and hopelessness (101, 102), while subjective well-being and meaning in life have been identified as protective factors for suicide in older adults (101). Innamorati et al. (103) in a study using psychological autopsy interviews studied 117 old-old adults who died by suicide and compared them to 97 young-old adults (6,574 years), 98 middle aged (50–64 years) suicide victims, and 117 psychiatric outpatients 75 years and older without a history of suicidal behaviors. They found that, in the elderly, unlike others stages of life, loneliness and lack of social support, were associated with risk of suicide. Physical illness, chronic severe pain, debilitating disease, and diagnosis of a terminal illness are common antecedents to suicide in older adults (104). Lee et al. (39) after analyzing age and sex-related features and suicide risk in the elderly stressed that the only stable risk factor for suicide in this age group was the negative perception of one's own health status.

Difficulties in interpersonal relations, social interactions, and social participation have been also linked to suicidal ideation and suicidal intent in the elderly (105). Mogensen et al. (106) reported that in the elderly, suicide risk appeared highest during the 6 months following the loss of a close relative and McLaren et al. (107) observed that widowhood was associated with suicidal ideation both in men and women. A longitudinal study on the importance of social support while adjusting to loneliness in bereaving elderly persons (108) and other studies examining on the importance of social supports reported that primary prevention programs designed specifically to increase social relations could decrease suicide risk (109). Older people are at risk for health decline and loss of independence that can affect social interactions negatively. Clark et al. (110) evaluated the effectiveness of lifestyle interventions in promoting well-being in independently living older people and Lapierre et al. (111) in a systematic review of 19 studies focusing on lifestyle programs for older adults, highlighted that psychoeducational programs and decreasing social isolation in this age group are effective interventions in the prevention of suicide. More recently, Okolie et al. (112) considered telephone counseling for vulnerable older adults and community-based programs incorporating education, gatekeeper training, depression screening, and group activities, as valid therapeutic options in preventing suicidal ideation. Lifestyle interventions in the areas of social interaction (113), personal goals (114), coping, and adaptive behavior (113), emotional

TABLE 1 | Lifestyle behaviors implicated in suicide risk (alphabetical order).

Lifestyle behaviors
• Difficulties in interpersonal relations
• Internet addiction
• Nutrition, dietary patterns
• Occupation and work stressor
• Sedentary
• Substance and alcohol abuse
• Tobacco's smoke
• Underweight, Obesity

TABLE 2 | Common Lifestyle behaviors implicated in suicide risk in different age ranges (based on results of studies included in this review).

Age range	Lifestyle behavior and suicide risk
Adolescents and young people (age 16–30)	Difficulties in interpersonal relations, substance and alcohol abuse, internet addiction.
Young adults and adults (age 30–65)	Substance and alcohol abuse, occupation and work stressor.
Older adults and elderly (age >65)	Difficulties in interpersonal relations, nutrition, dietary patterns.

TABLE 3 | Common Lifestyle behaviors implicated in suicide risk in psychiatric disorders (based on results of studies included in this review).

Psychiatric disorders	Lifestyle behavior and suicide risk
Psychotic disorders	Substance and alcohol abuse, difficulties in interpersonal relations, tobacco's smoke.
Depressive disorders	Substance and alcohol abuse, occupation and work stressor.

flexibility (115), social skills (116), self-esteem (117), sense of belonging (118), reasons for living (119), hope (120), meaning in life (101, 121), religion or spirituality (122) could became promising directions to prevent suicide in older adults.

Several studies have demonstrated the importance of a balanced diet to prevent depression (123, 124) and of sleep-based interventions to prevent suicide (125). Considering that hypnotics use in the elderly has been associated with an increased risk of suicide (126), behavioral treatment of insomnia represents an efficacious alternative to pharmacotherapy in this age group (127). O' Rourke et al. (128) studied specific predictors of suicide in a sample of 220 older adults affected by Bipolar Disorder (BD). Alcohol misuse, medication non-adherence, and cognitive impairment were found to be direct predictors of suicide in these patients, while sleep disturbances acts as a risk factor on suicide ideation via depressive symptoms. Contrary to what happens in other age groups, a link between smoking prevalence and suicide rates in the elderly has not been observed (129).

DISCUSSION

In this article, we reviewed a growing body of literature demonstrating a relationship between lifestyle behaviors, mental health, and suicide risk (**Table 1**) in differing stages of life (**Table 2**) and in severe psychiatric disorders (**Table 3**). Our review suggests that enhancing protective factors and reducing risk factors known to increase suicidal behaviors (75, 130–132) could help prevent suicide in some individuals. Given the high comorbidity between psychiatric disorders and medical illnesses that result from unhealthy lifestyle behaviors, lifestyle interventions to reduce medical diseases, and increase patient's well-being are urgently needed.

The relationship between lifestyle behavior and suicide is complex and multifactorial. Unhealthy lifestyle behaviors can directly increase the risk of suicide; at the same time increasing the risk for many medical diseases. It is well known that medical illnesses are associated with disability, social isolation and associated with an increased risk of suicide. Sedentary behaviors, underweight, obesity, cigarette smoking, and alcohol abuse are associated with cardiometabolic risk factors, poor mental health, and severe psychiatric disorders. These factors contribute to an increased risk of suicide. Sedentary behaviors, weight issues and fewer social supports contribute to social isolation, limiting the development of social relationships, which increase the risk of developing mental health problems and suicide. Adopting healthy lifestyle behaviors are indispensable for both, improving health and for the prevention of suicide at any stage in life.

Studies included in this article showed different lifestyle behaviors in different lifestages. In adolescent and young adults there are multiple important risk factors for suicide including psychosis, depression, low sleep satisfaction, high stress, substance abuse, alcohol consumption, smoking, sexual activity, internet addiction, interpersonal factors, personality disorders, anxiety or conduct disorders, eating disorders, and aggressive, irritable and antisocial tendencies (38, 39). Though it has been demonstrated that school-based suicide prevention programs increase knowledge on suicide without really preventing suicidal behaviors (133), it seems necessary to consider prevention programs that identify substance abuse, educational competencies (literacy, study skills, time management), educational environment, school programs, social interactions, academic attainment, cognitive progress, emotional control, behavioral expectations, physical and moral development, and encouragement of active engagement in sports.

In adults, lifestyle interventions on smoking, heavy alcohol consumption, physical inactivity, BMI, sedentarism, and eating habits should play a significant role in suicide prevention (17, 65). Effective lifestyle prevention programs in adults can be developed through screening programs identifying and assessing at-risk groups. These programs should include lifestyle training, psychoeducation, support/skills training and crisis response and referral resources (134). In patients with severe psychiatric disease, strategies that promote exercise and sport activities, that reduce caffeine consumption and other health-adverse behaviors are particularly important for the reduction of psychotic symptoms, depression, anxiety, low self-esteem, and life dissatisfaction, factors that increase suicide risk. Gallego et al. (135) suggested that in patients with either schizophrenia spectrum disorders or affective disorders, physicians should be alert for the presence of a previous suicidal attempts and financial or relationship losses, factors that can increase suicidal risk. Furthermore, psychiatric hospitalization, a close psychiatric follow up, collaboration with family would be important strategies in reducing the risk of suicidal behavior in patients affected by severe psychiatric disorders.

Finally, in the elderly, difficulties in interpersonal relations, social isolation and the consequences of physical disability can represent targeted and specific points for intervention. The concomitant presence of depressive symptoms and stressing life events including loneliness and physical illness should be considered warning signs for suicidal risk (136). In the elderly, innovative strategies should promote positive aging, involve family and community gatekeepers, and use telecommunications to identify older adult at risk of suicide (112). Psychosocial interventions influence depressive symptoms and considering that mental illness is one of the most significant factors in suicide; psychosocial interventions should be part of suicide prevention programs in the elderly. Further trials are warranted, especially for the most promising type of interventions for preventing suicide, that is, social activities (137, 138).

LIMITATIONS

When interpreting the results of this review, several limitations should be considered. First, this is a narrative review, therefore, studies were subjectively selected, which could have led to selection bias. Second, we only selected articles in English leaving relevant articles in other languages out of our review. Finally, we did not draw a distinction between gender and risk factors for suicide.

CONCLUSIONS

Lifestyle behavior is of paramount importance for suicide prevention as maladaptive maneuvers (such as drinking or drug abuse) as to face increased psychological pain and distress consistently reduce cognitive skill to solve source of suffering.

Furthermore, reduced quality of life as observed by impairment of some psychiatric disorders can be worsened by low exercise, excessive smoking, poor diet, and determinants associated with pharmacological treatment. Community mental health with proper programs such as assertive community treatment, psychoeducational family treatment, social skills training, and psychosocial therapies are important interventions that can incorporate education on lifestyle and ultimately reduce suicide risk.

AUTHOR CONTRIBUTIONS

IB and VC searched the literature and provided first draft. MH, AC, and DE independently reviewed the paper and added relevant information. MP provided the intellectual impetuous and supervised the entire process of development of the paper.

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Bringing an Effective Behavioral Weight Loss Intervention for People With Serious Mental Illness to Scale

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People with serious mental illnesses (SMIs) die 10–20 years earlier than the general population, mainly due to cardiovascular disease. Obesity is a key driver of cardiovascular risk in this group. Because behavioral weight loss interventions tailored to the needs of people with SMI have been shown to lead to clinically significant weight loss, achieving widespread implementation of these interventions is a public health priority. In this Perspective, we consider strategies for scaling the ACHIEVE behavioral weight loss intervention for people with SMI, shown to be effective in a randomized clinical trial (RCT), to mental health programs in the U.S. and internationally. Given the barriers to high-fidelity implementation of the complex, multi-component ACHIEVE intervention in often under-resourced mental health programs, we posit that substantial additional work is needed to realize the full public health potential of this intervention for people with SMI. We discuss considerations for successful "scale-up," or efforts to expand ACHIEVE to similar settings and populations as those included in the RCT, and "scale-out," or efforts to expand the intervention to different mental health program settings/sub-populations with SMI. For both, we focus on considerations related (1) intervention adaptation and (2) implementation strategy development, highlighting four key domains of implementation strategies that we believe need to be developed and tested: staff capacity building, leadership engagement, organizational change, and policy strategies. We conclude with discussion of the types of future research needed to support ACHIEVE scale-up/out, including hybrid trial designs testing the effectiveness of intervention adaptations and/or implementations strategies.

Keywords: exercise, diet, obesity, weight loss, serious mental health conditions

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INTRODUCTION

People with serious mental illnesses (SMIs) die 10–20 years earlier than the general population, primarily due to cardiovascular disease, and (1–6) obesity is one of the driving forces of cardiovascular risk in this group (7). As in the overall population, poor diet and low rates of physical activity are key contributors to obesity among people with SMI (8–16). In addition, most

people with SMI require long-term use of psychotropic medications, which can cause weight gain (17–21). A 2015 review concluded that tailored behavioral weight loss interventions can lead to clinically significant weight loss in this group (22). Spreading implementation of these evidence-based interventions to the mental health organizations that serve people with SMI is a priority for the field.

One intervention shown to be effective in a randomized clinical trial (RCT) is the ACHIEVE behavioral weight loss intervention for people with SMI (23). In this Perspective, we consider strategies for widespread implementation of ACHIEVE. We posit that substantial additional work is needed to realize the full public health potential of this behavioral weight loss intervention for people with SMI.

ACHIEVE RCT STUDY SETTING AND POPULATION

The ACHIEVE RCT has been described in detail previously and is summarized here (23, 24). The ACHIEVE RCT was conducted with adults with SMI participating in one of 10 psychiatric rehabilitation programs in Maryland. To be eligible for psychiatric rehabilitation services in Maryland, individuals must have impaired role functioning resulting in a need for rehabilitation services to develop or restore independent living skills. Overweight and obese adults with SMI ages 18+ were eligible to participate in the ACHIEVE RCT.

The study setting and population were intentionally selected and eligibility criteria were minimized in order to represent realistic mental health programs and diverse participants with SMI (25). The sample included people of diverse race/ethnicities (56% white, 38% black, 6% other race, 5% Hispanic ethnicity) and 52% of participants had a history of substance use, a common co-morbidity among people with SMI (23).

ACHIEVE BEHAVIORAL WEIGHT-LOSS INTERVENTION

The RCT evaluating the behavioral weight loss intervention found that ACHIEVE resulted in mean weight loss of seven lbs. over 18 months; this was the first trial to demonstrate that a behavioral intervention leads to clinically significant weight loss at 18 months among persons with SMI (23). In addition to ACHIEVE, one other behavioral weight loss intervention has been shown in a RCT to lead to weight loss among people with SMI: the STRIDE intervention resulted in mean weight loss of 5.7 lbs. over 12 months.[27] A RCT testing the InSHAPE behavioral weight loss intervention for people with SMI showed no effects of the intervention on weight loss among people with SMI over 12 months, but found 24% of participants with SMI randomized to the intervention had both an increase of at least 50 meters on the 6 min walk physical activity measure and a 5% or greater reduction in body weight, compared to 9% of control group participants (26). The ACHIEVE (23), STRIDE (27), and InSHAPE (26) RCT results have all been published previously. Scale-up of multiple effective behavioral weight loss interventions for people with SMI would be desirable. We focus on the ACHIEVE intervention here as a case study. ACHIEVE was developed based on a comprehensive lifestyle intervention for the general population shown to be effective in the PREMIER Trial (28). ACHIEVE integrates social cognitive, behavioral self-management and relapse prevention model theories, and fits well in the psychiatric rehabilitation framework of skill building and environmental supports.

ACHIEVE intervention components are shown in **Table 1**. Participants with SMI were encouraged to set a goal of 10 lbs. weight loss in 18 months; this goal was tailored as needed to individuals' preferences. The intervention was designed to address the neurocognitive deficits in working memory, verbal memory and executive function that are common in persons with SMI including teaching material in small, highly structured, repeated content units, emphasizing behavioral rehearsal and role-playing, hands-on activities, tailored simple self-monitoring, environmental prompts, and reinforcements. A 5–8th grade reading level was used for program materials. The ACHIEVE curriculum focused on repeated delivery of six key behavioral recommendations (e.g., "avoid sugary drinks"; see **Table 1**).

The study interventionist delivered the weight-management content through a 45 min group weight management session 3 weeks/month for the first 6 months and then monthly for months seven-18. While a portion of each session was didactic, the groups were interactive and emphasized goal-setting, role-playing and behavioral rehearsal of key concepts. Once-monthly individual weight management sessions with the study interventionist provided the opportunity for individualized cognitive tailoring and a personalized approach, where participants received feedback on weight loss progress, set and adjusted goals, and problem-solved as needed. For the duration of the 18 months intervention, ACHIEVE participants engaged in three group exercise sessions per week that gradually progressed to reach 40 min of moderate intensity physical activity with 10 min of warm-up and cool-down. In months one through six of the ACHIEVE intervention, group exercise classes were delivered by a study interventionist or certified exercise instructor. In months seven through eighteen, psychiatric rehabilitation program staff delivered one (months seven-12) or two (months 13–18) of the group exercise sessions, with support from a video, developed by study staff, that guided the content and pacing of the exercise class.

Participants were asked to filled out a simple tracking tool to monitor their diet and physical activity behaviors outside of the ACHIEVE intervention. In addition to group and individual sessions, regular weigh-ins with the study interventionist were recommended to support intervention goals. Intervention participation was reinforced with a point system. To receive a point for participation in a weight management group or individual visit, a participant had to attend the entire session. To receive a point for participation in group exercise, a participant had to be standing and engaged in the entire session. Points could be traded for small prizes, e.g., athletic socks or headphones.

TABLE 1 | ACHIEVE behavioral weight loss intervention core components.

Intervention components	Type and frequency of contact
Goal setting	Weight loss goal 10 lbs. in 18 months (tailored to individual)
Key behavioral recommendations	Avoid sugary drinks; avoid junk food; eat five servings of fruits/vegetables per day; portion control; smart snack habits/ and regular physical activity.
INTERVENTION CONTACTS	
Group weight management session	Months 1–6 45 min session 1x per week, 3 of 4 weeks, led by study interventionist Months 7–18 45 min session 1x per month, led by study interventionist
Individual weight management session	Months 1–18 15–20 min session, 1x per month, led by study interventionist
Group exercise classes	Months 1–6 50 min session, 3x per week, led by study interventionist. Months 7–12 50 min session, 3x per week led by study interventionist (2x per week) or psychiatric rehabilitation program staff, with video-assistance (1x per week). Months 13–18 50 min session, 3x per week led by study interventionist (1x per week) or psychiatric rehabilitation program staff, with video-assistance (2x per week).
Brief Weigh-ins	Months 1–6 1x per week Months 7–18 2x per month
Self-monitoring "tracker"	Participants fill out a simple tracking tool that records the number of servings of fruits and vegetables, whether they exercised outside of the group classes above for 30 min, and whether they drank sugar drinks; ate junk food; achieved smart portions; and achieved smart snacking goals.
Incentive program	Study participants were rewarded for participation in group and individual weight management sessions and group exercise classes with a point system, which participants could trade points for small prizes (e.g., athletic socks or headphones).
Environmental prompts	Reminders to be used at home: high impact behavioral goals on laminated card, refrigerator magnets, pre-printed grocery lists, water bottle, measuring cups, lunch bags.

ACHIEVE RANDOMIZED CLINICAL TRIAL INTERVENTION DELIVERY

The ACHIEVE intervention was designed for delivery by an interventionist with a bachelor's degree in a health-related field and by a certified exercise instructor. Staff received significant in-person initial and ongoing training on intervention content and motivational interviewing for weight management sessions. A leaders' guide and manualized procedures were used to ensure standardization of the intervention delivery. Staff were observed regularly to measure intervention fidelity. As noted above, psychiatric rehabilitation program staff delivered video-assisted group exercise sessions in months six through 18 of the study.

SCALING THE ACHIEVE INTERVENTION

The majority of interventions shown to improve health outcomes in RCTs are never widely implemented. In addition, the effectiveness of interventions often diminishes outside the high-resource, controlled environment of RCTs. This voltage drop in intervention effectiveness is particularly relevant for complex, multi-component interventions—like ACHIEVE—that can be challenging to implement with high-fidelity and the necessary level of intensity in real-world settings.

In a 2017 paper, Gregory Aarons and colleagues presented a framework for scaling up interventions, like ACHIEVE, which have been shown to be effective in RCTs but not yet widely implemented outside of the trial context (29). The authors helpfully distinguish between the concepts of "scale-up," which they define as efforts to expand an evidence-based intervention to similar settings and populations as those in which the trial was conducted, and "scale-out." Scale-out is defined as expanding an evidence-based intervention shown to be effective in one setting/population to a different setting and/or population.

In the context of ACHIEVE, scale-up would involve implementation of the intervention in psychiatric rehabilitation programs with similar staffing, programming, and client populations as those in the state of Maryland [while psychiatric rehabilitation programs exist in all 50 U.S. states, they take different forms, e.g., as day programs or "Clubhouses" (30)]. Scale-out of ACHIEVE might involve implementation of ACHIEVE in the outpatient mental health clinic, Assertive Community Treatment (ACT) or residential rehabilitation settings.

In the remainder of this piece, we propose considerations for ACHIEVE scale-up and scale-out. For both, we focus on two overarching steps: (1) adaptation of the ACHIEVE behavioral weight loss intervention and (2) development of implementation strategies to support scale-up/out. The existence of other

effective behavioral weight loss interventions for people with SMI including STRIDE (27) and InSHAPE, (26, 31) which share some core principles (e.g., tailoring to address cognitive deficits in SMI) but include varying components, could be an asset to scale-up/out efforts as adaptations to the components of one intervention could be informed by components of other effective interventions. Similarly, some implementation strategies for bringing behavioral weight loss interventions for people with SMI to scale may be intervention or setting-specific, but others are likely relevant across interventions. Strategies shown to result in high-fidelity implementation of the intervention, high rates of consumer participation, and weight loss in the population with SMI should be prioritized for broader use.

ADAPTATION OF THE ACHIEVE BEHAVIORAL WEIGHT LOSS INTERVENTION

Intervention Adaptation for Scale-Up

For scale-up of the ACHIEVE intervention to psychiatric rehabilitation programs similar to those included in the RCT, intervention adaptations should focus on facilitating intervention delivery by psychiatric rehabilitation program staff. Core intervention components (**Table 1**) should be retained, but changes to intervention contact schedule and adaptations and/or enhancements to delivery format are likely needed in order to enable the psychiatric rehabilitation program staff to deliver the sessions.

For example, the RCT-tested intervention included a total of 150 min per week of group aerobic exercise, delivered in three 50 min sessions, as well as weekly 45 min weight management sessions. For scale-up, the type (group aerobic exercise and weight management) and intensity of these intervention components should remain largely consistent, but the delivery schedule could shift to three 60 min combined weight management/exercise sessions per week, or another schedule that would be more efficient for each psychiatric rehabilitation program.

In addition, adaptations/enhancements to delivery format of the ACHIEVE intervention components are likely needed to support scale-up. For example, while study team interventionists delivered in-person group weight management sessions in the RCT, psychiatric rehabilitation program staff potentially could deliver group sessions supported by videos that are designed to alleviate some of the challenges PRP staff may face when implementing behavioral weight loss programs. These videos could be developed by the study team, and then the psychiatric rehabilitation program staff could utilize a curriculum that blends these tailored videos with the in-person interactive group weight loss sessions.

Intervention Adaptation for Scale-Out

The scale-up adaptations focused on facilitating intervention delivery by mental health program staff are also relevant for scale-out of the ACHIEVE intervention to different types of mental health programs. However, for scale-out, we suspect that changes to core components of the ACHIEVE intervention may also be required as described below.

For example, outpatient mental health clinic settings, many of which already deliver group and individual counseling, may be well-equipped to deliver to weight-management components of the ACHIEVE intervention. However, they may be less able, due to space and workflow constraints (i.e., shorter office-based clinical visits as opposed to several hour-long psychosocial rehabilitation programs), to deliver the group exercise component of ACHIEVE. The intervention could be adapted in multiple ways to address this issue. Exercise sessions could be shortened and paired with weight loss sessions in order to fit within standard programming time slots at outpatient clinics. Clinics could partner with personal trainers to provide individualized exercise coaching for participants, a strategy shown to be effective in the InSHAPE intervention (26, 31). Additional strategies could target other activities throughout the day, outside of the outpatient clinic setting, such as a pedometer/walking program and exercise videos to use at home.

Although the ACHIEVE intervention was developed and tested in a diverse group of consumers with SMI, changes may also need to be made to improve salience to specific sub-populations with SMI. For example, the intervention has not been translated into other languages. Translation of the ACHIEVE intervention into pediatric patients with SMI may also require modifications.

Development of Implementation Strategies

Implementation Strategies to Support Scale-Up

A multi-component implementation strategy (32) is needed to accomplish widespread scale-up of ACHIEVE to psychiatric rehabilitation programs. Within that multi-component strategy, we propose four key groups of strategies for consideration: staff capacity building strategies, leadership engagement strategies, organizational change strategies, and policy strategies.

Staff capacity building strategies are critical for ACHIEVE scale-up. While the RCT was performed in psychiatric rehabilitation programs, the ACHIEVE intervention was largely, with the exception of some group exercise classes, delivered by trained study team interventionists. To effectively implement ACHIEVE, program staff need training not only in delivery of the ACHIEVE intervention but also in motivational interviewing, the counseling technique used in ACHIEVE. Staff trainings on these topics will need to be developed and disseminated in a manner that allows busy staff members to participate. This training is a challenge given that typical motivational interviewing training involves, at a minimum, 2 days in-person workshops and repeated post-workshop feedback and coaching. Virtual training modalities and incentives for staff to participate, such as continuing education credits, need to be developed. In addition, performance coaching and audit-and-feedback strategies could support staff members' ability to deliver the ACHIEVE intervention. To ensure that the staff members delivering ACHIEVE are capable of doing so with high fidelity, a certification program could be created where staff become certified ACHIEVE interventionists after completing a specified level of training and demonstrating competency in intervention

delivery, similar to what is available with Center for Disease Control's National Diabetes Prevention Program (DPP) (33–35).

Leadership engagement strategies are needed to facilitate leaders' adopting and providing ongoing support for ACHIEVE implementation at their organization. An example of a potential strategy within this domain is the use of an opinion leader(s) (32)–i.e., a prominent psychiatric program rehabilitation leader at the local, state or national l level—to promote ACHIEVE.

Organizational strategies are needed to help psychiatric rehabilitation programs foster a culture that is supportive of ACHIEVE implementation and of good physical health more broadly. For example, many psychiatric rehabilitation programs serve food and could benefit from guidance on how to improve the healthfulness of their options. In addition, programs could benefit from guidance on creating safe places for group exercise. Organizational policies, e.g., tobacco-free policies and policies prohibiting vending machines offering sugar drinks, are also an important strategy in this domain.

Policy strategies are a key component of scale-up. Critically, a financing mechanism(s) is needed to allow psychiatric rehabilitation programs to cover the cost of ACHIEVE implementation. In Maryland, both weight management sessions and group exercise are reimbursable by Medicaid as psychiatric rehabilitation services; if this financing mechanism does not exist in other state Medicaid programs, it would need to be created. Creation of a parallel reimbursement mechanism in Medicare and among private insurers would further facilitate adoption and implementation. Medicare currently covers the Diabetes Prevention Program (33–36), setting a precedent for coverage of weight loss interventions, and the Medicare obesity counseling benefit (37) could potentially be expanded to cover the weight management components of the ACHIEVE intervention.

Financing mechanisms for implementation strategies also need to be developed, e.g., if research shows that external facilitation and audit-and-feedback are needed to support high-fidelity implementation of ACHIEVE by program staff, mechanisms to pay for these strategies need to be created. Other types of policies can also support ACHIEVE scale-up, for example accreditation standards requiring that programs have a certified ACHIEVE trainer on staff. Performance metrics are increasingly tied to payment through healthcare financing and delivery system reforms such Accountable Care Organizations (ACOs). Tying a metric measuring the proportion of overweight and obese people with SMI who lose weight through an evidence-based behavioral weight loss intervention like ACHIEVE to intervention reimbursement by insurers could facilitate implementation.

Implementation Strategies to Support Scale-Out

In some cases, the strategies developed for scale-up could also be used, with no or minimal adaptation, for scale-out. For example, an online motivational interviewing and weight management training program developed for psychiatric rehabilitation program staff could also be used for staff at other types of mental health programs. In other cases, new implementation strategies may need to be developed for scale-out, e.g., financing mechanisms may differ depending upon an organization's funding sources.

For scale-out, ACHIEVE intervention components may need to be implemented across different organizations, e.g., the outpatient clinic/community fitness center example above. Thus, implementation strategies to support the development of partnerships are likely needed for successful scale-out, e.g., development of model memorandum of understanding and financing strategies that organizations can use to facilitate effective collaborations.

Future Research to Support Scale-Up/Out

The key research questions around both scale-up and scale-out of ACHIEVE are which intervention adaptations and implementation strategies result in (1) adoption and sustained, high-fidelity implementation of the intervention in mental health programs and (2) clinically significantly weight loss among participants.

Aarons et al. describe a spectrum of potential research designs for scale-up/out (29). On one end of the spectrum are designs for scale-up scenarios where the setting and population are very similar to those in the RCT, and minimal adaptations to the RCT-tested intervention have been made. For these types of scenarios, a research design, like a hybrid type III trial design that focuses primary on evaluating implementation strategies, may be appropriate. One the other end of the spectrum is a scale-out scenario in which new implementation strategies have been developed and significant adaptations to the intervention have been made. In this scenario, a research design like a hybrid type II trial design that simultaneously tests both implementation strategy and intervention effectiveness (38) may be needed.

We posit that research to test implementation strategies for ACHIEVE scale-up and scale-out, which have not yet been developed or evaluated, should be prioritized. Given the barriers to high-fidelity implementation of complex interventions like ACHIEVE in often under-resourced mental health programs, implementation strategies should be shown to be effective through rigorous randomized trials before resources are invested in broad scale-up/out efforts. Financing mechanisms to support ACHIEVE scale-up and scale-out need to be developed and evaluated, and the cost-effectiveness of scaling ACHIEVE should also be studied. For both scale-up and scale-out, the degree to which the adapted ACHIEVE intervention differs from the original will be important in terms of deciding whether evaluation of weight change among participants with SMI is needed.

AUTHOR CONTRIBUTIONS

All authors contributed to the ideas presented in this Perspective and reviewed the final version of the article EM led manuscript writing.

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frontiers in Psychiatry

BRIEF RESEARCH REPORT
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Medically Unexplained Physical Symptoms in Hospitalized Patients: A 9-Year Retrospective Observational Study

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Introduction: "Medically Unexplained Physical Symptoms" (MUPS) defines a subgroup of patients presenting physical symptoms of unclear origin. The study aims to profile clinical and socio-demographic characteristics of patients with MUPS.

Materials and Methods: This 9-years observational retrospective study assesses all patients admitted between 2008 and 2016 in the divisions of neurology and gastroenterology. Socio-demographic and clinical variables were evaluated: gender, age, diagnosis or diagnostic hypothesis, presence of psychiatric comorbidities, psychiatric evaluation, pharmacological treatment, number of admissions/visits.

Results: Among 2,479 neurological patients 10.1% presented MUPS. Patients were more frequently women (63.5%), with a mean age of about 50 years. Reported symptoms were headache (22.6%), seizures (8.7%), vertigo (5.9%), fibromyalgia (5.5%), paresthesia (5.1%), visual disturbances (5.1%), amnesia (3.9%). The diagnosis was somatoform disorder in 6.3% of cases, conversion disorder in 2.7%, and somatic symptom disorder in 1.5% only. 2,560 outpatients were evaluated in gastroenterology division. 9.6% ($n = 248$) of patients had MUPS; 62.1% of them were women. The most affected age group ranged between 15 and 45 years. The most frequent diagnoses were functional abdominal pain (50%), dysmotility-like dyspepsia (26.6%), irritable bowel syndrome (10.4%), meteorism of unknown cause (2.4%), hiccup (1.6%), burning mouth syndrome (1.2%). No patients received a diagnosis of somatic symptom disorder.

Discussion: Patients with MUPS are more often women, of middle age, with self-referred specific symptomatology. While neurological patients received a diagnostic-therapeutic approach in line with the literature, gastroenterological patients mainly received antipsychotics. A more comprehensive assessment and a development of psychoeducational interventions are needed to improve patients' quality and quantity of life.

Keywords: somatic symptoms disorders, Medically Unexplained Physical Symptoms, psychosomatic medicine, consultative psychiatry, psychosocial interventions

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INTRODUCTION

The term MUPS (Medically Unexplained Physical Symptoms) is used as umbrella term to refer to conditions defined by physical symptoms not better defined by another disorder (1, 2). MUPS are extremely common, accounting for 15–30% of primary care patients and around half of secondary care patients (3–5).

MUPS can be partially explained by a complex interaction of physiological and psychological factors (1, 6) and they can cause disability persisting for at least 1 year in up to 30% of patients (3), affecting daily functioning, interfering with work productivity, and resulting in use of healthcare resources than in other patient groups (2, 7, 8).

Relations between physicians and patients with MUPS are often strained. Physicians often perceive patients with MUPS as difficult, frustrating, and demanding (9). Therefore, MUPS can be a challenging experience for clinicians with a high risk to develop symptoms of burn out (10). At the same time, patients with MUPS report feeling dissatisfied, disbelieved and dismissed by clinicians (1).

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revised* (*DSM-IV-TR*) the presence of MUPS was a criterion for the diagnosis of a somatic symptom disorder. In DSM-5 the somatoform disorders were replaced by the somatic symptom disorder, consisting of a new set of criteria including positive psychological ones (11, 12). The most important change was the focus on the importance of physical symptoms associated with significant distress and impairment (1). However, van Dessel et al. found a strong association between the presence of positive psychological criteria in DSM-5 and symptoms severity and physical functioning in patients with MUPS (13). Moreover, Huang et al. discussed the importance of recruiting settings, the comorbidity of pain disorder and undifferentiated somatoform disorder, and the impact of cultural factors in somatic symptoms disorder's diagnosis (14).

Some factors have been recognized as predictors of complexity of the clinical picture: high number of somatic symptoms, psychiatric comorbidity (particularly, depressive or anxious disorders), psycho-social risk factors such as history of child abuse or violence (8, 15).

The most frequently symptoms reported by patients are pain, fatigue, neurological, gastrointestinal, dermatological, and rheumatological symptoms. Although in most cases these symptoms resolve spontaneously (16), a small but significant percentage may worsen over time (8, 17–19).

Early detection of risk factors for the most complex or persistent types of MUPS is essential to provide adequate support to these patients (15). In view of the difficulties in the management of these disorders and of their impact on patients' quality of life, this 9-year retrospective observational study aims to profile clinical and socio-demographic characteristics of patients with MUPS and to identify the most frequent diagnoses of somatic complaints' disorders formulated in neurology and gastroenterology, and their clinical approach.

MATERIALS AND METHODS

In this observational and retrospective study all patients admitted between 2008 and 2016 in the divisions of neurology and gastroenterology in a teaching hospital in Northern Italy were assessed. Gastroenterology patients' data were available from 2011, year when the outpatient clinic was established.

The teaching hospital includes several hospital wards and outpatient clinics. MI, IC, LB, and FC were four Psychiatry Section clinicians (also authors of the manuscript) enrolled as investigator to collect data from hospital databases not directly involved in analyzed patients' treatment.

Data from patients presenting the following inclusion criteria were used: age $\geq$18 years, be an inpatient (neurology) or an outpatient (gastroenterology) of the teaching hospital; present symptoms with apparently no medical cause, or whose cause remains unclear; have a diagnosis of *Somatoform Disorder* or *Somatic Symptoms and Related Disorders* (according to *DSM-IV-TR* or *DSM-5* criteria, through ICD code Conversion Table; Italian statistical medical recoding system is *ICD*); present all instrumental and laboratory examinations clean.

Data from patients presenting only a psychiatric history were excluded. Patients' data were made anonymous obscuring sensitive data in the research to protect the recognizability of the patients. Moreover, data were anonymous because registered in electronic dataset and used in a collective form. The following socio-demographic and clinical variables were evaluated: gender, age, diagnosis or diagnostic hypothesis, presence of previous or concurrent psychiatric comorbidities, psychiatric evaluation, pharmacological treatment, number of admissions/visits. Patients data were collected through the medical records and the reports of the visits.

As data were made anonymous and unidentifiable, the Provincial Health Ethical Review Board (Ethics Committee of Insubria—*Azienda Socio Sanitaria Territoriale Sette Laghi*, Varese, Italy) consulted prior to the beginning of the study, has confirmed that, as it was a retrospective study, it did not need authorization from the Board.

