LIFESTYLE PSYCHIATRY: INVESTIGATING HEALTH BEHAVIOURS FOR MENTAL WELL-BEING

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LIFESTYLE PSYCHIATRY: INVESTIGATING HEALTH BEHAVIOURS FOR MENTAL WELL-BEING

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Editors of the Research Topic E-Book: Phil Ward, Brendon Stubbs, and Joseph Firth.
Image: Joseph Firth.

Recent years have seen a substantial increase in both academic and clinical interest around how 'lifestyle behaviors', such as exercise, sleep and diet, can influence mental health. The aim of this Research Topic is to produce a novel body of work contributing towards the field of 'Lifestyle Psychiatry'; i.e. the use of lifestyle interventions in the treatment of mental disorders. In this way, the Research Topic aims to (a) present important 'behavioral targets' for lifestyle modification in public health and/or clinical settings, and (b) examine the efficacy and implementation of lifestyle interventions for people with mental health conditions. Collectively, this research presented within this Research Topic can increase understanding and inform evidence-based practice of 'Lifestyle Psychiatry', while providing clear directions for future research required to take the field forward.

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Table of Contents

SECTION 3

PHYSICAL ACTIVITY AND EXERCISE

SECTION 4

MEASUREMENT AND HARNESSING NEW TECHNOLOGIES

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EDITORIAL
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Editorial: Lifestyle Psychiatry

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Keywords: physical activity, exercise, nutrition, diet, sleep

Editorial on the Research Topic

Lifestyle Psychiatry

WHAT IS LIFESTYLE PSYCHIATRY?

As the interface between physical and mental health becomes more widely acknowledged (1), the role of "lifestyle factors" (i.e., health behaviors, such as physical activity, diet, and sleep) in the onset and treatment of psychiatric disorders is also gaining increasing interest. Within this Research Topic on "Lifestyle Psychiatry" (a term popularized by Noordsy) (2), we set out to examine how multiple different aspects of our lifestyles relate to our mental health. More specifically, the articles in this collection set out to further articulate how symptoms of mental illness are related to typical health behaviors (including exercise, diet, and sleep) while also presenting new considerations for "lifestyle psychiatry," such as mindfulness, stress management techniques, and digital technology use. The main findings in each section are presented below.

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Traditional Health Behaviors and Lifestyle Psychiatry

Physical activity, nutrition, and sleep are all widely regarded as fundamental aspects of human health, for both the body and the mind. The role of physical activity in psychiatry is particularly well researched, with a number of recent meta-analyses showing that physical activity can aid in the prevention (3, 4) and management (5–9) of multiple symptoms of mental illness. Indeed, recent international guidelines now recommend exercise as a first-line treatment for mild/moderate depression and as an adjunctive intervention for severe mental illness (10). Building on this evidence, Hegberg et al. produce a new review on how exercise may also be helpful for those with PTSD. By drawing on data from 19 different studies, they explore the efficacy and underlying mechanisms of exercise as an intervention PTSD and present rationale for implementation. In further examination of the physical–mental health interface, Roeh et al. systematically review the evidence for using exercise to reduce symptoms of depression in those with *physical conditions* (rather than solely mental illness). Of the 39 meta-analyses examining this broad topic, 33 found positive effects of exercise on depressive symptoms as a comorbidity to cancers, cardiovascular diseases, and neurological conditions Roeh et al. Although more rigorous large-scale studies are needed, the existing evidence base shows that exercise is not only beneficial in the treatment of mental illnesses but can also be helpful for those experiencing subthreshold symptoms of mental illness as a comorbidity to physical illness.

Given the now substantial evidence base for exercise and mental health, the key outstanding question now becomes about motivating among individuals with mental illness to engage in sufficient exercise in order to feel these beneficial effects. Ho et al. shine new light on this with regards to severe mental illness, in a mixed-methods study of individuals with schizophrenia's experiences and reasons for exercise. Interestingly, participants with schizophrenia emphasized their core reasons for exercising were largely for the short-term improvements in mood, overall feelings of well-being, and boosting cognition (rather than for psychotic symptoms). The importance of understanding the motivations for exercise among those with mental illness is further emphasized by two other studies in this Research Topic, by Scheewe et al. and Engh et al. Together, these studies show how people with schizophrenia who engage in higher levels of physical activity have greater cardiorespiratory fitness, which is in turn associated with better physical and mental health outcomes of this condition.

Much like physical activity, our dietary food intake is a core determinant of physical health. Now, the potential impact of nutrition on mental health is also gaining increasing recognition due to large-scale meta-analyses of randomized controlled trials (RCTs) showing that both dietary interventions (11) and certain nutrient supplements (12) can significantly reduce symptoms of various psychiatric disorders. Adding to the evidence in this Research Topic, Marotta et al. present findings from a new double-blind, placebo-controlled RCT of probiotic supplementation. The findings confirm a beneficial effect of probiotics for self-reported mood and sleep quality after just 6 weeks, although further research is required to determine if these benefits extend to populations with clinically diagnosed psychiatric disorders.

In a longitudinal investigation of over 3,000 adolescents, Hoare et al. presents equivocal data on the link between nutrition and mental health, showing that the association between fruit/vegetable consumption in adolescents and reduced risk of depression is nonsignificant after adjusting for confounding factors. However, the relationship between healthy diet and healthy mind is unlikely to persist when examining only specific food groups—and may be better conceptualized through a "whole of diet" approach. Specifically, the overall "inflammatory potential" of the diet can now be calculated through scoring an individual's relative intake of "anti-inflammatory" nutrients (such as fruits, vegetables, and whole foods) against their intake of "inflammatory" foods (typically from calorie-dense processed foods and refined carbohydrates). Owing to the link between heightened inflammatory status and various mental disorders (including depression, bipolar disorder, and schizophrenia), the inflammatory potential of the diet is one key pathway thought to underlie associations between nutrition and mental health (13–15). A cross-sectional study by Shivappa et al. supports this link, showing that female adolescents with the most proinflammatory diets have around four times higher odds for moderate depressive symptoms compared to female adolescents with least inflammatory diets.

Despite these strong cross-sectional associations, there is now an urgent need to move beyond observational evidence of the link between nutrition and mental health, as such studies fail to tease out the bidirectional nature of poor diet and mental illness. Indeed, in this same Research Topic, Teasdale et al. examine the link from the opposite direction, presenting compelling new data to show that the poor diet and excessive energy intakes, which has previously been observed in those with long-term schizophrenia (13, 16), is also observed in young people undergoing initial treatment for this condition. Of note, Teasdale et al. discuss how this is a consequence (rather than cause) of their condition, due to the appetite-inducing effects of antipsychotic medications.

Similarly, sleep disturbance also holds bidirectional associations with mental illness, occurring both as a causal factor and consequence of mental ill-health (8, 17), which also interacts with other lifestyle factors. A first-in-field study by Waite et al. sheds new light on the reciprocal relations between sleep and psychological functioning in young people with indicated mental illness, using rigorous qualitative methods to detail both the impact of sleep disturbance, and need for sleep interventions, in high risk groups. Crucially, two further studies in this Research Topic confirm that exercise, diet, and sleep can all be addressed concurrently, with pilot data from Deenik et al. and Murphy et al. demonstrating the feasibility, along with potential physical and mental health benefits, of lifestyle interventions which combine exercise, diet, and sleep components into a single intervention for people with severe mental illness.

Emerging Considerations in Lifestyle Psychiatry

In the fast-growing field of Lifestyle Psychiatry, novel interventional approaches are emerging as potential self-management techniques for mental health and well-being. One such example is "mindfulness." In this Research Topic, Lu et al. found that mindfulness behaviors play a central role in alleviating the adverse mental health outcomes of stressful working conditions in intensive care nurses. Alongside mindfulness, Sarris et al. discusses how other interventions such as yoga, breathing techniques, nature therapies, and light, heat, and art-based therapies could be considered within the broader framework of Lifestyle Psychiatry. However, further RCTs are still required to establish if such interventions are only useful for promoting mental well-being in generally healthy samples or if these approaches can actually provide effective adjunctive treatment for those with severe mental illness.

Additionally, a "newer" aspect of our lifestyle which is currently overlooked in psychiatry is our engagement with digital technologies—particularly smartphones and connected devices. Whereas a recent major review has identified several pathways through which digital technology use can influence cognition (18), the role of these devices in mental healthcare is not well characterized. Nonetheless, the study by Hoffman et al. provide new insights on the applicability of these technologies for delivering behavioral health services, showing high acceptability and broad endorsement (among both patients and providers) for using digital devices for delivering mental health care through primary care settings. Considered alongside the indicated efficacy of digital interventions for both common and severe

mental disorders (14–21), now is clearly the time for more rigorous investigation into how these new tools can be integrated within existing care systems.

Along with providing new interventions options for "Lifestyle Psychology," digital technologies can also facilitate the gathering of lifestyle data. Indeed, papers by Berry et al. and Faulkner and Sidey–Gibbons, in this Research Topic highlight the inadequacy of existing measures, and Shoval et al., indicates a need for more fine-grain analysis of the relationship between physical and mental health status in people with mental illness. Capitalizing on the opportunities afforded by digital devices for passive and active data collection presents a promising path forward for Lifestyle Psychiatry in order to capture the level of detailed data necessary for better characterizing the dynamic relations between physical health behaviors and mental health symptoms.

Next Steps for Lifestyle Psychiatry

Overall, the studies within this Research Topic covers a broad range of health behaviors, which may play a central role in the prevention and self-management of mental illness. Along with the established fundamentals of human health (such as diet, exercise, and sleep), several other factors (such as stress management, nature time, and digital technology usage) should also be considered within Lifestyle Psychiatry, as this field continues to progress. The priorities for future research now lay with regards to i) moving from the wealth of observational studies to now focus on examining both the efficacy and implementation of lifestyle-focused approaches in mental healthcare, ii) harnessing digital technologies to facilitate the assessment of physical–mental health interactions, and delivery of lifestyle psychiatry interventions, and (iii) considering lifestyle factors in combination, rather than individual behaviors in isolation—in order to develop a more complete understanding of the interactions between our lifestyle and mental well-being. Ultimately, rigorous further research on the use and implementation of multicomponent lifestyle interventions could not only improve our understanding of the interface between physical and mental health but also align these existing individual fields of research (on physical activity, diet, etc.), to present more comprehensive and effective lifestyle treatment programs for individuals with mental illness.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the writing of this manuscript, and have approved the final version.

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ORIGINAL RESEARCH
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Is Obesity in Young People With Psychosis a Foregone Conclusion? Markedly Excessive Energy Intake Is Evident Soon After Antipsychotic Initiation

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Introduction: Antipsychotic medication (APM) initiation is associated with rapid and substantial weight-gain and high rates of obesity. Obesity leads to premature onset of cardiometabolic diseases and contributes to the 15–20 year shortfall in life expectancy in those experiencing severe mental illness. Dietary energy intake excess is critical to weight management but is yet to be quantified in youth with first episode psychosis (FEP) receiving APM. This study aimed to describe the degree of energy overconsumption and the food sources contributing to this in youth with FEP.

Materials and Methods: People aged 15–30 years with FEP receiving APM completed diet histories through qualified dietitians to assess energy imbalance and food sources. Outcome measures were: (i) energy balance; and (ii) intake of core and discretionary foods.

Results: Participants (n = 93) were aged 15–29 years (mean = 21.4 ± 2.9 years) and exposed to APMs for a median for 8 months (Interquartile Range (IQR) 11 months). Energy balance was exceeded by 26%, by a median 1,837 kJ per day (IQR 5,365 kJ). APM polypharmacy and olanzapine were linked to larger excesses in dietary energy intake. The greatest contributors to energy intake were refined grain foods (33%) and discretionary foods (31%).

Conclusion: Young people with FEP receiving APMs appear to have markedly excessive energy consumption, likely contributing to rapid weight-gain, and thereby seeding future poor physical health. Larger, prospective studies are needed to gain a greater understanding of dietary intake, and its effects on health, in people with FEP.

Keywords: weight gain, psychosis, antipsychotics, early intervention, diet

INTRODUCTION

People receiving antipsychotic medication (APM) for first-episode of psychosis (FEP) experience rapid, excessive weight gain and acquire risk factors for cardiometabolic disease (1, 2). Weight-gain is most rapid in the first few months of APM treatment, and accompanied by central obesity (3). Longitudinal data shows that mean weight gain is 12 kg over the first 2 years of APM treatment, increasing to a mean 19 kg over the first 4 years (4). The higher rates of abdominal obesity (OR 4.43), hypertriglyceridemia (OR 2.73), metabolic syndrome (OR 2.35), low HDL (OR 2.35), diabetes (OR 1.99), and hypertension (OR 1.36) compared to controls (5), culminates in a 20-year life expectancy gap compared to the general population (6, 7). Each of these drivers ill health are preventable lifestyle factors relating to dietary intake.

A recent prospective study followed people from their first episode of psychosis, and found that after 20 years, 62% of people with schizophrenia and 50% of people with bipolar disorder were obese, substantially higher than national averages (8). Interestingly, those with SCZ gained significantly more weight in the first 10 years compared to the subsequent 10 years, whereas those with bipolar disorder gained less weight in the first 10 years compared to years 10–20. Critically, this study monitored weight change for 20 years, significantly longer than other prospective studies, and showed for the first time that weight gain may not being to plateau until between 10 and 20 years post first hospitalization. The authors also suggested that participants could continue to gain weight, even after the 20-year observation period.

Appropriate dietary energy intake is fundamental to weight stability, management of weight excess, and managing cardiometabolic risk. It is yet to be explored, however, in people with FEP. APM are associated with increased appetite (9), unhealthy dietary intake (10), disordered eating behaviors (11) and sedentary behavior (reduced energy expenditure) (12), however mechanisms are not clearly understood. Dopamine, serotonin, muscarinic, and histamine receptors have all been implicated in APM-induced hunger changes, with APM with a high affinity for the 5-HT_{2C} and muscarinic receptors associated with the greatest risk for weight-gain (13). Evidence also suggests weight-gain mechanisms innate to the psychiatric illness, such as brain structural damages (14). The eating process in those experiencing psychosis is made difficult due to impaired executive functioning, which complicates restrained eating and facilitates disinhibition (15). It appears that both drug-naïve and those receiving APM treatment have insensitive rewards systems shifting the preference to less nutritious foods high in sugar, salt, and fat (14).

Whilst APM-induced changes in appetite, weight and obesity have been well-documented, the energy intakes, food preferences and dietary quality of youth with FEP receiving APM have yet to be clearly quantitated. Limited published data highlight unhealthy dietary habits in severe mental illness (10), with diets lower in fruit and fiber, and higher intake of sweet foods and drinks compared to the general population. Much remains to be delineated, including quantitation of energy excess, dietary quality, and shortfalls to national dietary guidelines.

In addition to energy consumption, diet quality also importantly contributes to health. Quality is inferred from the inclusion of essential fatty acids, protein, vitamins, minerals, and fiber, typically found in "core food groups" such as vegetables, fruit, wholegrains, milk, cheese, and yogurt, and protein-rich foods (meat, poultry, seafood, eggs, nuts, and legumes). On the other hand, "discretionary foods" are low- or non- nutritious foods typically found in "Westernized" diets, which are generally high in added sugars, salt and/or fat, and are identified risk factors for poor cardiometabolic health (16).

Understanding these food choices and preferences is fundamental to the development of dietary strategies to reverse and/or prevent APM-induced obesity in youth with psychosis. To the authors' knowledge no study has yet examined energy intake relative to individual energy requirement in order to estimate energy excess, in the early stage of APM-treatment when weight gain occurs most rapidly. Further, comparisons of diet quality against national standards are lacking.

AIMS OF THE STUDY

In youth with FEP receiving APM, this study aimed to (i) quantify energy intake against energy requirements to determine the degree of energy intake imbalance, and (ii) examine diet quality, compared to Australian national dietary recommendations.

METHODS

Design

We undertook a cross-sectional analysis of dietary intake in youth experiencing FEP. Inclusion criteria were: (i) 15–30 years of age, (ii) within 2 years of first onset of psychotic symptoms, and (iii) receiving APM. Exclusion criteria were having received dietary education and/or intervention since commencing APM. The treating psychiatrists provided data on psychotropic medications and Diagnostic and Statistical Manual for Mental Disorders (DSM-V) diagnoses (17). This study received ethical approval from the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC ref no: 14/276; LNR/14/POWH/614). This study was reported using the Strengthening the Reporting of Observational Studies in Epidemiology–Nutritional Epidemiology (STROBE-nut) guidelines (18).

Participants/Setting

Participants were patients who were referred, as part of routine care, to the *Keeping the Body in Mind* program between January 2015 and December 2017, from three allied community youth mental health services in urban Sydney. *Keeping the Body in Mind* is a lifestyle program involving a dietitian, exercise physiologist, and mental health nurse consultant, targeting the physical health of people with mental illness. On referral to the program, dietary intake was assessed by a dietitian using a comprehensive diet history (19), accounting for usual intake and variation. A food checklist was included to ensure all

food categories were evaluated. Portion size was estimated using food models and measuring cups. The frequency of various foods was evaluated, including the typical composition of meals (20). Individual diet histories were completed in a private consulting room, over 30–60 min. This dietary assessment formed part of a broader cardiometabolic lifestyle assessment (21), including anthropometric and physical activity measures and was conducted prior to the delivery of *Keeping the Body in Mind* intervention (22).

Outcome Measures

Estimated energy intake (EEI) was derived from kilojoule values assigned to food groups described in the Australian Guide to Healthy Eating (AGHE) (23). To determine energy balance, estimated energy requirement (EER) was calculated for each participant using the Schofield equation (24), adjusting for physical activity level (sedentary 1.3–1.4x BMR, light-moderate 1.5–1.6x BMR, active 1.7–1.8x BMR) (25) and using adjusted ideal body weight for participants with a body mass index (BMI) $\geq$25 kg/m^2 (see **Supplementary Material 1**) (26). Using Goldberg et al. cut-off limit for plausible intake, participants were considered to be underreporting if the EEI:BMR ratio was <0.9 (27).

Diet quality was measured by estimating serves of core food groups: (i) vegetables (separately for starch and non-starch vegetables), (ii) fruit, (iii) milk, cheese, yogurt, and alternatives, (iv) grain foods, (v) protein foods such as meat, poultry, fish, eggs, nuts and seeds, and (vi) discretionary foods as defined in the AGHE (23). These estimated intakes of food group servings were compared to the recommended serves, based on age and sex, also defined in the AGHE (23). Grain foods were further categorized into mostly wholegrain ($\geq$50% wholegrain products) or refined (<50% wholegrain products).

Weight (kg) was measured with participants barefoot in light street clothing. Height (m) was measured using a stadiometer with participants barefoot. Body mass index (BMI) was calculated using weight/ height x height, kg/m^2. Waist circumference (cm) was measured horizontally at the navel using a measuring tape to the nearest 0.1 cm. BMI was categorized using the World Health Organization classification (28). Central obesity was categorized using waist circumference and the International Diabetes Federation classification (29).

Statistical Analyses

We compared (i) estimated energy intake and recommended energy intakes, and (ii) estimated food group intake and recommended food group intakes. The Shapiro-Wilk test was run as a test of normality. Paired sample and/or independent samples *t*-tests were run to test for significance between variables for normally distributed data, and reported as mean and standard deviation. The Wilcoxon Signed Ranks Test was used to test for statistical significance for non-normally distributed data. Non-normally distributed data were reported as median and range. Chi-squared tests examined the weight and waist circumference status of participants. Kruskal-Wallis Tests with Pairwise Comparisons were used for subgroup analyses of excess energy intake by diagnosis and APM prescription. A Spearman's Rho correlation was run between excess energy intake and: (i) chlorpromazine equivalents, and (ii) duration of APM treatment. Statistical significance was set at $p < 0.05$. A Bonferroni correction was incorporated for *t*-test comparisons across multiple food groups, with a new statistical significance level set at $p < 0.007$. Analyses were performed using SPSS Version 24 (Chicago, IL, United States).

RESULTS

There were 93 participants (58 males, 62%), mean age 21.4 $\pm$ 2.9 years. Participants were predominantly Europids ($n = 52$, 56%) and, in decreasing frequency, Asian ($n = 27$, 29%), Maori/Pacific Islander ($n = 6$, 7%), Aboriginal/Torres Strait Islander ($n = 3$, 3%), Middle Eastern ($n = 3$, 3%), South American ($n = 1$, 1%), and African ($n = 1$, 1%). DSM-V diagnoses were: schizophrenia ($n = 32$), bipolar affective disorder ($n = 16$), psychosis not otherwise specified ($n = 15$), major depressive disorder with psychosis ($n = 10$), schizoaffective disorder ($n = 10$), substance-induced psychosis ($n = 4$), schizophreniform disorder ($n = 2$), delusional disorder ($n = 1$), organic psychosis ($n = 1$), brief reactive psychosis ($n = 1$), and psychosis due to another medical condition ($n = 1$). Demographic, diagnostic and medication data are provided in **Table 1**.

The majority of participants received APM monotherapy ($n = 81$, 88%): risperidone ($n = 28$), aripiprazole ($n = 19$), olanzapine ($n = 16$), quetiapine ($n = 8$), paliperidone ($n = 4$), clozapine ($n = 3$), amisulpride ($n = 2$), ziprasidone ($n = 2$). Eleven participants were prescribed dual APM: aripiprazole with olanzapine ($n = 5$), risperidone ($n = 1$), or quetiapine ($n = 2$); clozapine with amisulpride ($n = 1$), aripiprazole and quetiapine ($n = 1$); and quetiapine with paliperidone ($n = 1$). Mean dosage prescribed was 242 $\pm$ 186 mg chlorpromazine equivalents. Median APM exposure was 8 months (IQR 7 months). A range of mood stabilizer, antidepressant and benzodiazepine medications were also prescribed to some participants.

The mean BMI was 25.7 $\pm$ 5.0 kg/m^2 (males: 26.1 $\pm$ 4.4 kg/m$^{2;}$ females 24.9 $\pm$ 5.7 kg/m^2). Forty three participants had healthy BMI (48%), with large proportions overweight ($n = 31$, 33%) or obese ($n = 16$, 17%). One participant was underweight. Males (60%) were more frequently overweight or obese compared to females (34%), ($X^2 = 5.9$, $p = 0.01$). The percent of females with central obesity was numerically higher than for males ($n = 22$, 63% vs. $n = 30$, 52%), but this difference was not statistically significant, $X^2 = 1.1$, $p = 0.2$).

All participants met Goldberg's criteria for plausible energy intake reporting. Estimated energy intake (EEI) was significantly and substantively higher than estimated energy requirements (EER) ($Z = -5.1$, $P < 0.001$), with a median energy intake excess of 1,837 kJ per day (IQR 5,365 kJ). Median energy intake excess for males was 1,771 kJ per day (IQR 5,355 kJ), and for females 1,837 kJ per day (IQR 5,196 kJ) (**Table 2**). There was a significant difference for mean excess energy between different APM ($H = 15.7$, $p < 0.05$). Excess energy consumption was significantly higher in those prescribed APM polypharmacy when compared to those prescribed amisulpride ($p < 0.01$)

TABLE 1 | Demographic and clinical measures in young people with first episode psychosis.

		Males($n = 58$)	Females ($n = 35$)	Total($n = 93$)
DEMOGRAPHIC				
Age	mean (SD)	21.5 (2.8)	21.2 (3.2)	21.4 (2.9)
Ethnicity	*n* (%)			
Europid		37 (64)	15 (42)	52 (56)
Asian		13 (21)	14 (40)	27 (29)
Maori/Pacific Islander		5 (9)	1 (3)	6 (7)
Aboriginal/Torres Strait Islander		1 (2)	2 (6)	3 (3)
Middle Eastern		1 (2)	2 (6)	3 (3)
African		0 (0)	1 (3)	1 (1)
South American		1 (2)	0 (0)	1 (1)
PHYSICAL ACTIVITY LEVEL				
Sedentary		36 (62)	24 (68)	60 (64)
Light-Moderate		14 (24)	10 (29)	24 (26)
Active		8 (14)	1 (3)	9 (10)
ANTHROPOMETRIC MEASURES				
Weight	kg (SD)	82.4 (15.4)	66.8 (16.2)	76.5 (17.4)
BMI	kg/m^2 (SD)	26.1 (4.4)	24.9 (5.7)	25.7 (5.0)
BMI classification	n (%)			
Underweight (<18.5 kg/m^2)		1 (2)	0 (0)	1 (1)
Ideal weight (18.5–24.9 kg/m^2)		22 (38)	23 (66)	45 (49)
Overweight (25–29.9 kg/m^2)		27 (46)	4 (11)	31 (33)
Obese (≥30.0 kg/m^2)		8 (14)	8 (23)	16 (17)
Waist circumference	cm (SD)	93.7 (12.6)	86.7 (12.8)	91.0 (13.0)
Waist circumference classification	n (%)			
Ideal		28 (48)	13 (37)	41 (44)
Increased risk		30 (52)	22 (63)	52 (56)
DSM-V Diagnosis	n (%)			
Schizophrenia		25 (43)	7 (20)	32 (34)
Schizoaffective disorder		5 (8)	5 (14)	10 (11)
Schizophreniform disorder		0 (0)	2 (6)	2 (2)
Bipolar affective disorder		9 (16)	7 (20)	16 (17)
Substance-induced psychosis		3 (5)	1 (3)	4 (5)
Psychosis not otherwise specified		6 (10)	9 (25)	15 (16)
Major depression with psychosis		9 (16)	1 (3)	10 (11)
Delusion disorder		0 (0)	1 (3)	1 (1)
Organic psychosis		1 (2)	0 (0)	1 (1)
Brief reactive psychosis		0 (0)	1 (3)	1 (1)
Psychosis due to another medical Condition		0 (0)	1 (3)	1 (1)
PSYCHOTROPIC MEDICATIONS				
Antipsychotic	n (%)			
Risperidone		18 (31)	10 (29)	28 (30)
Aripiprazole		12 (21)	9 (26)	19 (20)
Quetiapine		4 (7)	4 (11)	8 (9)
Olanzapine		11 (19)	5 (14)	16 (17)
Clozapine		3 (5)	0 (0)	3 (3)
Amisulpride		1 (2)	1 (3)	2 (2)
Ziprasidone		1 (2)	1 (3)	2 (2)
Paliperidone		2 (3)	2 (6)	4 (4)
Antipsychotic polypharmacy		6 (10)	5 (14)	11 (12)
Chlorpromazine equivalent	mg (SD)	261 (208)	209 (138)	242 (186)
Duration of antipsychotic (months)	median (IQR)	8.7 (7.5)	7.0 (5.7)	8.1 (6.9)
Antidepressant	n (%)			
Yes		15 (26)	12 (34)	27 (29)
Mood stabilizer				
Yes		15 (26)	5 (14)	20 (22)
Benzodiazepine				
Yes		4 (7)	1 (3)	5 (5)
ADDITIONAL MEDICATION				
Metformin		1 (2)	1 (3)	2 (2)

and those prescribed risperidone ($p < 0.05$); those prescribed olanzapine reported significantly higher excess energy intake when compared to amisulpride ($p < 0.01$), risperidone ($p = 0.02$) and aripiprazole ($p = 0.04$). There was no relationship between medication dosage (chlorpromazine equivalents), or duration of treatment with APM, and excess energy intake in this sample ($r = -0.004$, $p = 0.97$; $r = 0.02$, $p = 0.85$). There was no significant difference between those prescribed: one APM only, APM polypharmacy, APM and mood stabilizer, APM and antidepressant, or APM, mood stabilizer and antidepressant ($X^2 = 3.8, p = 0.44$). There was no significant difference between all diagnoses within this sample ($H = 2.3$, $p = 0.81$), or major subgroups: (i) schizophrenia spectrum, (ii) bipolar affective and (iii) major depression with psychosis ($H = 0.6, p = 0.90$).