Descriptive analyses, which include means, standard deviation and demographic variables percentages, were used to summarize epidemiological and clinical characteristics. Fisher exact test at two-tailed was used to evaluate MUPS distribution between the two groups of patients and between genders. Significance threshold was set at p-value <0.05. Data analyses were performed using the IBM® SPSS® Statistics, version 22.0.

RESULTS

Sociodemographic and clinical data are reported in **Table 1**.

Neurology Patients

Data from 2,479 patients admitted to Neurology ward were evaluated and 252 (10%) presented MUPS; among them 63.5% were women. No statistically significant difference of MUPS distribution between genders emerged ($p = 0.88$). The most affected age group ranged from 36 to 45 years, while the middle age was 46 years for women and 50 years for men.

47.2% of patients had a clinical history of psychiatric disorder or a concomitant mood disorder. Reported symptoms were headache (22.6%), seizures (8.7%), vertigo (5.9%), fibromyalgia (5.5%), paresthesia (5.1%), visual disturbances (5.1%), amnesia (3.9%). The diagnosis was somatoform disorder in 6.3% of cases ($n = 16$), conversion disorder in 2.7% ($n = 7$), and somatic symptom disorder in 1.5% ($n = 4$). Furthermore, in 41.6% of cases, to emphasize the functional origin of the symptoms, it was declared that neuro-radiological and neurophysiological findings were all negative.

By evaluating the trend of data collected per year, it is interesting to note that the diagnoses have increased concomitantly with an increasing number of neuro-imaging negative assessments (as shown in **Figures 1**, **2**). The number of psychiatric consultations requested during hospitalization and the number of patients sent to the psychiatrist in the post hospitalization are unchanged over the years.

Although women are more represented than men, the medical examinations without evidences are comparable between genders, as well as psychiatric anamnesis and number of patients sent to psychologist or psychiatrist.

On the other hand, the presentation of symptoms appears to be different between the two genders: men have manifested the disorder in the form of paresthesia (17.3%) and epileptic crisis (15.2%); women lamented predominantly headache (30%), paresthesia (16.2%), epileptic crisis (10%), and vertigo (8%).

During hospitalization, a psychiatric consultation was requested for 24.6% of patients and for 21.8% of patients a continuation of care by psychiatric services was suggested; 42.8% of them received a treatment with a SSRI (35.1%) or a SNRI (7.7%); antipsychotics were prescribed in 9.9% of cases. Thirteen percent of patients received only benzodiazepine.

TABLE 1 | Socio-demographic and clinical characteristics.

	Neurology Inpatients *N* (%)	**Gastroenterology Outpatients** *N* (%)
Total number	2,479 (100%)	2,560 (100%)
Presence of MUPS	252 (10.1%)	247 (9.6%)
GENDER		
Men	92 (36.5%)	93 (37.5%)
Women	160 (63.5%)	154 (62.1%)
Mean age (years)	47	40
Men	50	35
Women	46	42

Gastroenterology Patients

Two thousand five hundred and sixty outpatients were evaluated in gastroenterology division. 9.6% ($n = 248$) of patients had MUPS, without significative statistical difference compared to MUPS distribution among neurological patients (chi-square 0.32; $p = 0.57$); 62.1% of them were women. No statistically significant difference of MUPS distribution between genders emerged ($p = 0.19$).

The most affected age group ranged between 15 and 45 years. Average age was 35 years for men and 42 years for women.

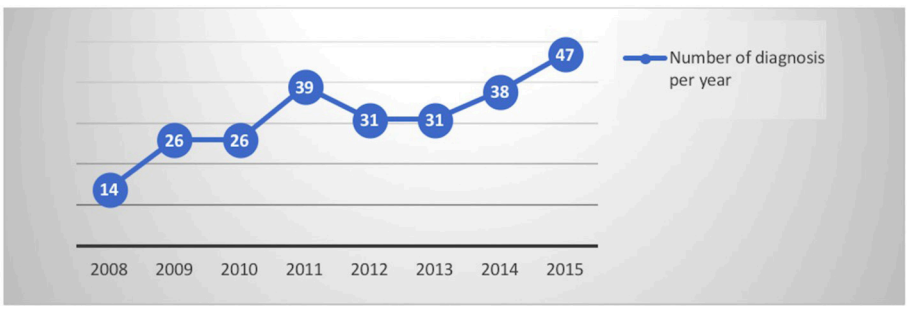

FIGURE 1 | Number of diagnosis per year.

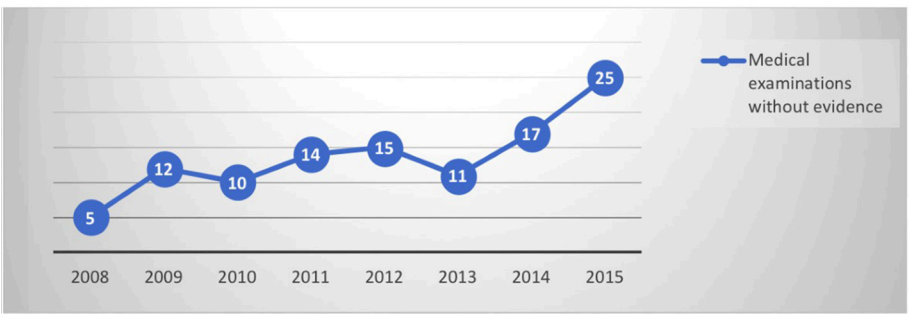

FIGURE 2 | Medical examinations without evidence per year.

Regarding gastroenterology patients: 22.9% of patients had a positive psychiatric history or a concomitant mood disorder. The most frequent diagnoses were functional abdominal pain (50%), dysmotility-like dyspepsia (26.6%), irritable bowel syndrome (10.4%), meteorism of unknown cause (2.4%), hiccup (1.6%), burning mouth syndrome (1.2%). No patient had received a diagnosis of somatic symptom disorder. During the assessment, a psychiatric visit was recommended in 1.6% of cases only.

Evaluating the diagnoses made per year, differently from neurological patients, an increase in data did not emerge, as for the negative investigations (as shown in **Figures 1**, **2**). The differences between the two genders seemed to be related to the anamnestic background: a greater presentation of previous or concurrent psychiatric disorders emerged among women.

Symptoms complained by patients in both genders are overlapping: dysmotility (23% among men and 28% among women), abdominal pain (41.9% among men and 27% among women), and irritable bowel syndrome (11.8% among men and 11.6% among women). The major differences related to symptoms between genders were dyspepsia, persistent hiccups, and jugular constriction more represented among men; vice versa burning mouth syndrome and hot flashes with chest-pain have been observed only among women.

Symptoms in gastroenterology group were not usually assessed through exams but were treated with Levosulpiride (38.7%) and antispasmodic (33.8%); only 8.1% of patients received an antidepressant (SSRI in 5.6% and or SNRI in 2.6% of patients) and only 1.6% of patients was sent to psychiatric care.

DISCUSSION

The notion that most MUPS are the result of a single process of somatization is no longer supported by the evidence. Physiology, personality traits, life experiences, health cognition, and interaction with healthcare professionals, in fact are all important in the development of medically unexplained symptoms, and a new model useful to understand MUPS is that of a complex adaptive system (20, 21).

Starting from patients' characteristics it is interesting to note that a significant number of patients visiting these hospital departments presents medical unexplained symptoms. This datum is partially in line with the literature showing higher percentage of patients with MUPS among general practice (25–50% of patients) and similar percentage in emergency department (18.5% of non-trauma patients visiting emergency departments) (22, 23).

According to the literature, patients with MUPS are more often women, of middle age, with self-referred specific symptomatology (23). In the neurology ward patients present a psychiatric history more frequently than in gastroenterology. From the largest study on comorbidity rates emerged that 50.6% of patients suffering from MUPS has a personality disorder. Other authors showed that MUPS are often associated to affective disorders, primarily depression, and especially in later life (24, 25). The role of inflammation in major depressive disorder (MDD) and the impact of exposure to early stressful events in increasing the vulnerability to develop psychopathologies may represent a possible common ground in developing physical symptoms, involving similar underlying pathogenic mechanisms (26–28). Additionally, the co-existence of MUPS and medical explained conditions in the same individuals tends to result in the exclusion of the MUPS episodes from the appropriate diagnostic code (29, 30).

Dealing with the diagnostic approach of somatic symptoms disorders, instead of neurological inpatients, among gastroenterology's outpatients no one received a diagnosis of somatic symptom disorder; this difference emphasizes the greater attention to psychopathological problems given in a department such as neurology.

Despite the numerous medical exams required, a psychiatric consult was prescribed in a minority of patients, remaining unchanged over the years in the whole sample. While neurological patients received a diagnostic-therapeutic approach in line with the literature, gastroenterological patients mainly received antipsychotics. In literature emerged that SSRIs are preferred, in monotherapy or in association with atypical antipsychotics (12, 31). However, from a Cochrane review emerged that the efficacy of new generation antidepressants has to be balanced with the long-term side effects that amplify the perception of somatic symptoms (32–34).

Psychotherapeutic treatments are varied; in literature emerged that approaches such as CBT can be helpful for these patients (35). However, practitioners often have not inadequate service opportunities (3). Focusing on the treatment of a psychiatric disorder can be useful for the resolution of physical symptoms (36). Different strategies, based on patient' risk profiles, as detected by consensus and expert opinion in the guideline working group, could be used in order to treat patients and reduce MUPS associated healthcare costs. In the Dutch Multidisciplinary Guideline for MUPS and Somatoform Disorder (SD), a disease management approach is recommended in which risk profiles are defined and a stepped care algorithm for treatment is described; in high risk patients a multidisciplinary team treatment is recommended (9, 36, 37). However, more researches are needed for validation of screening instruments for MUPS and SD, for preventive psychosocial interventions aimed at improvement of the patient-doctor relationship and at reduction of healthcare costs.

Strength and Limitations

The strength is the evaluation of a high number of data starting from a medical approach. Despite this point, retrospective data do not provide information on follow-up. Moreover, diagnosis of somatoform disorder or somatic symptom disorder was formulated by non-specialists. There are no data about costs; this point could represent a future goal for a study about psychoeducation and psychosocial interventions.

AUTHOR CONTRIBUTIONS

NP and CC conceptualized and wrote the first draft of the manuscript. MI, IC, LB, and FC contributed with commentaries and suggestions and collected the data. CI wrote the references. MI, IC, and CC also reviewed and supervised all the writing process.

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OPINION
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Physical Health Problems in Psychosis: Is It Time to Consider the Views of Family Carers?

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INTRODUCTION

People living with a diagnosis of psychosis have depleted social networks (1); a picture which is already evident at the first episode stage (2). The development of any psychotic illness (e.g., schizophrenia) will significantly and adversely impact multiple areas of a person's life and functioning, and leave many in socially marginalized positions, excluded from peer groups, and educational and employment opportunities (3, 4).

The vast majority of people living with psychosis reside in community based settings and receive the bulk of their care and support from informal carers, who are typically close relatives (e.g., parents, partners, children, siblings). Informal carers have long been recognized for the vital role they play in supporting patients with psychosis to recover, and their role in improving a broad range of outcomes (5). Such outcomes include reducing rates of relapse and need for inpatient care (6), and improving engagement in and outcomes from prescribed treatments (7, 8). For many, the time spent in caregiving duties can often exceed those recorded for a full-time job (9). Family carers are often the first to observe signs of deterioration in their relative's psychiatric health (10) and play an instrumental role in mobilizing appropriate service responses and treatments (11). Interestingly, recent developments in the literature have also highlighted that life expectancy in patients is significantly elevated in those with carer support compared to those without (12, 13). Reininghaus and colleagues, for example, completed a 10 years follow up of first episode psychosis cases in England. Their results suggested that patients with families were 90% more likely to be alive at follow up (i.e., less likely to have experienced a death attributable to unnatural cause e.g., suicide), compared to peers without no documented family support (12). Ran et al. (13) who assessed families living in China observed that over a 14 years follow up period, it was patients with family support who had improved survival rates at 70.9% compared to rates of 47.5% for those without support.

CAREGIVING AND PATIENT PHYSICAL HEALTH

There is an extensive body of literature documenting elevated rates of physical health comorbidity in people with psychosis and other severe mental illnesses (SMI) (14–16), and their significantly

reduced life expectancy rates compared to the general population (17–19). This gap is reported to be increasing (20) with some studies reporting a range between 10 and 30 years (14).

Though rates of deliberate self-harm and suicide are elevated in SMI (21); for the majority of people, the excess mortality rates are attributable to avoidable and treatable conditions that have modifiable lifestyle risk factors (e.g., sedentariness, tobacco use) (22–24), and inequality in access to healthcare and treatment (25). However, despite the role played by family carers in helping to optimize recovery outcomes for patients, carer experiences of patient physical health comorbidity in psychosis and other SMI have been largely overlooked by researchers and clinicians alike. To date, there have been only a handful of studies that have purposively sought the perspective of carers on matters related to patient physical health (26–29). Findings from our group (26), which were based on a combination of individual and group interviews with carers of adults with long-term psychosis, highlighted carers' exposure to a broad range of physical health conditions in patients. These included cancer and sexual health problems, alongside more frequently reported conditions of poor diet/high body mass index, diabetes, smoking and respiratory related concerns, and poor oral health. Five key themes capturing carers' experience of physical problems in patient groups were extracted from interviews. The themes focused on carers' perception and subjective experience of gaps in service provision for relatives with psychosis and concomitant physical health conditions, and the carer's role in meeting unmet service needs, including going to fitness classes with their relative. The identified themes also centered on the difficult conversations carers often found themselves having with their relative on physical health matters such as smoking cessation, dietary choices/weight management, seeing a general practitioner, how such conversations affected the quality of their caregiving relationship, and the consideration and forethought that preceded decisions to facilitate discussions. The impact of patient physical health on carers' own health and well-being were also noted as an important theme (26). Similar work from Happell and colleagues in Australia (27), as part of their qualitative investigations with a broad range of mental health carers, also highlighted the impact of patient physical health on carer health status. Their findings also identified a theme that reflected carers' beliefs about the fusion of mental and physical health problems. For example, it included concerns of how medication side-effects led to physical health problems (e.g., weight gain) which, in turn, impacted their mental health and ability to engage in strategies to improve their physical health. Lawn et al. (28) interviewed 12 family carers on their experiences of patient smoking behaviors. The results illustrated carers' struggles and perceived responsibilities for managing patient physical health, their own accommodation and facilitation of patient smoking, and the dissonance they experienced over their accommodation behaviors and their understanding of the negative health implications of smoking.

Though there will be overlapping features with other SMI conditions (e.g., BPAD), and with physical health problems that occur independent of co morbid severe mental health problems, the unique presentation of psychosis in an individual which, for many, can include the experience of paranoia, suspiciousness, hallucinations, and affective and cognitive disturbance, will impact their ability to communicate clearly and effectively with others. For example, hallucinatory experiences and paranoia can render it difficult for patients to first identify problems, articulate concerns or changes in their physical health and/or attribute changes in their functioning to possible physical health factors. Likewise, their style and patterns of communication (e.g., thought disorder) might increase the likelihood that others might misunderstand their communications. Patient symptomatology can also interfere with a carer's efforts and confidence to approach physical health issues in relatives through underlying concern and experience that their communications, behaviors, and intentions might be misunderstood and/or cause upset. Carers can find themselves feeling individually responsible for policing or modifying patient unhealthy behaviors and also accommodating behaviors to maintain calm and equilibrium (28). Given the complexity of patient symptoms, some carers might consider that in the "grand scheme" of things, trying to address the physical health issues faced by their relative are secondary to meeting the immediate challenges presented by their mental health problems [e.g., (9, 30)]. For example, if their relative is socially isolated with minimal activities and feelings of joy during the day, then encouraging their relative to refrain from consuming a favorite, yet calorific/low nutritional value, food item or smoking a cigarette can seem difficult to implement as it might mean their relative is left with no positive experiences during the day. It is these additional layers of complexity within the caregiver role and caregiving relationship that have been overlooked within the literature and, consequently, carers have been left to navigate this difficult terrain themselves without support and evidence driven guidance.

CARER AND PATIENT HEALTH

In comparison to the general population, poorer health status, including sleep disturbance, are also elevated in carers of patients with SMI (31–34), and patient physical and mental health problems have been linked to carer's poorer physical health (9, 26–28). Perlick et al. (32) reviewed the health status of 264 carers of people living with bipolar and psychosis spectrum disorders. The results highlighted that, in the preceding 5 years, approximately two thirds of carer participants reported experiencing health conditions such as hypertension and diabetes, and one third experienced at least two serious physical health conditions. The need for clinicians and researchers to extend discussions and service initiatives on patient physical health to incorporate carer needs are indicated. More recently, Poon et al. (33) assessed the mental and physical health status of 42 carers of patients with first-episode psychosis in Australia. Approximately one quarter of carers had high risk for Type 2 diabetes, one third had hypertension and just under 80% were overweight.

RECOMMENDATIONS FOR IMPROVING PHYSICAL HEALTH OUTCOMES IN SMI: SUPPORTING THE ROLE OF CARERS

In the United Kingdom, current treatment guidance recommends regular physical health monitoring in people with SMI (35, 36). However, monitoring rates can be variable (37) and the role played by carers in supporting these guidelines is unknown. Strategies to improve patient physical health have failed to acknowledge an ever expanding role carers adopt in supporting relatives, directly and indirectly, with their physical health (e.g., remembering appointments, escorting relatives to appointments, rebooking missed appointments, paying for gym membership). In light of emerging evidence, we argue that discussions on optimizing patient physical health and ensuring parity of esteem in physical and mental health provision must consider the role of carers, the impact of patient health on carer health and well-being and the caregiving relationship, and to consider what roles, (if any), carers might want in supporting improved physical health outcomes in patients.

The available literature suggests that mental health carers can all too often feel marginalized by service providers (38, 39) despite their reported need to be more involved and treated as partners in patient care, where their unique roles and expertise are recognized (40, 41). Though there are no specific guidelines on how best to support carers to address and cope with the impact of physical health comorbidity in SMI, the literature does offer some helpful indications. We already know that carers report a lack of information about physical health issues in psychosis and welcome opportunities to improve their understanding (26). It is conceivable, therefore, that carers might benefit from:

a. recognition of their caring role, knowledge and expertise about the patient, and their particular needs for information and support regarding physical health comorbidity,
b. psychoeducation interventions, from first onset, about what constitutes good physical health and identifying factors that help to encourage good health,
c. specific guidance on facilitating positive styles of communication on sensitive health issues (e.g., weight),
d. guidance on strategies (i.e., small, feasible) that could be used to promote improved patient health status. The strategies should be tailored toward the needs of a caregiving relationship and consider how psychosis can affect patient perceptions of events, people, and communication,
e. greater awareness of the research underpinning the global focus on decreasing physical health morbidity in SMI. This should be delivered with a balanced message of hopefulness and the potential for positive change and improvement avoiding the negative impacts of research and health messages focused exclusively on excess mortality and poorer outcomes.

Finally, there is an established evidence base detailing the broader impact of patient mental health problems on carer functioning such as burden (34, 42). However, a more nuanced understanding of how patient physical health problems interact with and impact carer health would seem a fruitful direction to follow [e.g., (31–34)]. Strategies to ensure carers have opportunities to reflect on the subjective impact of patient multi-morbidity on their own well-being and to access support in identifying adaptive coping and health management strategies (e.g. consulting with their own primary care physician, stress management, lifestyle interventions to maintain their own physical health) could be beneficial (43). These recommendations remain consistent with treatment and best practice guidance for providing carer focused interventions in SMI (35).

CONCLUSION

Informal carers are providing the bulk of care for people living with psychosis and many will reside in the same household and are therefore important figures in a patient's social network. Patient outcomes, including life expectancy, are enhanced where there is carer support and involvement, and overall care costs are reduced. There are sound clinical and economic arguments for the informal carer (family) perspective to be sought on discussions and strategies to develop and implement lifestyle interventions for improved patient physical health in SMI. These arguments remain strong given that carers are uniquely placed in the patient's immediate environment to impact change in patient environment and lifestyles. Carers want holistic and integrated approaches to patient care that are robust enough to take account of complex comorbid clinical presentations, and for this to occur irrespective of whether patients access mental or physical health services. Patient well-being, including optimal levels of physical health as part of that, are outcomes of interest and importance for carers. We have reached a stage where a more detailed understanding of carer needs, specifically as they relate to physical comorbidities in patients and their contributions to improving outcomes, are required.

AUTHOR CONTRIBUTIONS

JO prepared the first draft of the manuscript. DS and FG contributed to manuscript revision and approved the submitted version.

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REVIEW
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Effects of Aerobic Exercise on Metabolic Syndrome, Cardiorespiratory Fitness, and Symptoms in Schizophrenia Include Decreased Mortality

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Schizophrenia is a severe psychiatric disorder with a lifetime prevalence of about 1%. People with schizophrenia have a 4-fold higher prevalence of metabolic syndrome than the general population, mainly because of antipsychotic treatment but perhaps also because of decreased physical activity. Metabolic syndrome is a risk factor for cardiovascular diseases, and the risk of these diseases is 2- to 3-fold higher in schizophrenia patients than in the general population. The suicide risk is also higher in schizophrenia, partly as a result of depression, positive, and cognitive symptoms of the disease. The higher suicide rate and higher rate of cardiac mortality, a consequence of the increased prevalance of cardiovascular diseases, contribute to the reduced life expectancy, which is up to 20 years lower than in the general population. Regular physical activity, especially in combination with psychosocial and dietary interventions, can improve parameters of the metabolic syndrome and cardiorespiratory fitness. Furthermore, aerobic exercise has been shown to improve cognitive deficits; total symptom severity, including positive and negative symptoms; depression; quality of life; and global functioning. High-intensity interval endurance training is a feasible and effective way to improve cardiorespiratory fitness and metabolic parameters and has been established as such in somatic disorders. It may have more beneficial effects on the metabolic state than more moderate and continuous endurance training methods, but to date it has not been investigated in schizophrenia patients in controlled, randomized trials. This review discusses physical training methods to improve cardiorespiratory fitness and reduce metabolic syndrome risk factors and symptoms in schizophrenia patients. The results of studies and future high-quality clinical trials are expected to

lead to the development of an evidence-based physical training program for patients that includes practical recommendations, such as the optimal length and type of aerobic exercise programs and the ideal combination of exercise, psychoeducation, and individual weight management sessions.

Keywords: aerobic exercise, endurance training, high-intensity interval training, metabolic syndrome, mortality, schizophrenia, cognition, positive and negative symptoms

INTRODUCTION

Schizophrenia is a severe neuropsychiatric disease that affects ∼1% of the population (1, 2). It strikes young adults between 20 and 30 years of age (3), and symptoms persist throughout adult life in 30–50% of affected patients (4, 5). The disease leads to impaired social functioning; for example, only 20% of patients are able to have a job on the primary market, and only about 30% have a stable relationship (5). Because of the high hospitalization rates and high levels of both disease-related incapacity to work and early retirement, schizophrenia-related costs exceed even those of widespread diseases such as cardiovascular diseases (CVD) (6). According to the WHO report on the global burden of disease, schizophrenia is one of the most common conditions associated with a high rate of years lived with disability (YLD), one of the leading causes of disease burden (7), and among the 10 most costly illnesses worldwide (8).

COGNITIVE IMPAIRMENT AND UNDERLYING NEUROBIOLOGICAL PATHWAYS

Cognitive impairment is a frequent core feature of schizophrenia (9), in addition to positive and negative symptoms, and is related to the reported volume loss of the hippocampus, a region central to memory, learning, and cognitive integration (10). Cognitive deficits and negative symptoms are the most important predictors for poor social and functional outcome and are major contributors to disability (11). Cognitive deficits are present in domains such as executive function, episodic memory, attention, and social cognition (11–13), functions that are particularly dependent on the hippocampus and prefrontal cortex (14). In schizophrenia, neurodevelopmental disturbances in vulnerable periods of brain development are thought to lead to hippocampal-prefrontal pathway deficits, resulting in the onset of disease symptoms in young adulthood (15). Meta-analyses of structural magnetic resonance imaging (sMRI) studies revealed gray matter volume reduction of 5–10% in the prefrontal cortex and hippocampus in schizophrenia patients (16). In the polymorph layer of the dentate gyrus (CA4) of the hippocampus, decreased numbers of oligodendrocytes (17, 18)—an indicator of disturbed myelination—have been detected in schizophrenia. A meta-analysis of diffusion-tensor imaging (DTI) studies in schizophrenia revealed decreased fractional anisotropy in white matter tracts interconnecting the prefrontal cortex and hippocampus (19); such white matter disruption is known to play a crucial role in cognition and psychopathology (20). Of interest in this context is that schizophrenia patients with overweight and obesity showed disturbed white matter integrity, with lower fractional anisotropy than normal-weight schizophrenia patients (21).

Several environmental factors, such as psychosocial stress associated e.g., with an urban lifestyle or childhood trauma, interact with genetic factors to increase the risk of a chronic disease course (22). The prefrontal cortex and hippocampus are central to cognitive processing and are also involved in the regulation of the neuroendocrine control of stress hormone secretion, including glucocorticoids (23). Whereas, acute stress can increase fear-associated memory, chronic stress with cortisol-based stress reactivity levels has a negative impact on spatial-reference memory and cognitive flexibility, induces hippocampal volume loss, adversely alters dendritic morphology and reduces adult neurogenesis and synaptic plasticity (23). Chronic stress during the pubertal period up to young adulthood, when synaptic pruning and oligodendrocyte-related myelination take place, has been shown to induce symptoms of schizophrenia (24).

MORTALITY IN SCHIZOPHRENIA

Schizophrenia affects daily life and subjective well-being. Low physical activity, impaired physical health, and reduced activities of daily living (25, 26) are just some aspects of the disease. Compared with the general population, individuals with schizophrenia have a 12-fold higher mortality from all external causes (27), which can largely be explained by the high incidence of somatic comorbidities; unhealthy lifestyles, such as high rates of cigarette smoking and low physical activity; and increased rate of suicides (26, 28, 29). Estimates indicate that together these health-related risk factors and suicides reduce life expectancy by nearly 10–20 years compared with the general population (30, 31). A meta-analysis of data from 29 countries on six continents found that mortality was significantly higher among people with mental disorders and that, in 65 studies, the highest mortality rate (relative risk 2.54, 95% CI 2.35–2.75) was among patients with psychosis (31). The relative risk for natural causes, such as CVD, was 1.80 (95% CI 1.71–1.88), but that for unnatural causes, such as suicides, was even higher (7.22, 95% CI 6.43–8.12). Cardiovascular risk was higher in schizophrenia patients than in patients with depressive disorder or multiple psychiatric diagnoses (32). People with severe mental illness, including schizophrenia, had a higher risk of developing coronary heart disease than

controls (adjusted hazard ratio 1.54; 95% CI 1.30–1.82) and a higher rate of autonomic nervous system dysfunction, including diminished heart rate variability, hypertension, alterations of the QT interval, and lipid pattern abnormalities (33). During the year after the first diagnosis of psychosis, a study found that the relative risk for all-cause mortality was 54.6 (95% CI 41.3–68.0) per 10,000, whereby the highest relative risk of death was found for self-inflicted injury or poisoning; during this period, the relative risk of death due to heart disease or diabetes did not differ between the group of people with a psychotic disorder and the general outpatient group (34).

In schizophrenia patients, suicidal thoughts and suicide planning and attempts were significantly associated with completed suicide in the following year (35). In first-episode patients, more symptoms of depression, longer duration of untreated psychosis, and positive symptoms, such as hallucinations and delusions, were found to increase the odds of experiencing suicidal ideation (36). Another study found that the severity of negative symptoms was lower in schizophrenia patients who attempted suicide (37). With respect to cognitive performance, decreased global cognitive functioning and visual memory predicted suicidal behavior in non-affective psychosis (38). In a meta-analysis and meta-regression analysis in over 80,000 patients with schizophrenia, depressive symptoms, the Positive and Negative Symptom Scale (PANSS) general score, and the number of hospitalizations were higher in patients with suicidal ideation (39). A history of alcohol use, family history of psychiatric illness, physical comorbidity, history of depression, and depressive symptoms were associated with suicide attempts, whereas poor adherence to treatment, hopelessness, higher intelligence quotient, history of attempted suicide, and being male were most consistently associated with completed suicide (39).

This qualitative review will provide a current overview of clinical studies aimed at reducing the socioeconomic burden of schizophrenia and mortality by addressing metabolic risk factors and symptom severity in schizophrenia patients.

THE METABOLIC SYNDROME IN SCHIZOPHRENIA

The International Diabetes Federation defines the metabolic syndrome as a combination of increased waist circumference (a mandatory feature) and two of the following criteria: elevated triglycerides, high blood pressure, elevated fasting glucose, and low high-density lipoprotein (HDL) cholesterol (**Table 1**) (40). Metabolic syndrome is defined slightly differently by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (41) and the adapted Adult Treatment Panel III (ATP III-A) of the American Heart Association (42), both of which require 3 of 5 criteria to be fulfilled (**Table 2**). In the general population, the metabolic syndrome is associated with a 4-fold increased relative risk to develop type 2 diabetes mellitus (43) and a 2-fold increased relative risk to develop CVD, such as stroke and coronary heart disease (44). Schizophrenia patients have a higher prevalence of metabolic syndrome than the general population and a 2- to 3-fold increased risk for CVD, resulting in increased cardiac mortality (30, 45). Metabolic syndrome was present in 37.3% of schizophrenia patients treated with second-generation antipsychotics and associated with an increased 10-year risk of coronary heart disease (risk ratio 2.18, 95% CI 1.88–2.48) in both male and female patients (risk ratio 1.94, 95% CI 1.65–2.23). Among the criteria for metabolic syndrome, triglyceride levels and waist circumference were significantly associated with the 10-year risk of coronary heart disease events (46). A meta-analysis found that the overall rate of metabolic syndrome in schizophrenia patients was 32.5% (95% CI 30.1–35.0%) and showed only minor differences between treatment settings (inpatient vs. outpatient), country of origin, and gender. Duration of illness and older age had the strongest influence. Among the criteria for metabolic syndrome, waist circumference was the strongest predictor (47). Additionally, the prevalence of metabolic syndrome was higher in patients with negative symptoms, which are associated with a sedentary lifestyle and lack of physical activity (48). Furthermore, in schizophrenia patients metabolic syndrome was significantly associated with cognitive impairment and was found to contribute to cognitive deficits throughout the course of the disease (49).

One study found that the risk of metabolic syndrome was elevated in all patients with severe mental illness (32.6%, 95% CI 30.8–34.3%) and did not differ between patients with schizophrenia and those with bipolar disorder or between patients with bipolar disorder and those with major depression (45). In a meta-analysis of first-episode schizophrenia patients, the rate of metabolic syndrome was only 9.9%; the rate of overweight was 22%; hypertriglyceridemia, 19.6%; low HDL, 21.9%; hyperglycaemia, 6.4%; high blood pressure 24.3%; and smoking, 46.8% (50). This indicates that the cardiovascular risk is lower in first-episode than in multi-episode schizophrenia patients. Longer duration of illness is also predictive for longer

TABLE 1 | International Diabetes Federation criteria for metabolic syndrome.

Measure	Threshold (Waist circumference plus 2 other measures required)
Elevated waist circumference	
Men	≥94 cm
Women	≥80 cm
Elevated triglycerides	≥150 mg/dl
Elevated blood pressure*	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure
Reduced high-density lipoprotein cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Elevated fasting glucose**	≥100 mg/dl

*or treated with antihypertensive medication; **or treated with insulin or hypoglycaemic medication.

TABLE 2 | Adult Treatment Panel III and III-A criteria for metabolic syndrome.

Measure	Clinical criteria ATP III (3 of 5 required)	Threshold ATP III-A (3 of 5 required)
Elevated waist circumference		
Men	≥102 cm	≥102 cm
Women	≥88 cm	≥88 cm
Elevated triglycerides	≥150 mg/dl	≥150 mg/dl
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure
Reduced high-density lipoprotein cholesterol		
Men	<40 mg/dl	<40 mg/dl
Women	<50 mg/dl	<50 mg/dl
Elevated fasting glucose	≥110 mg/dl	≥100 mg/dl

treatment with antipsychotics, and treatment with second-generation antipsychotics in particular is a risk factor for developing metabolic syndrome (see below).

ANTIPSYCHOTIC TREATMENT AND METABOLIC SYNDROME

Despite reducing positive symptoms, first- and second-generation antipsychotics have demonstrated only poor or no efficacy in improving cognitive deficits and negative symptoms in schizophrenia (51, 52). Depending on the dose, users of typical and atypical antipsychotics had higher rates of sudden cardiac death than non-users (adjusted incidence rate 1.99, 95% CI 1.68–2.34) (53). Furthermore, atypical antipsychotics are known to prolong the QTc interval and increase resting heart rate, thereby affecting autonomic neurocardiac function (54). However, a decrease in heart rate variability has also been shown in unmedicated schizophrenia patients and is a cardiac risk factor, together with low physical fitness (55). A meta-analysis showed that second-generation antipsychotics have fewer extrapyramidal side effects than first-generation drugs, such as haloperidol (52). Many of the most effective second-generation antipsychotics, including olanzapine, clozapine, and risperidone (52, 56), however, are associated with substantial weight gain and sedation (52), leading to increased rates of the metabolic syndrome. In unmedicated and first-episode schizophrenia patients, the overall rate of the metabolic syndrome was only about 10%, the rate of diabetes was only 1–2%, and the rate of overweight was 22–26%. Therefore, the cardiovascular risk can be assumed to be higher in multi-episode patients with a long treatment history (50). A meta-analysis found that patients with severe mental illness who were treated with any antipsychotic had a significantly higher risk of metabolic syndrome than antipsychotic-naïve individuals. The risk was higher with olanzapine and clozapine than with other antipsychotics, especially aripirazole, and higher in patients on polypharmacotherapy than in those on monotherapy (45). Another meta-analysis also found the highest rates of metabolic syndrome in patients treated with clozapine (51.9%) and the lowest rates in unmedicated patients (20.2%) (47). One study found a positive association between a serotonin receptor gene (HTR2C) polymorphism and metabolic syndrome in patients treated with olanzapine, clozapine, and risperidone and that genetic factors may influence the prevalence of the metabolic syndrome in schizophrenia (57).

In summary, lifestyle changes can be assumed to be warranted, especially in multi-episode patients on long-term antipsychotic treatment. To reduce the risk for metabolic syndrome, subsequent CVD, and mortality, add-on therapeutic interventions aimed at improving symptoms of the disease, such as depression or negative symptoms; reducing the smoking rate; and increasing physical activity are needed (58).

PHYSICAL ACTIVITY IN SCHIZOPHRENIA

A worldwide analysis of adverse health conditions in the general population estimated that physical inactivity causes 6% of the burden of disease from coronary heart disease; 7%, from type 2 diabetes; and 10%, from breast cancer and colon cancer. Overall, inactivity causes 9% of premature mortality (59). The health benefits of physical activity in adults include reduced rates of metabolic syndrome, coronary heart disease, high blood pressure, type 2 diabetes, stroke, depression, and cancer. Additionally, there is strong evidence for increased cardiorespiratory fitness, healthier body mass and composition, and improved cognitive functioning (59). The high prevalence of the metabolic syndrome in schizophrenia may be a result of the disease itself and treatment with antipsychotics (see above) or of sedentary behavior and low physical activity and aerobic fitness, which play an important role in this patient group (60, 61), or a combination of these factors. Studies have repeatedly shown that schizophrenia patients show reduced cardiovascular fitness and physical activity (62). In a meta-analysis of 13 studies, sedentary behavior measured in hours per day was significantly higher in schizophrenia patients (hedges $g = 1.13$, 95% CI 1.47–4.1) than in healthy controls (63). According to a meta-analysis, schizophrenia patients engage in less moderate (hedges $g = -0.45$, 95% CI -0.79 to -0.1) and vigorous physical activity ($g = -0.4$, 95% CI -0.60 to -0.18) than healthy controls, and depressive symptoms and older age are associated with less vigorous physical activity (64). A meta-analysis of 212 schizophrenia patients and 132 healthy individuals confirmed that physical activity was lower in the patient group and showed that decreased physical activity was correlated with impaired quality of life and social functioning, increased social withdrawal, and lower motivation and employment rates (65). Furthermore, low physical fitness was associated with illness duration, smoking, the presence of the metabolic syndrome, and more severe negative, depressive, and cognitive symptoms (26). In schizophrenia patients, the duration of physical activity was negatively correlated with waist circumference and body

mass index, while food intake variables correlated with HDL cholesterol and triglyceride levels (66). A systematic review found that lifestyle interventions with psychoeducation, diet, and recommendations on physical activity were associated with significant weight reduction, reduced body mass index, decreased waist circumference, and lower blood glucose levels (67).

REQUIREMENTS FOR AEROBIC EXERCISE STUDIES IN SCHIZOPHRENIA

Compared with the healthy population, patients with schizophrenia have specific characteristics that decrease their motivation to perform physical activity; these characteristics include sedation related to antipsychotic treatment; schizophrenia symptoms, including anxiety and depression; a lower level of education; little experience with exercise; social withdrawal; and negative symptoms (68, 69). Therefore, it is essential that aerobic exercise interventions aimed at improving cardiovascular fitness are supervised by a sports scientist to increase patients' motivation to participate (70). Schizophrenia patients and healthy controls showed comparable adaptations to endurance training, as assessed by physical working capacity and maximal achieved power, but differences were found in changes of performance at a given lactate concentration (70). Under supervision by a sports scientist, endurance training was feasible and effective in both groups (70). The first studies to investigate aerobic exercise in schizophrenia patients had many methodological limitations (71). Major concerns included missing healthy or patient control groups or both, inadequate sample sizes, and non-randomized or non-controlled designs (72–74). In later endurance training studies, a minimum of 30 min per training session and at least three sessions per week were recommended in schizophrenia patients (75). According to the criteria of the American College of Sports Medicine, in healthy individuals 150 min of moderate training per week are necessary to improve cardiorespiratory fitness (76). A recent cross-sectional study examined the exercise behavior and mental health of 1,237,194 people aged 18 years or older in the USA and found that individuals who exercised had 43.2% fewer days of poor mental health in the past month and a lower mental health burden than the non-exercising groups. Interestingly, the largest effects were seen for popular team sports, cycling, and aerobic and gym activities and for durations of 45 min and frequencies of three to five times per week (77).

EFFECTS OF AEROBIC EXERCISE INTERVENTIONS ON THE METABOLIC SYNDROME

New add-on treatment options, such as aerobic exercise, are needed to reduce the risk of cardiometabolic diseases in schizophrenia. However, results of intervention studies examining the effects endurance training on parameters of the metabolic syndrome in schizophrenia patients were mainly negative. In a combined Weight Watchers intervention, exercise had no effects on weight loss (78). A randomized controlled trial in schizophrenia patients consisting of 2 h of aerobic exercise per week over a period of 6 months had no effects on body mass index, body fat percentage, or factors of the metabolic syndrome (79). A meta-analysis of aerobic exercise interventions in patients with bipolar or schizophrenia spectrum disorders found no effects of aerobic exercise on body weight or body mass index (80), and another meta-analysis also reported no effects of aerobic exercise on body mass index in schizophrenia patients (81). In contrast, in a small sample of schizophrenia patients aerobic exercise improved physical activity, blood pressure, and body composition (82). In a randomized study of an intervention comprising aerobic group exercise and individual weight management sessions in obese or overweight patients with schizophrenia, schizoaffective disorder, bipolar disorder, and major depression, weight loss in the intervention group increased progressively over the 18-month study period and differed from the control group (83). In summary, findings to date indicate that isolated exercise interventions are unlikely to induce weight loss in patients with schizophrenia (84). However, adding psychosocial interventions or diet to aerobic exercise programs seem to be a promising approach to reduce body weight. Increased physical activity (pedometer walking) plus motivational interviewing reduced body weight in obese schizophrenia patients after 12 weeks (85). In obese schizophrenia patients, a 3-month lifestyle intervention comprising psychosocial treatment, behavior therapy, and aerobic exercise reduced waist circumference, body weight, and body mass index but did not affect blood lipids or glucose levels (86). In a small study in multi-episode schizophrenia patients, an aerobic exercise program consisting of three 30-min sessions per week over a period of 24 weeks significantly reduced weight and body mass index (73). In a personalized diet and exercise program (3 exercise sessions per week) in 106 schizophrenia patients treated with antipsychotics, the months of participation correlated with weight loss (87) (**Table 3**).

Because of the need to improve the efficacy of aerobic exercise, higher intensity training, such as high-intensity interval training (HIIT), has been used in obese individuals. HIIT is a promising new method of intensified endurance training. A 12-week HIIT significantly improved metabolic parameters, such as waist circumference, body mass, fasting glucose, HDL cholesterol, and blood pressure, in mentally healthy patients with cardiometabolic risk factors and obesity (94–98). HIT has the highest potential to reduce visceral adipose tissue in obese individuals (99). Compared with continuous training, HIIT significantly reduced insulin resistance, HbA1c, and body weight in healthy adults and reduced fasting glucose in participants at risk of type 2 diabetes (100). However, a recent meta-analysis found no difference between HIIT and moderate-intensity continuous training for body fat reduction (101). This finding was supported by a meta-analysis of 12-month interventions in obese adults, which showed weight loss but found no difference between HIIT and moderate-intensity exercise (102). Another meta-analysis showed that HIIT performed as cycling or running significantly reduced abdominal and visceral fat mass but that running was more effective than cycling (103). In a group of

TABLE 3 | Effects of continuous endurance training on metabolic risk factor and symptoms of the disease in patients with schizophrenia.

Study	Participants	Training methods	Effects on cardio-respiratory fitness	Effects on metabolic partameters	Effects on symptoms
Dodd et al. (73)	8 chronic schizophrenia patients	24 weeks aerobic exercise program (treadmill, bicylcle, walking)		Body weight ↓ Body mass index ↓	
Methapatara and Srisurapanont (85)	64 schizophrenia patients with body mass index of 23 kg/m^2 or more	12 weeks randomized controlled trial with pedometer walking plus 1 week motivational inertviewing program vs. usual care		Body weight ↓ Waist circumference ↓ Body mass index ↓	
Pajonk et al. (88)	16 chronic schizophrenia patients 8 healthy controls	3 months randomized controlled trial with cycling vs. table football	VO_{2max} ↑ W_{peak} ↑		Short-term verbal memory ↑ Total symptoms ↓
Scheewe et al. (89)	63 schizophrenia patients, 55 healthy controls	6 months randomized controlled trial with cardiovascular aerobic exercise and muscle strength exercises vs. occupational therapy	VO_{2peak} ↑ W_{peak} ↑		
Daumit et al. (83)	291 overweight or obese patients with schizophrenia (58%), bipolar disorder (22%) or major depression (12%)	18 months group exercise sessions plus weight management sessions vs. standard information on nutrition and physical activity		Body weight ↓	
Scheewe et al. (79)	63 schizophrenia patients	6 months randomized controlled trial with cardiovascular aerobic exercise and muscle strength exercises vs. occupational therapy	W_{peak} ↑	Body mass index - Waist circumference -	Depressive symptoms ↓ Total symptoms ↓ Positive symptoms ↓ Disorganization ↓ Excitement ↓ Emotional distress ↓
Bredin et al. (82)	13 schizophrenia patients	12 weeks aerobic exercise (cycling, treadmill, elliptical training)	VO_{2peak} ↑ W_{peak} ↑	Body weight ↓ Waist circumference ↓	
Kuo et al. (86)	33 obese schizophrenia patients 30 healthy controls	10 weeks aerobic exercise, lifrestyle modification, psychosocial treatment, behavior therapy		Body weight ↓ Waist circumference ↓ Body mass index ↓	
Malchow et al. (90)	43 multi-episode schizophrenia patients, 22 healthy controls	3 months aerobic endurance training (cycling) plus cognitive remediation vs. table football plus cognitive remediation			Global functioning ↑ Social adjustment ↑ Negative symptoms ↓ Short-term verbal memory ↑ Cognitive flexibility ↑
Amiaz et al. (87)	106 schizophrenia patients	9 months fitness and diet program		Body weight ↓ Waist circumference ↓ Body mass index ↓ Body fat percentage ↓	
Armstrong et al. (91)	33 patients with schizophrenia	12 weeks randomized controlled trial with aerobic exercise vs. treatment as usual	VO_{2peak} ↑ W_{peak} ↑	Body weight - Body mass index -	
Jerome et al. (92)	291 overweight or obese patients with schizophrenia (58%), bipolar disorder (22%) or major depression (12%)	18 months group exercise sessions plus weight management sessions vs. standard information on nutrition and physical activity	Heart rate response ↓		
Firth et al. (93)	38 patients with first-episode schizophrenia	10 weeks individualized aerobic exercise vs. treatment as usual			Positive symptoms ↓ Negative symptoms ↓ Psychosocial functioning ↑ Short-term verbal memory ↑

VO_2peak, VO_2max,highest oxygen intake; W_{peak}, peak work rate/power output.

obese men, HIIT significantly improved insulin sensitivity and muscle mitochondrial content (increased muscle mitochondrial content is assumed to be a basic mechanism of effect of HIIT) compared with continuous aerobic training (104). To date, only two studies have applied HIIT interventions in patients with schizophrenia. One evaluated a 14-week program of 40 min HIIT twice a week in first-episode patients and showed a significant decrease in waist circumference and heart rate (105). The other studied an 8-week HIIT program comprising 25-min sessions three times a week in multi-episode patients and showed reduced body weight, body mass index, and resting heart rate (106) (**Table 4**). Overall, HIIT has the potential to improve parameters of the metabolic syndrome in patients with schizophrenia.

EFFECTS OF AEROBIC EXERCISE INTERVENTIONS ON CARDIORESPIRATORY FITNESS

In the general population, improving cardiorespiratory fitness is a key factor in preventing CVD and mortality (110, 111). Cardiorespiratory fitness can be measured by the highest oxygen intake (referred to as VO_{2max} or VO_{2peak}) and peak work rate/power output (W_{peak}). Aerobic exercise interventions seeking to improve cardiorespiratory fitness can prevent CVD and the associated mortality (112). In a randomized study in obese and overweight patients with severe mental illness, including schizophrenia, schizoaffective disorder, bipolar disorder, and major depression, participation in group exercise classes was associated with improved short- and long-term cardiorespiratory fitness, as indicated by a lower heart rate response (92). Significant increases in VO_{2max}, as a measure of aerobic capacity, and power output (W_{peak}) have been reported in schizophrenia patients after continuous exercise training compared with control conditions, such as occupational therapy or table soccer (73, 79, 82, 88, 89, 91, 113) (**Table 3**). In a meta-analysis, cardiorespiratory fitness was improved in schizophrenia patients after aerobic exercise ($g = 0.43$, 95% CI 0.05–0.82). Furthermore, in schizophrenia patients improved cardiorespiratory fitness was correlated with an increased volume of the hippocampus (88, 114), with decreased ventricular and increased cerebral gray matter volume, and with thickening in the frontal, temporal, and cingulate cortex of the left hemisphere (113).

In a meta-analysis of HIIT vs. moderate-intensity continuous training, HIIT was more likely to increase VO_{2peak} in adults with coronary heart disease, hypertension, metabolic syndrome, and obesity (115). In obese adults with hypertension, HIIT and continuous training both improved cardiorespiratory fitness, whereby an exercise intervention lasting at least 12 or 16 weeks was needed to achieve these effects (116). In schizophrenia patients, HIIT improved VO_{2peak} by 12% compared with playing computer games (107), and in a case report of a patient with schizophrenia HIIT was more effective than moderate continuous training in increasing heart rate variability and reduing resting heart rate (109). A decrease in resting heart rate and 38% increase in VO_{2max} was detected after a 14-week HIT program in schizophrenia patients (105). In summary, aerobic exercise is capable of improving cardiorespiratory fitness and thereby reducing risk factors for CVD and associated mortality (**Table 4**).

TABLE 4 | Effects of high-intensity interval training on metabolic risk factors and symptoms of the disease in patients with schizophrenia.

Study	Participants	Training methods	Effects on cardio-respiratory fitness	Effects on metabolic partameters	Effects on symptoms
Heggelund et al. (107)	25 inpatients	8 weeks HIIT vs. playing computer games	VO_{2peak} ↑		No change in positive, negative symptoms or depression
Abdel-Baki et al. (105)	25 first-episode patients	14 week HIIT	VO_{2max} ↑ Resting heart rate ↓	Waist circumference ↓ Body weight - Body mass index	
Heggelund et al. (108)	20 patients with schizophrenia, 13 patients with depression, 20 healthy individuals	1 day HIIT			Positive affect in all participants Patients with depression and schizophrenia had reduced distress and state anxiety
Herbsleb et al. (109)	Case report in one patient with schizophrenia	6 weeks HIIT vs. CET	Resting heart rate ↓ Heart rate variability ↑ VO_{2peak} ↑	Body weight - Body mass index – Body fat percentage -	
Wu et al. (106)	20 patients with chronic schizophrenia	8 weeks HIIT	Resting heart rate ↓ Pulse pressure ↓ Mean arterial pressure ↑ Diastolic blood pressure ↑	Body weight ↓ Body mass index ↓	Negative symptoms improved. General psychopathology improved. Depression and anxiety improved

HIIT, high intensity interval training; CET, continuous endurance training; VO_2peak, VO_2max, highest oxygen intake.

THE IMPACT OF AEROBIC EXERCISE ON SCHIZOPHRENIA SYMPTOMS AND COGNITION

Reduction of symptoms may help to decrease suicidality in patients with schizophrenia (see above), and there is evidence that aerobic exercise interventions can improve schizophrenia symptoms and cognitive deficits. Published data from our group show that a structured endurance training programme is feasible in multi-episode schizophrenia patients (70). Previously, we demonstrated that 3 x 30 min aerobic exercise per week alleviated negative symptoms, significantly improved short-term memory and increased hippocampal volumes in patients with schizophrenia (88). Furthermore, when we added cognitive training to aerobic exercise from week 6 up to 3 months negative symptoms and working memory improved (90). Importantly, in 45% of the multi-episode schizophrenia patients who performed aerobic exercise the Global Assessment of Functioning (GAF) score improved by about 20% from baseline to month 3 (90); thus, this study showed that aerobic exercise as add-on therapy fosters patients' capacity to improve in multi-epsode schizophrenia. In this study, we did not replicate the increase of hippocampal volume after aerobic exercise, although we did detect increased volume of the left temporal cortex (117). In a randomized clinical trial, a 6-month structured aerobic exercise intervention reduced total symptoms of schizophrenia, positive symptoms, disorganization, excitement, emotional distress, symptoms of depression, and need of care significantly more than occupational therapy (79). In first-episode patients, an individualized exercise training program revealed improvement of negative and positive symptoms, psychosocial functioning and verbal short-term memory (93).

The beneficial effects of physical exercise on brain function and structure and cognitive performance have been repeatedly reported in healthy individuals [e.g., (118)]. Beyond this, a meta-analysis showed that in schizophrenia patients aerobic exercise improves negative, positive, and depressive symptoms and global functioning, as measured by the GAF (119). Another meta-analysis focusing on cognition demonstrated improved global cognition, working memory, social cognition, and attention after aerobic exercise in schizophrenia patients (120). Findings from the literature are contradictory, but a meta-analysis of exercise interventions in schizophrenia indicated that symptoms improve with a higher intensity of training (81). Symptom improvement was prominent in interventions of 90 min of moderate exercise per week (81). In healthy adults, elderly people, or individuals with obesity, HIIT improved executive function and verbal and short-term memory (95, 121). A meta-analysis in healthy normal-weight and obese individuals showed that HIIT training improved affective psychological responses (122). In a first study in a small group of patients with different diagnoses that included only some schizophrenia patients, 8 weeks of HIIT did not decrease psychopathological symptoms, but it did have positive effects on physical fitness and anxiety (107, 108). In 18 patients with schizophrenia, an 8-week HIIT program significantly improved negative symptoms, general psychopathology, depression, and anxiety (106) (**Table 4**).

CONCLUSION

In summary, add-on therapy of endurance training combined with psychosocial interventions or diet may improve symptoms of the metabolic syndrome in schizophrenia patients, thereby reducing the prevalence of CVD and mortality. It has been shown that aerobic exercise programs are feasible in populations with severe mental illness and are accepted by schizophrenia patients who have weight gain and reduced physical fitness. However, specific complicating characteristics of patients with schizophrenia in comparison to the healthy population include fatigue and sedation (e.g., due to antipsychotic treatment), symptoms of the disease, a high level of anxiety and depression, antipsychotic-induced weight gain, a lower level of education, little experience with sport, and a lack of motivation for physical activity in case of negative symptoms (70). To increase patients' motivation to adhere to training sessions, a sports scientist must provide supervision, which in turn increases the cost of otherwise cheap training methods, such as biking and walking. Nevertheless, aerobic exercise programs still have a good cost-benefit ratio when one considers the high socioeconomic costs of metabolic risk factors in these patients. To date, physical exercise has no known serious side effects or safety issues that might pose any risk to the patients. Aerobic exercise can significantly contribute to improving symptoms of the disease, including cognitive deficits and psychosocial functioning. In addition, it may have positive effects on the residual symptoms that are known to be treatment resistant even after long-term therapy with antipsychotics; however, treatment recommendations will be given when the optimal dose and duration of the intervention has been found in randomized clinical trials. The reversibility of structural alterations in the brain and improvement of symptoms suggest that aerobic exercise may induce a regenerative process in patients with schizophrenia (123). Finally, HIIT can be hypothesized to have greater potential than conventional, aerobic endurance training to improve cognitive deficits, overall symptoms, and metabolic parameters in schizophrenia patients. Future studies should investigate the effects of HIIT on neuroplastic changes in the brain. Furthermore, treatment recommendations should include aerobic exercise in multimodal therapy regimes. The German S3 guideline "Schizophrenia" (124) and the NICE guideline (125) recommend exercise programs for patients with schizophrenia and weight gain. However, positive effects of aerobic exercise may be limited to the training periods (90), and long-term improvement of metabolic risk factors may require continuation of aerobic training in certified sports clubs. Overall, further high quality clinical trials are needed before statements can be made about the optimal length and type of aerobic exercise programs for routine clinical care.

AUTHOR CONTRIBUTIONS

PF, BM, AS, and IM designed this manuscript. ST, DK, BR, AS, BM, IM, MR, AR, AH, ML, MvW, and PF managed the literature searches, interpreted the data and prepared the manuscript. All

authors contributed to and approved the final manuscript and reviewed it critically for important intellectual content.

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Implementation of a Quit Smoking Programme in Community Adult Mental Health Services–A Qualitative Study

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Little is known about the experiences of people with severe mental health difficulties in smoking cessation interventions. This study aimed to review the implementation of a smoking cessation programme across 16 community mental health day services. The aim was to establish the experience from both service user and facilitator perspectives and refine implementation for future groups. In-depth interviews were conducted with 20 service users and four focus groups held with 17 facilitators. Thematic analysis was used to analyse the data for emergent themes in relation to key enablers and barriers to implementation. Data from service users and facilitators revealed that implementation was enabled by an open and engaged recruitment approach; the resourcefulness of facilitators; programme materials and group-based format; combining the cessation programme with other and broader health initiatives; and participants' motivations, including health and money. Barriers included the structure of the service; the lack of a joined-up approach across the health services; literacy issues and the serial/logical process assumed by the programme. Barriers perceived as more specific to those with mental health difficulties included the use of smoking as a coping mechanism, lack of alternative activities/structure and lack of consistent determination. The tobacco free policy, implemented shortly before the programme, interestingly emerged as both a barrier and an enabler. In conclusion, although this group-based cessation programme in community mental health settings was well-received overall, a number of key barriers persist. A joined-up approach which addresses the culture of smoking in mental health settings, inconsistencies in smoking policies, and provides consistent cessation support, is needed. Care needs to be taken with the timing as overall it may not be helpful to introduce a new smoking cessation programme at the same time as a tobacco free policy.

Keywords: smoking, smoking cessation, mental illness, mental health, community, qualitative analysis, implementation, intervention

INTRODUCTION

The increased prevalence of smoking among those with mental health difficulties (MHDs) has been well-established (1–4), as has its impact in terms of tobacco-related morbidity (4–11) and mortality (12–14). Evidence indicates that cessation may be more difficult for those with mental health difficulties (4, 15, 16), but mental health has been shown to improve in those with and without psychiatric disorders post quitting (17). Smoking cessation programmes in community mental health settings meanwhile remain understudied (18, 19). The studies which have been conducted tend to focus on quantitative methods (18, 20–24), brief outcomes data (18, 22–26), and had small samples (<30) (20, 22, 25).

Studies taking a more in-depth approach often include qualitative data for facilitators only (27, 28), omitting service user views (27), or rely on surveys with no in-depth exploration of their experience included (28). Conversely, Rae et al. provided rich qualitative data of the experience of those with severe mental illness on cessation interventions, yet included no data detailing the experiences of facilitators (29). The only prior study to qualitatively evaluate a cessation intervention for those with MHDs including both service user and facilitator perspectives was limited by including only service users who requested treatment, a sample of just 3 facilitators and no implementation data (30).

The available evidence does suggest that people with MHDs want to quit smoking and would benefit from doing so (17, 31, 32), that community programmes are able to reach a high proportion of smokers, and when tailored can be effective for those with mental illness for quitting (18, 24), or reducing smoking (21). Qualitative data from a provider perspective have revealed that a tailored tobacco cessation was feasible and well-received (28). Beyond implementation studies, qualitative data in relation to experiences of cessation interventions among those with severe mental illness have suggested the importance of flexibility and choice, a variety of treatment options, facilitators who understand mental health problems and responsivity to the changing needs and preferences of individual service users (29, 30).

EVE, a programme within Ireland's Health Service Executive (HSE) provides a network of services for adults with MHDs. In 2016, the Quit Smoking Programme (QSP) was implemented in 16 of these centers, but the implementation was not evaluated. The current study explores the implementation of this quit smoking programme in the EVE community setting. It is conducted in line with Medical Research Council guidelines (33), and aimed to provide qualitative data, integrating the views and experiences of both service users and facilitators, in relation to this programme's implementation. This study therefore provides richer accounts of the experiences of both staff and service users than that reported in the previous literature, taking full account of the complex issues which can shape the process of implementation in real world mental health settings.

MATERIALS AND METHODS

This study adopted an inductive approach, employing flexible interview guides based on the literature and study context but not restricted to fit the domains of a given theory or framework (34).

Quit Smoking Programme (QSP)

The QSP cessation programme was designed by the HSE Health Promotion Service to provide an accessible resource which sets out a stage-by-stage process to support smokers in the general population in their decision to stop smoking and to sustain the attempt, but was not specifically designed for those with mental health difficulties. Its introduction in EVE services represented the first implementation of this programme within mental health settings and the current study therefore explores its implementation and enablers and barriers to same.

QSP facilitators received a folder detailing the 7-week group programme including questionnaires/forms for attendees to complete regarding their smoking habit, the cost of same, individual quitting plans and personal coping strategies. A carbon monoxide monitor was also provided for attendees to ascertain their current expired CO breath levels. The programme was facilitated by frontline staff who had undergone training in brief interventions for smoking cessation as well as in QSP specifically. Two service users were also trained in QSP and acted as co-facilitators. The programme was introduced alongside a new Tobacco Free Campus Policy.

This study was approved by the Tallaght Hospital/St. James's Hospital Joint Research Ethics Committee on 28th April 2016. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Procedures

Recruitment of service user participants was conducted through EVE staff, who once briefed were asked to recruit those who smoke or who had recently quit smoking. A purposive sampling strategy was employed with efforts made to include a range of service users across eligible centers, in terms of age, gender, service use (full-time/part-time) and level of engagement with QSP (35), with a final sample of 20 service users across 9 centers interviewed. Facilitators were recruited by the researcher and an administrative assistant, with efforts made to include all trained facilitators still with the service. Seventeen (of nineteen) facilitators, across 15 centers, participated in focus groups, including both service user co-facilitators.

Service users were asked about smoking; barriers to and enablers of abstinence; feelings on the tobacco free policy and their experience of QSP, with interviews lasting 15–50 min. Facilitators were asked to discuss the recently implemented tobacco free policy; smoking in relation to those with MHDs and health service approach to same; QSP in relation to their training, the resource itself and their facilitation experience as well as initial and ongoing barriers and enablers to starting and running the programme at their centers. In line with the inductive approach taken, guides were reviewed in light of the knowledge gained from the initial round of interviews with

minor adaptations made. Focus groups ranged in size from 2 to 6 members and lasted around an hour (49–82 min) with the late arrival of one facilitator to a group managed through an extension add-on interview.

Analysis

All interviews and focus groups were digitally recorded and transcribed verbatim with identifying data removed and pseudonyms assigned. Data was analyzed using thematic analysis (36) with service user and facilitator data coded separately first prior to integration to produce a coding framework representing key enablers and barriers. Following an extensive familiarization process involving several close readings of transcripts initial codes were generated. Coding of interview transcripts was facilitated using Nvivo10 due to the large number of transcripts while focus group transcripts were coded manually. Once all data had been coded the researcher searched for major themes among these codes and developed an initial framework of themes and sub-themes representing key barriers and enablers. This framework was then discussed with a secondary coder (JS) before AB went on to review and refine these themes to ensure firstly each theme was based on coded data which formed a coherent pattern including exploration of deviant cases where present. Also, secondly and more broadly to ensure the key emergent themes were valid in their reflection of the dataset as a whole (36). A subset of transcripts were read by an additional coder (DR) to confirm that transcripts were coded consistently and that the key findings of the study were supported.

RESULTS

Enablers

A number of enablers for, and barriers to, the successful implementation of the smoking cessation programme were identified from the data (see **Table 1**).

Tobacco Free Campus Policy

The recently introduced policy emerged as an enabler, leading members to often find smoking more awkward and as a result for some, to find themselves smoking less:

> "It has been a little bit awkward so they've cut down…when the weather is bad in particular you'd need to really want your cigarette to go out." [Facilitator]

The policy also prompted replacements for smoking breaks in some centers with fruit and tea breaks offered to smokers or all members and thus serving as a distraction for smokers.

Resourcefulness of Programme Facilitators

The resourcefulness of staff facilitating QSP also emerged as an important enabler for implementation. This was revealed in extra-curricular efforts including the provision of additional individual support where required;

> "but I know the person who gave up was struggling hugely when he gave up so I linked in with him every day… just to keep the momentum going and so far he's at around six weeks now off." [Facilitator]

Facilitators were resourceful in dealing with missed weeks and service users progressing through the programme at different paces. This included meeting more often and building individual work into group sessions to deal with some service users catching up on missed weeks;

> "So we kinda go through it and then whether someone's on week 2 or week 3 I'd give them maybe ten minutes and if you're week 2 you get the week 2 little pack and if you're the week 3 and then you do your own little personal bit of writing." [Facilitator]

Some facilitators used the national quit line and quit website as an additional resource, used technology to support and empower attendees with low literacy, or had members who are former smokers come in to share advice;

> "I was just asked and I said I'll just go along…I thought maybe I could give back something" [Service user]

Novel approaches included running a stress management group and linking in with local services:

> "In between, rather than kind of doing, you know the same thing all over again the em, just you know the way I did one week about em, you know managing stress and whatever, I just did a relaxation group like." [Facilitator]
>
> "We got her to give talks and to work with the group as well you know to come in somebody different, we linked up with the local doctors for prescriptions and things like that we linked up with the local chemist as well to provide you know the patches and the different things and the cost and the consequences, so we kinda went out into community with it….yeah and that helped" [Facilitator]

An Active, Open and Engaged Recruitment Approach

A more active approach to recruitment seems to have helped get the programme up and running at centers. Facilitators mentioned the need to "sell" the programme a little and to encourage participation:

> "Having an initial chat with somebody what you don't want is to just put up a list and say you know 'Stick your name down there if you wanna do a quit smoking programme alright'...I think this needs to be sold for want of a better word quite rigorously…we are pushing it a little bit and I think if we're not pushing a little bit, we're not doing our job" [Facilitator]

Several service users discussed attending due to curiosity, or just to hear the advice on offer:

> "I thought, you know, it's not that I thought about stopping but, em, I thought it's
>
> good to sit down and listen to it and who knows if it gets me down on cigarettes,
>
> that's, why not, you know." [Service user]

TABLE 1 | Enablers for, and barriers to, the successful implementation of the smoking cessation programme.

Enablers for successful implementation	Barriers to successful implementation
Tobacco free campus policy	Implementation of tobacco free campus policy
Resourcefulness of programme facilitators	Structure of the service (scheduling, attendance and gaps in availability) and serial nature of programme
An active, open and engaged recruitment approach	Lack of a joined-up approach
Combining with other health initiatives	Literacy issues for some
Programme materials and format	Mental health difficulties
Health and money as motivators	

Opening the programme up to those not ready to quit led to greater uptake. And importantly appeared to spur on later quit attempts and personal goals, even if these were an intention to cut-down, but not quit:

> "We'd a couple of people who were still smoking coming to the group and no intention of giving up but then, it's like overnight something happens and they come in 'oh yeah I stopped last week.'" [Facilitator]

In general however, it seemed that while opening up the programme to those not necessarily ready to quit can work, it is best if these attendees have formed meaningful personal goals in advance or are at least somewhat self-motivated to attend. Forced or disengaged attendance may lead to frustration or affect overall atmosphere in the group:

> "I'd one who was just like really forcibly letting it be known that the only reason they were there was because people were told they had to be there whatever and …when you're talking about the health benefits and the whatever like and she'd say, '[Facilitator Name] I'm just not giving up there's no point in talking to me just I'm only here because people told me so just I don't want to hear any more of it' you know" [Facilitator]

> "They asked me to go on it.…I'm sitting in on one.… you don't, eh I don't really, you know, spend much time thinking about it" [Service user]

Combing With Other and Broader Health Initiatives

Facilitators also mentioned combining smoking cessation with other and broader mental and physical health initiatives and some seemed to feel this could be an effective approach:

> "Part of the whole conversation with the Tobacco Free Campus as well as the quit smoking programme is to say you know just to get that message out there consistently to everybody to say we are a HSE location and the HSE are part of the Healthy Ireland programme [a national framework for action to improve the health and well-being of the population of Ireland]…you know many of our centers now are doing healthy eating more often, they're doing mindfulness and quit smoking is just one of those things" [Facilitator]

In some centers service users themselves seemed to naturally start making goals in other areas and link cutting down on smoking with healthier eating or exercise goals:

> "[Staff member] in our center is doing the operation transformation with everybody and em some of the people have linked in smoking with that everybody's setting their goals from one week to the next or whatever could be to go for a walk or eat less sugar or whatever but some of them actually putting in to smoke less cigarettes." [Facilitator]

Programme Materials and Format

Easy to use, flows, colorful, good information, enjoyable

Facilitators found the pack helpful, with reports that it was easy to use, colorful, flowed well, had good information and was enjoyable:

> "What I liked about the document itself…it's you know if I put that down today and I went back and I read this in two months' time, you'd get into it very, very quickly and that's what is, it has to have a nice flow about it" [Facilitator]

Among service users, information and knowledge in relation to the effects of smoking; how to quit; and their own habit emerged as an important aspect of the programme. This knowledge was gained through leaflets and illustrations, teaching and filling in their own information:

> "There was very good knowledge. I mean it was about the carbon monoxide, and about your breathing and about the habit and eh there was leaflets about if you give up smoking, em, when you get the craving for a cigarette, how do you distract yourself from doing that, from having a cigarette, you know, do you listen to music, or have a meal or go for a walk, or bring the dog for a walk, or you know…I thought it was a good idea. Yeah it was very good knowing that. It was very good being taught that." [Service user]

Useful tools: questionnaires and carbon monoxide monitoring

Attendees and Facilitators referred specifically to the **questionnaires** that attendees filled in and their usefulness in promoting reflection and revealing habits to the attendee and facilitators;

> "There's questionnaires and there's little leaflets you can fill in and then it really points you to how much you smoke and why you smoke, and I think it's really good to understand why you smoke, you know" [Service user]

and also in highlighting the actual cost of their habit:

> "The part where you see how much you spend, that was useful, it was a shock to a lot of people how much they actually spent on cigarettes" [Facilitator]

Carbon monoxide monitoring in particular, seemed to stand out for service users;

> "That really is a wake-up call when you see your levels of nicotine or tar or whatever, em, I find that that's a good help. Then you can see well, you know, this is what you're doing to your lungs or to your body" [Service user]

It was also noted by several facilitators to be particularly useful in raising awareness and reinforcing quit attempts:

> "The carbon monoxide, they all loved that, that was a real buzz thing 'cause it was something real tangible they could actually really see, ok this is what my smoking is doing. . . there was a real sense of buzz and a few of them really were like, ok knuckling down, after seeing that." [Facilitator]

There was also however some indication that the carbon monoxide monitor vindicated the e-cigarette for people:

> "You get your carbon monoxide levels tested, and mine were the same as a non-smoker.. . . which I felt vindicated the electric cigarette" [Service user]

Doing it as a group–A sense of togetherness

Finally, the communal aspect also emerged as helpful for several attendees;

> "It was good to have a group of people that were going through the same thing as yourself, you know." [Service user]

while facilitators also noted it to be an advantage in attracting attendees, as well as during the programme:

> "I love the class I love the interactions in it." [Facilitator]

Health and Money as Motivators for Participants

Physical health appeared to be the main motivation for quitting smoking among service users in general, and an important motivation for joining the programme;

> "You know the physical health is suffering, you know, because em I don't have any breath, and I get out of breath. I get very tired, I get very tired and I get breathless very quickly and very easily you know...that's what's motivating me to go on the programme, and try and see if I can do something about it." [Service user]
>
> "Health is the big one, health is the biggest motivator, even over the financial one" [Facilitator]

Overall while health was the primary motivator, money also emerged, but was usually secondary;

> "and then definitely financial it adds to it as in somebody has more money then to go and treat themselves or to do something nice or to put it away or whatever." [Facilitator]
>
> "It's bad for your health first of all and secondly it's, it's money that I could use somewhere else." [Service user]

though notably for some, the financial aspect was in fact primary:

> "Eh money (Laughs), quit smoking have more money in my wallet. I wasn't too concerned with my health, eh but now I am so" [Service user]

Barriers

Implementation of Tobacco Free Campus Policy

Ongoing facilitation of smoking

Evidence of differential tobacco free campus policy implementation across settings pointed toward the ongoing facilitation of smoking at some centers. Smoking location did not appear to have been affected at all in one center, in another a service user described the erection of a smoking shelter in a new area, while at another there was the nomination of an alternative sheltered smoking spot for wet days.