The sources of energy intake were, in descending order of magnitude: grain foods (33%); discretionary foods (31%); protein-rich foods (17%); added unsaturated fats and oils including spreads (6%); dairy (milk, cheese and yogurt) (6%); fruit (4%); and vegetables (3%). Mean daily serves of food groups

TABLE 2 | Energy intake in young people with first episode psychosis.

	Mean energy intake kJ/day (SD)	Mean energy requirement kJ/day (SD)	Median difference kJ/day (IQR)	Wilcoxon signed ranks test
GROUP				
Male	13,651 (4,517)	11,167 (1,320)	1,771 (5,355)	Z=–3.6, $p < 0.001$
Female	11,513 (4,326)	8,479 (1,132)	1,837 (5,196)	Z=–3.8, $p < 0.001$
Total	12,846 (4,544)	10,155 (1,808)	1,837 (5,365)	Z=–5.1, $p < 0.001$

were: grain foods 7.2 ± 3.7, discretionary foods 6.6 ± 5.8, protein foods 3.7 ± 2.2, dairy foods 1.7 ± 1.4, fruit 1.7 ± 1.8, and vegetables 2.8 ± 1.8 (**Table 3**).

Reported intakes were compared to Australian national dietary recommendations. There was a significantly higher than recommended intake of discretionary [$t_{(92)} = 6.4$, $p < 0.001$]. In contrast, there were shortfalls in recommended intakes of vegetables [$t_{(92)} = -13.4$, $p < 0.001$], dairy [$t_{(92)} = -6.5$, $p < 0.001$], and unsaturated oils/spreads [$t_{(34)} = -14.9$, $p < 0.001$]. The majority of participants consumed grain-containing foods as refined/processed products (81%); only 19% consumed predominantly wholegrain products. The majority of participants had shortfalls in the recommended intakes of vegetables (86%), dairy (73%), and fruit (61%). The recommended intake of discretionary food intake was exceeded in 72% of participants.

DISCUSSION

To our knowledge, this is the first study to demonstrate that youth with severe mental illness receiving APM and other psychotropic medications have energy intakes that exceed individual requirements by some 26% on average. Further, excessive intakes of discretionary foods and refined grain-based foods were evident, along with insufficient intakes of vegetables, dairy and fruit. In combination with the sedentariness already documented in people with psychosis (12), this excessive energy intake is likely to contribute substantially to the rapid and excessive weight-gain observed in the years after APM initiation. The weight change dynamics paradigm of Hall and co-workers' (30) predicts that every 100 kJ (24 kcal) intake excess will have an eventual bodyweight change of 1 kg, with half this weight change occurring within 1 year, and 95% weight change occurring within 3 years. Applying this model to the excess daily energy intake of 1,837 kJ (439 kcal) found in our study an eventual bodyweight change of approximately 18 kg would be expected. This can help explain the mean 20 kg weight gain that has been observed in people receiving APM over the first 4 years of treatment (4).

Whilst increasing physical activity is important for reducing cardiovascular risk, and symptoms of depression and possibly psychosis (31, 32), increased physical activity alone is unlikely to adequately address this excessive energy imbalance: the hypothetical 70 kg person would need to walk an additional 3.5 h at 4 km/h or run for 1 h at 10 km/h each day to expend the observed energy surplus (33). Therefore, reduction of energy intake will be essential for preventing or reducing the weight gain that follows APM initiation and their long-term use.

The higher excess in dietary energy intake found for both APM polypharmacy and olanzapine is congruent with the literature, with both of these having higher weight gain potential compared to other second-generation APM (34, 35). Treatment with a mood stabilizer and some antidepressant medications can result in weight-gain. Given that our inclusion criteria were young people with FEP receiving APM, with no restriction on additional psychotropic medication prescription, it was difficult to disentangle the effects of mood stabilizer and antidepressant medication on dietary intake. Larger studies, with set psychotropic medication criteria would allow greater exploration of the effects of mood stabilizer and antidepressant medications (with and without APM) on food and dietary energy intake. Our study did not find a relationship between APM dosage and excess dietary energy intake, although it is conceivable that higher APM dosage would be associated with greater appetite and therefore higher dietary energy intake. Larger, appropriately designed studies would be needed to confirm the effect that APM dosage has on dietary intake.

Study limitations include the following: First, the cross-sectional design means that prospective studies that measure dietary intake at multiple time points are needed to confirm these findings. Second, while the program aims to assess all young people with FEP attending local health district services, there is potential for more health conscious consumers to engage in a dietary assessment. Third, there would be value in including a matched comparison group of youth not receiving APMs. Ideally, the comparator group would comprise sociodemographically-matched youth with mental health disorders that do not require treatment with APMs, such as depression and/or anxiety. Though it is worthy to note that the reported energy intake was substantially higher for both males and females in this study compared to data from the general population aged 19–30 years (36); 13,651 vs. 11,004 kJ/day for males, and 11,513 vs. 7,863 kJ/day for women. This reinforces the effects that impairments in executive function/reward system and increased appetite have on energy intake in people with psychosis. Fourth, important covariables such as symptom level/functioning, economic status, education, marital status, and metabolic/cardiovascular comorbidities, were not able to be included in this analysis and should be considered for future studies. Fifth, we could not determine if the nutritional issues predated APM use. Dietary data in pre-medicated FEP are required, but there are significant pragmatic obstacles to collecting such data pre-treatment, due to the nature of untreated severe mental illness and compliance with nutritional assessment. Sixth, dietary intake was estimated using the diet history method, a subjective measure that could lead to selective underreporting. The gold-standard objective biomarkers and the doubly labeled water technique are expensive and intensive for both the

TABLE 3 | Description of dietary patterns in young people with first episode psychosis.

	Percent of energy intake	Recommended servings/day*		Mean intake servings/day (SD)		Statistical test **	Percent of participants meeting national nutrition recommendations [11].
		Male	Female	Male ($n = 22$)	Females ($n = 13$)		
FOOD GROUPS							
Grain foods	33	6	6	7.1 (3.8)	7.4 (3.8)	$t_{(92)} = 2.5$, $p = 0.013$	19% choosing predominantly wholegrain
Protein-based foods	17	3	2.5	4.0 (3.2)	3.2 (1.9)	$t_{(92)} = 2.8$, $p = 0.009$	
Dairy and alternatives	6	2.5	2.5	1.8 (1.5)	1.6 (1.2)	$t_{(92)} = -6.5$, $p < 0.001$***	27%
Vegetables	3	6	5	2.6 (1.8)	3.3 (1.8)	$t_{(92)} = -13.4$, $p < 0.001$***	14%
Fruit	4	2	2	1.8 (2.2)	1.5 (1.2)	$t_{(92)} = 1.6$, $p = 0.103$	39%
Oils/spreads	6	4	2	2.0 (1.3)	1.8 (1.5)	$t_{(92)} = -14.9$, $p < 0.001$***	28%
Discretionary foods	31	0–3	0–2.5	7.6 (6.6)	4.8 (3.3)	$t_{(92)} = 6.4$, $p < 0.001$***	27%

** Recommended serves per day including serving sizes are described in the Australian Guide to Healthy Eating [11].*

*** Mean intake of all participants compared to recommended serves/day.*

**** Statistically significant after applying Bonferroni correction, with statistical significance set at $p < 0.007$.*

researcher and participant, and therefore not feasible in all studies. Studies that include these objective measures would help confirm findings using subjective measures. The final limitation is the conservative model used to calculate discretionary food consumption; the benchmark was set at the upper limit recommended, which would generally be reserved for those with higher energy requirements. This may have underestimated discretionary food intake. The dietary methodology did not enable us to estimate intake of trans and saturated fats, and free sugars, particularly relevant given the high intakes of discretionary foods.

Comprehensive care of youth with severe mental illness should incorporate lifestyle interventions to ameliorate cardiometabolic risk factors. Weight-gain prevention interventions implemented after APM initiation have larger effect sizes, compared to weight-loss interventions in people with enduring severe mental illness (37). Recognition of rapid weight-gain and cardiometabolic health decline soon after APM-initiation, together with evidence that lifestyle interventions in early psychosis programs prevent such outcomes (22), underpin the Healthy Active Lives (HeAL) Declaration (38), that defines 5-year targets for key lifestyle factors contributing to poor cardiometabolic health in severe mental illness (www.iphys.org.au). These include specific dietitian-led interventions for weight management, which have been shown to be effective in severe mental illness (37). Further exploration is also needed for the use of adjunctive nutrients in people experiencing FEP as a potential method of improving symptoms and functioning (39).

While not explored in this study, it is important to note that people at ultra-high risk for psychosis and APM naïve people with FEP also have high rates of cardiometabolic abnormalities (40). This may be explained, at least in part, by the impaired executive functioning and reward system complicating the eating process and increasing the preference for non-nutritious foods high in sugar, salt and fat (14). Further exploration of the effectiveness of weight-gain preventative measures in those at ultra-high risk for psychosis and APM naïve people with FEP are needed.

In summary, this cross-sectional study suggests excessive consumption of discretionary and processed foods and numerous shortfalls in essential quality requirements are likely contributing not only to rapid weight gain, but also to other longer-term health sequelae in people in the early stages of APM treatment. Addressing the energy intake excesses observed in people with FEP receiving APM may assist in preventing weight-gain in the early stages of APM treatment. Larger, prospective studies, measuring dietary intake at multiple time points would assist in providing a greater understanding of the dietary intake, and its effects on health, in people with FEP.

AUTHOR CONTRIBUTIONS

ST, PW, AW, JC, and KS conceived the study and sought ethical approval. ST, RJ, TW, and ER completed the assessments. JC and JL provided psychiatry input and confirmed diagnoses. ST, PW, and KS analyzed the data. ST led manuscript preparation. PW, JC, JL, and KS added scientific intellect. RJ, TW, ER, and AW assisted with clinically relevant components. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00725/full#supplementary-material

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Does Fruit and Vegetable Consumption During Adolescence Predict Adult Depression? A Longitudinal Study of US Adolescents

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The relationship between better diet quality and decreased depression across the life span is consistent and compelling. Fruit and vegetable consumption has been of particular interest. The nutritional benefits from the consumption of fruits and vegetables may mitigate non-communicable diseases and promote brain and mental health. This study aimed to determine whether fruit and vegetable consumption during adolescence was associated with a reduced risk of developing depression in adulthood in a large, representative sample of US individuals. Data from the Add Health Study were analyzed, which included 3,696 participants who were aged approximately 17 years at baseline (1994–1995), and 29 years at follow-up (2007–2008). The Center for Epidemiologic Studies Depression Scale was used to assess depression and a self-report item asked how many times the participant consumed fruit/vegetables on the previous day. Individuals who were depressed at both times points had the highest proportion who failed to consume any fruit (31%) or vegetables (42%) on the previous day. Fruit and vegetable consumption did not predict of adult depression in fully adjusted models. Cross sectional associations existed for diet and adolescent depression only. Our initial findings supported fruit and vegetable consumption as being protective against adult depression, but this association was subsequently attenuated on adjustment for other relevant factors. Future research will benefit from more precise measures of dietary intakes.

Keywords: depression, adolescents, fruit, vegetables, adulthood

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INTRODUCTION

Healthful diets for the prevention and treatment of depression is a current major focus in nutritional psychiatric research. In particular, the Mediterranean Style Diet, traditional wholefood diets, and anti-oxidant rich foods have been promoted as supportive of positive mental health (1–4). Depression is a highly complex mental disorder and is the leading contributor to the global burden of disease (5). The causes and risk factors of depression span individual, familial, environmental, societal and other domains, thus prevention strategies are needed that account for the complexity

within which depression occurs (6). Individuals experiencing depression are at greater risk of experiencing comorbid lifestyle driven diseases such as overweight/obesity, cardiovascular disease and some cancers (7). These conditions are all associated with underlying poor diet and it is therefore highly plausible that prevention strategies that target healthier diet could hold dual physical and mental health benefits. It is recognized that experiencing depression and associated symptoms such as low motivation, can also lead to poor dietary choices and overall unhealthy eating habits particularly as a form of coping (8). Indeed the typical diet of individuals living with mental illness is poorer at the population level, compared to individuals without mental illness (9). The diet and depression relationship is therefore assumed to be bi-directional. Whilst the etiology of depression is highly complex, targeting diet for prevention holds great promise given the population reach and the known dual benefits for physical health and non-communicable disease prevention.

The underlying components of diets considered beneficial for mental health are all similar in that they all promote the regular consumption of fruits and vegetables (4). Fruits and vegetables are micronutrient and anti-oxidant rich, which is thought to be protective against oxidative stress in the body (10, 11). In addition, vitamins and minerals found in fruit and vegetables have been shown to support healthy emotional and cognitive functioning (12). Diets high in fruit and vegetables have also been shown to impact directly on brain health. A study published in 2015 found that healthier dietary patterns, high in fruit and vegetables, were associated with larger hippocampal volume over time, compared to Western-style, unhealthy diets, low in fruit, and vegetables (13).

Evidence suggests that both low rates of common mental disorders including depression, low mood, stress, and anxiety (14, 15), and higher rates of positive mental health including life satisfaction, positive mood, and perceived life flourishing (16), co-occur with fruit and vegetable intake. Furthermore, research suggests that a dose-response relationship exists, whereby each serve increase in fruit and vegetables is associated with an improvement in mental health (17, 18). Given the evidence to date, treatment trials have been conducted examining the impact of dietary changes, including increased fruit and vegetable consumption, on depressive symptoms with significant positive outcomes being reported (3, 19).

Despite evidence to date, there are some research gaps in terms of the relationship between fruit and vegetable intake for the prevention of depression at a population-level. In particular, while it is known that a life span approach should be adopted, it remains unknown what the unique preventive potential of fruit and vegetable consumption during adolescence might be for reducing the risk of depression later in adulthood. This may be particularly critical given that depression often first occurs during adolescence (20). In addition, dietary habits formed in adolescence often track into adulthood, which has important implications for physical health later in life (21). Investigating the predictive potential of fruit and vegetable consumption during adolescence and adult depression outcomes thus has important implications for population-level prevention initiatives.