The culture of the center also seemed to impact on the Tobacco Free Campus Policy. At Center Q the culture meant that the policy involved only a change in location and there were no limits to when service users could smoke;

> "People leave our gates, walk across the road and there's a big congregation of people there, em almost constantly. . . there's a lot of people who aren't engaged you know and em, they just come in and out constantly you know and that's the way the center was historically, like it's very kind of family orientated environment very easy going and we don't tend to kind of do parent child stuff." [Facilitator]

The ongoing facilitation of smoking at some centers, which in some cases was due to having a shared campus, was, it seems, in some casesa barrier to service users trying to cut down or quit smoking.

Associated forced/'herded' attendance at QSP

At Center F, the ongoing facilitation of smoking was more apparent as Tobacco Free Campus Policy was not implemented due to feasibility issues relating to location and traffic. Instead, a derogation was granted, with the trade-off that attendance at QSP was compulsory for all smokers:

> "Well there was a derogation in our center, em it was an issue, going out onto the road would be dangerous like with that but it's also very far away but em, we'd a derogation that we could still use the smoking shelter em, if on the condition that everybody did the programme." [Facilitator]

While attendance was not compulsory at any other center, others also felt that the timing in relation to QSP following the policy may have had a negative effect on morale:

> "When the ban came in it was like the two were at the one go you're trying to force me to stop smoking and you're trying to make me do this course to get me off. . . yeah it was kinda just because the two of them did happen at the same time . . . just gave it a negative slant." [Facilitator]

TABLE 2 | Summary of barriers related to mental health difficulties with sample quotes from service users and facilitators.

MHD barrier	Sample quote
Perceived association between MHDs and smoking	"There was eight of us in the family, and I'm the only smoker and I put it down to my anxiety" [Service user]
	"When I became a teenager I said to myself I'm not going to ever smoke, and I'm not, I want to be fit and keep myself fit and healthy, you know, and em, it didn't happen that way, with the illness [schizophrenia] I had, it just didn't materialize like that." [Service user]
	"There's no doubt it is, it is far more difficult for them to give it up." [Facilitator]
Coping mechanism	"It's a safety net, isn't it yeah" [Facilitator]
	"Like the cigarettes are just such a big crutch" [Facilitator]
	"It helps me calm down…it helps, em, I'd have a cigarette when I'm stressed or anxious, and I'd have a cigarette and I'd feel grand then for a long, for a few hours...it makes me feel better…it helps me relax. It helps me to, you know, get my bearings sometimes." [Service user]
Lacking self-belief/ self-esteem	"And some of them again when they say I don't want to give up or I'm happy smoking they might even be saying, do you know what I'd love to give up, but I'm just not able to, you know I'm not able to do that." [Facilitator]
Lack of consistent determination/willpower	"It's not having the willpower to stop doing something that's very bad for you…if you have a mental health problem it's harder to give up smoking because I just haven't got the mind, I haven't got the willpower and I'm not able to make a decision to say I'm going to quit, and then just quit. I can't, I find that difficult to do." [Service user]
Smoking among peers and past culture	"Just about everybody I know in the psychiatric services, service users, people with mental health, people with mental illness, they all smoke." [Service user]
	"Here in the clubhouse I have contact with smokers, and we all go together for our smoke, if we can, especially the women, you know, who smoke and they get it together. That's in a way nice. It's chatty you know. Yeah." [Service user]
Lifestyle: lack of structure/alternative activities	"A lot of it was to do with like boredom" [Service user]
	"They actually said it to me…yeah when I'm in the flat on my own at the weekends, that's when I tend to smoke a lot." [Facilitator]
MHDs as an excuse rather than an actual barrier?	"Em I think depending on the groups sometimes the ones with the mental health difficulties will use it as a tool to not move forward and they'll kind it use it as a as you know, an excuse almost" [Facilitator]
Timing	"What he's going through at the minute, there's no way that he's ready or there's no way he wants to yet but that's not saying down the line" [Facilitator]

Structure of Service (Scheduling, Attendance, Gaps in Availability) and Serial Process Assumed

Scheduling

Scheduling barriers emerged around finding the right start date and day for the programme as service users do not all attend 5 days a week:

> "There's people attending 3 days, and there's people attending 2 days, and there's people attending 4 days and whatever and to try and find the spot where you were trying to get as many like, I changed the timetable recently…there was only 3 people the last week…I'll have to look at the timetable again but it's very hard." [Facilitator]

Facilitators also commented on the clubhouse structure (which permits flexible attendance) and several felt that this in particular meant it was difficult to know when to start a programme, as attendance can be irregular in general.

Contractual obligations

Contractual obligations also meant smoking cessation groups had to be run in the afternoon when attendance is lower. In general smoking cessation was less of a priority meaning that it was also the "first thing that will go":

> "That was the biggest thing for ourselves, it was just em, although it's part of policy and now the actual quitting smoking, but facilitating it is the first thing that will, I'll be honest in our center, if something's to go in the timetable, it'll be the first thing that will go." [Facilitator]

Staff sickness, leave or moves leading to gaps in availability

Staff shortages, sickness and other leave were often the reasons something had "to go" in the timetable and facilitators discussed how sickness or leave often meant the programme simply did not happen in their absence. This was also observed by service users;

> "There was a few stops in it. One of the, the person that was giving it mightn't be in that day or on holidays or sick or something." [Service user]

Serial/logical process

Some facilitators felt the 7-week programme assumed a very swift, logical and serial process that was perhaps unrealistic. In reality, service users were not always ready to quit, or even to set a quit date on the designated week:

> "Yeah, we didn't get past week 3. I would say yeah no we didn't em, again so we get, so we started first we had a good first week if you like, and the second week was fine and then the third week we'd no-one setting dates" [Facilitator]
>
> "They want you to stop after seven weeks. I wouldn't be able to" [Service user]

Facilitators were sometimes left feeling stuck and unsure what to do. There was a seeming lack of clarity on how to move forward when these issues arose in this real world setting:

"It would be helpful within this [pack] or whether EVE kind of have an addendum to this saying what to do if you if this scenario happens, you get stuck at week 3." [Facilitator]

While some felt they had to stop, other facilitators made the decision to keep going. Some centers also made efforts to tailor the programme so that it was at individuals' own pace, and this together with decisions by some service users to re-attend a second or even third time, illustrates the longer more circular process quitting could be for some service users:

Inconsistencies and the Need for a Joined-Up Approach

Lack of healthcare professional (HCP) advice

Smoking cessation did not emerge as strongly addressed by healthcare professionals. Several service users and staff reported a complete lack of smoking cessation advice from HCPs:

Facilitator 1: I did specifically ask one of my keyworkers about that, he'd been to his nurse for his injection and ah…I just said aw did your nurse ever mention your smoking or does your psychiatrist you know, he only sees him every 2 or 3 months now, no no it's never mentioned…

Facilitator 2: They never mention it

This was also supported by several service user interviews where service users commented in relation to HCP advice that "It never happened." The exception to this was two service users who reported in their interviews that their GP had continually raised smoking as a health issue.

Inadequate HCP Advice

Some of the interactions around smoking that did occur were revealed to be ill-informed in relation to inaccurate advice as recounted by one facilitator;

"Some were told by their doctors and I know this is wrong information that they couldn't use any of the smoking, giving up smoking aids because it would affect their medication." [Facilitator]

or ill-advised approaches in terms of a seeming focus on restriction of access to cigarettes rather than offer of person-centered support to quit:

"Actually one of the last times I was in [specialized neuro-psychiatric hospital], just to be noted, they said we're going to have to take your e-cigarette off you, I said why? We're putting everyone on the patches" [Service user]

Several service users reported bringing up smoking and Nicotine Replacement Therapy (NRT) themselves;

"Yeah, no he [GP] didn't suggest it [patches]. No I did" [Service user]

while many HCPs seemed to avoid actual recommendations of quitting. These ranged from vague almost neutral references to smoking, to advice to cut-down rather than quit, to advice that they did not need to quit;

"I always said I'd give them up if the doctor told me to...But he never did. He'd say, 'You're still smoking'" [Service user]

"I go to a psychiatrist and I told him that I'm trying to give up the cigarettes, and he told me to cut down. [Service user]

"Yeah my doctor discussed it one day and he asked me and I said, I have a few, andhe said that's no harm, he said…He said don't mind, have a few if you want to yeah."[Service user]

Lack of a joined-up approach to cessation support

There were calls for a more joined-up approach;

"If everybody does a little bit and they're all going in the same direction, they don't all have to be singing on the same page, but if everybody's going the same direction, you're planting seeds as you go along." [Facilitator]

and the need for smoking cessation support to be brought into hostels and hospitals:

"Help with quitting. Not just shut down completely like. I mean just introducing as much as they can into hospitals and there might be like half the patients might want to quit, half of them might not want to and at least give people a chance, you know." [Service user]

Facilitator 2 used the example of the person-centered plan, which is made for each service user at meetings including doctors, nurses and hostel staff and queried why smoking could not be addressed here when weight already is;

Facilitator 2:When you're doing a person-centered plan for someone and the hostel staff are there, the doctor's there, or the CPN is there or whoever, that the health, if a person had weight issues that would be to the fore at every single meeting…but if we do that for weight, well why not do that for smoking [agreement], it's the same thing d'you know so you should be, it should be, like I think smoking and if if it, it is affecting a person's health, you can't say if it is affecting the health, it should be in that PCP.

while Facilitator 1 noted that this joined-up approach should be at policy level as given under-resourcing and lack of staff services are unlikely to "opt in." The lack of a current joined-up approach also meant that for service users due to leave EVE the availability of continued smoking cessation support is a gray area, an uncertainty which emerged in several service user interviews.

Exemptions and inconsistencies in relation to tobacco free policies

In addition to a frequent lack of advice and joined-up cessation support, there were also inconsistencies in relation to smoking policies in hostels and psychiatric hospital settings;

"I was in a smoke free hospital…but [the] psychiatric unit had their own yard…there's a smoking shed" [Service user]

and the maintenance of smoking as a social activity in these settings seems to lead to service users increasing consumption and even relapsing to smoking at times:

> "If she went out for a cigarette she'd have someone to talk to outside, so she found when she came out of [acute mental health unit] and into here, she was after increasing about 20 on top of what she was smoking." [Facilitator]
>
> "I was meeting loads of new people and I felt oh God I can't, I need something to take the edge off, so I started smoking again, because everyone was out there talking and chatting and I was saying aw me sitting in here. I want to be out with them, you know…yeah, I went back on them." [Service user]

Facilitators need to be linked

Within EVE itself, the lack of a linked-up approach to QSP was a barrier, as an opportunity for facilitators to collaborate and share knowledge was lacking.

> "Maybe the organization would be happy enough to, to okay us to meet up, once or twice a year to kind of get together and share experiences and share feedback…just give each other a call and the knowledge is there (Facilitator).

Literacy Issues for Some Participants and Need to Add Technology Component in General

Participant literacy was an issue for some facilitators and could cause difficulties with engagement and pacing, while Facilitator 8 found the questionnaires involved and group format meant she felt she was effectively revealing any literacy issues:

> "One of my problems as well…I'd two people that couldn't read, write or spell and that was very difficult now I have to say, because I was more or less filling it out for them and I don't know if I felt uncomfortable, because you know it was sort of em, you were letting the rest of the group know that they couldn't read or spell and that you know, I just felt it was awkward." [Facilitator]

Technology could help

There was suggestion from several that additional use of technology could not only help with literacy issues but also overcome issues like missing questionnaires. This might lead to enhanced ownership with service users even able to log in at home. In relation to centers, the point was made that many of the resources in terms of computers and equipment are already in place.

MHDs

An explicit association between MHDs and smoking emerged among service users, in relation to both their own and others' smoking:

It was reported as a specific reason for starting;

> "I became unwell [developed psychosis and depression], em, and I went on medication and I started smoking regularly then every day." [Service user]

for relapsing; and at times described as the reason for becoming a smoker despite wishes not to be, seemingly taking the choice out of their hands somewhat.

Although a few facilitators felt that quitting smoking was no different for those with MHDs;

> "I just think they're the same as everybody else, I don't think because of the mental health difficulties it's any harder to, to quit." [Facilitator]

many felt that it can indeed be more difficult for this group.

A number of factors were felt to contribute to this:

Coping mechanism

Smoking emerged strongly as a coping mechanism from the perspectives of both facilitators and service users themselves.

Coping mechanism for stress

Its role as a coping mechanism for stress was evidenced when initiation, increases and relapses were described in the context of acute stressors in the past. These acute stressors included health scares, family members falling ill and bereavements:

> "The first time ever, because my father actually gave me bad news at the time. My mother was in hospital and she was in a bad way in hospital." [Service user 1 on starting smoking]

In addition to acute stressors, smoking was also used to cope with the everyday stresses of life:

> "What doesn't help me quit smoking, em, day-to-day living, you know, being caught in traffic jams, or you know, being short changed in a shop or dogs barking at me, or if it's gale-force winds and pouring rain, and I'm after forgetting my umbrella, and you know, things like that. Just day-to-day living, you know, that would make it difficult to stop smoking" [Service user]

Coping mechanism for MHDs

Its role as a coping mechanism also emerged specifically in relation to MHDs such as anxiety;

> "If I'm anyway anxious I, I tend to unfortunately, and I used to be real confident and I'm losing my confidence a bit again, em, but if I'm worried about anything, (whispers) oh God I need a cigarette, and then I'd be grand for a while, you know" [Service user]

and schizophrenia or psychosis;

> "[smoke] to keep me calm…well [pause] there's mood changes. People with schizophrenia have mood, mood changes, and em, eh a cigarette calms it down a little bit. You'd, you'd enjoy because it just calms you down, you know." [Service user]
>
> "I've psychosis…it [smoking] makes me feel easy, and em it kind of [pause] it kind of relaxes me that bit" [Service user]

with a dose response relationship again seemingly emerging for some;

"She said like, when I'm very unwell I smoke extra" [Facilitator]

"I probably would have become more anxious in the last few years...so I think that would be the cause of [becoming a heavier smoker]" [Service user]

Effectiveness as a coping mechanism

While many service users strongly believed in smoking's effectiveness in relieving and calming stress and symptoms related to MHDs;

"They help to relieve stress" [Service user]

some facilitators and service users expressed doubts regarding its effectiveness as a coping mechanism;

"You know it doesn't help, it's never, there's no actual evidence to say it supports em, your stress levels" [Facilitator]

"I don't think it makes a difference" [Service user 11 (who here contradicted her earlier report that smoking helps with her depression)]

and thought rather than help it could be an added source of stress or anxiety;

"I don't believe that em, smoking, even having smoked, I think you can delude yourself that it does em, when you're smoking, I don't believe that smoking helps you with stress…if I'd no cigarettes…then you have a stress on top of the stress" [Facilitator]

"Of more recent times, the smoking causes my anxiety...because it makes me think I'm going to get cancer, or I'm going to take a heart attack, or I'm going to take a brain hemorrhage or something."[Service user]

and overall, even if effective, the trade off in terms of physical health perhaps outweighs any benefit:

"I just think it's a general mind-set change of saying, you know, the easy thing to do is say 'Look carry on smoking because otherwise you're going to be mentally distressed' or whatever it is and you know there might be an element of truth to that, but longer term you're going to, you know one in two of them are going to die" [Facilitator]

"They help to relieve stress, you know…yeah, de-stress but I found you…I'd say that ah overall you know, that they probably weren't, they're probably having a bit of a negative effect on me...my overall health would have, would have changed…you know, I wasn't as physically active as I was a couple of years ago you know. So, I suppose, the smoking doesn't help that, you know. It could help to, to solve stress a bit, you know, but physically it probably isn't such a great stress helper." [Service user]

Perceived as "Need"

In a couple of cases, the notion that smoking is a coping mechanism or crutch for this group went a step further and it was labeled a "need."

"I need it for my mental health" [Service user]

This occurred at service user and family levels and actually led to a relapse to smoking for Service user 2:

"My mother knew I was bored after my dad died, and she knew I, she thought I needed something so she bought me cigarettes" [Service user]

Lacking self-belief/self-esteem

Another barrier which emerged among both facilitators and service users, related to a lack of self-esteem or self-belief among service users. Several facilitators described this lack of self-belief;

"Some people's self-esteem and their belief in themselves wouldn't be at a high point, so you'd be trying to encourage and that they can you know, so that that might be a barrier with some of the mental health." [Facilitator]

with a lack of perceived ability also emerging in some service user interviews:

"I knew deep down that I wouldn't be able to…will I try? Will I be able to try?" [Service user]

For others a lack of self-belief did not emerge and two service users were in fact particularly clear on their ability to quit, but simply not ready at the moment. In both cases, this self-belief seemed to be the result of previous quitting.

Lack of consistent determination/willpower

There was some suggestion from facilitators and service users that those with MHDs experience a barrier to quitting in the form of an associated lack of determination or consistent motivation:

"You have to be motivated and motivation is always a kind of a critical factor as well and while the, person may be motivated one week, you know 2 or 3 weeks in they may not feel so good and then that's their downfall then that it falls, it falls you know, it doesn't necessarily work for them" [Facilitator]

While not an issue for Service user 12, he again seemed to associate mental illness more generally with decreased strength or determination:

"I am a very strong minded person even though I have mental illness and all...I'm very strong minded in the sense if I say I'm starting Monday, no smoking. I will start Monday and there'll be no smoking." [Service user]

In general, he seemed to need the assistance of the programme less with a clear focus on his own plan and preparation. This contrasted with Service users 18 and 14 whose reports suggested they wanted or needed more external pressure to quit or set a date:

"People like that, facilitators need to give me a good boot in the backside, and say, "[Name] get in there and buy them patches." [Service user]

"I would have like that they pinpoint a bit more out on stop the smoking. It's to stop smoking and they don't do that either

there, you know, they are very careful with not to say that [you have to stop smoking], you know. . . and I find that amazing that they don't, even a cessation group, they don't do that either, you know. I think I need that. I think I need that somebody says to me you stop smoking now." [Service user]

Service user 14 did go on to state however, that she would prefer to be given a quit date in the future rather than told to stop straight away:

"I'd rather have a date in the future so that I can get used to it, you know" [Service user]

Smoking among peers and past culture

The prevalence of smoking among people with MHDs may also represent a barrier given the culture of smoking this creates among peers.

There was also some evidence of this increased prevalence and a culture of smoking at EVE centers:

"You get shanghaied into going out for a cigarette. . . ah no there's, there's one or two that smoke here and if they go outside, they'll give you a cigarette and you have one." [Service user]

Centers also experience issues such as a culture of money lending and borrowing to buy cigarettes;

"One other thing, em, came up there, just thinking em, people who smoke like that financially they don't have as much money, so that, there was a knock on effect so they wouldn't have as much money and like [Facilitator 2] said they'd do anything to get a cigarette so borrowing became an issue. . . and as a result there's problems then people are not giving back the monies so there was huge knock on effects from that." [Facilitator]

as well as trading of counterfeit cigarettes;

"and then the dodgy ones as well, a guy going in [to town] buying them, and I've seen it in centers, coming in on Monday with like 200 cigarettes and doling them out." [Facilitator]

Other reports however contradicted this and overall there was a sense the culture of smoking was waning:

"Smoking has kind of died down here." [Service user]

"I think it was a lot higher when I first started. This is even well before smoking cessation and now it's, I'd say we're twenty, twenty percent maybe smoking twenty-five maybe." [Facilitator]

Facilitators commented on the lower prevalence among younger service users;

"There was a culture of go and have a cigarette I think going back but that's definitely not the case with the younger people coming in. I don't think we have as many smokers definitely with the younger em variety." [Facilitator]

while for some the past culture of smoking also seemed to serve as an extra motivator to provide support now:

"We have a responsibility to address this I believe, because our services have condoned this for so long and the medical community probably exacerbated it over the years, made it worse so we have a responsibility to kind of, maybe be a little more of campaigners about it." [Facilitator]

Lifestyle: lack of structure/activities

Inactivity, lack of structure and time spent alone emerged as particular barriers for service users from both facilitators and service user perspectives. Service users discussed inactivity, boredom, time alone and filling a vacuum as prompts to smoke:

Interviewer: And if I was to ask you why did you smoke, what would you say?

Service user 7: Em, I'd say the vacuum after I got sick, and being off work, having that time on my hands.

This was mirrored in the accounts of several facilitators, who also noted a lack of structure and time alone as key barriers for individuals with MHDs.

Hobbies, work, and being otherwise busy often emerged as distractions;

"There are places I smoke less. Yeah. When I'm doing something I get it done, you know" [Service user]

Service user 15 referred to the years when he stopped smoking as partially down to being busy with work;

"Well I was working away like and there was no point to be smoking while you were working, you know, I'd be stopping every 5 min if I had of been smoking at the time, so it helped me as regards work as well." [Service user]

while Service user 12 described how his hobby serves as a powerful distraction;

"I smoke an awful lot less when I'm gigging" [Service user]

There were calls from service users and facilitators for more activities;

"I think someone mentioned it, just in terms of structure I think structure is, if a person's day can be filled and it doesn't matter whether it's you know within the center, outside the center, in terms of leisure activities and social activities, that's obviously going to help in in a big way" [Facilitator]

and some felt there was a need in particular for specific replacement activities though concrete suggestions were limited:

"What to do when they do give up cigarettes. I found like, I started doing myself knitting and reading more and doing things like that, I think something like that could be put into the book, what to do, [murmuring] ideas and suggestions. . . I feel what we need to do is encourage people to change their lifestyle, I think that would help an awful lot." [Facilitator and Former Smoker]

"Something to do with their hands, you know, knitting or sewing or something like that. . . but my, my hands shake so it's very difficult for me to, to do things." [Service user]

MHDs as an excuse rather than an actual barrier

There was also some suggestion from facilitators that in some cases, MHDs can act as an excuse at the individual level rather than a barrier in terms of actual ability to quit smoking. This is perhaps unsurprising given the past culture discussed above.

> "I think there can be some people who might use their, their mental health as an excuse… they might be in a system where they might have a nurse or a key worker who is facilitating and done a lot for them and now they're signed up to a smoking cessation programme but now it's them that has to do it, nobody else is going to quit for them." [Facilitator]

Facilitator 7 addressed this by highlighting the equality between service users and staff;

> "I've used me as an example in my groups 'So you're different to me because you have a MHD? Nah you're no different to me you're able to do loads of things I can't do… so if you I think if we hit it at that level and then all of a sudden they're looking at you and they start laughing, they know straight away, they're like alright I'm not gonna use that." [Facilitator]

which is also central to the structure and ethos of the service more generally.

Timing

While many felt MHDs can indeed make quitting harder facilitators felt timing can be a really important factor as a barrier to attending the programme at all;

> "The interesting thing about the first session was that the person, it was Christmas time it was the wrong time and they found by, I think we got to week 5, they found that week 5 they had to stop because their cigarette smoking had increased! Because of Christmas and stresses and all that kinda thing and all so" [Facilitator]

but also to actual quitting in those that did attend:

> "I did the course 3 times in [name of location] and she sat on each one of them, but she had something going on in her life that she just wasn't ready and...it was a bit her mental health was a bit unstable at the time, yeah and she had family issues she had to get sorted out and she just felt she needed that cigarette." [Facilitator].

Table 2 summarizes the sub-theme MHD barriers discussed in this paper providing further sample quotes.

DISCUSSION

This study aimed to identify key enablers of, and barriers to, the implementation of a quit smoking programme in community adult mental health services. By exploring an ongoing group smoking cessation intervention in a real world mental health setting, from both facilitator and service user experiences of its implementation, this study filled an important gap in knowledge.

The emergence of health and money as important motivators is consistent with previous research in relation to the enablers of smoking cessation among individuals with severe mental illness (37, 38), and is similar to other populations (39–41). The use of carbon monoxide monitors makes use of biofeedback, which is arguably one of the strongest behavior change techniques (42), and appeared to be a powerful, and appropriate, aspect of this programme also, spurring cessation efforts as well as reinforcing those already quit. Interestingly however the monitor also appeared to vindicate the use of e-cigarettes in service user's eyes, presumably an unintended consequence given the HSE have not endorsed e-cigarettes as a cessation aid (43).

The emergence of facilitator resourcefulness and tailoring of the programme to individuals' needs as an enabler is consistent with previous studies among mental health patients. These studies found flexible, personalized and responsive approaches to be helpful with benefit emphasized by both facilitators and service users (30, 44). Notably, this flexible, individualized approach is also consistent with the person-centered philosophy underpinning delivery of EVE programmes in general. An active, open and engaged recruitment approach seemed to work best as opening up to those not ready to quit, but interested in attending, sometimes led to unexpected wins by spurring on later quit attempts. Non-voluntary attendance without personal goals however appeared to lead to disengagement, frustration for both service users and facilitators and potentially affected overall group atmosphere.

The recently introduced Tobacco Free Campus Policy emerged as both an enabler and barrier to programme implementation and participant quitting. The identification of the partial nature of the ban and its varying implementation as barriers supports other studies which show partial smoke-free policies are less successful than total smoke-free policies. A partial ban creates additional problems and has a limited impact on the staff and service user culture of smoking (45). Moreover, the timing of implementing cessation support, following or alongside the introduction of a smoke-free campus policy, may have negatively affected morale.

Conflicting priorities and a lack of prioritizing smoking cessation support as part of staff workload has previously emerged as a barrier among HCPs in Ireland and internationally (46–48). As well as in relation to mental health services more specifically especially in the context of outpatient settings (38).

The emergence of the current lack of a joined-up approach as a barrier producing inconsistencies in relation to lack of cessation supports and also in relation to exemptions from tobacco free policies echoed the conclusions of a recent review of qualitative studies which called for cessation to be addressed at all levels (systemic, health provider, and individual) among people with severe mental illness (37). Although there is a lack of evidence relating to the effectiveness of advice for those with serious or severe mental illness (49, 50), the motivational impact of HCP advice, where it did occur, was important. This is not surprising, given prompts from health professionals have been shown to be an important driver in quit attempts among smokers in general (51–53).

In line with previous research, barriers relating to MHDs including smoking as a coping mechanism (44, 54–57); lack of self-belief (29, 54, 56); lack of consistent motivation (30, 38, 44);

prevalence of smoking among peers and the culture within mental health settings (37, 44, 58); and lack of structure or alternative activities (59–61), also emerged from the data. Timing was also perceived to be an important factor by facilitators and some service users felt an inpatient stay was the wrong time for cessation. Evidence is still however lacking in this area due to the ongoing tendency for smoking cessation studies to recruit from psychiatrically stable rather than acutely unwell populations (50, 62).

Implications

There was some evidence in the current study, of knowledge among service users and facilitators of the ineffectiveness of smoking as a coping mechanism and the ability of those with MHDs to quit. Overall, however, findings suggest that integrating education on the proven ability of people with MHDs to quit smoking, and the benefits of quitting for mental health, into facilitator training and resources for service users could be beneficial. It is also crucial that the service continue to present this opportunity to quit on an ongoing basis, especially given the accounts of non-attenders who also expressed the wish that this service remain as they may use it in future.

A stronger focus on replacement coping mechanisms and activities may be needed. It is important however to ensure these replacements are healthy. Given the increased physical health risks in general seen among those with MHDs (4, 63), the introduction of well-intentioned replacements such as biscuit breaks seem ill-advised. Rather, a focus on overall wellness and combining smoking cessation with broader health initiatives, a proven enabler, should continue; as should the open recruitment of those not ready to quit but interested in attending and perhaps cutting down. In light of the potential changing levels of motivation among those with MHDs, which were also reported in the current study, Williams and Ziedonis have previously recommended reduction toward abstinence as a method of harm reduction (64). Smoking cessation support should also ideally be in place in advance of the introduction of any new smoke-free policies. Appears that the introduction of a smoke-free policy alone is insufficient. Appropriate implementation by enthusiastic staff with environmental barriers addressed in advance is required.

Finally, attending the cessation programme and attempting to quit turned out to be a longer and more circular process than anticipated for some, providing support for the idea that some individuals with MHDs may require more intensive, modified or tailored cessation support (25, 37, 65). It is important to note however that some service users in the current study needed little support to quit particularly in the early stages of implementation. Perhaps the introduction of new smoking policies and a support programme produce quick initial gains or "low-hanging fruit" in terms of the quitting of more motivated and less dependent smokers after which those more dependent smokers, needing greater support, remain. Regardless, there was a clear need to sufficiently equip facilitators, through enhanced training, guidelines or a nominated support contact, for attendees or groups getting "stuck" in order to avoid feelings of uncertainty and frustration. Beyond a support person, a forum for facilitator communication and collaboration could also be beneficial in sharing knowledge and approaches to obstacles.

Future research may wish to explore how the provision of evidence of successful smoking cessation in those with MHDs, as well as a greater focus on replacement coping mechanisms and activities, might enhance a smoking cessation programme for this population. Studies which include exploration of experience of use at both participant and provider levels in addition to cessation outcomes would be particularly useful.

Strengths and Limitations

This study was strengthened by the participation of a high number of service users across a large number of the eligible centers as well as the inclusion of almost all facilitators, meaning results should have good external validity. Including the 16 sites meant contextual factors were well accounted for and barriers and enablers that emerged were truly cross-site. Previous qualitative studies of smoking cessation and other lifestyle interventions in individuals with serious or severe mental illness have at times involved very small samples of service users (66, 67), while others have failed to include the service user voice at all (38, 44).

Beyond the inclusion of both voices, the triangulation of sources, combining both service user and staff perspectives and experiences, also serves to validate study findings (68), adding credibility and strengthening confidence in the conclusions drawn (69). Lambert et al. have also found that the integration of focus group and interview data in particular, assists in the identification of individual and contextual circumstances, thus adding to interpretation and ultimately enhancing trustworthiness of results (70). The two-phase sequential design also allowed for the refinement of the facilitator focus group interview guide and thus allowed service users to set the agenda somewhat before facilitator data collection commenced. Unfortunately, due to incomplete data collection by staff, quantitative data on programme outcomes were unavailable so we were unable to include a mixed methods triangulation element to the data.

As this was a qualitative study, findings are not generalizable beyond the study population and conclusions drawn refer to the sample itself (71). Practical issues around staff availability led to pragmatic decisions including conducting a focus group with just two members and allowing a facilitator to join another focus group late. The recruitment of participants through HSE staff may have meant they did not believe the researcher was truly neutral and interview data confidential, although this was restated at the beginning of each interview and focus group, it is unclear if this affected findings.

CONCLUSIONS

A group-based smoking cessation programme with an open recruitment approach and the provision of individual support, where needed, appeared to work well in community mental health services. Findings indicated that implementation of cessation programmes in community mental health settings may be best when done in advance of new tobacco free policies,

when it is prioritized and sustained and when the cessation care provided also addresses the key barriers perceived as specific to those with mental health difficulties. More broadly, a joined-up approach across the health service seems necessary to address ongoing inconsistencies and support those with MHDs in their efforts to quit.

AUTHOR CONTRIBUTIONS

AB designed the research instruments, completed all data entry and data analysis and wrote the manuscript as part of her PhD. JS provided feedback on research instruments, supervised AB in the conduction of thematic analysis and assisted in review of the current paper. LC provided feedback on research instruments, supervised AB in completing the study and assisted in review of the current paper. MW, GS, and TO'B provided original research ideas, designed the protocol and applied for research ethics approval, contributed to the design of research instruments and assisted in review of the current paper. DR contributed to the data analysis of the manuscript, and assisted in review of the current paper. FD was the principal investigator for this project. He supervised the project, provided feedback on the design of research instruments, qualitative analysis and assisted in review of the current paper. All authors revised the original manuscript and provided critical input.

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Stop Turning a Blind Eye: Tobacco Smoking Among Egyptian Patients With Schizophrenia

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Background: Patients with schizophrenia have considerably higher rates of mortality than general population. Multiple factors may play a role in this. Despite being a major preventable cause of death, smoking is usually overlooked when dealing with patients with schizophrenia. Understanding the pattern of smoking, its severity, and the reasons to quit might be helpful in managing patients with schizophrenia and decreasing the mortality gap.

Subjects and Methods: The study included smokers divided into two groups; the first included 346 patients with schizophrenia while the second group had 150 smokers with no mental illness. Both groups were assessed and compared regarding sociodemographic variables, pattern of smoking, severity of nicotine dependence, and motivation to quit smoking.

Results: Earlier age of starting to smoke, higher number of cigarettes per day, and lower dependency scores were noted in patients with Schizophrenia. Positive correlation was found between positive symptoms and severity of dependence. Specific positive symptoms were correlated to number of cigarettes per day and time before first cigarette. Patients with Schizophrenia showed a significant difference in intrinsic reasons to quit (health concerns and self-control), which were also positively correlated to their positive symptoms score. Linear regression analysis for predictors of FTND score revealed that only age, sex, and schizophrenia were significant predictors of FTND score.

Conclusion: Patients with schizophrenia smoke at earlier ages and smoke more cigarettes per day, yet, have less severe dependence than non-schizophrenic counterparts. Positive symptoms play a role in their smoking pattern and severity. Health concerns and self-control are their main motives to quit smoking.