The aim of this study is to determine whether adolescent fruit and vegetable consumption predicts adult depression, and whether this predictive potential is independent of other factors known to be related to both diet and mental health outcomes, such as overweight/obesity, socio-economic status, and physical activity.

METHODS

Study Design

Add Health is a longitudinal, US population-based study of adolescent health (22). During the 1994–1995 school year, 132 secondary schools participated in a questionnaire data collection, which reflected a nationally representative sample of students aged between 12 and 18 years ($n = 20{,}745$). Additionally, four waves of in-home interviews were conducted in 1994–1994 (Wave 1), 1996 (Wave 2), 2001–2002 (Wave 3), and 2007-2008 (Wave 4), spanning a total of 18 years. The sampling strategy was stratified random sample that represented the entire US in regards to region, urban/rurality, size, and ethnicity. Further detailed information has been published elsewhere (22).

Our study examined data from the original participating adolescents from Wave 1, who also completed follow-up data collection at Wave 4, and had complete, public accessible data available ($n = 4{,}807$). Sample weights were employed to account for the baseline probabilities and potential clustering effects of school to which participant attended. Ethics approval for the Add Health study was approved by the Institutional Review Board of the University of North Carolina, Chapel Hill. Public-use data are available for research purposes and were accessed from http://www.cpc.unc.edu/projects/addhealth

Depression

Depression was measured by the Center for Epidemiologic Studies Depression Scale (CES-D) (23) at baseline in Wave 1 (1994–1995, mean age 16 years) and at Wave 4 (2007–2008, mean age 29 years). The CES-D is often used in population level epidemiological studies to measure the presence of symptoms typically resembling depression. The questionnaire includes items relating to how often in the past week the individual experienced symptoms such as restless sleep, feelings of loneliness and trouble in concentrating. Responses range from 0 to 3, where 0 = rarely or never and 3 = most or all of the time. Higher scores reflect greater depressive symptoms. The CES-D shows good sensitivity, specificity and high internal consistency and has been previously used across a broad range of age groups including adolescents (24). Reliability and validity has been previously shown.

At Wave 1, the 20-item CES-D was administered, and at Wave 4, participants received the 10-item version. A score of 16 or higher on the CES-D-20 and 11 or higher on the CES-D-10 was used to define probable depression, as per recommendations (23, 25). Adult (Wave 4) depression was the main outcome of interest and adolescent depression was controlled for as a covariate in analyses. We also ran models to examine the cross-sectional relationship between adolescent depression and fruit and vegetable consumption.

Fruit and Vegetable Consumption

Fruit and vegetable consumption was the main predictor of interest in this study. During Wave 1, participants completed questionnaires on habitual dietary intake including items asking whether they had eaten fruit or vegetables on the previous day. Specifically, participants were asked "How often did you eat fruit or drink fruit juice yesterday?" with responses "didn't eat," "ate once" or "ate twice or more." The same item with response options was asked for vegetable consumption. Single-item dietary measures for fruit and vegetable consumption are widely used in population level epidemiological questionnaires and have been shown to be indicative of overall dietary quality (26).

Covariates

Demographic, health behavioral, and anthropometric variables were selected for inclusion, based on evidence demonstrating potential to confound the relationship between diet and depression. Wave 1 questionnaires asked information relating to participants age, sex, total household income during 1994 (reported by parents) and ethnicity. Health behaviors including smoking status and physical activity levels were assessed at Wave 1 asking participants to report the number of times during the past week they did exercise, such as jogging, walking, karate, jumping rope, gymnastics, or dancing. Smoking status was also self-reported. Height and weight were objectively measured at Wave 4 and converted into body mass index, which was further converted into healthy weight and overweight/obese weight status categories (27). Because objective measures were only taken at Wave 4 (and not Wave 1), these data were used to control for weight status in analyses.

Statistical Analyses

All analyses were conducted in Stata/SE 15.0 (Stata Corporation) and significance was assumed at $p < 0.05$. Total CES-D scores were calculated and dichotomised using the cut off $\geq$16 for Wave 1 (CES-D-20) and $\geq$11 for Wave 4 (CES-D-10) as recommended by previous research (28).

Logistic regression models were used to examine whether adult depression was significantly predicted by adolescent fruit and vegetable consumption. Odds ratios with 95% confidence intervals assessed these relationships, with outcomes being whether or not depression was present (0 = no depression, 1 = depression present). Models were sex-specific given the known unique experiences of depression specific to sex. Univariate relationships were examined (Model 1) and then baseline depressive status were added (Model 2). Covariates age, household income during adolescence, ethnicity, physical activity, smoking status, and weight status were adjusted for in Model 3.

RESULTS

Participants were approximately 16 years at adolescence (baseline) and 29 years at adulthood (follow-up) (**Table 1**). Most participants were of Caucasian decent and depression significantly varied by ethnicity. The mean household income during adolescence was significantly lower among those with adult depression compared to those without adult depression. Physical activity and smoking status during adolescence, and adult overweight/obesity did not differ between those depressed as adults and those not depressed.

TABLE 1 | Participant characteristics, expressed as n (%) unless otherwise specified.

	Not depressed in adulthood (n = 3,003)	Depressed in adulthood (n = 693)	Total (n = 3,696)
Age, mean (SD)			
Baseline	15.9 (1.7)	15.9 (1.8)	15.9 (1.7)
Follow-up	28.9 (1.7)	28.9 (1.8)	28.9 (1.7)
Ethnicity			
Caucasian	2189 (72.9)	436 (62.9)	2625 (71.0)
African American	591 (19.7)	193 (27.9)*	784 (21.2)
Native American	34 (1.1)	Supressed	Supressed
Asian/pacific islander	85 (2.8)	Supressed	Supressed
Other	104 (3.5)	38 (5.5)	142 (3.8)
Household income during adolescence m SD ('000s)	50.8 (57.0)	40.2 (45.6)*	48.8 (55.2)
Smokers	565 (18.7)	150 (21.7)	712 (19.3)
Physical activity[a]			
Not at all	508 (16.9)	108 (15.6)	616 (16.7)
1 or 2 times	942 (31.4)	212 (30.6)	1,154 (31.2)
3 or 4 times	761 (25.3)	177 (25.5)	938 (25.4)
5 or more times	792 (26.4)	196 (28.3)	988 (26.7)
Overweight/obese in adulthood	2,013 (67.0)	469 (67.7)	2,482 (67.2)
Depression during adolescence	491 (16.4)	289 (41.7)*	780 (21.1)

Significant ($p < 0.05$) difference between groups not depressed in adulthood and depressed in adulthood.

Abbreviations: Standard deviation, SD.

[a] *Participants were asked the number of times during the past week they did exercise, such as jogging, walking, karate, jumping rope, gymnastics, or dancing.*

Individuals who never experienced depression were the highest consumers of fruit and vegetables during adolescence (**Figure 1**; **Supplementary Table 1**). Most (80%) of the individuals who did not ever experience depression ate fruit on the previous day. The proportion not eating fruit on previous day was higher among those who had depression during adolescence, and among those who went on to experience depression in adulthood. One third of those depressed at both time points did not consume fruit and 42% did not consume any vegetables on the previous day. Vegetable consumption was highest among those who did not experience depression at either time point (**Figure 2**).

Fruit consumption among males and vegetable consumption among females was prospectively associated with a reduced risk of adult depression in unadjusted models (**Table 2**). The association between vegetable consumption among females and the risk of adult depression remained significant after controlling for adolescent depression; however, this relationship was attenuated after controlling for age, household income, ethnicity,

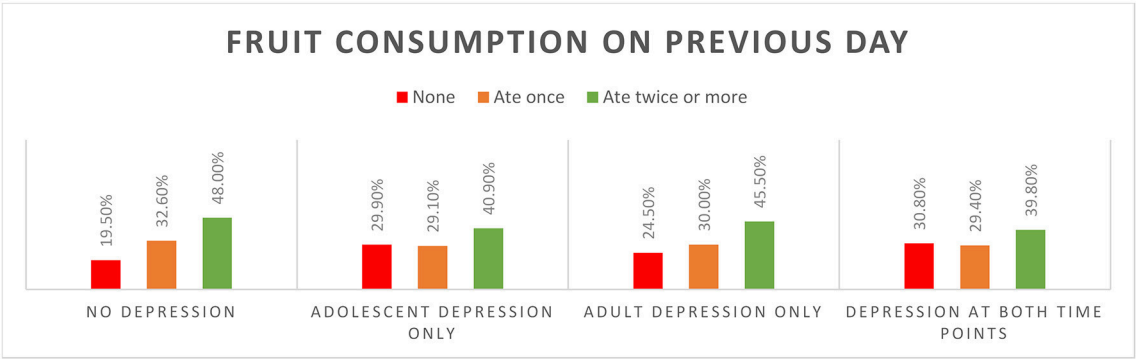

FIGURE 1 | Fruit consumption on previous day by depression status.

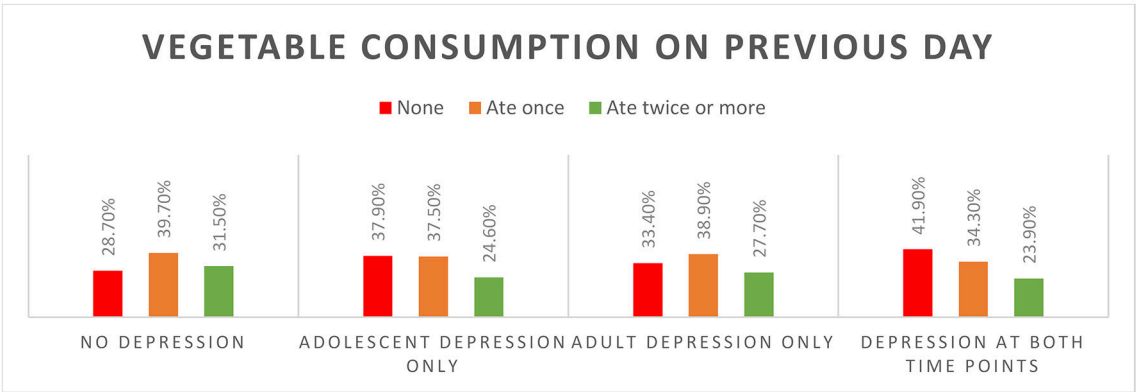

FIGURE 2 | Vegetables consumption on previous day by depression status.

physical activity and overweight/obesity. Fruit consumption was cross-sectionally related to reduced odds of depression in adolescence in both males and females, both before and after controlling for covariates (**Table 3**). Vegetable consumption among females was cross-sectionally associated with reduced odds of depression in adolescence.

DISCUSSION

Fruit and vegetable consumption during adolescence was predictive of adult depression in univariate models, however, this relationship was attenuated once adjusted for adolescent depression in males and by further adjustment for key confounding variables in females. In cross-sectional analyses, fruit (males and females) and vegetable (females only) consumption was related to adolescent depression, both before and after controlling for covariates. Consumption patterns by depressive status were as expected; fruit and vegetable consumption was highest among individuals who did not experience depression during adolescence or adulthood.

Our findings are somewhat inconsistent with previous literature that suggests that diet during adolescence is predictive of both concurrent and future mental health outcomes (26, 29). It has been suggested that it is fruit and vegetables, as a component of wider healthy diet, that promotes and supports mental and brain health (15, 26, 30). This was highlighted in research by (4) who proposed that it is the combination of foods and habitual dietary patterns over time, that hold implications for inflammation and oxidative stress which are contributing pathways to mood and emotional dysfunction that underpins depression (4). In light of the current results, it is possible that failing to incorporate the wider diet beyond fruit and vegetables, resulted in failure to capture potential predictive potential of future depression. In particular, given the established relationship between unhealthy diets and adolescent (31) and adult (1) depression, failure to assess and model the intake of other food groups, including processed and "junk" foods, may have limited our findings. This suggests that promoting fruit and vegetable consumption alone may not be enough to support prevention efforts. It is also known that mental health and diet relationship is considered bi-directional in that depressed states can impact upon appetite, hedonic capacity and food and dietary decisions (32). Recent evidence demonstrates poorer diet quality at a population level, among those living with mental illness, compared to those who do not experience mental illness (9). This relationship has been shown to be independent of relevant confounders

TABLE 2 | Prospective logistic regression models of adult depression (dependent variable) and associations with fruit and vegetable consumption during adolescence (independent variable).

Depress	Model 1						Model 2						Model 3					
	Males			Females			Males			Females			Males			Females		
Adult	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***
Fruit																		
0	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Once	**0.62**	**0.41, 0.94**	**0.025**	0.81	0.57, 1.15	0.239	0.71	0.46, 1.10	0.123	0.93	0.65, 1.35	0.715	0.72	0.46, 1.11	0.139	0.92	0.63, 1.33	0.645
Twice +	**0.64**	**0.44, 0.94**	**0.021**	0.76	0.55, 1.05	0.098	0.73	0.49, 1.09	0.123	0.89	0.63, 1.26	0.526	0.71	0.47, 1.07	0.097	0.88	0.62, 1.26	0.478
Veg																		
0	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
Once	0.96	0.65, 1.40	0.815	**0.66**	**0.48, 0.89**	**0.007**	1.00	0.68, 1.48	0.986	**0.72**	**0.53, 1.00**	**0.047**	1.07	0.72, 1.57	0.752	0.74	0.54, 1.02	0.068
Twice +	0.97	0.64, 1.46	0.870	**0.68**	**0.49, 0.94**	**0.019**	1.01	0.66, 1.55	0.951	0.79	0.57, 1.10	0.168	1.02	0.66, 1.56	0.936	0.80	0.57, 1.12	0.201

Unadjusted (Model 1), adjusted for adolescent depression (Model 2) and further adjusted for age, household income, ethnicity, physical activity, and BMI (Model 3) models are presented.
BMI, body mass index; CI, confidence interval; OR, Odds ratio.
Bolding indicates significance at $p < 0.05$.

including age, gender, BMI, education, and social deprivation. The cross-sectional findings here during adolescence supports this bi-directionality.

Eating vegetables once a day during adolescence was predictive of reduced odds of depression as an adult among females, compared to females who did not consume vegetables on the previous day. Sex differences have been established both in experiences and trajectory of depressive disorders, and also in health behaviors across the life span (5, 33). For example, our recent study showed that adolescent females were close to twice as likely to meet fruit and vegetable consumption recommendations compared to males (33). In emerging adulthood (18–30 years), females were less likely to be habitual sugar sweetened beverage consumers and more likely to meet physical activity recommendations, compared to emerging adult males. It is possible that young females who are regular consumers of vegetables are also engaging in other protective behaviors that might in combination offset depression. This finding is particularly important with a disproportionate risk of depression increasing with age among adolescent females compared to adolescent males (5). Males and females experience similar level of risk of depression in early adolescence, and by early adulthood females are twice more likely to experience depression than males of the same age (34).

It is possible that the influence of socio-economic circumstances were inadequately captured in this study. For example, whilst household income was included in fully adjusted models, participants' socio-economic circumstances may have changed with their transition from adolescence to adulthood. It is possible that life experiences occurring in early adulthood such as leaving school, living independently, commencing studies or full-time employment, may have influenced adult mental health and the potential contribution of these factors was not adequately captured. Higher rates of depression are consistently seen in neighborhoods experiencing disproportionate socio-economic disadvantage (35). There are environmental challenges in such communities, such as greater density of fast food outlets in place of fresh wholefood stores (36). The influence of socio-economic circumstances on mental and physical health outcomes are well-established, and it is possible that the failure to identify significant relationships in this study was due to inadequate capturing of such circumstances.

The expectation for fruit and vegetable consumption to impact upon current and future mental health is supported by physiological mechanistic pathways. Several plausible mechanisms have been proposed as to why fruit and vegetable consumption may confer protective benefits. Fruits and vegetables are rich in essential micronutrients such as folate, magnesium and selenium. Deficiencies in nutrients, such as folate, have been implicated in the pathogenesis of depression (37). Folate is an essential co-factor in metabolic pathways required for the synthesis of neurotransmitters, such as noradrenaline and serotonin (38), and may further exert protective benefits by decreasing homocysteine levels (39). Further, adequate intake of magnesium may reduce inflammation (40), and protect against chronic, low-grade inflammation which is implicated in depression (11).

TABLE 3 | Cross-sectional logistic regression models of adolescent depression (dependent variable) and associations with fruit and vegetable consumption in adolescence (independent variable).

	Model 1						Model 2					
Depress	**Males**			**Females**			**Males**			**Females**		
Adoles	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***	**OR**	**95%CI**	***p***
Fruit												
None	Ref.			Ref.			Ref.			Ref.		
Once	**0.48**	**0.33, 0.70**	**<0.001**	**0.59**	**0.43, 0.81**	**0.001**	**0.53**	**0.36, 0.77**	**0.001**	**0.68**	**0.49, 0.95**	**0.025**
Twice +	**0.50**	**0.35, 0.71**	**<0.001**	**0.54**	**0.40, 0.73**	**<0.001**	**0.55**	**0.38, 0.80**	**0.002**	**0.62**	**0.45, 0.85**	**0.003**
Veg												
None	Ref.			Ref.			Ref.			**Ref.**		
Once	0.79	0.56, 1.11	0.171	**0.65**	**0.49, 0.85**	**0.002**	0.80	0.56, 1.13	0.206	**0.69**	**0.52, 0.93**	**0.014**
Twice +	0.79	0.54, 1.16	0.232	**0.54**	**0.39, 0.73**	**<0.001**	0.87	0.59, 1.28	0.475	**0.64**	**0.46, 0.88**	**0.006**

Unadjusted (Model 1), and adjusted for age, household income, ethnicity, physical activity, and BMI (Model 2) models are presented. BMI, body mass index; CI, confidence interval; OR, Odds ratio.
Bolding indicates significance at $p < 0.05$.

Non-nutrient components of fruits and vegetables, such as polyphenols, also strengthen our rationale for fruit and vegetables to protect against depression. Polyphenols refers to a wide class of compounds that as antioxidants, may protect cells against oxidative damage (41) to positively influence brain health (42). Polyphenols may also act as prebiotics within the gut, and along with other dietary fibers, may contribute to the health of the commensal bacteria that reside within the gastrointestinal tract (i.e., the gut microbiota). Numerous studies suggest that the gut microbiota may play a key role in the pathophysiology of depression (43); thus, modulation of the microbiome by prebiotics and dietary fibers may have associated mental health benefits.

STRENGTHS AND LIMITATIONS

There were study design elements that limited this study. In particular, the measurement of fruit and vegetable consumption was self-reported, and this is likely to have introduced biases to the analysis such as social desirability bias. Moreover, there is large measurement error arising from dietary questionnaires and this would have attenuated the strength of the detected associations (44). On the other hand, single item fruit and vegetable consumption items have been shown to correlate with comprehensive dietary recall measures, and are widely used in population health research (44). In addition, our study examined fruit and vegetable consumption during adolescence only, and our findings could have been further explored with the inclusion of adult dietary behaviors. It is possible that dietary habits changed over time, but we did not have data to assess this. As identified, this study accounted for household income as a proxy for socio-economic status during adolescence. However, it is likely that social and economic changes were likely to have affected health behavioral and depressive outcomes in the transition from adolescence to adulthood. Our study failed to account for the impact of such changes. Our study was strengthened by the use of longitudinal cohort data, which were sampled to be representative of the US population. Despite this, the extent to which findings can translate to current adolescent health is limited. For example, the social environment and daily habitual lifestyle of adolescents is different to that experienced two decades ago and such experiences are likely to impact upon health outcomes adulthood. Lastly, the CES-D is a self-reported measurement of depression and our study was limited in that no clinical depression assessment was available. However, it has been commonly used in epidemiological studies and is widely accepted as an appropriate tool for the measurement of depression (23, 45).

CONCLUSION

The findings of this study offer further support for the role and importance of lifestyle behaviors, and in particular diet, for understanding experiences of mental health during adolescence. The wider evidence to date suggests that fruit and vegetable consumption could be an important predictor of future depression, and our null findings may be due to the limitations of our dietary assessment, which failed to capture overall dietary patterns and was likely affected by measurement error. Increasing consumption of fruit and vegetables is a highly valuable public health message in terms of preventing chronic and non-communicable diseases. The potential for prevention of depression to be included in this public health messaging is promising, given the current burden associated with depression and lifestyle-driven diseases. Given that diet and other lifestyle behaviors are largely shaped by social and economic circumstances, we propose that such factors, in addition to comprehensive dietary and other lifestyle behaviors, are incorporated into population-level mental health prevention research. Optimal prevention strategies are likely to be achieved through assuming complex interconnecting relationships between such drivers of health across the lifespan.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of University of North Carolina School of Public Health Institutional Review Board guidelines that are based on the Code of Federal Regulations on the Protection of Human Subjects 45CFR46: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html Add Health participants provided written informed consent for participation in all aspects of Add Health.

AUTHOR CONTRIBUTIONS

EH developed the study design, conducted the analyses, and drafted the manuscript. MH contributed to the manuscript and revised for intellectual content. AR and FJ revised the manuscript for intellectual content. All authors read and approved the final draft for submission.

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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.2018.00581/full#supplementary-material

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A Pro-Inflammatory Diet Is Associated With an Increased Odds of Depression Symptoms Among Iranian Female Adolescents: A Cross-Sectional Study

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Background: The relation between dietary inflammation and risk of depression has not been widely explored. We examined the association between the inflammatory effect of the diet and the odds of depression among Iranian female adolescents.

Methods: Using a stratified cluster sampling technique, 300 female adolescents aged 15–18 years were recruited from schools in Tehran between years 2014–2015. Depression was assessed using the Depression, Anxiety and Stress Scale (DASS)-a 21-point scale. The dietary inflammatory index (DII®) was used to evaluate the inflammatory potential of the diet. Dietary intake was assessed using a validated food frequency questionnaire. In addition to descriptive statistics, multivariable linear and logistic regression were used to calculate confounder-adjusted beta estimates and odds ratios.

Results: In total, 88 females (30%) had at least a moderate level of depressive symptoms (DASS > 6). Females with the most pro-inflammatory diet had higher DASS depression score ($\beta = 1.67$; 95% CI = 0.03, 3.31) and were at 3.96 (95% CI = 1.12, 13.97) times higher odds of having at least moderate depressive symptoms, compared to females with the least anti-inflammatory diets.

Conclusion: These data suggest that Iranian adolescent females eating a pro-inflammatory diet, as indicated by higher DII scores, had greater odds of having at least moderate depressive symptoms.

Keywords: dietary inflammatory index, diet, inflammation, depression, Iran

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INTRODUCTION

Depression is expected to become the world's second leading disease burden, after cardiovascular disease, by 2020 according the World Health Organization (1). Women are more than twice as likely to be diagnosed with depression compared with men (2). In Iran, major depression is the most prevalent mood disorder, with a prevalence rate of 2.98% among the entire population and 4.38% among women (3). The peak prevalence is between 25 and 44 years of age; however, recent data indicate that depression is occurring at younger ages (4, 5). Several metabolic and inflammatory processes, such as reduced insulin sensitivity, elevations in plasma homocysteine levels and, perhaps more importantly, increased production of pro-inflammatory cytokines and endothelial dysfunction, seem to be the major factors responsible for the depression (3, 4). Proinflammatory cytokines like c-reactive protein and interleukin-6 act by reducing brain monoamine levels, activating neuroendocrine responses, promoting excitotoxicity (increased glutamate levels), and impairing brain plasticity modulate mood behavior which can result in depression (6). Various dietary components have different effects on inflammation (7–9). A prudent dietary pattern high in fish, yogurt, pulses, rice, fruit, vegetables, and pasta has been shown to be associated with lower concentrations of intermediary inflammatory markers (10).

Various studies have been conducted to evaluate dietary exposures in relation to depression (11–15). In general, prospective cohort studies have shown that dietary patterns rich in anti-inflammatory components such as fruits, vegetables, olive oil, and legumes may be protective against depression (16–19). By contrast, increased risk has been observed with "pro-inflammatory" dietary patterns rich in saturated fat, omega 6 fatty acids, and refined carbohydrates (20, 21). A literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual's diet (22). DII has previously been shown to be associated with various inflammatory markers in different populations (23–28) including among Iranians (29, 30). With respect to health outcomes, DII was significantly associated with different health outcomes ranging from cardiovascular diseases (31–33), cancer (34–37), overall and disease-specific mortality (38–42) to various mental health disorders (43–47). Previously, DII has been shown to be associated with depression in various studies conducted in Western population (48–53) but no study has been conducted in Iran whose dietary habits and culture are very different from Western populations. Our aim was to assess the association between the inflammatory potential of diet of adolescent Iranian females, as indicated by higher DII scores, and dimensions of depression as measured by Depression Anxiety Stress Scale-21 (DASS-21) (54).

METHODS AND MATERIALS

Study Population

This cross-sectional study of 300 adolescents females aged 15–18 years was carried out in Tehran (capital of Iran) from 2014 to 2015. Participants were randomly chosen by stratified cluster sampling. We first stratified the high schools based on socioeconomic status of the districts (low, intermediate, and high). Then we randomly selected 8 high schools from each stratum. Finally, subjects were chosen from a registration list (in each selected high school) by simple random sampling to fulfill the sample size requirement ($n = 300$).We did not include participants who reported major depression and anxiety disorder, using of any anti-depressant or sedative medication and who were pursuing a distinct diet, because there is a high probability that people with these disorders and taking antidepressant or sedative medications would have made lifestyle changes like adopting a healthier diet that may bias the results. The study protocol was approved by the research council of the Research Institute for Nutrition and Food Sciences, Shahid Beheshti University of Medical Sciences. All subjects gave written informed consent in accordance with the Declaration of Helsinki (approval number is 054577).

Assessment of Dietary Intake

Food consumption was based on a reliable and valid Food Frequency Questionnaire (FFQ) consisting of 168 food items with standard serving sizes typically used in Iran (55). FFQs were collected by specifically trained professional interviewers through private face-to-face interviews. Participants reported their daily, weekly, monthly or yearly of intake frequency for each food item. Daily frequencies for each item were computed. Then, by applying the manual for household measures the daily grams of food intake were calculated (56).

Anthropometric Measurement

Body weight was assessed to the nearest 0.1 kilogram by using digital scales (Seca 881® Germany) while participants were in light clothes with bare feet. Height was evaluated by using a stradiometer in the standing position and was recorded to the nearest 0.1 cm. Body Mass Index (BMI) was computed as weight divided by height squared (kg/m^2).

Socio-Demographic Information

Characteristics including age (years), ethnicity (Fars,Tork, Gilak, others), father/mother job (Unemployed, grade 3 (e.g., laborers), grade 2 (e.g., clerks), grade 1 (e.g., managers and higher), father/mother education (<diploma, diploma, university education), marital status of parents (married, unmarried), salary (USD), chronic disease (yes/no) diet supplement (yes, no), and smoking status (never, previous, current) were collected by a general questionnaire for all subjects.

Physical Activity Assessment

Physical activity was assessed using a valid self-reported questionnaire (57) that has been used previously in a sample of Iranian women and demonstrated consistent outcomes (58). Participants were asked to check the activities in which they had participated during the last year. From these reports, the total time spent in particular activities were summed and mean durations were calculated. Total physical activity was expressed as metabolic equivalent-hours per day (Mets/d).

TABLE 1 | Characteristics of participants according to different categories of depressive symptoms, Study of Diet-Inflammation and Depression in Iranian Adolescent Females, 2014 to 2015.

Characteristics[a,b]	Normal symptoms (DASS ≤9) *N* = 257	At least mild level of depressive symptoms (DASS > 9) *N* = 43	*P*-value
Age, (years) (mean ± *sd*)	16.2 ± 1.0	16.3 ± 1.1	0.69
Physical Activity (METs/d)(mean ± *sd*)	36.2 ± 5.7	34.7 ± 5.0	0.11
BMI (kg/m2)(mean ± *sd*)	22.3 ± 4.6	22.3 ± 4.9	0.98
Smoking (%)			0.002
Never	96.9	90.7	
Current/Past	3.1	9.3	
Chronic disease (%)			0.38
Yes	2.3	4.6	
No	97.7	95.4	
Diet supplement use (%)			0.47
Yes	34.0	39.5	
No	66.0	60.5	
Parental marital status (%)			0.20
Yes	95.3	90.7	
No	4.7	8.3	

[a] *Significance testing was based on t-test for continuous variables.*
[b] *Chi-square test was used for categorical variables.*

TABLE 2 | Participant characteristics by tertiles of dietary inflammatory index (DII)[C], Study of Diet-Inflammation and Depression in Iranian Adolescent Females, 2014 the 2015.