Keywords: tobacco smoking, nicotine, schizophrenia, motivation to quit, mortality, positive symptoms, PANSS

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INTRODUCTION

Mortality gap in schizophrenia is a significant issue (1). Physical illness is associated with the problem, which may be related to the adoption of unhealthy lifestyle behaviors (2).

Smoking is one of the main factors adding to the mortality gap in patients with schizophrenia being one of the leading causes of premature mortality in them (3). Yet, it is usually overlooked.

Tobacco smoking is common in schizophrenia (4). Patients with schizophrenia have high reported smoking rates of 58–90% (5). This is considerably higher than smoking rates of 24% in the general public (6) and of ∼50% in people with other psychiatric diagnoses (7). Patients with schizophrenia are not only more likely to smoke, but also smoke more heavily, have longer smoking duration, and have lower rates of cessation compared to individuals without schizophrenia (8). Among different factors that may explain the high rates of smoking among patients with schizophrenia is the shortage of smoking cessation services in mental health treatment programs (9).

Smoking is a major preventable cause of death (10). In patients with schizophrenia, the risk of mortality is doubled, and the risk of cardiac-related morality is increased about 12-fold in smokers compared to non-smokers (1, 11). However, despite the high frequency of smoking in schizophrenia, little is known about clinical correlates or pharmacological treatments associated with tobacco smoking in patients with schizophrenia (12).

The relation between schizophrenia and smoking has been the subject of many studies for years. Some showed smoking to be associated with both positive and negative symptoms of schizophrenia, others found relationship with just one of these domains (13), while some found no relationship with either (14). Some authors suggest that Schizophrenia does not only increase the possibility of smoking but increases the risk of severe smoking as well (15).

Consequently, the high rates and severer patterns of smoking in patients with schizophrenia are suggested to contribute to reduction in life expectancy and to excess morbidity and mortality among them. Moreover, cigarette smoking has also been demonstrated to be associated with more frequent hospital readmissions, increased financial burden, and higher rate of attempted suicide (16). Addressing several factors like lack of resources, smoking, physical illness, and lifestyle modification may help decreasing the mortality gap in schizophrenia (1).

On the other hand, studies suggest that patients with schizophrenia are at least as motivated to quit as the general population but have lesser chance to quit attempts (17, 18). Moreover, several studies suggest that tobacco dependence treatment is effective in patients with mental illness (9, 19, 20), with some exploring the safety and efficacy of pharmacological treatment in this group (21, 22). Despite that, most psychiatric services do not address smoking cessation in patients with schizophrenia. This may be due to the lack of a consensus on certain recommendations to treat tobacco dependence in this patients group. Moreover, only modest results are achieved with the available regular approaches for smoking cessation (23). However, specific programs that promote healthy living, e.g., LIFESTYLE trial (2) are emerging recently. Those programs might play a key role in helping patients with Schizophrenia getting rid of harmful habits like smoking which might decrease mortality rates.

Therefore, as smoking appears to be one of the major factors contributing to the mortality gap in patients with schizophrenia, this study aims at shedding the light on smoking patterns among a sample of patients with Schizophrenia in Egypt and to highlight the patients' willingness to quit.

MATERIALS AND METHODS

This is a comparative cross-sectional study between two different groups; the first included smokers with schizophrenia and the second had smokers without mental illness. The sample was a convenient sample collected over a 1-year period. The sample size was also calculated prior to the study using PASS version 15.0, setting the power at 80% and the significance level (α- error) at 0.05, to make sure the study reaches the minimal sample size. Data from previous study (24) reported that the mean immediate reinforcement score for patients with schizophrenia was 2.0 ± 1.1 compared to 2.3 ± 0.9 for normal controls. Calculation according to these values produced a minimal sample size of 139 subjects per group, rounded to 150 in each.

The first group; included 346 patients with schizophrenia who were collected during the study period using a convenient sampling method. Patients fitting the inclusion criteria were approached in both inpatients and outpatients departments, at the Institute of Psychiatry, Faculty of Medicine, Ain Shams University, and those who consented were included. This group included both sexes, older than 18 at the time of the study, with the diagnosis of Schizophrenia according to DSM IV-TR criteria and had been smokers for at least 12 months. Presence of any other Axis I psychiatric diagnosis was an exclusion criterion.

As for group two; 150 subjects were recruited from the smoking cessation clinic and we also called for volunteers from employees and students through an announcement in the university hospitals. This group included both sexes, above the age of 18 with exclusion of those with any Axis I psychiatric disorder.

Required ethical approvals were obtained prior to the study. Informed written consents were requested from all participants, including detailed description of the study procedures. Socio-demographic data were collected using a questionnaire based on the admission sheet of the Institute of Psychiatry, Ain Shams University.

Further assessment was done using the following. (a) Structured Clinical Interview for DSM-IV Axis-I disorders (SCID) (25), an Arabic version validated in Egyptian studies was used (26) to confirm the diagnosis of Schizophrenia and to exclude other Axis I psychiatric disorders in both groups. (b) Positive and Negative Syndrome Scale (PANSS) (27). The Positive and Negative Syndrome Scale is one of the most widely used methods for standardized measurement of schizophrenic core symptoms. The PANSS consists of 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology items. All 30 PANSS items are rated on a 7-point symptom severity scale, ranking from 1 (absent) to 7 (extremely severe). (c) Fagerström Test for Nicotine Dependence (FTND) Arabic version which has been validated for use among Arabic speaking population (28). In this study, nicotine dependence was classified into two categories; low dependence (LD; FTND < 4) and high dependence (HD; FTND ≥ 4). (d) Reasons for Quitting scale (RFQ) (29), which gathers information about motivations and reasons of smokers to quit smoking. The RFQ is composed of 20 self-report items and measures intrinsic and extrinsic motivation for quitting smoking. It consists of two intrinsic motivation

subscales, self-control (e.g., "To show myself I can quit if I really want to") and health concerns (e.g., "Because I'm concerned that smoking will shorten my life"), and two extrinsic motivation subscales, immediate reinforcement (e.g., "To save money that I spend on cigarettes") and social pressure (e.g., "Because someone has given me an ultimatum to quit").

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 20). Data was presented, and suitable analysis was done according to the type of data obtained for each parameter.

i Descriptive statistics:

1. Mean and Standard Deviation (±SD) for numerical data.
2. Frequency and percentage for non-numerical data.

ii. Analytical statistics:

1. Student *T*-Test was used to assess the statistical significance of the difference between two study group means.
2. Chi-Square test was used to examine the relationship between two qualitative variables.
3. Correlation analysis (using Pearson's and Spearman's methods): To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" for Pearson correlation and "rs" for Spearman correlation defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.
4. Linear regression was used to test and estimate the dependence of a quantitative variable based on its relationship to one or more independent variables.

RESULTS

Sample Description

The study included two groups; a group of patients with schizophrenia ($n = 346$; males 232, females 114) and a group of individuals with no mental illnesses ($n = 150$; males 93, females 57). The mean age of the group with schizophrenia was 33.28 years (±9.57 SD) and for the other group 36.97 years (±10.52 SD). The levels of illiteracy (13.9%) and unemployment (21.7%) were higher among patients with schizophrenia than in non-schizophrenia group (0.7 and 6.7%, respectively) (**Table 1**).

As regard patients' symptoms profile, they had higher positive scale scores (Mean ± SD = 25.01 ± 5.08) than negative scale scores (Mean ± SD = 18.64 ± 8.05).

Pattern of Use and Severity of Tobacco Dependence Among Patients

Comparing the two groups, a statistically significant difference in the age of starting smoking was detected as the patients started at an earlier age than the other group (mean: patients with schizophrenia 22.15 ± 6.17 SD, non-schizophrenics 23.93 ± 5.89 SD, $p = 0.003$). However, patients with schizophrenia had statistically significant lower dependency scores using FTND (cases 6.6 ± 1.56, controls 7.12 ± 1.43, $p = <0.001$) (**Table 2**).

The number of cigarettes per day was significantly ($P < 0.001$) higher among patients group as 39.9% of patients with schizophrenia smoked more than 20 cigarettes per day compared to only 20.6% of the group without schizophrenia. Moreover, patients preferred their first cigarette within 5 min of awakening (39%) compared to the other group (14.7%) ($P < 0.001$).

On the other hand, there is a statistically significant negative correlation ($r = -0.158$) between positive scale score and age of starting smoking (the younger the age of start smoking, the higher the positive scale score), and a statistically significant positive correlation between positive scale score and FTND score ($r = 0.246$) (the higher the FTND score, the higher the positive scale score). This suggests that patients with more positive symptoms start smoking early and have more dependency score on FTND. However, no significant correlations were detected with negative scale and general scale scores (**Table 3**).

Upon performing linear regression analysis for predictors of FTND score, it was revealed that only age (0.041, 95% CI: 0.03–0.05), sex (−0.917, 95% CI: −1.18 to −0.65, ref. male), and schizophrenia (−0.398, 95% CI: −0.69 to −0.1) were significant predictors of FTND score (**Table 4**). Moreover, in the patients group, linear regression analysis for predictors of FTND score revealed that only age (0.043, 95% CI: 0.03–0.06), sex (−1.145, 95% CI: −1.45 to −0.84, ref. male), positive score (0.11, 95% CI: 0.08–0.14), and negative score (0.041, 95% CI: 0.02–0.06) were significant predictors of FTND score (**Table 5**).

Moving to specific symptoms, this study found statistically significant positive correlation, between number of cigarettes and severity of delusions, conceptual disorganization, hallucination, excitement, hostility, anxiety, preoccupation, and poor impulse control and statistically significant negative correlation with motor retardation and poor attention (**Table 6**).

Regarding correlation between symptomatology and time spent before the first cigarette, this study found statistically significant negative correlation between time spent before the first cigarette and severity of delusions, conceptual disorganization, hallucination, excitement, persecution, hostility, somatic concern, anxiety, preoccupation, and poor impulse control. While a statistically significant positive correlation was found with motor retardation (**Table 6**).

Reasons for Quitting

Assessing the reasons for quitting, significant differences in intrinsic reasons were detected. This includes "health concerns" (mean: patients group 2.63 ± 1.02, non-schizophrenic group 2.17 ± 1.13) with a *P*-value of <0.001 and "self-control" (mean: patients group 1.92 ± 1.06, non-schizophrenic group 1.69 ± 0.88) with a *P*-value of 0.017. Patients with schizophrenia were more concerned with health risk and to gain self-control over smoking than their counterparts from the other group. However, no statistically significant differences were detected as regard extrinsic factors; immediate reinforcement and social pressure as reasons to quit.

Moreover, regarding PANSS positive scale score, statistically significant positive correlation with health concern subscale and

TABLE 1 | Comparison between smokers with schizophrenia and smokers with no mental illness regarding socio-demographic data.

		Smokers with no mental illness		Smokers with schizophrenia		*t*-test	
		Mean	**SD**	**Mean**	**SD**	***p*-value**	**Sig.**
Age		36.97	10.52	33.28	9.57	<0.001	S
		N	**%**	***N***	**%**	**Chi square test**	
						***p*-value**	**Sig.**
Gender	Male	93	62.0	232	67.1	0.277	NS
	Female	57	38.0	114	32.9		
Marital	Unmarried	60	40.0	165	47.7	0.114	NS
	Married	90	60.0	181	52.3		
Education	Uneducated	1	0.7	48	13.9	<0.001	S
	Basic	10	6.7	64	18.5		
	High school	26	17.3	63	18.2		
	Diploma	56	37.3	119	34.4		
	College	57	38.0	52	15.0		
Job	Non functioning	10	6.7	75	21.7	<0.001	S
	Functioning	140	93.3	271	78.3		
Income	Not adequate	72	48.0	195	56.4	0.086	NS
	Adequate	78	52.0	151	43.6		

TABLE 2 | Comparison between smokers with schizophrenia and smokers with no mental illness regarding age, pattern of smoking and FTND score.

		Smokers with no mental illness		Smokers with schizophrenia		*t*-test	
		Mean	**SD**	**Mean**	**SD**	***p*-value**	**Sig.**
Age of smoking		23.93	5.89	22.15	6.17	0.003	S
FTND		7.12	1.43	6.60	1.56	<0.001	S
		N	**%**	**N**	**%**	**Chi Square**	
						***P*-value**	**Sig.**
1st Cig	After 60 min	17	11.3	64	18.5	<000.1	S
	30–60 min	52	34.7	52	15.0		
	6–30 min	59	39.3	95	27.5		
	Within 5 min	22	14.7	135	39.0		
No. of cig/d	<10	3	2.0	78	22.5	<0.001	S
	11–20	116	77.3	130	37.6		
	21–30	17	11.3	95	27.5		
	>30	14	9.3	43	12.4		

with self-control subscale were detected. On the other hand, negative correlations with immediate reinforcement subscale and social pressure subscale were also found. This suggests that patients with more positive symptoms are more concerned with intrinsic reasons (i.e., health and self-control) to quit smoking and less concerned with extrinsic reasons (i.e., less affected by immediate reinforcement and social pressure) (**Table 3**).

Furthermore, statistically significant positive correlation between general scale score and health concern subscale and negative correlation with immediate reinforcement subscale were detected. This implies that patients with schizophrenia who have higher scores on the general scale of PANSS are more concerned with health but less concerned with immediate reinforcement (**Table 3**).

DISCUSSION

Schizophrenia is associated with mortality rates that are two to three times higher than the general population. The number of deaths due to cardiovascular disease is high and could be reduced by lifestyle modification (2, 30). Kelly et al. (11) reported a significant risk of increased mortality from smoking in patients with schizophrenia which was mainly evident in the middle ages (35–54 y). This implies the importance of a better understanding

TABLE 3 | Correlations between age of starting smoking, FTND score, RFQ scale, and PANSS.

N = 346		Age of starting smoking	FTND-S	RFQ-INH	RFQ-INS	RFQ-EXI	RFQ-EXS
Positive score	R	−0.158	0.296	0.483	0.245	−0.109	−0.123
	p-value	0.003	<0.001	<0.001	<0.001	0.043	0.022
Negative score	R	0.068	0.038	0.070	−0.042	−0.102	0.002
	p-value	0.205	0.485	0.191	0.433	0.056	0.970
General	R	0.014	0.085	0.265	0.048	−0.109	0.028
	p-value	0.793	0.114	<0.001	0.377	0.043	0.607

TABLE 4 | Linear regression analysis for predictors of FTND score in both groups.

	Regression coefficient	95.0% confidence interval	*p*-value
Schizophrenia (Ref.: Non-schizophrenic)	−0.398	−0.69 to −0.1	0.008
Sex (Ref.: Male)	−0.917	−1.18 to −0.65	<0.001
Age	0.041	0.03 to 0.05	<0.001
Marital (Ref.: Unmarried)	−0.202	−0.49 to 0.08	0.163
Job (Ref.: Non-Functioning)	−0.341	−0.69 to 0.01	0.054
Basic (Ref.: uneducated)	0.223	−0.3 to 0.75	0.402
High school (Ref.: uneducated)	0.333	−0.17 to 0.84	0.196
Diploma (Ref.: uneducated)	0.320	−0.15 to 0.79	0.183
College (Ref.: uneducated)	0.441	−0.07 to 0.95	0.091

TABLE 5 | Linear regression analysis for predictors of FTND in patients with Schizophrenia.

	Regression coefficient	95.0% confidence interval	*p*-value
Gender (Ref.: Male)	−1.145	−1.45 to −0.84	<0.001
Age	0.043	0.03 to 0.06	<0.001
Positive score	0.111	0.08 to 0.14	<0.001
Negative score	0.041	0.02 to 0.06	<0.001
marital (Ref.: Unmarried)	−0.294	−0.62 to 0.04	0.082
job (Ref.: Non-Functioning)	−0.154	−0.51 to 0.2	0.395
Basic (Ref.: uneducated)	0.139	−0.38 to 0.65	0.597
High school (Ref.: uneducated)	0.455	−0.05 to 0.96	0.078
Diploma (Ref.: uneducated)	0.321	−0.15 to 0.79	0.178
College (Ref.: uneducated)	0.155	−0.39 to 0.7	0.574

of the smoking problem among patients with schizophrenia, and the inclusion of the assessment, and management of smoking in routine treatment strategies (9).

When assessing age of starting smoking, this study found that patients with schizophrenia start in a younger age, which may suggest that smoking might be involved in pathophysiology of schizophrenia or smoking may be an early sign of prodromal symptoms. A birth cohort study (31) links cigarette smoking to the prodromal phase of schizophrenia and suggested that impaired nicotinic neurotransmission is involved in the pathophysiology of schizophrenia. However, another study conducted by Wade et al. (32), reported that patients with schizophrenia began smoking around the same age as healthy controls, i.e., in their teenage years.

On the other hand, the current study found that patients with schizophrenia had lower dependency scores on FTND compared to the other group. A possible explanation for this is the high prices of cigarettes due to increased taxes especially in the recent years, which is a burden to the patients with schizophrenia who already suffer from financial problems. Another possible explanation is that most of patients with schizophrenia in Egypt live with their families who control their cigarettes supply. This result comes in concordance with several studies that indicated that nicotine dependence and the number of cigarettes per day are not higher and even sometimes similar to those without schizophrenia (33). However, other studies (3, 34, 35) found that people with schizophrenia are heavier smokers and had high levels of nicotine dependence scores.

The relation between smoking and positive and negative symptoms have always been debatable. Results of different studies have yielded various outcomes (4, 36, 37) with some reporting smoking related to positive symptomatology, to negative, to both positive, and negative symptomatology (38, 39) or to neither positive nor negative symptoms (37).

On assessing patients with positive symptoms, this study found that patients with more positive symptoms start smoking early and have more dependency score of FTND of cigarettes smoking. Yet, no significant correlations between negative symptoms or general symptoms severity and age of patients, age of start smoking, or cigarettes dependency were detected. This comes in concordance with work done by Ziedonis et al. (40) who found that heavy smokers (here defined as >25 cigarettes per day) had the most positive symptoms and a significantly lower number of negative symptoms. In addition, a cohort study done by Aguilar et al. (41) found that highly dependent smokers had the most severe positive symptoms of schizophrenia. Moreover, it was reported that tobacco use, and weight gain/obesity were associated with increased severity of symptoms of schizophrenia and decreased functioning (42).

However, upon performing linear regression analysis, both positive and negative scores were significant predictors of FTND score. This comes in concordance with study done by Patkar et al. (13) for assessments of nicotine dependence in relation to PANSS

TABLE 6 | Correlation between symptoms of schizophrenia (PANSS) and the number of cigarettes and time spent before first cigarette.

	Number of cigarettes $N = 346$		Time before 1st cigarette $N = 346$	
	rs	*p*	rs	*p*
Delusions	0.147	0.006	−0.160	0.003
Conceptual disorganization	0.428	< 0.001	−0.417	< 0.001
Hallucinations	0.213	< 0.001	−0.201	< 0.001
Excitement	0.287	< 0.001	−0.286	< 0.001
Grandiosity	0.055	0.307	−0.085	0.115
Suspiciousness/ Persecution	0.085	0.115	−0.106	0.048
Hostility	0.185	0.001	−0.227	< 0.001
Blunt affect	0.018	0.740	−0.002	0.968
Emotional withdrawal	−0.010	0.852	0.042	0.434
Poor rapport	−0.029	0.591	0.049	0.361
Passive/apathetic social withdrawal	0.003	0.950	0.005	0.922
Difficulty in abstract thinking	0.035	0.513	0.011	0.837
Lack of spontaneity & flow of conversation	−0.019	0.726	0.025	0.643
Stereotyped thinking	0.042	0.434	−0.030	0.584
Somatic concern	0.079	0.143	−0.125	0.020
Anxiety	0.157	0.003	−0.138	0.010
Guilt feelings	0.013	0.816	−0.055	0.306
Tension	−0.051	0.343	0.053	0.326
Mannerism & posturing	0.099	0.067	−0.087	0.107
Depression	0.035	0.519	−0.020	0.704
Motor retardation	−0.178	0.001	0.165	0.002
Uncooperativeness	0.011	0.843	0.001	0.985
Unusual thought content	−0.035	0.518	0.031	0.563
Disorientation	0.045	0.408	−0.087	0.106
Poor attention	−0.138	0.010	0.157	0.003
Lack of judgment & insight	0.029	0.587	−0.008	0.883
Disturbance of volition	0.096	0.074	−0.076	0.157
Poor impulse control	0.226	< 0.001	−0.219	< 0.001
Preoccupation	0.150	0.005	−0.139	0.010
Active social avoidance	0.014	0.796	−0.043	0.422

who found significant positive correlations between Fagerstrom scores and the total negative symptom score and scores on the negative symptom subscales of blunted affect, social withdrawal, difficulty in abstract thinking, and stereotyped while positive symptoms were not significantly associated with smoking.

On the other hand, morning smoking preference was positively correlated to conceptual disorganization and excitement in this sample. As regard the correlation with conceptual disorganization, this may be explained by the possibility that nicotine use enhances performance in several domains of cognitive functioning which may be reflected on process of thinking and goal-directed sequencing. Thus, morning smoking may be preferred because it might improve this thinking processing from the start of the day. The relaxing effect of nicotine may also explain the correlation between morning smoking and excitement (43). This study also linked the number of cigarettes and time spent before the first cigarette to certain symptoms including delusions, hallucinations, conceptual disorganization, excitement, hostility, anxiety, and poor impulse control.

When it comes to quitting, Evins et al. (44) observed that persons with schizophrenia are often highly motivated and persistent in their attempts to quit smoking despite having long histories of smoking. This study found that patients with schizophrenia are more concerned with intrinsic factors, i.e., heath risk and self-control as reasons to quit. These results are in concordance with a study done by Addington et al. (45) who found the chief reasons for quitting smoking in patients with schizophrenia could be health concerns, which ultimately reinforce these individuals to quit. However, this is not in concordance with other studies (46) which found that people with schizophrenia were significantly less likely to consider quitting for health concerns.

On correlating positive and negative symptoms with reasons for quitting, we found that patients with more positive symptoms are more concerned with intrinsic reasons (with health and self-control) and less concerned with extrinsic reason (less affected by immediate reinforcement and less affected by social pressure). However, no significant correlation between negative symptoms and the subscales of reasons for quitting was detected.

LIMITATIONS

The main limitation of the study is its non-generalizability. It included a not well-representative community sample; as the sample was only collected from Institute of Psychiatry, Ain Shams University Hospitals.

CONCLUSION

Tobacco is one of the major contributors to major health issues in patients with schizophrenia. It seems that there is some sort of a link between some positive symptoms of schizophrenia and severity of tobacco dependence, number of cigarettes, and morning smoking preference. It also appears that patients with schizophrenia who have more severe positive symptoms are more inclined to quit smoking; mainly for health concerns. Thus, it is important for psychiatrists to investigate these issues when assessing patients with schizophrenia especially their readiness to quit. Addressing tobacco use during the course of treatment might have positive outcomes on schizophrenia and health related issues and consequently lead to decreased morbidities and mortalities.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethical committee of Faculty of Medicine, Ain Shams University. The protocol was approved by the ethical committee of Faculty of Medicine, Ain Shams University. All subjects gave written informed consent.

AUTHOR CONTRIBUTIONS

NN, GT, ME, HE, and LA contributed to conception and design of the study. LA was the researcher responsible for the field work and organized the database. MY revised all the collected data and performed the statistical analysis. HE collated all results and wrote the first draft of the manuscript. All authors contributed to the revision, read and approved the submitted version.

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Physical Exercise in Major Depression: Reducing the Mortality Gap While Improving Clinical Outcomes

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Major depression shortens life while the effectiveness of frontline treatments remains modest. Exercise has been shown to be effective both in reducing mortality and in treating symptoms of major depression, but it is still underutilized in clinical practice, possibly due to prevalent misperceptions. For instance, a common misperception is that exercise is beneficial for depression mostly because of its positive effects on the body ("from the neck down"), whereas its effectiveness in treating core features of depression ("from the neck up") is underappreciated. Other long-held misperceptions are that patients suffering from depression will not engage in exercise even if physicians prescribe it, and that only vigorous exercise is effective. Lastly, a false assumption is that exercise may be more harmful than beneficial in old age, and therefore should only be recommended to younger patients. This narrative review summarizes relevant literature to address the aforementioned misperceptions and to provide practical recommendations for prescribing exercise to individuals with major depression.

Keywords: depression, mortality, exercise, physical activity, efficacy, cardiovascular disease

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INTRODUCTION

Depression exerts an enormous impact on different domains of individual functioning, as well as physical health (1, 2). Physical exercise is increasingly recognized as an effective intervention to improve these outcomes.

Patients with major depression seldom receive adequate treatment. When they do, there is a high likelihood they remain depressed or relapse after first-line treatment (3, 4). Whereas, a substantial proportion of patients go on to receive intensive pharmacological care (5, 6).

Besides mental health outcomes, recent studies cast great concern on the physical health of depressed individuals. Depression is, in fact, accompanied by behavioral and biological features that are deleterious for physical health, particularly in the cardiovascular system (7). Moreover, when depression arises as a consequence of pre-existing physical problems, it may amplify disability, anticipate recurrences, and increase disease-related mortality (8, 9). Recently it was estimated that individuals with major depression die, on average, about 10 years earlier than those who are not depressed, even when excluding deaths by suicide (10–12).

There is wide agreement that current research and clinical efforts to address these issues are arguably not proportional to their gravity. There is an urgent need to develop and implement novel treatments that are effective to treat symptoms of depression and, at the same time, are beneficial for physical health (13). One such intervention is physical exercise, which is increasingly recognized as both an antidepressant agent (14) and a potent tool to delay mortality (15). The aim of this perspective article is to provide a concise update on the effectiveness of exercise for depression and cardiovascular mortality reduction. A specific section is dedicated to treatment of elderly patients, in consideration of their increasing demographic relevance (2). English-language reviews and meta-analyses published in the last 10 years were considered, identified with the following search string in the Pubmed database: (exercis*[ti] OR "physical activity"[ti]) AND depress*[ti] AND (review*[pt] OR review*[tiab]).

DEPRESSION IS ASSOCIATED WITH A SHORTER LIFESPAN

Even if a direct causal role is still debated (16), depression could increase mortality through several mechanisms (10). First, it negatively impacts lifestyle choices. Individuals with depression tend to be sedentary (17, 18) and less physically fit than their non-depressed counterparts (19). Moreover, they exhibit higher rates of cigarette smoking (20–22), consume more alcohol (23), adopt low-quality dietary regimens (24), and become overweight (25, 26). Of note, some of these associations seem underlined by bi-directional causal links.

Second, depression is accompanied by dysregulation of several homeostatic systems (27). Depressed individuals commonly display dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis (28–30), immune (31, 32), and autonomic nervous system (33), as well as metabolic imbalances (34).

Third, depression can raise mortality risk by increasing the incidence of physical illnesses or worsening the outcomes of existing ones. For instance, the presence of clinically significant depression has been found to increase the incidence and mortality of cardiovascular diseases (35, 36), as well as the mortality due to diabetes (37) and stroke (38). This phenomenon could stem, among other reasons, from placing additional stress on disorder-specific pathophysiologic mechanisms, but may also reflect poor adherence to medications or problematic health behaviors (39–41). In this regard, **Table 1** reports an overview of the relationship between depression, cardiovascular risk factors, and mortality.

EXERCISE IS EFFECTIVE FOR THE PHYSICAL HEALTH OF DEPRESSED PATIENTS

Physical activity and exercise have a wide range of beneficial effects (72) that involve both "body" and "mind." Bearing in mind this is an artifactual and anachronistic convention, here we provide an overview of exercise effects on the body "from the neck down" that could be relevant to individuals with depression. **Table 1** reports recent literature addressing this issue.

Together with dietary caloric restriction, exercise is the main component of interventions that are effective at reducing and managing weight (73–75). The positive effect of exercise is likely mediated by enhanced regulation of appetite hormones (76) and by increased metabolic rate (47, 77, 78). Moreover, exercise improves sleep quality and duration (79).

Exercise also causes beneficial adaptations in homeostatic systems involved in the response to stress, including the HPA axis (80–82). Moreover, it dampens inflammatory processes while delaying the aging of the immune system (51–53). Exercise also improves the autonomic visceral control by restoring sympathovagal balance (57, 83, 84) Finally, it improves cardiorespiratory fitness both in healthy individuals (47) and individuals with depression (85).

While the formal acknowledgment of the salutary effects of exercise in the medical sciences has been a lengthy process, regular exercise is now recognized as an important lifestyle behavior that can ameliorate the negative impact of chronic diseases (86). Overall, it is estimated that exercise can reduce mortality to a similar extent as medications in individuals with coronary heart disease, stroke, heart failure, and diabetes (15). It would be urgent to verify if such findings can be translated to depressed subjects.

Among the many salutary effects of exercise, arguably the least researched—and probably the most controversial—are its effects on other lifestyle and health behaviors. Both the number of randomized controlled trials and the methodological quality of the trials in this area are rising. While concepts and methods continue to evolve, some early results related to smoking cessation and reducing problem drinking among individuals with mental health disorders show promise (87–89). However, at this stage, systematic reviews of the evidence on the effectiveness of exercise in promoting abstinence from smoking (60) or alcohol (58) indicate no beneficial effect. On the other hand, the effect of exercise on reducing the use of illegal substances is significant (90). In addition, whether a structured exercise intervention can reduce sedentary behavior or encourage engagement in subsequent physical activity remains hotly debated (64).

EXERCISE IS EFFECTIVE AGAINST SYMPTOMS OF MAJOR DEPRESSION

Physical exercise has been shown to be an effective treatment for major depression in adults (14, 91) in several randomized controlled trials comparing it to a wide range of other treatments, including usual care, psychological interventions, and antidepressant medications (14, 92). Although there have been contrarian meta-analytic findings [e.g., (93)], closer inspection of methodological details reveals a pattern of debatable choices (91).

Exercise interventions consisting of three sessions per week for 12–24 weeks typically result in a medium to large reduction in the severity of depression, measured by symptom

TABLE 1 | Literature examining the relationship between depression, cardiovascular risk factors, cardiovascular mortality, and physical exercise in adults.

Cardiovascular risk factor	Association between depression and risk factor	Effect of exercise on risk factor among non-depressed populations
Obesity—overweight	Depression had a 37% increased risk of becoming obese (RR: 1.37, 95%CI: 1.17–1.48); risk was highest for young and middle aged women. Nineteen prospective studies (26, 42)	Exercise was effective to reduce body weight (although less effective than hypocaloric diet) and visceral adipose tissue (more effective than hypocaloric diet). 117 trials (43)
Type 2 Diabetes	Depression was associated with an increased risk of having T2DM (RR: 1.49; 95%CI: 1.29–1.72). Ten studies, only one prospective (44)	Exercise improved Hb1AC levels and insulin resistance. 27 trials (45)
Unbalanced diet	Two out of three studies supported an association between depression and unbalanced diet. Three studies, all cross sectional (24)	na
Blood metabolic parameters	Depression was associated with a higher prevalence of Metabolic Syndrome (OR: 1.54, 95% CI 1.21–1.97), hyperglycemia (OR: 1.33, 95%CI: 1.03–1.73), hypertriglyceridemia (OR: 1.17, 95% CI 1.04–1.30). Eighteen studies, all cross-sectional (34). Depression was associated with lower serum LDL levels (mean difference: 3.15 mg/dL, 95%CI: 6.05–0.24). Eighteen cohort studies (46)	Exercise lowered fasting insulin, HOMA-IR, and Hb1AC levels. TG and APOA1 levels, increased HDL levels; trend-level effects for reductions of LDL and fasting glucose. 160 RCTs (47)
Hypertension	Depression was associated with an increased risk of incident hypertension (RR: 1.42, 95% CI: 1.09–1.86). Nine prospective studies (48)	Exercise reduced blood pressure. The magnitude of the effect changed according to exercise type and was greater for hypertensive subjects. 93 RCTs (49)
Inflammation	Depression was associated with abnormal levels of peripheral cytokines and chemokines compared to HCs. IL-6, TNF-a, IL-10, sIL-2R, CCL-2, IL-13, IL-18, IL-12, and sTNFR2 were significantly elevated, IFN-gamma was slightly reduced. Eighty-two case-control studies (50)	Exercise reduced IL6 and CRP levels in T2DM. Fourteen RCTs (51). Similar results in CAD. Twenty-six trials (52). Possible effect enhancing immune competence and delaying the aging of the immune system (53)
Autonomic dysfunction	Untreated depression was associated with reduced Heart Rate Variability (g: −0.349, 95%CI: −0.51 to−0.19). Twenty-nine case-control studies (54)	Exercise increased HRV in 9 out of 15 trials on T2DM (55). Exercise improved HRV in CAD. Sixteen RCTs (56). Exercise improved HRV in HF. 19 trials (57)
Alcohol use	Depression was associated with increased risk of Alcohol Use Disorders (aOR: 2.09, 95%CI: 1.29–3.38). Seven studies, two of which prospective (23)	Exercise did not reduce daily alcohol consumption or AUDIT total scores. 21 trials (58)
Cigarette smoking	Among adolescents, depression increased the risk of beginning smoking (RR: 1.41, 95% CI: 1.21–1.63). Twelve prospective studies (20). Depressed smokers had lower odds of short-term (OR: 0.83, 95%CI: 0.72–0.95) and long-term abstinence (OR: 0.81, 95%CI: 0.67–0.97). Forty-two clinical trials on smoking cessation (59)	No effect of exercise on smoking cessation. 19 RCTs (60)
Adherence to medications	Depression was associated with an increased likelihood of non-adherence to medications (OR: 1.76, 95%CI: 1.33–2.57). Thirty-one U.S. based cross-sectional studies on chronic diseases (61)	na
Physical inactivity/sedentary behavior	Depression was associated with less time spent for total Physical Activity (SMD: −0.25, 95%CI: −0.03–0.15), higher levels of Sedentary Behavior (SMD: 0.09, 95%CI: 0.01–0.18) and lower likelihood to meet physical activity levels recommended by guidelines (OR: −1.50, 95%CI: −1.10 to −2.10). Twenty-four cross sectional studies (17). A recent large study confirmed the association between mental health and physical activity levels (62)	Exercise interventions yielded uncertain and/or small effects increasing subsequent physical activity (63–65)
Cardiovascular mortality	**Association between depression and mortality**	**Effect of exercise on mortality among non-depressed populations**
Coronary heart disease	Depression was associated with an increased risk of myocardial infarction-related death (HR: 1.31, 95%CI: 1.09–1.57) and coronary death (HR: 1.36; 95%CI: 1.14–1.63). Nineteen prospective studies (66). Quality of evidences appraised as "highly suggestive" (16)	Exercise reduced mortality in coronary heart disease (OR: 0.89, 95%Credible Interval: 0.76–1.04) with no difference in magnitude from ACEi, beta-blockers, ARBs and diuretics. Thirty-four RCTs (15). Exercise-based Cardiac Rehabilitation reduced cardiovascular, but not overall mortality (RR: 0.74, 95%CI 0.64–0.86). 27 RCTs (67)
Arrhythmias related mortality	Depression was associated with an increased risk of Sudden Cardiac Death (HR: 1.62; 95%CI: 1.37–1.92), ventricular arrhythmias (HR: 1.47; 95%CI: 1.23–1.76) recurrence of Atrial Fibrillation (HR: 1.88; 95%CI: 1.54–2.30). Seventeen studies, of which 15 prospective (36)	No clear effect of exercise on mortality in Atrial Fibrillation (RR: 1.00; 95%CI: 0.06–15.78). 6 RCTs (68)

(Continued)

TABLE 1 | Continued

Cardiovascular mortality	Association between depression and risk factor	Effect of exercise on risk factor among non-depressed populations
Mortality in Heart Failure	Depression was associated with an increased risk of all-cause mortality (HR: 1.20; 95%CI: 1.10–1.31). Increased risk was driven by studies on participants older than 65. 14 prospective studies (35). Quality of evidences was appraised as "highly suggestive" (16)	Exercise reduced mortality in heart failure (OR: 0.79; 95%Credible Interval: 0.59–1.00) to a greater extent than ACEi, beta-blockers, ARBs, but less than diuretics. 18 RCTs (15)
Mortality after Cardiac Surgery	Perioperative depression was associated with an increased risk of early (RR: 1.44; 95%CI: 1.01–2.05) and late postoperative mortality (RR: 1.44; 95%CI: 1.24–1.67). Sixteen prospective studies (69)	Insufficient evidence to establish a significant effect of exercise on mortality after heart valve surgery. 2 RCTs (70)
Overall mortality	Depression was associated with an increased risk of mortality relative to non-depressed participants (RR: 1.52, 95%CI: 1.45–1.59). Excess mortality risk was of similar magnitude in patients from the community vs. those with specific diseases. Two hundred and ninety-three prospective studies (10). Quality of evidence was however appraised as inadequate to support a direct causal association (16, 71)	The network meta-analysis estimated that exercise can reduce mortality to a similar extent to medications among individuals with coronary heart disease, stroke, heart failure, and diabetes. 305 RCTs (15).