Characteristics[a,b]	Tertile 1	Tertile 2	Tertile 3	*P*-value
Age, (years) (mean ± *sd*)	16.1 ± 1.0	16.3 ± 1.0	16.2 ± 0.9	0.83
Physical activity (METs/d)(mean ± *sd*)	36.3 ± 5.9	36.2 ± 5.0	35.4 ± 5.9	0.28
BMI (kg/m2)(mean ± *sd*)	21.4 ± 4.8	22.7 ± 4.4	23.0 ± 4.6	0.02
Smoking (%)				0.39
Never	97.0	97.0	93.0	
Current/Past	3.0	3.0	7.0	
Chronic disease (%)				0.59
Yes	2.0	4.0	2.0	
No	98.0	96.0	98.0	
Diet supplement use (%)				0.17
Yes	42.0	30.3	32.0	
No	58.0	69.0	68.0	
Marital status (%)				0.29
Yes	95.0	97.0	92.0	
No	5.0	3.0	8.0	

[a] *Significance testing was based on ANOVA for continuous variables.*
[b] *Chi-square test was used for categorical variables.*
[c] *Tertile 3 indicates the group with the most pro-inflammatory diet and tertile 1 indicates the group with most anti-inflammatory diet.*

Other Variables

Further information on body image was collected by using 28-items of eating disorder examination questionnaire (EDE-Q-28) (59). The Persian version of EDE-Q-28 which was used in this study (60).

Dietary Inflammatory Index (DII®)

The development and validation of the DII are described in detail elsewhere (22). Briefly, developing the DII involved reviewing and scoring nearly 2,000 scientific articles representing cell culture and laboratory animal experiments, and a variety of human studies on diet and six inflammatory markers (i.e., CRP, interleukin (IL)-1b, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α). Developing the DII also entailed creation of a world standard database that involved obtaining 11 data sets from around the world to which individuals' intakes of 45 food parameters (consisting of nutrients, spices and whole foods) on which the DII is based, could then be compared.

FFQ-derived dietary data were used to calculate DII scores for all participants. Dietary data were first linked to the previously described regionally representative world database that provided a robust estimate of a mean and standard deviation for each parameter (22). These then became the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This score was computed by subtracting the "standard global mean" from the amount reported and dividing this value by the "global standard deviation" of the world population as represented by the 11 data sets used for comparative purposes. To minimize the effect of "right skewing," this value was then converted to a centered proportion score.

For each individual food parameter, this score was multiplied by the respective food parameter effect score, derived from the literature review, in order to obtain a food parameter-specific DII score (22). All of the food parameter-specific DII scores were then summed to create the overall DII score for each participant in the study, DII = b1*n1+b2*n2.....b31*n31, where b refers to the literature-derived inflammatory effects score for each of the evaluable food parameters and n refers to the food parameter-specific centered percentiles, which were derived from the FFQ-derived dietary data.

For the current study, data on 31 of the 45 DII food parameters could be derived from the FFQ and were thus used for DII calculation. These include: Pro-inflammatory components (energy, carbohydrate, protein, fat, saturated fat, iron, cholesterol, trans-fat, vitamin B12) and anti-inflammatory components (alcohol, fiber, mono-unsaturated fat, poly-unsaturated fat, omega-3, omega-6, niacin, thiamin, riboflavin, magnesium, zinc, vitamin A, vitamin C, vitamin E, vitamin D, vitamin B6, folic acid, beta-carotene, tea, turmeric, garlic, and onions).

Psychological Assessment of Depression, Anxiety and Stress

The Persian version of Depression, Anxiety, Stress Scale-21 (DASS-21) which was introduced by Lovibond and Lovibond (61) has been used to determine the level of depression, anxiety

TABLE 3 | Beta estimates and odds ratios and confidence intervals for the association between DII as tertiles and depressive symptoms, Study of Diet-Inflammation and Depression in Iranian Adolescent Females, 2014 to 2015.

	Beta Estimates for depressive symptoms expressed as continuous DASS-21 score				Odds Ratios for at least moderate level of depressive symptoms (DASS-21 > 9)			
DII[d]	Tertile 1	Tertile 2	Tertile 3	*P*-trend[c]	Tertile 1	Tertile 2	Tertile 3	*P*-trend[c]
DASS-21 > 9/DASS ≤ 9					12/88	17/82	14/87	
Model 1[a]	0	1.47 (0.04, 2.89)	1.97 (0.30, 3.64)	0.03	1	2.70 (1.03, 7.12)	3.01 (0.94, 9.59)	0.09
Model 2[b]	0	1.57 (0.19, 2.94)	1.67 (0.04, 3.31)	0.07	1	3.03 (1.11, 8.26)	3.96 (1.12, 13.97)	0.03

[a] *Adjusted for age and energy.*

[b] *Mode 1+physical activity, BMI, smoking, presence of chronic disease, diet supplement use, salary and marital status.*

[c] *Tests for linear trend were performed by assigning the median value of each category to each participant in that group.*

[d] *Tertile 3 indicates the group with the most pro-inflammatory diet and tertile 1 indicates the group with most anti-inflammatory diet.*

and stress in our sample population. This questionnaire has three subscales and each of them consists of seven items. The score of each subscale is attained by adding the scores of relevant questions. The Persian version of the DASS-21 was found to be a reliable and valid tool to examine the level of depression, anxiety and stress among Iranian adolescents (62).

Statistical Analysis

Study participants' characteristics were described according to two parameters: (1) reporting of at least depressive symptoms and (2) tertiles of the DII. Comparisons were carried out using *t*-tests and ANOVA for continuous variables and chi-square test for categorical variables. Multiple linear and logistic regression analysis were then used to calculate adjusted beta estimates and odds ratios (ORs) and 95% confidence intervals (CIs) for both DASS-21 as continuous and as categorical variable (DASS-21 > 9) in relation to DII in 2 separate models. Model I adjusted for total energy intake and age, model 2 additionally adjusted for physical activity, marital status, income, smoking, BMI, and presence of chronic disease.

RESULTS

Table 1 describes distribution of characteristics across categories of DASS-21 scores. Females with at least moderate level of depressive symptoms had lower level physical activity and greater dietary supplement use and were either past/current smokers. **Table 2** shows distribution of characteristics across tertiles of DII. Females in tertile 3 had higher BMI compared to females in tertile 1. **Table 3** describes the results for depression as a continuous score and as a dichotomous outcome where the scores were categorized on having at least a moderate level of depression symptoms (DASS > 9). Significant associations were observed for both types of outcomes for both models. Results are described for the full model, females in the third tertile had significantly higher depression scores (β = 1.67, 95% C.I. 0.04, 3.31); odds of having at least moderate depressive symptoms (DASS-21 > 9) (OR = 3.96, 95% CI 1.12, 13.97) compared to females in tertile 1 **(Table 3)**.

DISCUSSION

In this study we report a significant positive association between increasing inflammatory potential of diet and depressive symptoms among adolescent females in Iran. To date, this is the first study to examine this association in adolescent females. A case-control study conducted in Iran showed that a healthy dietary pattern is protective against major depressive disorders, while no such association was observed with the unhealthy dietary patterns. The healthy pattern was characterized by high intakes of fish, poultry, low fat dairy, high fat dairy, coffee, fruits, and nuts, fruit juices, vegetables, legumes, and olives, and low intakes of refined grains, fats, and soft drinks. The unhealthy dietary patterns, on the other hand, were characterized by high intakes of processed meats, red meat, tea, fried potatoes, whole grains, refined grains, snacks, cookies, oils, sugar, and soft drinks (63). Previous reports suggest that men are more likely to have mental health problems than women (64). The current work shows an association between inflammatory potential of diet and depressive symptoms, among the female adolescents. While some of the earlier studies also reported associations between dietary inflammation potential and risk of depression among women; these were female-only cohorts where inflammatory potential of diet was determined by two different methods (inflammatory dietary pattern and DII) (14, 53). Results from the Nurses' Health Study revealed a 30–40% increased risk of depression, among women in the highest quintile compared to women in the lowest quintile of inflammatory dietary pattern (14). Twelve-years' follow-up of middle-aged women in Australia (n = 6,438) identified a 20% lower risk of depression among those whose diets were in the highest DII quartile compared to those in the lowest DII quartile (53).

This study is unique because for the first time this association has been examined in a Middle-Eastern population whose dietary habits and culture is very different from the Western population where this relationship has previously been examined (48–53). Traditional Iranian diet consist of food like cooked rice, mixed pilaf, rice, and stew, rice, high protein dishes and stuffed vegetables (65).

In agreement with our findings, the results of the only other study that examined the association between inflammatory

potential of diet and depression showed that the hazards ratio for participants in the highest quintile of the DII (strongly pro-inflammatory) was 1.47 (95% confidence interval (CI): 1.17–1.85) compared with those in the bottom quintile, with a significant dose-response relationship (p for trend = 0.01) (66).

The DII, thus far, has been shown to be associated with several inflammatory markers and various chronic inflammation related outcomes. For instance, higher DII scores were positively associated with various inflammatory markers, including C-reactive protein (67, 68), interleukin-6 (69, 70), and homocysteine (69). Additionally, the DII has been shown to be associated with bone mineral density among postmenopausal women in Iran (70), two colorectal cancer case-control studies in Spain and Italy (71, 75) and in a cohort study in women in the USA (37, 71), esophageal cancer (72–74), breast cancer (75), pancreatic cancer (76), prostate cancer (77, 78), cardiovascular diseases (79, 80) and biomarker of aging (81).

The direct association between the DII and the odds of depression observed in this study could be explained by the fact many of the anti-inflammatory components of the index, namely zinc, omega 3 fatty acids, and coffee, have been shown to be negatively associated with the risk of depression (13). On the other hand, pro-inflammatory components of the index, such as energy and carbohydrate, have been linked to a higher risk of depression. For instance, results from a large cohort study conducted in the USA showed that frequent consumption of sweetened beverages, especially diet drinks, increases the risk of depression among older adults, whereas coffee consumption lowered the risk (11). Various studies have been conducted examining the association between dietary pattern and depression. In a systematic review conducted on 21 studies high intakes of fruit, vegetables, fish, and whole grains may be associated with a reduced depression risk (82). There is substantial evidence linking inflammation and depression (83–86).

Despite its strengths, our study had some limitations, which should also be considered in interpreting the results. First, the validity and reliability of FFQ has not been established in the context measuring dimensions of depression measured using DASS-21. Second, we could not directly infer causality due to the cross-sectional nature of the study design. Other limitations include small sample size, and the possibility of recall bias. Fourth, in this study, data were available on 31 of the 45 food parameters; absence of information on the remaining food parameters can be considered as a limitation. Additionally, validity and reliability of FFQ has not been established in the context measuring dimensions of depression measured using DASS-21. Another limitation is the inability to evaluate the history of stressful life events in the last 12 months. Self-reported dietary methods like the FFQ is subjected to bias of under reporting and implausible values for energy intake, the inability to measure this bias and adjust for it in the analyses is a limitation.

In conclusion, female adolescents with a pro-inflammatory diet have greater odds of having at least a moderate level of depressive symptoms. So, promoting diets with a higher concentration of anti-inflammatory foods, such as vegetables and fruits, at younger age may be protective against the development of depression. However, further studies analyzing the link between diet, inflammation and depression are warranted among both men and women to further elucidate the role of diet in the development of depression and other mental disorders.

AUTHOR CONTRIBUTIONS

NS calculated the DII, ran the analyses and also wrote the first draft of the manuscript. Upon receiving comments from the co-authors he also made changes to the manuscript and finalized it. JRH, AN, BB, FN, and BR reviewed and provided important input to the paper.

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Conflict of Interest Statement: JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. NS is an employee of CHI.

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Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality

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Recent demonstration that probiotics administration has positive effects on mood state in healthy populations suggests its possible role as an adjunctive therapy for depression in clinical populations and as a non-invasive strategy to prevent depressive mood state in healthy individuals. The present study extends current knowledge on the beneficial effects of probiotics on psychological well-being, as measured by changes in mood (e.g., cognitive reactivity to sad mood, depression, and anxiety), personality dimensions, and quality of sleep, which have been considered as related to mood. For this double-blind, placebo-controlled study 38 healthy volunteers assigned to an experimental or control group assumed a daily dose of a probiotic mixture (containing *Lactobacillus fermentum* LF16, *L. rhamnosus* LR06, *L. plantarum* LP01, and *Bifidobacterium longum* BL04) or placebo, respectively, for 6 weeks. Mood, personality dimensions, and sleep quality were assessed four times (before the beginning of the study, at 3 and 6 weeks, and at 3 weeks of washout). A significant improvement in mood was observed in the experimental group, with a reduction in depressive mood state, anger, and fatigue, and an improvement in sleep quality. No between-groups differences were found. These findings corroborate the positive effect of probiotics on mood state and suggest that probiotics administration may improve psychological well-being by ameliorating aspects of mood and sleep quality.

Keywords: psychological well-being, probiotics, mood, sleep quality, personality traits

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INTRODUCTION

Gut and brain communicate with each other via the gut-brain axis, a specific pathway that involves the neural, endocrine, and immune systems (1–4). The intestinal microbiota plays a crucial role in this bidirectional communication, since it can influence mood and cognitive functions by producing neurotransmitter precursors that reach the brain through the endocrine and the autonomic nervous systems where they regulate the level of specific neurotransmitters (5, 6).