This table summarizes recent literature on: (a) the relationship between depression, cardiovascular risk factors and mortality due to cardiovascular diseases; (b) the effectiveness of exercise modifying such risk factors and mortality. The latest reviews for each topic were identified through multiple searches of the Pubmed database. Quantitative reviews or meta-reviews were preferred over qualitative or narrative ones. The number and type of primary studies is specified (cross-sectional vs. longitudinal; RCTs vs. controlled trials).
Na, not available; RCTs, Randomized Controlled Trials; T2DM, Type 2 Diabetes Mellitus, CAD, Coronary Artery Disease; HF, Heart Failure; ACEi, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin II Receptor Blockers; OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; SMD, Standardized Mean Difference; CI, Confidence Intervals.

rating scales (91). Moreover, exercise interventions have been found to result in 22% higher likelihood of remission from depression than treatment as usual (93), the latter in turn being associated with the remission of about a third of patients (3, 4). Generally, exercise is well-tolerated and leads to about 18% of dropout rates (94). Based on the available data, the efficacy of exercise seems greater if it is aerobic, delivered in groups, and supervised by an instructor (95). Although there are relatively few head-to-head comparisons and duration of treatment may be different, the efficacy of exercise may be comparable in terms of magnitude to that of psychotherapies (3, 94–97) or antidepressant medications (98).

Some authors claim the psychological effects of exercise largely depend on "placebo," or "non-specific" psychosocial effects, such as attention by staff (99, 100). Consistently, exercise is still listed among "alternative and complementary" therapies in some guidelines [e.g., (101)]. Skepticism has been fueled, among other reasons, by difficulties to demonstrate a clear dose-response relationship, such as would be expected in drug trials. Recent studies, however, have started to detect significant associations between the intensity and length of exercise interventions, and their antidepressant efficacy (102, 103); of note, such relationship is likely to follow non-linear patterns (104). Another long-held belief among clinicians is that exercise does only ameliorate non-specific somatic symptoms, such as sleep and appetite changes. Whereas, extant results suggest that exercise indeed reduces core symptoms of depression, such as depressed mood, anhedonia, and suicidal ideation (105, 106). On the other hand, studies examining the effects of exercise interventions on cognitive function among individuals with depression [e.g., (107)] at present do not indicate substantial benefits (108–110).

Exercise may be effective improving several biomarkers that have been implicated in depression (e.g., impaired neuroplasticity, autonomic, and immune imbalances). However, at present, evidence derived from non-depressed individuals still needs to be replicated among clinical populations (111). Nevertheless, recent trials have begun to show efficacy in treating patients with severe mood disorders (112–114) and individuals with treatment-resistant depression, either alone or as an add-on to medications (115, 116). Lastly, exercise can be effective for individuals who may present concerns about drug treatment, such as women with pregnancy or post-partum depression (117) and adolescents (118, 119).

At present, research is still needed to establish the efficacy of exercise in the long-term course of major depression. Some analyses suggest that the antidepressant effects may diminish beyond the duration of the exercise intervention (92). However, individuals who regularly engage in moderate physical activity maintain reduced risk of incurring depressive episodes (120, 121).

EFFECTIVENESS OF EXERCISE IN LATE LIFE DEPRESSION

The clinical features and pathophysiology of late-life depression are largely distinct from that encountered among younger adults (122–124). Specifically, depression in late life is associated with a higher prevalence of physical illnesses, greater prevalence of cognitive impairments and inadequate response to antidepressant drugs (125–128). Despite these differences, late-life depression seems to respond to exercise as well as adult depression (129–131). Moreover, among studies appraised in recent meta-analyses, participants receiving exercise

did not report any significant side effects. More recently, the SEEDS study showed that exercise was an effective add-on to antidepressant drugs for mild to moderate depression (132). Interestingly, adding exercise to antidepressant drugs primarily affected core symptoms of depression rather than somatic symptoms (133). Moreover, individuals receiving aerobic exercise plus antidepressants displayed greater improvements in cognition and autonomic balance compared to those only receiving antidepressants (134, 135). The intervention was well-received by patients and physicians alike (136).

Despite these promising results, the available evidence remains insufficient to conclude whether exercise can improve cognition in patients with late-life depression (108, 109). At present, studies suggest that exercise may not improve cognition among non-impaired, non-depressed individuals (137), but it may, to some extent, improve cognitive performance among individuals diagnosed with cognitive impairment (irrespective of depression), dementia, or physical diseases (138–141).

HOW SHOULD EXERCISE BE PRESCRIBED TO INDIVIDUALS WITH DEPRESSION?

Depression is usually treated by primary care physicians, psychiatrists, and psychologists. Exercise interventions can be delivered by professionals with a variety of disciplinary backgrounds, including group exercise leaders, personal trainers, clinical exercise physiologists, wellness specialists, and physical therapists. Given the challenging cognitive and affective features of depression, it is recommended that exercise for individuals with depression should be delivered by professionals with specific experience in mental health care (142). In other words, a well-integrated, collaborative approach is essential.

A collaborative approach begins with physicians willing to introduce the idea of exercise as a possible treatment options to individuals expressing depression complaints. However, proposals to introduce exercise to the armamentarium of interventions for the treatment of depression are often met with skepticism by physicians due to various perceived barriers (143, 144). These barriers may stem, at least in part, from high-profile reviews and treatment recommendations that downplay the relevant evidence. A recent review, for example, characterized any benefits of exercise, even against non-active control interventions, as merely "modest," alleged that "high-quality clinical studies investigating the effect of exercise for treating depression among older patients are lacking," and raised doubt about whether older individuals with depression would be "willing to participate actively in an exercise program" (145). A counterpoint is that, to a large extent, such statements reflect a limited or outdated assessment of the evidence (146, 147). While the evidence base continues to evolve, there are already several randomized controlled trials with positive results that satisfy the standard criteria for high methodological quality (91). Furthermore, provided that proper therapeutic alliances are established within a stepped-care collaborative framework (136), many individuals with subthreshold, mild, and moderate depressive symptoms will opt for exercise and will demonstrate satisfactory adherence.

Several groups have published recommendations for developing exercise prescriptions for individuals with depression, based on both empirical evidence and clinical experience (148–152). While we endorse these recommendations, we should note that the optimal exercise prescription for the treatment of depression remains unknown, insofar as the relation between the "dose" of exercise (i.e., intensity, frequency, session duration) and the therapeutic response remains understudied. Therefore, any prescription recommendations at the present stage are essentially derived from general exercise prescription guidelines, which were developed primarily for the improvement and maintenance of physical fitness and cardiometabolic health (153). Therefore, we wish to highlight an emerging trend in exercise prescription, which may be especially relevant to the treatment of depression, namely affect-based exercise prescription (154). This method expands the traditional focus of exercise prescriptions from the dual goal of maximizing fitness gains while minimizing risk to a model that also aims to ensure that participants consistently derive pleasant affective experiences. The inclusion of pleasure as a central consideration is intended to enhance what is often the Achilles' heel of lifestyle or behavior-change interventions, namely adherence. In a typical affect-based prescription, the exercise participant is shown a simple rating scale (e.g., one ranging from +5: "I feel very good" to −5: "I feel very bad") and is instructed to self-regulate his or her exercise intensity and duration to maintain a rating of +3 or higher.

Individuals with depression can experience exercise as pleasant and affect-enhancing (155–157). Among non-depressed adults, affective responses to a bout of exercise have been found in correlational studies to be associated with the amount of physical activity individuals choose to do (158), while experimental manipulations resulting in improved affective responses have been shown to increase the amount of physical activity performed over a subsequent period of 6 months (159). Early evidence among individuals with depression indicates that affective responses to a bout of exercise may predict treatment response (160, 161). While randomized controlled trials investigating the efficacy, effectiveness, and cost-effectiveness of affect-based exercise prescriptions for the treatment of depression are not yet available, this method seems to hold promise for clinical application due to its simplicity, making it appealing to physicians who lack specialized training in exercise and to healthcare organizations concerned about implementation costs.

CONCLUSIONS

The premature mortality of individuals with depression is an alarming public health concern, which is exacerbated by the present inability to offer satisfactory treatments. Physical exercise represents an underutilized intervention that may uniquely address both concerns at the same time.

First, exercise offers numerous physical benefits, which can counteract several mechanisms postulated to increase mortality risk in depression. Second, if prescribed and delivered correctly, exercise can be as effective as other first-line treatments, while being mostly free of adverse side-effects.

While there is a need of pragmatic trials to evaluate the long-term effects of exercise and its cost-effectiveness, clinicians in the mental health sector should acknowledge this ancient, yet new treatment option and should start to use it to the benefit of patients.

AUTHOR CONTRIBUTIONS

MB and PE conceived and drafted the work. MM, DZ, SC, PC, LC, GS, SZ, and MA contributed to revising it critically and approving the content.

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Metabolic Syndrome in Psychotic Disorder Patients Treated With Oral and Long-Acting Injected Antipsychotics

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Background: Severe mental illnesses are associated with increased risks for metabolic syndrome (MetS) and other medical disorders, often with unfavorable outcomes. MetS may be more likely with schizoaffective disorder (SzAff) than schizophrenia (Sz). MetS is associated with long-term antipsychotic drug treatment, but relative risk with orally administered vs. long-acting injected (LAI) antipsychotics is uncertain.

Methods: Subjects (n = 151 with a DSM-IV-TR chronic psychotic disorder: 89 Sz, 62 SzAff), treated with oral or LAI antipsychotics were compared for risk of MetS, initially with bivariate comparisons and then by multivariate regression modeling.

Results: Aside from measures on which diagnosis of MetS is based, factors preliminarily associated with MetS included antipsychotic drug dose, "high-risk" antipsychotics associated with weight-gain, older age and female sex. Defining factors associated with diagnosis of MetS ranked in multivariate regression as: higher fasting glucose, lower LDL cholesterol, higher diastolic blood pressure, and higher BMI. Risk of MetS with antipsychotics ranked: quetiapine ≥ clozapine ≥ paliperidone ≥ olanzapine ≥ risperidone ≥ haloperidol ≥ aripiprazole. Other associated risk factors in multivariate modeling ranked: higher antipsychotic dose, older age, and SzAff diagnosis, but not oral vs. LAI antipsychotics

Conclusions: SzAff diagnosis and higher antipsychotic doses were associated with MetS, whereas orally vs. injected antipsychotics did not differ in risk of MetS.

Keywords: metabolic syndrome, antipsychotics, long-acting injected, schizoaffective, schizophrenia

INTRODUCTION

Persons with severe mental illnesses have increased risk for metabolic disorders, including metabolic syndrome (MetS), characterized by obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension (1). Such disorders appear to be related to an unhealthy diet, lack of regular exercise, adverse effects of psychotropic drugs, and possibly to undefined risk factors associated with the illnesses themselves (2, 3). Much of the research on this topic has involved patients diagnosed with chronic psychotic or mood disorders, particularly schizophrenia (Sz) and bipolar disorder

(2, 4–6). Few studies have compared physical health of subjects diagnosed with schizoaffective disorder (SzAff) to that of other patients with other psychotic-disorder diagnoses, including Sz, but SzAff patients may have a greater risk of MetS than those with other major psychiatric disorders (6). SzAff patients are characterized by emotional and behavioral instability over time as well as psychotic features, and often are treated with relatively complex pharmacological regimens (7). Both emotional instability and complex treatments may contribute to an increased risk of metabolic disorders (1).

Also uncertain is whether specific types of medicines differ appreciably in their associations with risks of metabolic disorders. In particular, the extent to which relative metabolic risks of modern or second-generation antipsychotics (SGAs) and their long-acting injected (LAI) preparations differ from older or orally administered antipsychotics remains uncertain (1, 8–10).

The preceding considerations led us to compare clinical measures, in particular indices of metabolic health, among SzAff vs. Sz patient-subjects to identify factors associated specifically with MetS, including comparison of orally administered vs. LAI antipsychotics. We hypothesized that SzAff subjects would have a higher risk of MetS than Sz subjects, and that the risk might be lower with LAI antipsychotic treatments.

METHODS

From June 2014 to February 2017, we enrolled study subjects as part of a program monitoring the health of psychotic disorder patients attending the Day Hospital Service for Severe Mental Disorders in the Psychiatric Department at the University of Foggia Medical Center. A total of 151 consecutive patients were enrolled as study-subjects, including 89 diagnosed with Sz and 62 as SzAff by two expert clinicians (AB, AV) based on DSM-IV-TR (Diagnostic and Statistical Manual of mental disorders-Text Revision) criteria (11). Treatments were selected clinically and included oral antipsychotics ($n = 64$, with or without mood-stabilizers or antidepressants) as well as LAI antipsychotics ($n = 87$, usually as monotherapy).

All subjects provided written informed consent to participate, after study procedures approved by the University of Foggia medical center ethics committee were explained to them. Patients were enrolled in a stable phase of their illness and treatments; candidates who required psychiatric hospitalization, had revised treatment protocols within the previous 6 months, were actively abusing alcohol or drugs (confirmed by urine assays), or were pregnant, were excluded from the study.

Current psychiatric morbidity was assessed and rated with the Positive and Negative Syndrome Scale (PANSS) (12), and Brief Psychiatric Rating Scale (BPRS) (13) by two experienced psychiatrist-investigators (AB, AV). Raters were held unaware of treatments given, and their ratings yielded high, independent, interrater agreement ($\chi^2 \geq 0.90$). Being considered "mildly ill" corresponded to a PANSS total score of ≤58 or BPRS score of ≤31, "moderately ill" corresponded to PANSS ratings of 59–75 or BPRS scores of 32–40, "moderately severely ill" corresponded to PANSS of 76–95 or BPRS of 41–53, and "severely ill" corresponded to a PANSS of 96–116 or BPRS of 54–126 (12, 13).

We also collected data on: demographics (sex, age, employment status), current pharmacological treatments (oral or LAI antipsychotics, mood stabilizers [MSs], and antidepressants [ADs]), and their doses; anthropometric and metabolic measures (height [cm] and weight [kg] for body-mass index [BMI]), systolic and diastolic blood pressure (mm Hg), pulse (beats/min); serum concentrations of fasting glucose (FBS; mg/dL), %-glycated hemoglobin (Hgb-A1c), total cholesterol (mg/dL), low density lipoproteins (LDL; mg/dL), high density lipoproteins (HDL; mg/dL), triglycerides (mg/dL); waist circumference (cm), electrocardiographic rate-corrected QT repolarization interval (QTc, msec); serum levels of prolactin (ng/dL), thyroid stimulating hormone (TSH, mIU/L), and free thyroxin and triiodothyronine. We also recorded adverse events associated with treatment, and rated treatment-adherence with the 30-item Drug Attitude Inventory (DAI-30) (14).

We rated subjects for the presence of MetS defined by current, revised International Diabetes Federation (IDF) criteria, American Heart Association and International Association for the Study of Obesity (15, 16). MetS required meeting ≥3 of the following 5 criteria: [a] large waist circumference (≥102 cm in men, ≥88 cm in women); [b] elevated serum triglycerides (≥150 ng/dL); [c] low HDL-cholesterol (<40 mg/dL in men and <50 in women); high blood pressure (≥130 mm Hg systolic or ≥85 mm diastolic); elevated glucose as fasting blood sugar (FBS >100 mg/dL).

To facilitate comparisons, we converted antipsychotic doses to approximate oral daily mg-chlorpromazine-equivalents (CPZ-eq); LAI antipsychotic doses were estimated as total mg doses per days of injection cycles for conversion to CPZ-eq (17, 18). For MSs, we converted dosages to approximate daily mg-equivalents of lithium carbonate (Li-eq) (18, 19). Antidepressants were noted as being prescribed or not.

We compared measures collected among subjects diagnosed with SzAff and Sz, treated with LAI and oral antipsychotics, emphasizing comparisons of subjects with vs. without MetS. Data analyses used commercial statistical programs (Statview-5, SAS Corp., Cary, North Carolina, USA for spreadsheets; Stata.13.0, Stata Corp., College Station, Texas, USA). Data are presented as means ± standard deviation (SD) or with 95% confidence intervals (CI), or as percentages (%), unless stated otherwise. Continuous data were compared using nonparametric Mann-Whitney rank-sum test (z-score) to avoid problems of non-normal distribution of values, and categorical data were tested with contingency tables (χ^2). Factors yielding $p < 0.10$ in preliminary bivariate comparisons were considered in multivariate logistic regression modeling, with presence of MetS as the outcome measure.

RESULTS

Sample Characteristics and Treatments

The 151 patient-subjects were aged 42.1 ± 12.4 years; 52.9% were men, 18.5% were employed. Diagnoses included Sz ($n = 89$; 58.9%) and SzAff ($n = 62$; 41.1%). More men than women were

diagnosed with Sz ($\chi^2 = 6.76$; $p = 0.009$). Treatments included oral antipsychotics in 42.3%, and LAI antipsychotics in 57.7% (none received both). Antipsychotics were combined with mood-stabilizers (MSs) in only 14.5%, or with antidepressants (ADs) in 12.3% (ranking by use: duloxetine > paroxetine > citalopram or *S*-citalopram > sertraline). Both adjunctive treatments were given selectively with oral antipsychotics, by 6.4- (MSs) or 7.0-times more (ADs; both $p \leq 0.006$) among SzAff than Sz subjects. Antipsychotic doses averaged 313 ± 329 mg/day CPZ-eq, and MS (carbamazepine, lithium carbonate, sodium valproate) total daily Li-eq doses averaged 650 ± 244 mg. Overall, clinical ratings averaged 75.0 ± 34.7 for PANSS and 51.6 ± 23.6 for BPRS; both indicate moderate symptomatic severity, even though all patients reported clinical and treatment stability for at least six continuous preceding months. Prolonged, stable dosing assured that even the LAI antipsychotics were at pharmacokinetic steady-state.

Subjects who received LAI vs. oral antipsychotics had significantly lower levels of symptomatic morbidity. PANSS scores were, respectively, 58.0 ± 27.6 vs. 98.1 ± 29.9, and BPRS scores averaged 40.1 ± 15.0 vs. 67.1 ± 24.5 (z-scores = 7.76 and 6.85, both $p < 0.0001$).

No subject was considered to have a substance-use disorder, as was supported by urine drug assays, consistent with current substance abuse as an exclusion criterion. Adherence to prescribed treatments was considered good, as supported by a DAI-30 score of 9.64 ± 2.19 (of a total maximum of 30). There was a moderate rate of reported, treatment-associated, adverse events (19.8%), most of which involved motor slowing or mild tremor.

Risk and Measures Associated With Metabolic Syndrome

Of the entire sample, 31.8% met diagnostic criteria for MetS (**Table 1**): 42.3% of women and 22.5% of men. Overall, BMI averaged 27.7 ± 5.72 kg/m^2, in the nearly obese range. However, 35.8% of subjects (38.0% of women and 33.8% of men) had BMI of ≥28.8 kg/m^2, taken to indicate obesity (15, 16).

Other factors possibly associated with MetS included: female sex, older age, SzAff vs. Sz diagnosis, higher BPRS psychosis score (which was associated with greater APD doses: Spearman $r_s = 0.252$, slope = 1.68 [0.653–2.72], $p = 0.002$), treatment with antipsychotics with relatively high risk of obesity and MetS (clozapine, olanzapine, paliperidone, quetiapine; **Table 2**), higher CPZ-eq antipsychotic dose, but not orally administered vs. LAI antipsychotics (**Table 1**). Additional metabolic and cardiovascular measures did not differ between subjects with vs. without MetS, including assays of TSH and thyroid hormones, prolactin, pulse rate, and ECG repolarization interval (QTc), nor did BPRS or PANSS ratings of psychosis-severity differ (**Table 1**).

As expected, measures that contributed to its diagnosis were highly deviant among subjects with MetS, including obesity, waist circumference, blood pressure, FBS, hemoglobin glycation, serum concentrations of cholesterol (higher total and LDL, lower HDL) and triglycerides (**Table 1**). BMI was not used to define MetS but was markedly elevated in subjects with MetS (**Table 1**). We also tested the strengths of association of such measures with the diagnosis of MetS using logistic regression modeling (**Table 2**). These ranked as: higher FBS ≥ lower HDL ≥ higher diastolic blood pressure ≥ higher BMI ≥ female sex (BMI and sex were not included in diagnostic criteria for MetS).

Treatments and Metabolic Syndrome

LAI antipsychotics were more prescribed than oral agents (57.7% vs. 42.3%), particularly among Sz vs. SzAff subjects (65.5% vs. 34.5%; $\chi^2 = 3.67$, $p = 0.055$), whereas oral agents were used in half of both diagnostic groups. Average CPZ-eq daily doses of oral and LAI antipsychotics among Sz (295 mg) and SzAff subjects (338 mg) did not differ significantly. LAI paliperidone palmitate was the most prescribed antipsychotic agent in both diagnostic groups (Sz 34.8%; SzAff 27.4%; 31.8% overall); other LAI antipsychotic usage ranked: risperidone extended release (10.6%) > aripiprazole long acting (9.28%) > olanzapine palmitate (4.64%). Usage of oral antipsychotics ranked: risperidone (Sz 11.2%, SzAff 12.9%, 11.9% overall) > haloperidol (7.28% overall) = olanzapine (7.28%) > aripiprazole (5.30%) > quetiapine (3.98%) ≥ paliperidone (3.31%) = clozapine (3.31%) > ziprasidone 1.32%.

Several metabolic measures were somewhat more favorable with use of LAI vs. oral antipsychotics, including total cholesterol (192 vs. 223 mg/dL), LDL cholesterol (125 vs. 175 mg/dL), triglycerides (148 vs. 188 mg/dL); waist circumference (103 cm [40.6 in] vs. 117 cm [46.1 in]); the cardiac QTc repolarization interval (399 vs. 413 msec); and circulating prolactin (42.7 vs. 61.3 ng/dL).

We compared the prevalence of MetS among subjects treated with different antipsychotic agents. Relatively high-risk drugs were quetiapine (83.3%), clozapine (60.0%), paliperidone (34.0%) and olanzapine (33.4%; **Table 3**). Of note, these risks were not accounted for by dose as prevalence of MetS and CPZ-eq doses were not significantly correlated (**Table 3**).

Multivariable Modeling: Factors Associated With Metabolic Syndrome

We used multivariable logistic regression modeling to identify factors associated independently with MetS. In order of significance, associated factors ranked: CPZ-eq antipsychotic dose, older age, and SzAff > Sz diagnosis, but not oral vs. LAI antipsychotics (**Table 4**).

DISCUSSION

This study involved 151 patient-subjects with chronic psychotic disorders who had been clinically stable on constant medication regimens for at least 6 months. LAI antipsychotics were given to 57.7%, and oral agents to 42.3%. LAI agents were more often given to Sz subjects, whereas use of oral antipsychotics was similarly prevalent in both SzAff and Sz subjects. SzAff subjects were also 6–7-times more likely to be given co-treatment with a mood-stabilizer or antidepressant. All subjects were rated at moderate symptomatic severity by PANSS and BPRS. Adherence to prescribed treatments was rated as good by DAI-30 score, and the risk of adverse effects was moderate at 19.8%.

TABLE 1 | Factors associated with metabolic syndrome in 151 psychotic disorder patients.

Factor	Metabolic syndrome		Statistic	*p*-value
	Present	Absent	(*z* or χ^2)[a]	
All cases (*N* = 151)	31.8 [24.5–39.9]	68.2 [60.1–75.5]	–	–
Women (%)	62.5 [47.4–76.0]	39.8 [30.3–49.9]	6.77	0.009
Older age (years)	45.0 [42.0–48.0]	40.8 [38.2–43.4]	2.18	0.03
Unemployed (%)	83.3 [69.8–92.5]	80.6 [71.6–87.7]	0.67	0.69
Schizoaffective diagnosis (%)	52.1 [37.2–66.7]	35.9 [26.7–46.0]	3.53	0.06
Psychosis				
BPRS score	57.1 [49.8–64.4]	49.0 [44.6–53.4]	1.96	0.05
PANSS score	81.7 [71.1–92.3]	71.9 [65.3–78.5]	1.55	0.12
Substance abuse (%)	4.17 [0.51–14.3]	1.94 [0.24–6.84]	0.63	0.43
High-risk antipsychotics (%)[b]	29.2 [17.0–44.1]	14.6 [3.39–22.9]	4.50	0.03
LAI antipsychotics (%)	50.0 [35.2–64.8]	50.0 [35.2–64.8]	1.67	0.20
Antipsychotic dose (CPZ-eq, mg/day)	423 [266–580]	261 [235–287]	2.14	0.004
Treatment adherence (DA130)	9.95 [9.25–10.7]	9.59 [9.12–10.1]	0.86	0.39
Adverse drug effects (%)	22.9 [12.0–37.3]	18.4 [11.5–27.3]	0.41	0.52
Mood-stabilizers given (%)	18.8 [8.95–32.6]	12.6 [6.89–20.6]	0.99	0.32
Antidepressants given (%)	2.08 [0.05–11.1]	6.80 [2.28–13.5]	1.45	0.23
BMI (kg/m^2)	30.3 [28.3–32.3]	26.6 [25.7–27.5]	3.43	0.0006
Obesity (% BMI≥28.8)	64.6 [49.5–77.8]	22.3 [14.7–31.6]	25.4	<0.0001
Waist circumference (cm)	117 [110–124]	105 [100–110]	2.74	0.006
Systolic BP (mm Hg)	120 [117–123]	116 [114–117]	2.28	0.02
Diastolic BP (mm Hg)	76.5 [75.5–81.5]	73.7 [71.7–75.8]	2.58	0.01
Pulse rate (per min)	85.0 [82.7–86.1]	84.4 [82.4–87.6]	0.37	0.71
ECG repolarization (QTc, msec)	409 [401–417]	407 [403–411]	0.13	0.90
Glucose (FBS, mg/dL)	105 [99.6–110]	88.8 [87.2–90.4]	4.91	<0.0001
HgbA1c (%)	5.95 [5.71–6.19]	5.62 [5.49–5.75]	2.79	0.005
Total cholesterol (mg/dL)	217 [206–228]	200 [193–207]	2.50	0.01
LDL cholesterol (mg/dL)	161 [148–174]	140 [132–148]	2.75	0.006
HDL cholesterol (mg/dL)	42.9 [40.3–45.5]	50.2 [47.9–52.5]	3.86	0.0001
Triglycerides (mg/dL)	204 [181–227]	147 [135–159]	4.31	0.0002
TSH (nU/L)	2.56 [2.07–3.05]	2.14 [1.89–2.39]	1.65	0.10
Free thyroxin (ng/dL)	1.13 [1.07–3.05]	1.30 [1.09–1.51]	1.09	0.27
Free triiodothyronine (ng/dL)	0.358 [0.340–0.376]	0.353 [0.340–0.366]	0.86	0.39
Prolactin (ng/dL)	42.9 [41.4–54.5]	50.2 [47.1–65.9]	1.53	0.12

BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; LAI, long-acting injectable antipsychotics; CPZ, chlorpromazine; DAI, Drug Attitude Inventory; BMI, body-mass index; BP, blood pressure; ECG, electrocardiogram; Hgb, hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone. [a]*Mann-Whitney (z-score) or contingency table (χ^2).* [b]*Clozapine, olanzapine, paliperidone, quetiapine.*

The overall prevalence of MetS (31.8%) was moderate, but ranged from 18.2% with aripiprazole to 83.3% with quetiapine (**Table 3**). By comparison, reported prevalence of MetS in patients with psychotic disorders has ranged from 30 to 67% (1, 7, 20, 21). Based on multivariate modeling, factors associated with MetS were antipsychotic dose, older age, and SzAff diagnosis, but not oral vs. LAI antipsychotics.

Of note, the present finding of significantly greater risk of MetS with SzAff vs, Sz diagnoses supports one hypothesis of this study, and adds to a previous suggestion of such a relationship (6). Although use of complex medication regimens was much more prevalent among SzAff subjects, these were infrequent and not significantly associated with risk of MetS. In addition, CPZ-eq antipsychotic doses were somewhat higher among SzAff subjects, although both factors appeared to operate somewhat independently (**Table 4**). Nevertheless, we suggest that the relative instability of SzAff disorders contributes to the use of more complex treatments (7) and this feature as well perhaps as intrinsic characteristics of such patients may contribute to risk of MetS.

In addition, contrary to prediction, we did not find a significant difference in risk of MetS in association with treatment with oral vs. LAI antipsychotics. This finding appears to be consistent with other recent reports indicating that LAI agents may not be safer than oral antipsychotics (8, 10). However, several measures tended to be less abnormal with LAI treatments (including lower total and LDL cholesterol, triglycerides and prolactin, smaller waist-circumference, and

TABLE 2 | Multivariable logistic regression modeling: diagnostic measures associated with metabolic syndrome.

Measure	OR [95% CI]	χ^2	*p*-value
Higher FBS	1.12 [1.07–1.17]	25.2	<0.0001
Lower HDL	1.16 [1.08–1.24]	17.0	<0.0001
Diastolic blood pressure	1.10 [1.04–1.16]	10.3	0.001
Higher BMI	1.17 [1.06–1.29]	9.53	0.002
Female sex	5.72 [1.85–17.7]	9.21	0.002

Model fit $\chi^2 = 93,5$, $p < 0.0001$. Not associated, age, LDL level, waist-circumference.

TABLE 3 | Risk of metabolic syndrome: antipsychotic agents and doses.

Drug	Metabolic Syndrome Prevalence (% [CI])	Daily dose (CPZ-eq mg [CI])
Quetiapine	83.3 [35.9–99.6]	229 [89.9–368]
Clozapine	60.0 [14,7–94.7]	615 [196–1034]
Paliperidone	34.0 [21.5–48.3]	298 [265–330]
Olanzapine	33.4 [13.3–59.0]	378 [309–448]
Risperidone	23.5 [10.7–41.2]	266 [232–301]
Haloperidol	18.2 [2.28–51.8]	259 [197–321]
Aripiprazole	18.2 [5.19–40.3]	121 [95.4–146]

Risk of MetS is not significantly associated with CPZ-eq dose (Spearman $r_s = 0.402$, $p = 0.325$), but the drugs differ overall ($\chi^2 = 13.4$, $p = 0.04$). Relatively high-risk drugs are quetiapine, clozapine, paliperidone and olanzapine.

TABLE 4 | Multivariable logistic regression modeling: risk factors associated with metabolic syndrome.

Factor	OR [95% CI]	χ^2	*p*-value
Antipsychotic dose (CPZ-eq)	1.003 [1.001–1.005]	4.80	0.028
Older age	1.03 [1.01–1.07]	4.76	0.029
Diagnosis: Schizoaffective	2.28 [1.06–4.90]	4.46	0.035
Oral vs. LAI antipsychotics	1.01 [0.46–2.24]	0.001	0.98

Model fit $\chi^2 = 17.9$, $p = 0.001$. Not associated, sex, diagnosis, psychosis severity. (BPRS rating).

shorter QTc interval). In addition, we found marked differences in risk of MetS between particular antipsychotic agents, with higher risk associated with quetiapine, clozapine, paliperidone, and olanzapine, which are known to be associated with relatively high risks of weight-gain (1, 2, 18, 22, 23).

Limitations

The study included a relatively small number of subjects and its findings may not generalize to other sites. Its cross-sectional design supports associations with MetS, but precludes causal inferences. In addition, estimates of CPZ-eq doses of LAI antipsychotics are not adjusted for probable but uncertain differences in bioavailability of injected vs. orally administered drugs.

CONCLUSIONS

This observational study of 151 patient-subjects with chronic psychotic disorders found a moderate prevalence of MetS (31.8%), which was associated with being overweight or obese and with antipsychotic agents prone to leading to weight-gain, as well as higher antipsychotic CPZ-eq doses, and older age. Notably, risk of MetS was somewhat greater among SzAff than Sz subjects, but did not differ significantly between treatment with oral and LAI antipsychotics nor with the relatively infrequent use of adjunctive mood-stabilizers or antidepressants. However, several metabolic measures tended to be less abnormal among SzAff than Sz subjects. The association of MetS with SzAff (more than with Sz) probably reflects the complexity of SzAff disorders and their pharmacological treatment, including somewhat higher antipsychotic doses and more co-treatment with mood-stabilizers and antidepressants, but may also reflect other unknown characteristics of the disorders themselves.