It has been hypothesized that modifying the microbial environment by means of probiotics, for instance, may help to improve mood and cognitive functions. This hypothesis is supported by studies using animal models. Li et al. (7) found an improvement in spatial memory and problem solving in rats after probiotics supplementation. Other studies using rodent models showed beneficial effects of probiotics on anxiety and depression (8, 9). Research involving human participants is still scant. Among the existing literature on this topic, some studies showed no effects of probiotics on mood (10), but other found promising data. For instance, a recent fMRI study

demonstrated that 4 weeks of probiotic intake reduced the activity of brain regions involved in emotional processing (11). Moreover, a recent triple blind, randomized, placebo-controlled study showed reduced cognitive reactivity to sad mood after a 4-week intervention with multispecies probiotics (12). Sleep quality also seems to benefit from probiotic supplementation. Takada et al. (13) reported an improvement in sleep quality in academic students during a period of increasing stress after 11 weeks of probiotics consumption. Beneficial effects of probiotics were also reported in studies involving clinical populations. For instance, Rao et al. (14) found that anxiety in patients with chronic fatigue syndrome was reduced after 2 months of probiotics intake. Overall, these studies suggest that probiotics administration might be used to improve mood and cognitive functions (e.g., emotional processing).

The aim of the present explorative study was to extend our current knowledge about the beneficial effects of probiotics on psychological well-being by investigating different aspects of mood (e.g., cognitive reactivity to sad mood, depression, and anxiety) and various dimensions of personality related to mood, including optimism, pessimism, and motivational drive. Also, we investigated the potential effects of probiotics on sleep quality, which is also known to affect mood (15). In line with previous findings, we expected an improvement in mood only in the group that received the probiotics. Additionally, we hypothesized an improvement in perceived sleep quality and personality dimensions known to be related to anxiety and depression.

Examining the ways in which probiotics influence mood, personality traits, and sleep may help to gain a better understanding of the relationship between the gut and the brain and to develop new applications for psychological well-being.

MATERIALS AND METHODS

Participants were recruited from students of the University of Verona (Italy) where the investigation took place and where data were collected. Computation of the sample size was performed with G-Power 3.1 (16), considering *F*-test within-between interaction with two groups (experimental and control) and four evaluation sessions (T0, T1, T2, T3) (see the procedure for details). Assuming a priori medium effect size of 0.25 (17), an α error probability of 0.05, and a power (1-β error probability) of 0.90, the resulting total sample size is 30. We recruited more participants to prevent reduction in statistical power due to potential drop-outs.

Thirty-eight male and female adults volunteered for the study (13 women, mean age ± SD, 22.00 ± 3.02, age range, 19–33 years). Inclusion criterion was an age between 18 and 35 years. Exclusion criteria were: psychiatric or neurological disorders, celiac disease, lactose intolerance, or allergies or other ongoing illnesses (i.e., irritable bowel syndrome, diabetes, ulcerative colitis, etc.) or recent antibiotic treatment (i.e., <3 months before the beginning of the study). Participants who smoked more than 10 cigarettes per day were excluded.

Participants were screened via structured interviews by three experimenters (MF, AM, ES) who collected data on demographics and physical activity. In order to account for potential bias due to premenstrual syndrome, the women were also asked about their monthly physical and emotional changes.

Participants were assigned to receive probiotics or placebo by means of stratified randomization method. Since the amount of physical activity can influence cognitive functions, mood and sleep quality (18, 19), we took this covariate into account in the randomization process. More precisely, we applied the stratified randomization method to address the need of balancing the groups for the amount of physical activity (20, 21). Following this method, participants were stratified into two blocks (Highs and Lows) of 19 participants each depending on the amount of physical activity. More precisely, according to the mean value of physical activity per week of the whole sample (2.87 ± 0.99 h), the block of Highs was made of participants with more than 2.87 h per week and the block of Lows was made of participants with <2.87 h per week). Then, participants were allocated to the experimental or control group by means of simple randomization through a computer generated list that guarantees the same number of subjects and equivalent physical activity by type of intervention. In this way, sample size and amount of physical activity were balanced in the experimental and control group. After randomization, we confirmed that the level of physical activity was balanced between the two groups [$t_{(34)} = 1.031$, $p = 0.310$]. Two experimenters (MA and ES) enrolled participants, generated the random allocation sequence, and assigned participants to interventions. The experimenters and the participants were blinded for group allocation.

The study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Ethical committee of Verona Hospital (Azienda Ospedaliera Universitaria Intregrata, AOUI Verona, 766CESC). Written informed consent was obtained before the start of the study. The protocol is registered in ClinicalTrials.gov with the number ID: NCT03539263. The full trial protocol can be accessed upon request at Probiotical S.p.A. and to the principal investigator MF.

Procedure

The probiotic product or placebo was administered for 6 weeks followed by a 3-week washout period for a total duration of 9 weeks. The experimental group received 42 sachets of the product (one for each day), each containing 4×10^9 colony forming unit/active fluorescent unit (CFU/AFU) 2.5 g freeze-dried powder of the probiotic mixture containing *Lactobacillus fermentum* LF16 (DSM 26956), *L. rhamnosus* LR06 (DSM 21981), *L. plantarum* LP01 (LMG P-21021), and *Bifidobacterium longum* BL04 (DSM 23233) (Probiotical S.p.A., Novara, Italy).

The mixture was composed with commercially available probiotic strains extensively used for food supplement formulations.

The study materials were analyzed by Biolab Research S.r.l., Novara, Italy, via flow cytometry (ISO 19344:2015 IDF 232:2015, $> 4 \times 10^9$ AFU) and plate count method (Biolab Research Method 014-06, $>4 \times 10^9$ CFU) to confirm target cell count. The control group received 42 sachets of placebo, each containing 2.5 g of maltodextrin in powder form. The placebo powder was indistinguishable from the probiotics powder in color, taste, and

smell, but contained no probiotic bacteria. Participants were instructed to dissolve the powder in water or milk and drink it in the morning with breakfast.

A mobile application developed *ad hoc* (AgendaQR, Bussola Labs, Verona, Italy) was installed on the participants' phones at the beginning of the study; adherence to the study protocol was facilitated by means of a daily reminder to take the probiotics product or placebo and to scan the QR code attached to the sachet. If a participant failed to scan the code, the application kept a record of the missed daily intake.

All participants completed an extensive battery of psychological questionnaires (see next paragraph for a details) at four time points: before intake of the probiotics product or placebo (baseline) (T0), at 3 (T1), and 6 (T2) weeks after the first intake, and then at 3 weeks of washout (T3). E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, PA, USA) was used to present the questionnaires and record the responses. Each session lasted about 45 min.

Questionnaires Measuring Mood-Related Aspects

Leiden Index of Depression Sensitivity-Revised Test

The primary outcome of our study was the difference in the scores at the Leiden Index of Depression Sensitivity-Revised test (LEIDS-R) (22) between the experimental and control groups. The LEIDS-R is a self-report questionnaire that tests cognitive reactivity to sad mood, which is an index of cognitive vulnerability to depression. It consists of 34 items describing different situations. Before answering the items, participants are asked to take a few minutes to imagine their feelings and thoughts when they experience a sad mood. They then rate how much each item applies to themselves on a 5-point scale ranging from 0 (*not at all*) to 4 (*very strongly*). Of note, the experimenter emphasizes that each item describes a situation happening on *a day that is not good, but you don't feel depressed*. The LEIDS-R consists of 6 subscales: Hopelessness/Suicidality (5 items), Acceptance/Coping (6 items), Aggression (5 items), Control/Perfectionism (6 items), Risk aversion (6 items), and Rumination (6 items). The total score for each subscale is obtained by adding the scores from the corresponding item. The range of the total score for the Aggression and Hopelessness/Suicidality subscales is from 0 to 20. The range of the total score for the other three scales is from 0 to 24. The higher the total subscale score, the higher the vulnerability to the assessed dimension.

State Trait Anxiety Inventory

The State Trait Anxiety Inventory, STAI, (23) is a self-report questionnaire that measures the presence and severity of current symptoms of anxiety and the propensity to be anxious (24). There are separate subscales for two anxiety components: state anxiety (STAI—form Y1) and trait anxiety (STAI—form Y2). Each subscale contains 20 items. The STAI—Y1 measures the current anxiety state by asking participants to rate how they actually feel (e.g., calm, tense, worried) on an intensity scale from 1 (*not at all*) to 4 (*very much so*). The STAI—Y2 measures the propensity to anxiety by asking participants to rate how they generally feel in their life (e.g., confident) on a frequency scale from 1 (*almost never*) to 4 (*almost always*). The total score for each subscale is obtained by adding the scores of all items. The score for the anxiety-absent items are reversed. The range of the total score for each subscale is 20–80, wherein the higher the score, the higher the degree of state or trait anxiety. Scores of 39–40 have been defined as a cut-off for clinically relevant symptoms of state anxiety (24).

Beck Depression Inventory

The Beck Depression Inventory, BDI-2 (25), is a self-report questionnaire that measures the occurrence and severity of current depressive symptoms. It consists of 21 groups of sentences describing different depression-related feelings and thoughts (e.g., self-dislike, loss of interest, irritability, changes in sleep pattern). Participants are asked to choose the statement from a group of sentences that best describes how they have been feeling in the past 2 weeks including the current day. Each statement corresponds to a specific severity score (range, 0–3). The total score is obtained by adding the statement scores (range, 0–63), wherein the higher the total score, the higher the severity of depressive state (minimal depression, 0–13; mild depression, 14–19; moderate depression, 20–28; severe depression, 29–63).

Profile of Mood State

The Profile of Mood State, POMS, (26) is a self-report questionnaire that assesses mood. It consists of 58 items (words or sentences) that describe feelings that people usually have. For each item, participants rate on a 5-point scale from 0 (*not at all*) to 4 (*extremely*) how they have been feeling the past week including the current day. The items are grouped in 6 subscales: Tension (9 items), Depression (15 items), Anger (12 items), Fatigue (7 items), Confusion (7 items), and Vigor (8 items). The Vigor scale is in inverted relationship with the other scales since it assesses positive feelings (e.g., to be lively, active, energetic). The total score for each scale is obtained by adding the related item, wherein the higher the total score of the scale, the higher the level of the related mood.

Sleep Quality Questionnaire

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index, PSQI, (27, 28) is a self-report questionnaire that assesses sleep quality for the majority of days and nights in the past months. It consists of 19 questions. The first four investigate usual bedtime, the number of minutes needed to fall asleep, the usual getting up time, and the hours of sleep per night. The other questions are related to other aspects of sleep quality rated on scales appropriate for the specific question. The items are weighted on a 0–3 interval scale and grouped in seven component scores (i.e., subjective sleep quality, sleep latency, sleep duration, use of sleeping medication, daytime dysfunction, sleep duration, habitual sleep efficiency). A global PSQI score (range, 0–21) is obtained by adding up the component scores, wherein the lower the PSQI global score, the better the sleep quality.

Questionnaires Measuring Personality-Related Aspects

Temperament and Character Inventory

The Temperament and Character Inventory, TCI, (29) is a self-report, true-false questionnaire that measures two components of personality: temperament and character. Temperament refers to automatic responses to perceptual stimuli likely reflecting hereditable biases in information processing (29). It consists of four dimensions: novelty seeking (system of behavioral activation), harm avoidance (system of behavioral inhibition), reward dependence (system for maintenance of ongoing behavior), and persistence (system of partial reinforcement and active behavior despite fatigue and frustration). Based on the psychobiological model of personality (29), each dimension is related to specific neurotransmitters: dopamine for novelty seeking; GABA and serotonin for harm avoidance; noradrenaline and serotonin for reward dependence, and glutamate and serotonin for persistence. Character refers to dimensions determined by the environment rather than by inheritance. These dimensions regulate the cognitive processes of perception and emotion defined by the person's temperament (30). The character dimensions are: self-directedness (identification with autonomous self and ability to solve situations); cooperativeness (extent to which other people are viewed as part of the self); and self-transcendence (identification with a unity of all things). Based on this model of personality, the TCI consists of 240 items grouped on four temperament scales (40 items for novelty seeking; 35 for harm avoidance; 24 for reward dependence; 8 for persistence) and three character scales (44 items for self-directedness; 42 for cooperativeness; 33 for self-transcendence). The total score for each scale is obtained by adding the related items (range of total scores: novelty seeking, 0–40; harm avoidance, 0–35; reward dependence, 0–24; persistence, 0–8; self-directedness, 0–44; cooperativeness, 0–42; self-transcendence 0–33). The higher the total score, the higher the level of the personality dimension described by the scale.

Cope Orientation to the Problems Experienced—New Italian Version

The Cope Orientation to Problem Experienced—New Italian Version, COPE-NIV, (31) is a self-report questionnaire that measures coping strategies: the cognitive and behavioral strategies people use to manage stressful situations (32). The COPE-NIV consists of 60 items that describe different coping strategies. Participants are asked to rate each item on a frequency scale from 1 (*I usually don't do this*) to 4 (*I usually do this*). The items are grouped in five essentially independent components: social support (12 items), avoidance strategies (16 items), positive attitude (12 items), problem solving (12 items), and turning to religion (8 items). The total score for the subscales is obtained by adding the corresponding item scores. The higher the total subscale score, the higher the frequency in adopting the coping strategy described by that subscale.

Behavioral Inhibition System and Behavioral Activation System Scale

The Behavioral Inhibition and Behavioral Activation Scale, BIS/BAS, (33) is a self-report questionnaire that measures an individual's sensitivity to behavioral inhibition and behavioral activation systems. The behavioral inhibition system (BIS) mediates responses to potential punishment and suppresses behavior that is expected to lead to threat, punishment or non-reward (34). Conversely, the behavioral activation or approach system mediates responses to rewards expectancy (34) and facilitates behavior that brings the person closer to expected rewards. The BIS/BAS scale consists of 24 items grouped in four subscales: BIS (7 items), BAS Drive (4 items), BAS Fun seeking (4 items), and BAS Reward responsiveness (5 items). Four items serve as control. Participants rate how much each statement describes themselves from 0 (*It does not describe me at all*) to 5 (*It completely describes me*). The total score for each scale is obtained by adding the items of the respective scale; the total BIS score ranges from 1 to 35 and the total BAS score ranges from 1 to 65. The higher the total score, the higher the sensitivity of behavioral inhibition and behavioral activation systems.