AUTHOR CONTRIBUTIONS

AV, GV, IB, AC, AR, and AP recruited patients and collected data. AV and RB wrote the paper. AB supervised clinical work and the manuscript drafting.

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Need for Cardiovascular Risk Reduction in Persons With Serious Mental Illness: Design of a Comprehensive Intervention

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Persons with serious mental illness (SMI) comprise a high-risk group for cardiovascular disease (CVD)-related mortality with rates at least twice those of the overall US. Potentially modifiable CVD risk behaviors (tobacco smoking, obesity, physical inactivity, unhealthy diet) and risk factors (hypertension, diabetes, dyslipidemia) are all markedly elevated in persons with SMI. Evaluations of programs implementing integrated medical care into specialty mental health settings have not shown meaningful effects on CVD risk factor reduction. Rigorously tested, innovative interventions are needed to address the large burden of CVD risk in populations with SMI. In this article, we describe the design of a comprehensive 18-month intervention to decrease CVD risk that we are studying in a randomized clinical trial in a community mental health organization with psychiatric rehabilitation programs. The individual-level intervention incorporated health behavior coaching and care coordination/care management to address all seven CVD risk behaviors and risk factors, and is delivered by a health coach and nurse. If successful, the intervention could be adopted within current integrated care models and significantly improve the physical health of persons with SMI.

Keywords: serious mental disorder, cardiovascular risk, intervention, care coordination, behavioral coaching

INTRODUCTION

Persons with serious mental illness (SMI) comprise a high-risk group for cardiovascular disease (CVD)-related mortality with rates at least twice those of the overall US (1–5). Potentially modifiable CVD risk behaviors (tobacco smoking, obesity, physical inactivity, unhealthy diet) and risk factors (hypertension, diabetes, dyslipidemia) are all markedly elevated in persons with SMI (6–10). The American Heart Association set strategic goals to improve cardiovascular (CV) health to ideal levels for each risk factor and reduce CVD mortality by 20% for all Americans by 2020 (11). However, persons with SMI often have challenges in everyday functioning due to cognitive impairment and ongoing psychiatric symptoms (12, 13). Together with high prevalence of substance use, unemployment, low-income and social isolation, these factors make implementing effective CVD risk reduction interventions challenging for this population (13–17). Adapted

behavioral weight loss interventions and smoking cessation interventions tailored to persons with SMI have shown to be efficacious in clinical trials (18–21), however, evidenced-based interventions are needed that address more than one CVD risk factor. Without special efforts to develop interventions that promote CV health and control risk factors in persons with SMI, health disparities will persist and likely worsen.

While in the general population there is substantial evidence that non-physician interventionists (e.g., care managers) who facilitate and coordinate treatment with primary care physicians (PCPs) can improve multiple CVD risk factors (22–28), evidence for effective interventions in populations with SMI is needed. To address the premature mortality from CVD and other medical causes (3, 29–32) and need for improved access to quality care for physical health conditions (33, 34) among people with SMI, there has been a recent increase in implementation of programs integrating medical care into mental health settings (35–45).

In the US, one such model is the behavioral health home (BHH), which incorporates primary care coordination and management into the specialty mental healthcare setting (35–42). However, results from evaluations of BHHs and other integrated programs to-date have been mixed with either no or minimal effects on actual CVD risk factors (37, 46–51).

Thus, rigorously tested, innovative interventions are needed to address the large burden of CVD risk in populations with SMI. Here we describe the design and implementation of a comprehensive risk reduction intervention incorporating health behavior coaching and care coordination/care management to address all CVD risk factors in persons with SMI that we are studying in a randomized clinical trial.

TRIAL STUDY DESIGN

This community organization-based two-arm randomized clinical trial (the IDEAL trial) tests an 18-month comprehensive, practical risk reduction program compared to control in reducing CVD risk as assessed by the global Framingham Risk score (52) in persons with SMI. Participants were randomized to receive a control condition or the active intervention, which incorporates health behavior coaching and care coordination/care management to improve CVD risk behaviors and factors. Individual CVD risk behaviors and factors comprise secondary outcomes.

PARTICIPANTS AND SETTINGS

Two hundred sixty-nine participants with SMI 18 and older and at least one CVD risk factor (hypertension, diabetes mellitus, dyslipidemia, current tobacco smoker, or BMI $\geq$ 25 kg/m^2) were enrolled in the study. Exclusion criteria included having a CVD event in the prior 6 months, a serious medical condition limiting life expectancy, or an active alcohol or substance use disorder, pregnancy, planning on leaving the community in 6 months or the geographic area in 18 months. Serious mental illness diagnosis was assessed by chart review. The study was conducted in partnership with a large community mental health organization that provides outpatient services including psychiatric rehabilitation programs (PRPs). PRPs serve persons with SMI offering vocational and skills training, coordination of behavioral health and social services, and normally provide breakfast and lunch to attendees. We implemented the study at four organization sites with PRPs. As part of our partnership with the community mental health organization and to encourage environments conducive to healthy behaviors, we provided training and resources to promote group physical activity classes open to all program attendees, and a dietician to consult with PRP kitchen staff to provide healthier meals.

INTERVENTION OVERVIEW

We adopted the American Heart Association (AHA) Life's Simple 7 goals and modified some (e.g., 10 lb. weight loss instead of BMI $<$ 25) to provide intermediate targets achievable over the 18-month intervention (11). (**Table 1**) To work toward these goals, participants in the active intervention met individually with a health coach and a nurse who provided: (1) tailored CVD risk reduction education and counseling; (2) collaboration with physicians to advocate for appropriate management of CVD health risks; and (3) coordination with mental health staff and social supports to encourage and motivate participants to reach individually tailored CV health goals.

THEORETICAL APPROACH

Behavioral aspects of the IDEAL intervention incorporate social cognitive theory and behavioral self-management concepts (54, 55). Motivational interviewing, is well suited for adults with SMI in that it is patient-centered, and uses a guiding style to enhance intrinsic motivation to improve CVD risk-related behaviors and promote medication adherence (56–59). The intervention also used solution-focused therapy, a positive-oriented, goal-directed technique emphasizing solutions rather than problems (60, 61). These approaches are useful in helping individuals gain confidence from small successes while staying focused on positive long-term changes.

The intervention fits well within a psychiatric rehabilitation framework because rehabilitation models emphasize skill building and goal setting and incorporate reinforcements as part of a behavioral change strategy (62–65). Evidence demonstrates the success of points/reward systems for persons with SMI in improving social interactions, work-related task performance, and other adaptive behaviors (66–74). The IDEAL intervention uses a point system to reward recommended behaviors (e.g., low carbon monoxide (CO) values consistent with no recent smoking, attending group exercise classes). Points can be traded for inexpensive items (e.g., pen, key chain) or saved for larger rewards (e.g., CD player).

The intervention is tailored to meet the cognitive needs of adults with SMI, characterized by memory and executive function deficits (75, 76). Participant materials have high readability and simplicity of messages, and streamlined paper tracking logs correspond to the intervention's lifestyle change

TABLE 1 | Intervention approaches in comprehensive cardiovascular risk reduction intervention for adults with serious mental illness.

CVD risk behavior or risk factor targets	Evidence-based goals*	Intervention approach
Tobacco smoking	Quit smoking	• Smoking cessation behavioral counseling tailored to readiness to quit • Communication with psychiatrist about pharmacotherapy • Contingency management with CO testing
Diabetes mellitus	Control blood sugar, HbA1c < 7%	• Diabetes self-management education • Behavioral counseling to support medication adherence, healthy diet and exercise • Regular monitoring of blood glucose and communication/coordination with physician, mental health program staff and caregivers
Hypertension	Control blood pressure, systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg	• Hypertension education • Behavioral counseling to support medication adherence, healthy diet and exercise • Regular blood pressure monitoring and communication with PCPs about monitoring and treatment goals.
Dyslipidemia	Lower cholesterol, total cholesterol <200 mg/dl, LDL<130 mg/dl**	• Behavioral counseling to support medication adherence, healthy diet and exercise • Communication with the PCP around guideline-concordant treatment with lipid lowering medications.
Overweight/obesity	Healthy weight, encourage 10 pound weight loss for those overweight or obese	• Lifestyle behavioral counseling including simplified dietary messages (e.g., avoid junk food, avoid sugar drinks, limit snacking, limit portion sizes), exercise, weekly weigh-ins, and self-monitoring using paper trackers. • Reinforce the role of weight management in the relevant CVD risk.
Unhealthy diet	Customized based on clinical condition	• Lifestyle behavioral counseling with clear message for healthy diet in context of other risk factors • Self-monitoring to increase awareness and accountability of food choices • Role playing and skill building to support decisions for healthy choices
Physical inactivity	Moderate intensity physical activity, 150 min/week	• Encourage participation in group exercise at PRP • Identify additional exercise strategies e.g., providing pedometers and setting daily step goals, exercise DVDs to guide home-based workouts • Link the role of exercise to the relevant CVD risk.

Based on AHA Strategic Goals and prevailing national guidelines modified for the trial, and tailored to participant needs.
***CVD risk-based target also used (53).*

approach. In addition, in-person sessions include techniques such as emphasizing learning through repetition, modeling and demonstrating a few specific skills repeatedly; breaking material into small units; and rehearsing behavioral skills (12, 77, 78).

The intervention utilizes concepts drawn from the overlapping constructs of care management and care coordination. Care management is a patient-centered, team-based approach to increase delivery of evidenced-based care for chronic medical conditions (79). Care coordination emphasizes the deliberate organization of patient activities and the sharing of relevant information among all concerned parties to achieve better patient care (80). The IDEAL intervention team includes a nurse and a health coach, who work together to facilitate communication and coordination between participants, providers, and mental health program staff for all aspects of CVD risk factor management.

INTERVENTION STAFF

The health coach is a facilitator with training in health behavior change and individual-level counseling with a skill level typical for a community health educator. When possible, the coach is an employee of the mental health organization; the position is modeled after one that would be feasible and sustainable in a community mental health setting. The coach, embedded in the PRP, is well-positioned to work with (other) community mental health program staff and take advantage of everyday interactions with staff and participants to encourage and support health behavior change and facilitate coordination of care for CVD risk factors. The registered nurse is an intervention team member who serves as a clinical resource addressing all aspects of CVD risk factor status. The coach and nurse report to an intervention director with motivational interviewing and health behavior change expertise. The intervention director implements quality assurance (**Table 2**), and may also provide direct services to participants.

INTERVENTION APPROACH

The core elements of the intervention include health behavior coaching, coordination of care and care management.

Health Behavior Coaching

Participants received 20–30 min individual coaching sessions, with weekly sessions for the first six months and at least biweekly thereafter, based on participant need. Guided by the participant's abilities and interests, the health coach addressed CVD risk and

TABLE 2 | Quality assurance techniques used in comprehensive cardiovascular risk reduction intervention for adults with serious mental illness.

Quality assurance technique	Intervention approach
Training	• Coaches receive initial training on CVD risk behaviors and risk factors • All staff trained on behavior change theories, working with persons with SMI, motivational interviewing, implementing the intervention according to the manual of procedures • Quarterly follow-up training • Follow up training topics determined from trends observed during case management and fidelity observations.
Case Management Meetings	• Used to review each participant's CVD risk factors and current treatment plan and to help facilitate behavior change and/or appropriate monitoring or treatment • Ensure that all participants are reviewed regularly; those with uncontrolled risk factors are prioritized. • Facilitated by intervention director, attended by intervention team and as needed by investigators with expertise in CVD risk reduction strategies
Intervention Fidelity	• Health coach and nurse sessions are either observed in person or audio recorded and reviewed by the intervention director for adherence to the protocol. • Fidelity reviews occur more frequently initially and then at least quarterly to identify skills in need of improvement.

targeted behaviors either simultaneously or sequentially. The sessions used motivational interviewing strategies with an initial focus on building rapport and establishing a working alliance. Sessions included a review of the participant's risk behaviors to identify knowledge deficits and to set short-term behavioral goals. The coach used solution-focused therapy to support attainment of individual goals. Participants were encouraged to self-monitor with simple tracking tools as appropriate for their cognitive abilities. The coach reviewed tracking data with participants to reinforce progress, identified triggers and high-risk situations, and formulated new behavioral plans. The nurse provided educational and counseling sessions related to specific CVD risk factors (e.g., diabetes). The intervention sessions may include family members or peers to support the participant for better control of risk factors (e.g. tobacco smoking).

Care Management and Care Coordination

The nurse mets with participants for medication-related counseling to address issues with adherence and plan for physician appointments, prioritizing those with uncontrolled risk factors. He/she shared information on participant's CVD risk factor profile with the primary care physician (PCP) and accompanied the participant on selected office visits. The nurse provided information on guidelines for diabetes, hypertension, dyslipidemia and smoking cessation as needed to participants' physicians, and advocated for evidenced-based monitoring and treatment (19, 53, 81–91). If the participant smoked and was interested in pharmacotherapy, the nurse communicated with the psychiatrist or PCP about prescribing smoking cessation medication and supported the participant through the process. The intervention staff coordinated with mental health staff, therapists, caregivers, physicians and/or office staff to support and reinforce participant health goals. This included facilitating the scheduling of and participant attendance at medical appointments, and removing barriers to obtaining medications and supplies as needed.

Approaches by Risk Factor

Participants received intervention sessions tailored to their individual CVD risk profiles and readiness to address each risk factor. When participants had multiple risk factors, in keeping with a patient-centered approach, intervention staff worked collaboratively with the participant to identify the focus of the sessions. They used options tools, cards with pictures, for possible conversation topics based on the participant's risk factors (e.g., for someone who smokes and has diabetes the options listed would read: Smoking, exercise, medication, sugar drinks). These tools gave the participant the autonomy to choose specific behaviors to discuss, while also allowing the coach to provide direction to the session.

Tobacco Smoking Cessation

Intervention staff assessed the motivation of participants who smoke with questions based on the transtheoretical stages of change (92) and placed them in one of three tracks: interested in quitting in 30 days; interested in quitting/reducing smoking but not ready to set a quit date; and expressing no interest in quitting. Those ready to quit within the next month received smoking cessation sessions and those interested but not ready to set a quit date received a motivational enhancement program (19, 93–95). The programs identified personalized reasons to stop smoking, provided training in strategies to respond to urges to smoke (The 4Ds: delay, do something else, deep breathe, drink water), and educated patients about the benefits of quitting and of using smoking-cessation pharmacotherapy. Those in the motivational enhancement program transitioned to quit smoking sessions when ready. These interventions incorporated a breathalyzer that measures expired CO as a marker of recent smoking, with incentives for low CO values. For those willing to consider recommended pharmacotherapy, the nurse worked with participants' physicians to facilitate prescription of varenicline or bupropion, and/or provided dual form nicotine replacement therapy as appropriate. Participants who expressed no interest in quitting smoking focused on other behavior change topics, however, the coach recommended change in smoking behavior monthly and re-assessed willingness to quit. If participants expressed interest in quitting smoking or were ready to set a quit date, they transitioned to another track.

Diabetes

Intervention staff helped participants optimally manage their diabetes through self-management education sessions, supporting medication adherence, and encouraging self-monitoring of blood sugar as appropriate. They facilitated hemoglobin A1c monitoring and other guideline concordant

care for diabetes with the PCP. For those with uncontrolled diabetes, the nurse and coach coordinated care as needed to decrease barriers to blood glucose control (e.g., obtaining and using glucometer) with mental health staff, caregivers, PCPs and/or specialists. They encouraged high impact dietary behaviors (e.g., no sugar drinks), participation in regular exercise, and weight loss when appropriate.

Hypertension

The nurse met with participants for hypertension education sessions including discussion of medication adherence. Intervention staff monitored blood pressure regularly and communicated with participants and PCPs about monitoring and treatment goals. The nurse also reinforced the dietary (e.g., avoid salty/processed foods) weight loss and exercise goals set with the coach.

Dyslipidemia

The nurse met with participants who met recommended guidelines for lipid lowering therapy for medication education and counseling before communicating with the PCP for guideline-concordant treatment. Both the coach and nurse encouraged high impact dietary behaviors (e.g., no greasy foods), participation in regular exercise, and weight loss if needed.

Overweight/Obesity

The coach used lifestyle strategies that have proven effective in previous clinical trials including individual counseling sessions, weekly weigh-ins, simplified dietary messages (e.g., avoid junk food, avoid sugar drinks, limit snacking, limit portion sizes) and paper trackers to help monitor these behaviors (18). The nurse also linked the roles of weight management to the participant's other CVD risks.

Unhealthy Diet

Intervention staff provided guidance on ways to eliminate unhealthy dietary choices and incorporate healthier options in the context of other CVD risk factors and the participant's health goals. The conversations used simplified messages and incorporate paper trackers to facilitate awareness and goal setting. Dietary topics included: Avoiding salty/greasy foods, sugar drinks, sweets and processed foods, and eating smart portions and more fruits and vegetables. The coach used role playing and hands-on activities (e.g., visiting the soda machine) to model decision making for healthy diet choices.

Physical Inactivity

The intervention staff encouraged participation in regular moderate-intensity physical activity. We trained PRP staff to deliver site-wide group exercise classes using either a study-made DVD or commercially available walking DVD and recommend that classes are offered three times per week. The health coach encouraged exercise class attendance for intervention participants, participated in some of the classes, and substituted for PRP staff if requested. The coach worked with intervention participants to identify additional strategies to meet physical activity recommendations, for example, providing pedometers and setting daily step goals, and providing exercise DVDs to guide home-based workouts. The nurse reinforced exercise goals set with the coach and linked the importance of exercise as an independent health behavior and to the relevant CVD risks.

DISCUSSION

Given the extraordinarily high and persistent burden of CVD risk factors and resultant CVD in persons with SMI, there is an urgent need for tailored, effective interventions to promote CV health. We describe a comprehensive health behavior coaching and care coordination/care management intervention designed to address each CVD risk behavior and risk factor for adults with SMI in community mental health settings. The IDEAL intervention design has important strengths. First, the intervention uniquely focuses on addressing all of the seven CVD risk factors and behaviors with strategies directed at reaching clinically significant targets consistent with treatment guidelines. Second, the health coach is embedded in the PRP, facilitating coordination and communication with mental health staff in the everyday community mental health outpatient environment. This provides a practical real-world design to optimize future implementation feasibility and sustainability.

The IDEAL intervention faces some challenges to success. The intervention is ambitious in its attempt to address multiple risk factors in persons with SMI given that accomplishing reduction for a single risk factor in those without SMI often takes intensive efforts (96). Fortunately, the intervention's lifestyle-based recommendations to help address risk factors such as high blood pressure or high blood glucose involve similar approaches. Having both a coach and nurse use a coordinated approach for each participant should help to address this challenge. Another potential barrier to success is that the intervention team does not prescribe medications, and PCPs in the community have no specific incentive to participate in the intervention's care coordination efforts.

If shown to be effective in the RCT, the IDEAL intervention could be implemented through programs, like the BHH, which provide a financing mechanism for staff (e.g., nurse) and infrastructure to integrate care coordination and management into specialty mental health settings. BHHs are currently operating in 15 U.S. states and D.C. through the Affordable Care Act's Medicaid health home waiver program, and have been implemented through the Substance Abuse and Mental Health Services Administration's Primary Behavioral Health Care Integration initiative and other local programs (35, 36, 38).

However, BHHs generally do not require use of a specific care coordination/management protocol or intervention, thus the strategies currently employed in BHH models vary considerably across sites; they also typically do not emphasize evidenced-based behavioral counseling for CVD risk behaviors (35–44). These features likely contribute to the mixed results to-date for BHHs. The two US RCTs evaluating BHHs found the programs improved quality of primary care delivery; while one showed small reductions in cardiovascular risk among a subset

of participants, the second showed no effects on CVD health outcomes (37, 48). These findings suggest that care coordination alone, while potentially capable of improving processes of care, may not be enough to achieve improved clinical outcomes. In Denmark, the CHANGE trial tested care coordination vs. care coordination plus lifestyle coaching vs. control and found no change in CVD risk or individual risk factors over 2 years (97). These null results may be due to the high quality of the health system in Denmark such that many participants at baseline had controlled risk factors; also, the lifestyle coaching may not have been as intense as needed to affect additional CVD risk reduction.

The IDEAL intervention may be well suited for integration into and could improve the effectiveness of models like the BHH. When embedded into a BHH-like structure with its financing, the intervention with its standards of procedure for all aspects of care coordination and tailored, evidenced-based behavioral counseling, could make considerable progress in improving the CVD health for a population that is not routinely receiving quality CV care.

CONCLUSION

Unless effective interventions that effect CV health outcomes are implemented, populations with SMI will continue to lag far behind the nation's CVD goals. Interventions and models incorporating CVD risk factor treatment in mental health settings to-date have not shown meaningful changes in CV risk factors. The IDEAL intervention incorporates care coordination and care management concepts with intensive health behavior change coaching to address all CVD risks in persons with SMI in community mental health outpatient program settings. If successful, the intervention could be adopted within current integrated care models and significantly improve the physical health of persons with SMI.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Johns Hopkins Medicine IRB with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by The Johns Hopkins Medicine IRB.

AUTHOR CONTRIBUTIONS

AD, GD, and GJ wrote the manuscript. GD, LA, GJ, FD, N-YW, DY, JC, RC, AD, SG, JG, CC, EE, and AH contributed to the conception, design and implementation of the study. EM wrote a section of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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The Influence of Continuous Exercising on Chronotropic Incompetence in Multi-Episode Schizophrenia

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People with schizophrenia die on average 15–20 years earlier than age and gender matched controls in the general population. An essential part of this excess mortality in people with schizophrenia is caused by physical illnesses. Among the physical illnesses, cardiovascular disease (CVD) has been identified as the most common natural cause of death in up to 40–45% of the cases. Chronotropic incompetence (CI) is defined as the inability of the heart to increase its beating frequency in proportion to increased physical activity or higher metabolic demand. It is an established independent cardiovascular risk factor for major cardiac events and overall mortality and might explain adaptation intolerance of the cardiovascular system to even minor exercise courses. CI needs objective exercise testing for definitive diagnosis and therefore represents a biological marker indicating the integrity of the cardiovascular system. It was recently described in patients with schizophrenia and might help explain the reduced physical fitness in these patients and the inability of a subgroup of patients to benefit from exercise interventions. In this study, we tried to replicate the occurrence of CI in an independent sample of patients with schizophrenia and evaluated whether CI can be influenced by a continuous endurance training of 12 weeks. Therefore, we re-analyzed the fitness testing data of 43 patients with schizophrenia and 22 aged and gender matched healthy controls. Parameters of aerobic fitness and chronotropic response to exercise were calculated. Patients with schizophrenia were less physically fit than the healthy controls and displayed a significantly higher heart rate at rest. 10 of 43 patients with schizophrenia and no healthy control subject were classified as chronotropically incompetent. Chronotropic response to exercise did not change significantly after 12 weeks of continuous aerobic exercise training. No differences were observed for baseline heart rate and peak heart rate in both subgroups of schizophrenia patients. Aerobic fitness did not improve significantly in the patients with schizophrenia classified as chronotropically incompetent. Our results confirm the occurrence of CI in patients with multi-episode schizophrenia. This should

be taken into account when planning an exercise or lifestyle intervention studies in this population. Schizophrenia patients with CI do not seem to benefit as well as schizophrenia patients without CI from aerobic exercise training interventions. Larger, prospective randomized controlled clinical trials with different training interventions are urgently needed to address the topic of schizophrenia patients not responding to exercise and the relationship to the illness itself.

Keywords: schizophrenia, exercise, chronotropic incompetence, cardiac autonomic dysfunction, heart rate response

INTRODUCTION

There is a solid body of evidence underpinning the notion that people with schizophrenia die on average 15–20 years earlier than age and gender matched controls in the general population (1–3). This mortality gap between the general population and patients with schizophrenia seems to increase instead of converge over the last decades (4–6). An essential part of this excess mortality in people with schizophrenia is caused by physical illnesses (7–9). In several studies, cardiovascular disease (CVD) has been identified as the most common natural cause of death in up to 40–45% of cases (7, 10). It has been suggested that coronary heart disease is the main contributor to CVD, which is exacerbated by the high-risk profile (obesity, poor diet, lack of exercise, smoking) of most patients with schizophrenia. In addition, patients with schizophrenia take antipsychotic medication on a regular basis, which is known to affect the cardiovascular system additionally (11). Some of the risk factors are potentially reversible by changing the lifestyle and even by considering side effects of some antipsychotics. A non-pharmacological interventional approach to impact cardiovascular risk factors is regular physical exercise (12, 13). As mentioned above, studies have shown that people with severe mental illness like schizophrenia engage in significantly more sedentary behavior and significantly less physical activity compared to healthy controls (14). Additionally to somatic health benefits, aerobic exercise positively impacts core features of the disease itself like cognitive deficits (15–17) and negative symptoms (18). However, although the above-mentioned risk factors seem to be plausible they do not explain the excess mortality of patients with schizophrenia satisfactorily. Moreover, psychiatrists and researchers seem to overlook to some extend the solid body of evidence describing cardiovascular dysregulation in patients with schizophrenia both at rest and during physical activity. It has been shown that young unmedicated patients with schizophrenia show increased heart rates at rest caused by severe autonomic dysfunction (19). An increase in heart rate of 5 beats per minute corresponds to a significant increase in the atherosclerosis progression (20). Life expectancy in animals and humans shows a close relation to the medium heart rate (21). Increased resting heart rate has been shown to be a risk factor for reduced life expectancy in both the general population (22, 23) and in populations with cardiovascular diseases (24, 25). In patients with schizophrenia, the protective vagal component seems to be profoundly impaired leading to reduced heart rate variability or an insensitive baroreflex. While similar findings have been described in patients with depression (26), alcohol withdrawal (27), or anxiety disorders (28) the pronounced degree of changes leads to a unique pattern in patients with schizophrenia. Most of the described alterations in the autonomic nervous system are associated with reduced life expectancy previously shown in various conditions such as diabetes (29), survival after myocardial infarction (30, 31) or in cardiac artery disease (CAD) (32). Thus, more research is needed to better explain cardiovascular dysregulation in schizophrenia because in contrast to patients suffering from severe CAD the cardiac autonomic dysfunction in schizophrenia is not caused by structural or functional alterations of the heart itself but moreover by abnormalities in the brain—heart interaction (33).

More recently, we investigated the putative link between autonomic dysfunction and physical incapacity in these patients. And indeed, Herbsleb et al. (34) were able to present evidence that about half of the tested population of patients with schizophrenia showed a strikingly absent heart rate acceleration during physical exercise. This phenomenon is called chronotropic incompetence of the heart (CI) and was again described in various cardiac conditions (35–38). It is defined as the inability of the heart to increase its beating frequency in proportion to the increase in physical activity or higher metabolic demand and therefore needs an exercise testing of the patients for definitive diagnosis (37). This finding is of paramount importance since CI is a well-described cardiac risk factor of mortality (39–43), it is associated with physical incapacity and might explain to some extend that patients with schizophrenia encounter difficulties to enjoy physical activities. However, this new finding warrants further studies to identify patients at risk and to investigate treatment options.

Therefore, the aim of the current investigation was to examine if the previously revealed impaired heart rate response to physical exercise is a consistent finding, which can be also detected in a further cohort of patients with schizophrenia. Here, we used a different exercise test protocol in order to elucidate the possibility to include data from various studies and to generalize findings. In addition, we evaluated, whether heart rate responses to exercise can be influenced by a moderate-intensity continuous endurance training of 12 weeks in our patients.

We hypothesized that (i) our re-analysis of fitness testing data would reveal CI in a substantial portion of patients with multi-episode schizophrenia, (ii) that CI is again related to

reduced physical fitness in this subset of patients, and (iii) that an continuous aerobic exercise training ameliorates or reverses the CI of the heart in the subset of schizophrenia patients affected.

MATERIALS AND METHODS

Subjects

The evaluated cohort consisted of forty-three multi-episode schizophrenia patients and twenty-two healthy controls who successfully completed an interventional, single center continuous aerobic exercise study which took place at the Department of Psychiatry and Psychotherapy at the University Medical Center Göttingen between 2010 and 2013 (44–48). The local ethics committee approved the study protocol, which was in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to inclusion in the study. The trial was registered at www.clinicaltrials.gov (NCT01776112). Briefly, 43 patients with multi-episode schizophrenia and 22 healthy controls were assessed for endurance capacity using an incremental exercise test on a bicycle ergometer before and after the study intervention. The study intervention consisted of standardized continuous endurance training on cycle ergometers three times a week for 30 min over a total intervention period of 12 weeks. A group of 21 patients with schizophrenia played table soccer (also known as foosball is the US) as an additional active control intervention. Healthy controls were matched regarding age and gender to patients in the endurance group (see **Table 1**). Inclusion criteria were a diagnosis of schizophrenia according to ICD-10, stable psychopathology and antipsychotic medication for 2 weeks prior to the intervention and age between 18 and 60 years. Exclusion criteria were substance abuse (alcohol and illicit drugs (cannabis, amphetamines, cocaine, benzodiazepines, and opioids) assessed with urine drug tests), a worsening of psychopathological symptoms within 2 weeks of the screening period, pregnancy, lactation, or contraindications for endurance training or maximal cardiopulmonary exercise testing (CPET).

TABLE 1 | Baseline characteristics as well as parameters of aerobic fitness in the control and patient group.

Baseline characteristic	Controls	Patients	*P*-value
	n = 22	*n* = 43	
EPIDEMIOLOGICAL DATA			
Age; years	37.6 ± 11.3	36.3 ± 12.9	0.589
Gender: male/female	16/7	31/12	0.743
Body mass; kg	80.8 ± 13.6	90.4 ± 19.2	0.052
BMI; kg/m^2	26.0 ± 3.7	28.4 ± 4.9	**0.023**
DISEASE SPECIFIC DATA			
Duration of disease (years)	NA	10.9 ± 9.3	-
PANSS	NA	69.3 ± 6.3	-
MEDICATION			
Chlorpromazine equivalents, CPE *(mg/d)*	NA	658 ± 674	
Clozapin (yes/no)	NA	5/38	
PARAMETERS OF AEROBIC FITNESS			
Peak oxygen uptake; ml/kg/min	35.9 ± 7.5	29.5 ± 8.7	**0.011**
Peak oxygen uptake; % pred	93 ± 22	113 ± 26	**0.001**
Peak power output; W/kg	2.54 ± 0.48	1.87 ± 0.54	**<0.001**
PWC 130; W/kg (patients: *n* = 40)	1.32 ± 0.36	1.09 ± 0.32	**0.013**
PWC 150; W/kg (patients: *n* = 42)	1.76 ± 0.38	1.44 ± 0.44	**0.009**
Power output at Lactate Threshold; W/kg	1.28 ± 0.24	1,00 ± 0.32	**0.001**
OBJECTIVE EFFORT			
Peak blood lactate, mmol/l	9.6 ± 2.7	7.6 ± 2.6	**0.005**
HEART RATE DATA AND CHRONOTROPIC RESPONSE			
Baseline heart rate; 1/min	78 ± 10	90 ± 15	**0.001**
Peak heart rate; 1/min	180 ± 14	171 ± 18	0.069
% pred. heart rate reserve	98 ± 12	88 ± 18	**0.017**
Slope metabolic-chronotropic relationship	1.05 ± 0.11	0.91 ± 0.20	**<0.001**
Chronotropic incompetence (yes/no)	0/22	10/33	**0.014**

Data are shown as mean ± standard deviation or absolute number.
n, number of participants if not all are include in calculation because of excluded or missing data (e.g., failure to reach a given heart rate); NA, not applicable.
Bold values indicate significant differences between groups.

Exercise Testing

In order to measure aerobic endurance capacity before and after the 12-week intervention, participants performed incremental CPET until subjective exhaustion on an electronically braked bicycle ergometer (Ergoselect 200 K, Ergoline GmbH, Bitz, Germany). After a resting period of 3 min, the incremental bicycle protocol started at a power output of 25, 50, or 75 W on the basis of the anamnestic information for 3 min. The power output was then increased in steps of 25 W every 3 min until the subject reached his or her limit of tolerance. During the CPET, ventilatory indices and gas exchanges and heart rate were measured continuously on a breath-by-breath basis using an automatic mobile wireless ergospirometer (MetaMax 3B, Cortex, Biophysik GmbH, Leipzig, Germany, and T31, Polar Electro Oy, Kempele, Finland). Before each test, the turbine (flow and volume) was calibrated with a syringe (Hans Rudolph Inc., Kansas City). For data analysis, the breath-by-breath gas exchange and ventilatory data were smoothed using a 15-breath moving average, aligned to the time of the central breath. Peak oxygen consumption (VO_2peak) was defined as the highest value of 15-breath average occurring during CPET. Capillary whole-blood samples of 0.2 µl were obtained for lactate measurements from the ear lobe when the patient was at rest, and again at the end of the third minute of each 3-min period of the CPET. The blood lactate concentrations were measured by Lactate SCOUT Solo Plus, SensLab GmbH, Leipzig, Germany).

Parameters of Aerobic Fitness

A set of different physiological maximal and submaximal indices was used to describe the aerobic fitness. We calculated the power output at a fixed heart rate of 130 and 150 (known as physical working capacity; PWC 130, PWC 150), as well as the power output at the Lactate Threshold (LT), which are both submaximal indices of aerobic fitness. The time course of lactate was graphically interpolated using an equalizing spline procedure.

The LT was defined as the minimum lactate equivalent (the lowest value of the quotient lactate to power output) as describes the first sustained increase in blood lactate concentration above resting level during incremental exercise (49). The evaluation of the LT and the power output achieved at a blood lactate concentrations of 2 mmol/l (for training prescription) were done examiner independent by using a software for performance diagnostic (Ergonizer, Germany, www.ergonizer.de). Moreover, we determined the achieved peak power output (Ppeak) and peak oxygen uptake (VO_2peak). More details for the calculation of the PWC, VO_2peak, and Ppeak are given in Keller-Varady et al. (45).

Continuous Endurance Training

The interventions in the patients with schizophrenia consisted of a 12-week training procedure. Participants participated in three training sessions per week lasting exactly 30 min each. The sessions consisted of moderate-intensity endurance training on cycle ergometers. The exercise intensity was set to the individual power output achieved at a blood lactate concentrations of 2 mmol/l, determined during the preceding CPET. Power output was than increased gradually, corresponding to improvements in endurance performance, by a mean of 8 $\pm$ 1 % after 11 $\pm$ 6 training sessions, controlled by lactate concentration monitoring.

Assessment of Heart Rate Responses to Exercise

To assess chronotropic response, the metabolic-chronotropic relationship (MCR; also known as the chronotropic index) was calculated according to (50) using the ratio of heart rate reserve (predicted HRpeak (220—age)—HR at rest) to metabolic reserve (VO_2peak—VO_2 at rest) during the CPET. The MCR adjusts for age, physical fitness and functional capacity and is unaffected by the exercise protocol as well as effort-independent (37). The increase in percentage heart rate reserve in relation to the increase in percentage metabolic reserve (also known as oxygen uptake reserve) was obtained by linear regression analysis using the least squares method of the mean values acquired for VO_2 and HR data in the last 30 s of each incremental step of the CPET. In healthy adults, the percentage of heart rate reserve achieved during exercise equals the percentage of metabolic reserve achieved, so that the median MCR slope is near around 1.0 with a 95% confidence interval between 0.8 and 1.3 (50).

Statistics

For statistical analysis, SPSS for Mac (version 25.0.0.1) was used. All parameters were tested for normal distribution with the Kolmogorov–Smirnov test or with Shapiro-Wilk-Test by subgroup analysis. Epidemiological data and objective effort during exercise testing of patients and controls as well as subgroups of patients (CI vs. non CI patients) were compared by either using parametric or non-parametric two-sample tests as well as Chi-squared tests for comparison of nominal data. To investigate basic differences of aerobic fitness and heart rate parameters between all patients and controls, we performed two separate multivariate analyses of variance (MANOVAs). We conducted a first MANOVA for aerobic fitness parameters with the inter-subject factor GROUP (patients vs. controls) including VO_2peak, Ppeak, PWC 130, PWC 150, as well as LT (all normalized to body mass) followed-up by univariate analysis of variances (ANOVAs). The second MANOVA for all participants was performed by applying the factor GROUP (patients vs. controls) and included the following heart rate parameters: baseline heart rate, peak heart rate, and percentage of the predicted heart rate reserve (% pred. heart rate reserve). ANOVAs were then calculated for single parameters. To investigate the main hypothesis of our study, the metabolic–chronotropic relationship slope (MCR slope) of patients and controls was analyzed. Controls and patients with a MCR slope below the cut-off value of 0.8 were referred as chronotropic incompetent whereas subjects with a MCR slope above a value of 0.8 were classified as chronotropic competent (50). Group differences of the MCR slope between patients and controls were verified with a parametric two-sample *t*-test. We repeated a MANOVA with respect to physical fitness for the factor SUBGROUP (CI vs. nonCI patients) followed-up by univariate ANOVAs. Due to the influence of chronotropic incompetence on the heart rate derived fitness indices PWC 130 and PWC 150, we abstained form including these parameters in the analysis. The effects of the continuous aerobic endurance training on aerobic fitness indices (including VO_2peak, Ppeak, PWC 130, PWC 150, and LT) in subgroups of patients (CI vs. nonCI) were examined using the dependent sample *t*-test or the Wilcoxon matched pairs signed rank test as the nonparametric alternative. We applied the same procedure to investigate the effects of training MCR-slope in CI and non-CI patients. The significance level was set 0.05 (two-sided) and fitted using Bonferroni adjustment procedure to account for inflation of alpha level by multiple testing.

RESULTS

Physical Fitness

The MANOVA for aerobic fitness indices (VO_2peak, Ppeak, PWC 130, PWC 150, LT) revealed a significant difference [$F_{(5, 56)} = 5.66$; $P < 0.001$] between all schizophrenia patients and healthy controls. The follow-up univariate ANOVAs indicated significant differences for VO_2peak ($F = 6.93$; $P < 0.05$), Ppeak ($F = 21.84$; $P < 0.001$), PWC 130 ($F = 6.57$; $P < 0.05$), PWC 150 ($F = 7.35$; $P < 0.01$ and LT ($F = 11.38$; $P < 0.01$; see **Table 1**).

Heart Rate

The second MANOVA for heart rate parameters revealed a significant effect for the factor GROUP [$F_{(3, 61)} = 6.45$; $P < 0.01$]. As depicted in **Table 1**, the ANOVAs showed significant differences between all patients and controls for baseline heart rate ($F = 11.60$, $p < 0.01$) and percentage of predicted heart rate reserve ($F = 6.02$, $P < 0.05$), whereas only a trend was found for peak heart rate ($F = 3.42$, $P < 0.069$).

Metabolic–Chronotropic Relationship

Based on cut-off values by Burbaker and Kitzman, (37) and Wilkoff and Miller, (50), 10 of 43 patients with schizophrenia

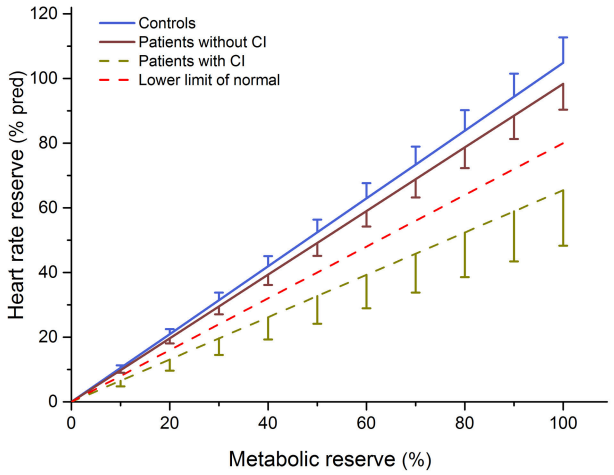

FIGURE 1 | Mean ± 90% confidence limit of the metabolic–chronotropic relationship of patients with (CI) and without (non-CI) chronotropic incompetence as well as control subjects. The dotted line represents the lower limit of normal (slope < 0.8).

had an impaired heart rate response to exercise and were classified as chronotropically incompetent, whereas no healthy control subject was below the cut-off value. Furthermore, a significant difference was observed between the mean MCR slopes of patients and controls ($P < 0.001$, see **Table 1** and **Figure 1**). The MANOVA that compared aerobic fitness indices (VO_2peak, Ppeak, and LT) between subgroups of patients (CI vs. nonCI patients) revealed no significant difference between groups [$F_{(3, 39)} = 1.76$; $P = 0.170$] (see **Table 2** and **Figure 2**).

Influence of the Moderate Intensity Continuous Aerobic Exercise Training on Heart Rate Response to Exercise

The MCR-slope as an index of chronotropic response to exercise did not change significantly in both, the CI and the non-CI subgroup after 12 weeks of continuous aerobic exercise training compared to baseline (see **Table 3**). Furthermore, no differences were observed for baseline heart rate and peak heart rate in both groups.

Responses of Aerobic Fitness to Continuous Aerobic Exercise Training

Of the 22 schizophrenia patients who underwent the 12-week continuous aerobic exercise training intervention, 6 were classified as chronotropic incompetent based on the MCR-Slope as described above. The epidemiological data, aerobic fitness and heart rate parameters are highlighted in **Table 3**. Aerobic fitness improved significantly (as indicated by Ppeak, PWC 130, PWC 150) in the non-CI group, but contrary to our initial hypothesis it did not change significantly in the CI-group (see **Table 3**). However, no significant responses to training in both groups were observed for VO_2peak and LT.

TABLE 2 | Baseline characteristics as well as parameters of aerobic fitness in patients with schizophrenia with (SZ-CI) and without chronotropic incompetence (SZ-nonCI).

Parameters	NonCI-patients	CI-patients	*P*-value
	n = 33	*n* = 10	
EPIDEMIOLOGICAL DATA			
Age; years	37.4 ± 13.5	34.0 ± 11.3	0.542
Gender: male/female	22/11	9/1	0.150
Body mass; kg	87.2 ± 15.4	101 ± 27	0.204
BMI; kg/m^2	27.6 ± 4.1	31.3 ± 6.2	**0.033**
DISEASE SPECIFIC DATA			
Duration of disease (years)	10.7 ± 9.8	11.6 ± 8.0	0.702
PANSS	70.0 ± 6.6	67.1 ± 5.5	0.724
MEDICATION			
Chlorpromazine equivalents, CPE (mg/d)	624 ± 632	767 ± 822	0.687
Clozapin (yes/no)	2/31	3/7	**0.039**
PARAMETERS OF AEROBIC FITNESS			
Peak oxygen uptake; ml/kg/min	30.9 ± 8.6	25.2 ± 7.5	0.067
Peak oxygen uptake; % pred	98 ± 21	74 ± 19	**0.003**
Peak power output; W/kg	1.97 ± 0.52	1.54 ± 0.49	**0.027**
Power output at Lactate Threshold; W/kg	1.06 ± 0.33	0.83 ± 0.21	**0.017**
PWC 130; W/kg (CI: *n* = 9; nonCI: *n* = 31)	1.08 ± 0.33	1.14 ± 0.29	0.601
PWC 150; W/kg (CI: *n* = 9)	1.39 ± 0.45	1.61 ± 0.34	0.188
OBJECTIVE EFFORT			
Peak blood lactate, mmol/l	7.9 ± 2.6	6.4 ± 2.3	0.089
HEART RATE DATA AND CHRONOTROPIC RESPONSE			
Baseline heart rate; 1/min	88 ± 15	92 ± 7	0.629
Peak heart rate; 1/min	177 ± 14	154 ± 17	**<0.001**
% pred. heart rate reserve	95 ± 13	64 ± 13	**<0.001**
Slope metabolic-chronotropic relationship	0.98 ± 0.14	0.65 ± 0.15	**<0.001**

Data shown as mean ± standard deviation or absolute numbers.
n, number of participants if not all are include in calculation because of excluded or missing data (e.g., failure to reach a given heart rate).
Bold values indicate significant differences between groups.

DISCUSSION

Our study shows in agreement with previous reports that healthy controls show better fitness levels than patients with schizophrenia, despite being age and gender matched and engaging in no sports 2 years before entering the study (45). In addition, this study confirmed in 10 out of 43 patients the pattern of chronotropic incompetence in patients with schizophrenia and thus corroborates the first description in the disease although studied in a different fitness test design. Most intriguingly, we did not observe a significant impact of a twelve-week moderate continuous exercise training on CI values in patients.

In the present study, we identified impaired chronotropic responses with a step-wise incremental exercise test in contrast

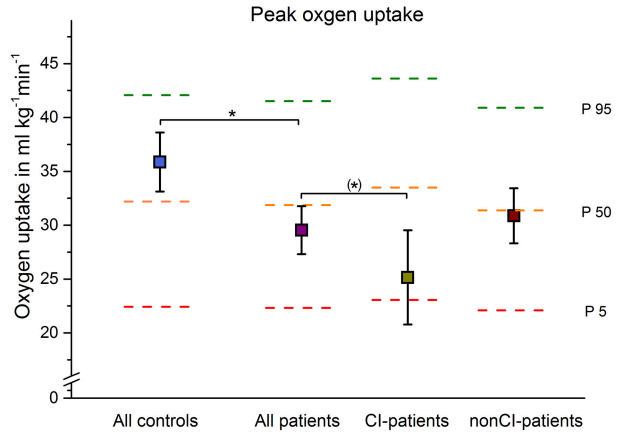

FIGURE 2 | Mean ± 90% confidence limit of peak oxygen uptake of all patients, and patients with (CI) and without (non-CI) chronotropic incompetence are depicted in comparison to controls. The dotted horizontal lines represent contemporary age, gender, and body size specific reference percentiles (51). Significant or a trend differences are indicated by $^{*}p < 0.05$ or $(^{*})$ $p < 0.1$, respectively.

TABLE 3 | Differences to baseline in disease specific data, indices of aerobic fitness, and heart rate data after a 12-week moderate-intensity aerobic training in patients without (SZ-nonCI) and with (SZ-CI) chronotropic incompetence.

	Training nonCI-patients	Training CI-patients
	***n* = 16**	***n* = 6**
EPIDEMIOLOGICAL DATA		
Body mass; kg	−0.9 ± 5.2	−0.5 ± 9.1
BMI; kg/m^2	−0.2 ± 1.6	0.0 ± 2.6
DISEASE SPECIFIC DATA		
PANSS	**−8.9 ± 18.6***	7.0 ± 13.5
MEDICATION		
Chlorpromazine equivalents, CPE (mg/d)	−2 ± 473	212 ± 552
PARAMETERS OF AEROBIC FITNESS BEFORE AND AFTER TRAINING		
Peak oxygen uptake; ml/kg/min	1.52 ± 5.24	0.45 ± 5.42
Peak oxygen uptake; % pred	4.8 ± 15.7	2.0 ± 16.0
Peak power output; W/kg	**0.18 ± 0.23*#**	0.09 ± 0.43
PWC 130; W/kg (non CI: *n* = 15, CI: *n* = 5)	**0.20 ± 0.26*#**	−0.00 ± 0.37
PWC 150; W/kg (CI: *n* = 5)	**0.22 ± 0.26*#**	0.08 ± 0.43
Power output at Lactate Threshold; W/kg	−0.02 ± 0.32	0.05 ± 0.24
OBJECTIVE EFFORT		
Peak blood lactate; mmol/l	0.83 ± 1.66	0.83 ± 2.83
HEART RATE DATA AND CHRONOTROPIC RESPONSE		
Baseline heart rate; 1/min	−4.7 ± 13.4	−6.1 ± 7.1
Peak heart rate; 1/min	0.0 ± 10.4	−0.5 ± 18.8
% pred. heart rate reserve	0.1 ± 13.1	3.4 ± 17.0
Slope metabolic-chronotropic relationship	0.01 ± 0.14	0.02 ± 0.20

Data are shown as mean ± standard deviation.
*n = number of participants if not all are include in calculation because of excluded or missing data (e.g., failure to reach a given heart rate), * and # indicates statistically significant difference from baseline values, P < 0.05 (*not adjusted/*#adjusted for multiple testing).*
Bold values indicate significant differences before and after training within a group.

to the ramp-wise protocol used in the previous study by Herbsleb et al. (34). However, in this independent sample only 23% of the multi-episode patients with schizophrenia showed CI. This is lower than in our previous study where the proportion of SZ-CI consisted of 43% (34). The difference to higher share of CI cases in our previous study may relate to the composition of groups rather than other causes given the small sample size. It seems not plausible that the cause of the higher occurrence of CI in the study of Herbsleb et al. (34) is mainly explained by the different exercise test protocols that were used. Although the ramp-wise protocol results in lower mean HR as well as VO_2 values at the common power output than step-wise tests [(52), the impact of the test protocol on the MCR slope (which is the relationship of HR and VO_2 values) is considered to be negligible. A variety of exercise testing protocols and modes of testing have been used to evaluates the MCR relationship (37) since the originally description by Wilkoff and Miller (50), that used a step-wise incremental treadmill exercise test. However, in order to adequately assess the chronotropic response to metabolic stress of exercise the following points should be considered in future study designs: (i) participants should be encouraged to exercise until the subject reaches his or her limit of tolerance, (ii) exhaustion levels should be objectively evaluated by either measuring blood lactate values or the respiratory exchange ratio (ratio of carbon dioxide output to oxygen uptake), (iii) a sophisticated gas-exchange analysis is needed or specific test protocols (e.g., Bruce treadmill protocol, Chronotropic Assessment Exercise Protocol) should be applied and iv) a step-wise incremental exercise test with stage durations ≥3 min is recommended to obtain a near steady-state heart rate and to satisfy the equations conditions.

Since CI is known to be a cardiac risk factor larger trials might even elucidate possible clinical key factors associated with CI. To date, we were unable to find a substantial difference between CI and non-CI patients with respect to psychopathology, body mass index, duration of disease or the prescribed medication (see **Table 1**). However, it should be noted that patients taking clozapine were not included in the first analysis and the putative influence of clozapine on cardiovascular regulation should be investigated separately in future studies.

Various pathophysiological mechanisms have been proposed leading to chronotropic incompetence in cardiac conditions. For instance, Bristow and colleagues found a 50% or greater reduction in β-adrenergic receptor density in the left ventricular myocardium of failing hearts explanted during transplant surgery (53). These and other findings suggest that in heart failure patients, a decrease in β-receptor density leads to a diminished sensitivity of the β-adrenergic pathway and a decrease in β-agonist–stimulated muscle contractility. We would like to speculate that the long lasting augmented sympathetic drive might lead to a reduction of β-receptor density in patients with

schizophrenia. In addition, we cannot exclude that the chronic stress of a multi-episode disease such as schizophrenia might be associated with reduced excretion of catecholamines during an exercise bout. Although we have not observed a difference between both patient groups with respect to medication (34), we cannot completely exclude that anti-dopaminergic activity of some antipsychotics might influence the acute stress response. Since the definite pathophysiology of schizophrenia remains unclear, concepts of neuroinflammation and specifically autoimmune encephalitis or autoimmune psychosis have again gained more ground recently (54–57). However, the definite contribution is still discussed controversially, especially in those cases with no neurological symptoms (58). For the diagnosis of Autoimmune-Encephalitis clinical, imaging and CSF criteria have been proposed (59). Autoimmune antibodies are known to cause autonomic dysfunction in a lot of diseases like Sjögren syndrome or Guillain–Barré syndrome but also in conditions called pure autonomic failure (60). To the best of our knowledge the patients with multi-episode schizophrenia included in this study showed no yellow or red signs pointing to autoimmune etiology (61). Nevertheless, autoimmune antibodies were not studied specifically in the cerebrospinal fluid prior to inclusion in the study and hence cannot be ruled out to cause or promote autonomic dysfunction, here described as CI, in a subgroup of the patients. Nevertheless, CI could be a relatively easy to obtain objective biological marker to study the conjunction with inflammation pathways. Thus, this should be elucidated in further studies in this field and shift the focus on pathophysiological mechanisms to understand regulatory problems in patients with schizophrenia. This might help to decrease some obstacles impeding patients to engage in physical activities on a regular basis and to benefit from it (62). If CI is of importance in a substantial subset of patients with schizophrenia then one needs to think about other routines to accustom patients with schizophrenia to regular physical activity.

It is therefore intriguing that 12 weeks of continuous aerobic exercise training had no impact on CI measures in this study and that patients with multi-episode schizophrenia and CI did not benefit from the regular aerobic exercise in terms of fitness parameters or heart rate at rest. More studies are urgently needed to learn how to modulate the cardiac risk factor CI in patients with schizophrenia. One needs to consider different exercise protocols, longer durations of exercise and adjustments as well as an optimal assessment of CI in the first place. In addition, we need to learn the influence of antipsychotic medication on CI. Especially promising might be the application of high intensity training, which seems to be feasible in patients with schizophrenia (63–66). Herbsleb et al. (67) showed in an case report that a 6-week high intensity training improved autonomic function substantially while no such effect was observed after 6 weeks of continuous training in a patient with schizophrenia. Most intriguingly, the previously observed pattern of autonomic dysfunction returned after 6 weeks of detraining. This study underlines the importance of the choice of the training method as well the introduction of long-lasting training concepts in psychiatry.

Some limitations need to be taken into account. This is an exploratory secondary analysis of the fitness testing results of previously published data (44–46). Though the initial study protocol (44) was not primarily designed to reveal CI it contained thorough fitness testing [executed by a trained sports scientist (KKV)] to objectively assess cardiovascular fitness levels in the included patients with schizophrenia before and after the exercise intervention. However, the obtained data allowed us to calculate the metabolic-chronotropic relationship and hence CI *post-hoc*. As outlined above, the presence of CI can detected regardless the protocol (continuous or step-wise increase of the workload) during formal exercise testing and a variety of exercise testing protocols can be used (37, 52). This is of high interest when re-analyzing fitness testing data of existing exercise studies to shed more light on the phenomenon of exercise intolerance in patients with schizophrenia and to determine to which extend CI might be a contributing factor. The sample size is relatively small, especially those of SZ-CI that underwent 12 weeks of continuous aerobic exercise training.

CONCLUSION

Our results confirm the occurrence of CI in patients with multi-episode schizophrenia. Thorough fitness testing is necessary to reveal CI, but it does not seem to make a difference if the workload during the test is raised continuously or stepwise every 3 min. This should be taken into account when planning an exercise or lifestyle intervention study in patients with schizophrenia. Further studies are also needed to confirm CI in a prospective sample of patients with schizophrenia and to examine the underlying pathology of CI in patients with schizophrenia, i.e., by performing additional structural and functional examinations of the heart, as CI might rely to a specific cardiovascular pathophysiology in patients with schizophrenia. Furthermore, schizophrenia patients with CI do not seem to benefit as well as schizophrenia patients without CI from moderate continuous aerobic exercise training interventions, which may explain mixed results in this population in the literature. Larger, prospective randomized controlled clinical trials with different training interventions are urgently needed to address the topic of schizophrenia patients not responding to exercise and the relationship to the illness itself.

AUTHOR CONTRIBUTIONS

MH analyzed the data and wrote the first draft of the study. KK-V designed and performed the study and critically analyzed the data. TW, AH, and AS designed the study, gave critical comments, and revised the first draft of the study. PF and BM designed and performed the study, critically analyzed the data, gave critical comments, and revised the first draft of the study. HHWG gave critical comments and critically analyzed the data. K-JB designed the study, gave critical comments, critically analyzed the data, and revised the first draft of the study.

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BRIEF RESEARCH REPORT
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Prevalence and Correlates of Vitamin D Deficiency in a Sample of 290 Inpatients With Mental Illness

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Introduction: Vitamin D inadequacy or deficiency (VDID) has been reported in a high percentage of otherwise healthy individuals. Factors that may contribute to the high prevalence of VDID in people with mental disorders include diet low in vitamin D, poor sunlight exposure, decrease in cutaneous vitamin D synthesis, intake of certain medications, poor mobility, excessive alcohol intake, and tobacco smoking. VDID has been correlated to a host of adverse conditions, including rickets, osteoporosis, osteomalacia, muscle diseases, depression, cognitive dysfunction, and even certain cancers.

Objectives: The purpose of this study was to report the prevalence and correlates of vitamin D inadequacy in a sample of 290 psychiatric patients admitted to inpatient or day hospital treatment at the University of Siena Medical Center.

Methods: We retrospectively evaluated the prevalence of VDID in 290 psychiatric inpatients' medical records during the year 2017 and evaluated the correlates of VDID in patients with mental illness.

Results: Two hundred and seventy two out of two hundred and ninety patients (94%) showed VDID. Physical activity and regular diet were positively correlated with vitamin D levels whereas age, tobacco smoking, PTH, alkaline phosphatase levels were negatively correlated. Statistically significant differences were found among smokers and non-smokers in all study groups.

Conclusions: VDID was highly prevalent in our sample. In addition to vitamin D supplementation, psychosocial intervention able to promote and help sustain physical activity, appropriate diet, quitting smoking and sensible sun exposure to prevent and treat VDID in patients with mental health should be implemented, tested, and introduced in our clinical practice.

Keywords: mood, psychiatric, mental, inadequacy, deficiency, vitamin D, depression, bipolar

INTRODUCTION

Vitamin D (vit D), also known as sunshine vitamin is an essential component for a number of physiological functions such as muscle performance, bone metabolism, calcium and phosphorus omeosthasis and immunity. Vit D may be produced via sun exposure or obtained from food (1). According to Clinical Practice Guidelines from the US Endocrine Society, vitamin D deficiency is defined as serum 25-OH D <50 nmol/l (below 20 ng/ml). Vit D insufficiency is defined as serum levels of 25-OH D ranging between 50 and 75 nmol/l (21–29 ng/ml) (2, 3). Vit D deficiency is a global health issue affecting individuals of all ages (4). There are number of factors causing deficiency, with lack of sunlight exposure and poor dietary intake being the most important (5). The mean prevalence of Vit D deficiency in US population has been reported to be 37.5% (6). It is associated with various metabolic, neoplastic and immunological disorders such as atherosclerosis, diabetes mellitus and colon cancer (2, 7).

Vit D also plays an important role in mental health and cognitive functions (8, 9). Vit D receptors are present in various parts of the brain, including the amygdala, which is associated with the regulation of emotions and behavior (10). Vit D regulates intra and extracellular calcium concentration in neurons (11). Researchers found that patients with low vitamin D levels suffer from mood disorders (12, 13). In addition, vit D deficiency has been associated with neuropsychiatric conditions such as Parkinson's disease, schizophreniform disorder, multiple sclerosis (MS), Alzheimer's disease and autism spectrum disorders (14–16). Other studies have found significant relationships between deficiency of vitamin D and depressive symptoms or cognitive impairment (17, 18).

The main reasons for vitamin D deficiency in patients with psychiatric disease are low exposure to sunlight and poor diet (19). Anticonvulsant therapy may play a role as well (20). Although it is not a common practice to screen psychiatric patients for vitamin D deficiency, evidence suggests that vit D levels should be included in routine screening. For example, a study conducted in UK found that 100% psychiatric male inpatients were vitamin D deficient during hospital treatment (21). In another study conducted in the same country, researchers found that 83% of hospitalized inpatients were Vitamin D deficient (22).

The purpose of the study was to report the prevalence and correlates of vit D deficiency in a sample of 290 psychiatric patients admitted to inpatient or day hospital treatment at the University of Siena Medical Center.

METHODS

We retrospectively evaluated the medical records of 290 patients admitted to inpatient or day hospital treatment from January to December 2017.

The following information was extracted from the clinical charts: socio-demographic variables (age, sex, date, and place of birth); main psychiatric diagnosis; vitamin D serum levels and other parameters of the phosphocalcic metabolism (PTH, alkaline phosphatase, calcium, magnesium, and phosphorus); prolactin serum levels; body weight, height and body mass index (BMI); regular diet (as expressed by at least two meals per day); regular physical activity (as expressed by aerobic activity >20 min at least 2 days per week); smoking tobacco; medical comorbidities. All data above was collected retrospectively and no exam was specifically conducted for the purposes of this study. For the reasons above, the study was exempt from informed consent. The study was approved by the Regione Toscana - Area Vasta SudEst Ethical Committee Board.

We excluded confounding conditions that may contribute to low vitamin D levels such as malnutrition (eating disorders and/or wasting syndrome due to medical reasons) or malabsorption (celiac disease, inflammatory bowel disease, exocrine pancreatic insufficiency from cystic fibrosis and/or short bowel syndrome). Subjects with metabolic bone diseases (such as osteoporosis, rickets, osteomalacia, osteopetrosis, Paget disease of bone, and fibrous dysplasia) and pathological hyperprolactinemia not drug induced (such as pituitary micro- and macroadenomas, prolactinoma, chronic renal failure, and patients on hemodialysis) were also excluded.

Descriptive statistics were used to summarize the participant characteristics. Participants were then divided into three groups based on their vit d Levels: (1) vit D deficiency (vit D levels <10 ng/ml); (2) vit D insufficiency (vit D levels = 10–29.99 ng/ml); (3) vit D adequacy (vit D levels greater ≥30 ng/ml). The three groups were compared with chi-square tests on categorical variables such as gender, physical activity, smoke, diagnosis (bipolar disorder vs. other disorders), season (other seasons vs. summer) and drug treatment, and with Kruskal-Wallis test on quantitative variables (age, BMI, PRL, Magnesium, Calcium, Phosphorus, Alkaline phosphatase, and PTH) because they showed a non-normal distribution, as assessed using Shapiro-Wilks test. The significance level was set at $p < 0.05$. Variables that differed significantly among the three groups of vitamin D levels were entered as independent variables in a logistic regression model with a forward stepwise procedure. In this model, vitamin D was used a dependent variable, coded as deficiency vs. no deficiency. Statistical analyses were performed using SPSS for Windows version 22.0 and PRISM GraphPad.

RESULTS

The sample consisted of 290 patients, of which 127 were males (43.8%) and 163 females (56.2%). The mean age was 47.8 years. The majority of patients had a diagnosis of mood disorders ($n = 251$, 86.6%): among these 243 (83.8%) had a diagnosis of bipolar disorder and 8 (2.8%) of major depressive disorder; other diagnoses were schizophrenia or psychosis ($n = 8$; 2.8%), post-traumatic stress disorder ($n = 17$; 5.9%), other mental disorders (anxiety disorders, neurodevelopmental disorder) ($n = 14$; 4.8). The mean values for the anthropometric parameters of the sample were: weight 75 kg, height 169 centimeters, BMI 26.2 kg/m^2. About three quarters of patients (219/75.5%) followed a regular diet, 147 (50.7%) were smokers, and 75 (25.9%) reported to practice regular physical activity.

TABLE 1 | Demographic and clinical characteristics of study participants according to vit D levels.

Variables	Deficiency <10 ng/ml	Insufficiency 10–30 ng/ml	Adequacy ≥30 ng/ml	*P*-value
N	89	183	18	–
Males, *n* (%)	39 (43.8)	82 (44.8)	6 (33.3)	$\chi^2 = 0.87677$, df = 2, $p = 0.645$
Physical activity, *n* (%)	10 (11.2)	49 (26.8)	16 (88.9)	**FET, $p < 0.0001$**
Smoke, *n* (%)	68 (76.4)	*79 (43.2)*	0 (0.0)	***$\chi^2 = 46.189$, df = 2, $p \leq 0.0001$***
Age (Median)	54.4	45.2	48.1	**KW = 13.284, df = 2, $p < 0.01$**
BMI (Median)	26.2	26.1	26.9	KW = 0.295, df = 2, $p = 0.863$
Drug treatment, *n* (%)	81 (91.0)	161 (88.0)	15 (83.3)	FET, $p = 0.524$
PRL (Median)	275.3	272.5	318.2	KW = 0.1223, df = 2, $p = 0.941$
Magnesium (Median)	2.1	2.0	2.1	KW = 3.476, df = 2, $p = 0.176$
Calcium (Median)	9.4	9.5	9.5	KW = 1.3197 df = 2, $p = 0.517$
Phosphorus (Median)	3.2	3.2	3.3	KW = 0.47053, df = 2, $p = 0.790$
Alkaline phosphatase (Median)	68	59	61	**KW = 12.585, df = 2, $p < 0.01$**
PTH (Median)	37.0	28.0	25.5	**KW = 18.558, df = 2, $p < 0.0001$**

BMI, Body Mass Index; df, degrees of freedom; FET, Fisher Exact Test; KW, Kruskal-Wallis; N, Number; ng/mL, Nanograms Per Milliliter; PRL, Prolactin; PTH, parathyroid hormone; χ^2, chi-square. Bold values statistically significant.

Ninety-four percent ($n = 272$) of the 290 study subjects showed vit D levels below the normal range (vit D ≥30 ng/ml). Specifically, 31% met criteria for vit D deficiency (vit D levels <10 ng/ml), and 63% had vit D insufficiency (vit D levels = 10−30 ng/ml). The mean vitamin D levels was 15.3 ng/ml (±7.7 ng/ml). Not surprisingly, vit D levels were higher in samples collected in the months of July and August. Vit D levels were inversely proportional to age ($p < 0.001$). No significant relationship between vitamin D levels and gender was found ($p = 0.481$). Physical activity ($p < 0.001$) and regular diet ($p < 0.01$) were found to be positively and significantly related to vitamin D levels. Tobacco smoking had a negative association with vitamin D levels ($p < 0.001$). No statistically significant correlations were found between vitamin D levels and calcium, magnesium, phosphorus and prolactin. However, PTH ($p < 0.001$) and alkaline phosphatase ($p < 0.001$) were inversely and significantly related to vitamin D levels. Psychiatric medications were unrelated with vitamin D levels ($p = 0.935$). Demographic and clinical features of the study sample divided in three groups based on vitamin D levels (deficiency: <10 ng/ml; insufficiency: 10–30 ng/ml; adequacy: ≥30 ng/ml) are presented in **Table 1**.

In the multiple logistic regression model, smoking was the strongest predictor of vit D deficiency (OR = 5.033, 95% CI 2.684–9.435) after adjusting for the effect of season. Older age and higher PTH values were also significantly associated with an increased likelihood of vit D deficiency, while physical activity was associated with a lower likelihood of vit D deficiency (the *p*-value was borderline significant, $p = 0.053$).

DISCUSSION

We found a very high prevalence of VDID, with only 18 (6%) out of 290 patients with mental illness (mostly bipolar disorder) showing adequate levels of vitamin D. Our results are in line with similar studies (20, 21) and indicate that VDID is much greater in patients with mental illness than in the general population (6). A recent study evaluated vitamin D serum levels in a representative sample of 55,844 European individuals, and found that 13.0% had serum vit D concentrations of less 30 nmol/L (23). The authors concluded that these rates are concerning and call for action from a public health perspective.

Our findings highlight a much higher degree of concern in individuals with mental illness and point to the need of routinely screening for vitamin D deficiency, as a part of the standard assessment of patients with mental illness. However, given that almost all patients resulted deficient in vitamin D, the possibility to offer vitamin D supplementation to every patient with mental illness could be considered, as a cost-effective alternative to general screening. In addition to other benefits, vit D supplementation may improve the outcomes of illnesses like depression (24).

It is well-known that the main factors behind vitamin D deficiencies include the lack of sunlight exposure, poor dietary intake, smoking, and lack of physical exercise (5). Several studies have shown that a high number of patients with bipolar illness smoke tobacco, run a sedentary lifestyle, and have unhealthy dietary habits (25–28), similarly to what has been described in patients suffering from schizophrenia (27). Consistently with other studies in non-psychiatric patients [for instance; (29)], smokers were more likely to show VDID than non-smokers, despite the fact that outdoor smoking likely increased the sun light exposure. Of interest, in the multiple logistic regression model, smoking was the strongest predictor of vit D deficiency. This may be due to the fact that the negative influence of smoking on vitamin D levels is higher than the positive influence of a few minutes of sun exposure wen people smoke outdoors. Also, this could be due to the fact that our patients smoked primarily indoor. In fact, in our inpatient unit, people are allowed to smoke in a designated smoking area consisting of a fenced and shaded balcony, with no direct sunlight exposure. It is likely that our patients smoked indoors before being admitted as well,

given that a comprehensive smoking ban (e.g., no smoking policies in apartment buildings) is not widely adopted/enforced in Italy. Although we did not find a significant relationship between VDID and specific medications, we cannot rule out this possibility, because polytherapy was common. For instance, the effect of antiepileptic drugs on vitamin D levels has been widely demonstrated.

Our study has several other limitations, including the retrospective design of the study, the evaluation of vit D levels via blood samples collected in different seasons of the year, and the heterogeneity of the sample in terms of psychiatric diagnosis and socio-demographic features.

CONCLUSIONS

VDID is highly prevalent in patients with mental illness and is significantly influenced by lifestyle factors, such as diet, physical inactivity and tobacco smoking (this last with a strong and negative influence). As we already demonstrated (29) for other conditions affecting patients with mood disorders, the development and testing of standardized psychosocial healthy lifestyle interventions is warranted, as a key tool to promote and sustain physical and mental well-being of our patients.

DATA AVAILABILITY

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

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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