Life-Orientation Test-Revisited

The Life Orientation Test-revisited, LOT-R, (35) is a self-report measure of dispositional optimism and pessimism. It consists of 10 items: 3 are worded positively; 3 are worded negatively; and 4 are control items. Participants rate their agreement with each item on a 5-point scale from 0 (*strongly disagree*) to 4 (*strongly agree*). The LOT-R total score is obtained by adding all items except the 4 control items. The three negatively worded items are related to pessimism and are reverse scored. The LOT-R total score ranges from 0 to 24. The higher the total score, the higher the degree of optimism (high optimism, 19–24; moderate optimism, 14–18; low optimism, 0–13).

Data Analyses

Distribution of age and gender was analyzed with an independent sample *t*-test and a chi-square test, respectively. Questionnaire data were first checked for normality by means of the Shapiro–Wilk test ($p > 0.05$). Since the data were not normally distributed, non-parametric tests were used. The Friedman test was used to compare questionnaire scores across time points (T0, T1, T2, T3) separately for each group (experimental and control). *Post-hoc* comparisons were performed using the Wilcoxon signed-rank test. Bonferroni correction was applied and the adjusted critical level of significance for multiple comparisons was set at $p < 0.017$. The Mann–Whitney *U*-test was used to compare questionnaire scores between-groups. $P < 0.05$ were considered statistically significant. Spearman correlations were used to explore the relationship between mood and sleep quality, separately for each group. Mean and standard deviation of questionnaire data are reported in **Tables S1, S2**.

RESULTS

Nineteen participants assumed probiotics and made up the experimental group (7 women, mean age ± SD, 21.47 ± 2.22 years); 19 participants received placebo and made up the control group (6 women, mean age, 22.53 ± 3.64 years). One subject from the experimental group and four subjects from the control group did not complete the study because they underwent therapeutic interventions with antibiotics. The final study sample was 33

subjects: 18 in the experimental group (7 women, mean age, 21.61 ± 2.2 years) and 15 in the control group (5 women, mean age, 21.67 ± 2.19 years). The two groups did not differ by age [$t_{(31)} = -0.115$, $p = 0.909$] or gender distribution [$\chi^2_{(1)} = 0.109$, $p = 0.741$].

Recruitment started 28 November 2016 and follow-up finished 15 June 2017.

Mood-Related Aspects

Leiden Index of Depression Sensitivity-Revised Test

No significant time effect on the total score and subscale scores of the LEIDS-R was noted for the experimental and the control group. There was a significant between-group difference in the *acceptance* subscale scores at 6 weeks (T2). This difference was due to the higher scores recorded in the experimental group (mean ± SD, 5.33 ± 5.11) as compared to the control group (mean ± SD, 2.93 ± 3.51) ($Z = -2.162$, $p = 0.031$, effect size $= -0.376$) (**Figure 1**).

State Trait Anxiety Inventory

No significant time effect on STAI scores in the experimental and the control group was found: STAI-Y1 (state anxiety) (experimental group, $p = 0.612$; control group, $p = 0.412$) and STAI-Y2 (trait anxiety) (experimental group, $p = 0.161$; control group, $p = 0.085$). Moreover, there were no between-group differences in STAI-Y1 (all time points, $p > 0.218$) and STAI-Y2 (all time points, $p > 0.436$). The state and trait dimensions of anxiety remained constant in both groups at all four time points, discarding a potential effect of probiotics intake on both anxiety components.

Beck Depression Inventory

No significant time effect on BDI-2 scores in the experimental ($p = 0.137$) and the control group ($p = 0.409$) was found; there were no between-group differences at any of the four time points (all time points, $p > 0.383$). Probiotics intake had no effect on depressive symptoms as assessed by the BDI-2.

Profile of Mood State

A significant time effect on the *depression* subscale scores for the experimental group [$\chi^2_{(3)} = 12.43$, $p = 0.006$] was found. *Post-hoc* comparisons with Wilcoxon signed rank test (after Bonferroni correction, $p < 0.017$) showed that this result was due to lower scores after 6 weeks of treatment (T2) (mean ± SD, 6.22 ± 7.26) compared to baseline (T0) (mean ± SD, 11.00 ± 9.45) ($Z = -2.596$, $p = 0.009$, effect size $= -0.433$). Moreover, the effect was maintained after 3 weeks of washout, as revealed by a significant difference between T3 (mean ± SD, 5.67 ± 7.15) and T0 ($Z = -2.452$, $p = 0.014$, effect size $= -0.409$). These results suggest that the experimental group experienced a reduction in depressive mood state and that this effect remained nearly stable after 3 weeks of washout (**Figure 2A**).

A significant time effect [$\chi^2_{(3)} = 17.52$, $p = 0.001$] was also found on the *anger-hostility* scale scores for the experimental group. *Post-hoc* comparisons showed that this effect was due to lower scores after 3 weeks of probiotics intake (T1) (mean ± SD, 6.56 ± 4.87) compared to baseline (T0) (mean ± SD, 10.39 ± 6.79) ($Z = -2.695$, $p = 0.007$, effect size $= -0.449$), and after 6 weeks of probiotics intake (T2) (mean ± SD, 6.78 ± 5.11) compared to baseline ($Z = -2.411$, $p = 0.016$, effect size $= -0.402$), as well as after 3 weeks of washout (T3) (mean ± SD, 5.28 ± 4.66) compared to baseline ($Z = -2.921$, $p = 0.003$, effect size $= -0.487$) (**Figure 2B**).

A significant time effect was noted for the *fatigue* subscale scores [$\chi^2_{(3)} = 11.75$, $p = 0.008$]. This effect was due to a lower score at T2 (mean ± SD, 7.06 ± 4.24) compared to T0 (mean ± SD, 8.89 ± 4.30) ($Z = -2.802$, $p = 0.005$, effect size $= -0.467$) and at T3 (mean ± SD, 5.33 ± 4.12) compared to T0 ($Z = -2.556$, $p = 0.011$, effect size $= -0.426$) (**Figure 2C**). A significant time effect was also observed for the subscale *confusion* [$\chi^2_{(3)} = 14.45$, $p = 0.003$]. This effect was not further confirmed at *post-hoc* analysis, however ($p > 0.022$ for all comparisons). No significant time effect on any of the subscales for the control group. Finally, no between-group differences were found ($p > 0.079$ all-time points and subscales).

Sleep Quality

Pittsburgh Sleep Quality Index

A significant time effect in the experimental group [$\chi^2_{(3)} = 12.16$, $p = 0.007$] was found. *Post-hoc* comparisons showed that this effect was due to lower scores after 6 weeks of probiotics intake (T2) (mean ± SD, 4.00 ± 1.64) compared to baseline (T0) (mean ± SD, 5.61 ± 2.17) ($Z = -2.820$, $p = 0.005$, effect size $= -0.470$) (**Figure 3**). No significant time effect was noted for the control group nor were between-group differences found.

Correlations Between Mood and Sleep Quality

In the experimental group significant positive correlations were found between PSQI scores and STAI Y2 (T0, $r = 0.716$, $p = 0.001$; T1, $r = 0.623$ $p = 0.006$) and BDI2 (T2, $r = 0.634$, $p = 0.005$). PSQI positively correlated also with several scales of LEIDS-r: Hopelessness (T3, $r = 0.502$, $p = 0.034$); Acceptance (T3, $r = 0.834$, $p < 0.001$); Aggression (T0, $r = 0.544$, $p = 0.020$); Risk aversion (T0, $r = 0.472$, $p = 0.048$). Significant correlations were also found with different scales of POMS as well. Precisely, PSQI positively correlated with Tension (T0, $r = 0.628$, $p = 0.005$; T2, $r = 0.643$, $p = 0.004$), Depression (T0, $r = 0.709$, $p = 0.001$; T2, $r = 0.549$, $p = 0.018$), Anger (T0, $r = 0.829$, $p < 0.001$; T2, $r = 0.679$, $p = 0.002$), Fatigue (T0, $r = 0.595$, $p = 0.009$; T2, $r = 0.560$, $p = 0.016$), and Confusion (T0, $r = 0.595$, $p = 0.009$) subscales. Negative correlations, instead, were found with the Vigor subscale (T0, $r = -0.545$, $p = 0.019$; T3, $r = -0.507$, $p = 0.032$). As stated before, the higher the scores at PSQI, the lower the sleep quality. Thus, positive correlations with measures of anxiety (i.e., STAI Y2) and depression (i.e., BDI2) suggest that the lower the sleep quality, the higher the anxiety and depression. Similarly, poor sleep quality is related to higher hopelessness, acceptance, aggression, risk aversion as measured by the LEIDS-r subscales, and tension, depressive mood state, anger, fatigue, and confusions as measured by the POMS subscales. Conversely, the negative correlation with the Vigor subscale suggests that the better the sleep quality, the higher the level of vigor experimented by participants. In the control group PSQI positively correlated

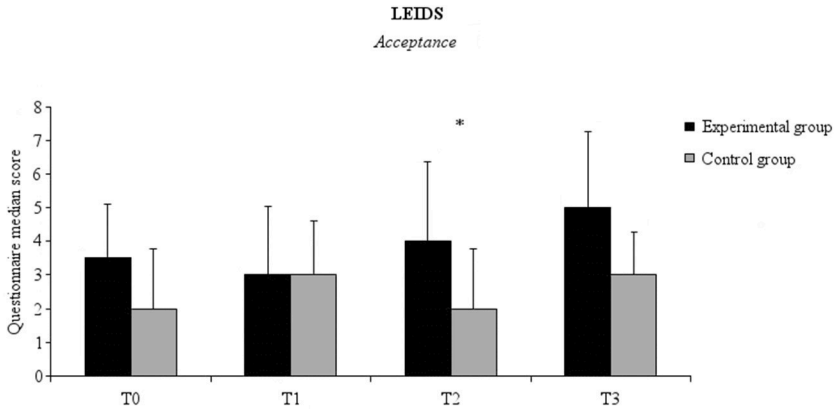

FIGURE 1 | Median LEIDS−R score, Acceptance subscale for the experimental (black columns) and the control (gray columns) groups at all-time points. Error bars represent 95% Confidence Interval. Asterisks indicate between-groups significant differences ($p < 0.05$).

with STAI-Y1 (T1, $r = 0.550$, $p = 0.034$; T2, $r = 0.638$, $p = 0.010$), STAI-Y2 (T1, $r = 0.707$, $p = 0.003$; T2, $r = 0.738$, $p = 0.002$) and BDI2 (T1, $r = 0.710$, $p = 0.003$). Significant correlations were also observed for several subscales of POMS. More precisely, sleep quality positively correlated with Tension (T0, $r = 0.537$, $p = 0.039$; T1, $r = 0.601$, $p = 0.018$; T2, $r = 0.595$, $p = 0.019$), Anger (T1, $r = 0.615$, $p = 0.015$), Fatigue (T2, $r = 0.677$, $p = 0.006$), and Confusion (T1, $r = 0.694$, $p = 0.004$) subscales, while negatively correlated with the Vigor subscale (T1, $r = -0.771$, $p = 0.001$; T2, $r = -0.537$, $p = 0.039$). These results suggest that a poor sleep quality relates to higher anxiety, depression, tension, anger, fatigue, and confusion. Conversely, a good sleep quality relates to higher vigor.

Personality-Related Aspects

Temperament and Character Inventory

No significant time effect on any of the TCI subscale scores in either the experimental or the control group was found. Significant between-group differences were found for four subscale scores at different time points. There was a significant group effect for the *novelty seeking* subscale score only at T3 ($Z = -2.209$, $p = 0.027$, effect size $= -0.385$), where the scores were higher for the experimental group. This finding might suggest that at the last assessment the participants who had taken probiotics for 6 weeks were more prone to look for new experiences; in other words, they may have been more activated by novel stimuli as compared to the controls. In addition, the *persistence* subscale scores differed between the groups; the difference was due to lower scores for the experimental group at all-time points (T0, $Z = -3.127$, $p = 0.002$, effect size $= -0.544$; T1, $Z = -2.906$, $p = 0.004$, effect size $= -0.506$; T2, $Z = -2.948$, $p = 0.003$, effect size $= -0.513$; T3, $Z = -2.820$, $p = 0.005$, effect size $= -0.491$). This means that starting from baseline, the experimental group was less persistent and that these differences remained constant independent of probiotics intake.

A significant group effect was found for the *self-directedness* subscale scores at T3 ($Z = -2.497$, $p = 0.013$, effect size $= -0.435$). This difference was due to the lower scores for the experimental group, suggesting that at 3 weeks since their last intake of the probiotic the experimental group was less self-directed than the controls.

Finally, there was a significant between-group difference in *cooperativeness* subscales scores at T2 ($Z = -2.233$, $p = 0.026$, effect size $= -0.389$), with lower scores noted for the experimental group. This finding might suggest that after 6 weeks of probiotics intake, the participants who had taken the probiotics were more self-focused than those who did not.

Coping Orientation to Problem Experienced

No significant time effect on any of the COPE subscale scores in either the experimental or the control group was noted. Significant between-group differences were found for the *Avoidance Strategies* subscale scores at T2 ($Z = -2.590$, $p = 0.010$, effect size $= -0.451$) and T3 ($Z = -2.728$, $p = 0.006$, effect size $= -0.475$), where the scores were higher for the experimental group, suggesting that they were more apt than the control group to use avoidance strategies after 6 weeks of probiotics intake and after 3 weeks of washout.

Moreover, there was a significant between-group difference in the *Positive Attitude* subscale scores at T1 ($Z = 2.412$, $p = 0.016$, effect size $= -0.420$) due to lower scores for the experimental group, suggesting that after 3 weeks of probiotics intake, the experimental group had a lower positive attitude toward problem solving than the controls. This difference was not observed at the other time points, however.

Behavioral Inhibition System and Behavioral Activation System Scale

No differences between time points for either group nor between-group differences were found. These results suggest that probiotics intake did not affect the inhibition or the activation system.

Life Orientation Test-Revisited Test (LOT-R)

No significant time effect on either group was found. Moreover, no differences between-groups were found. These results suggest

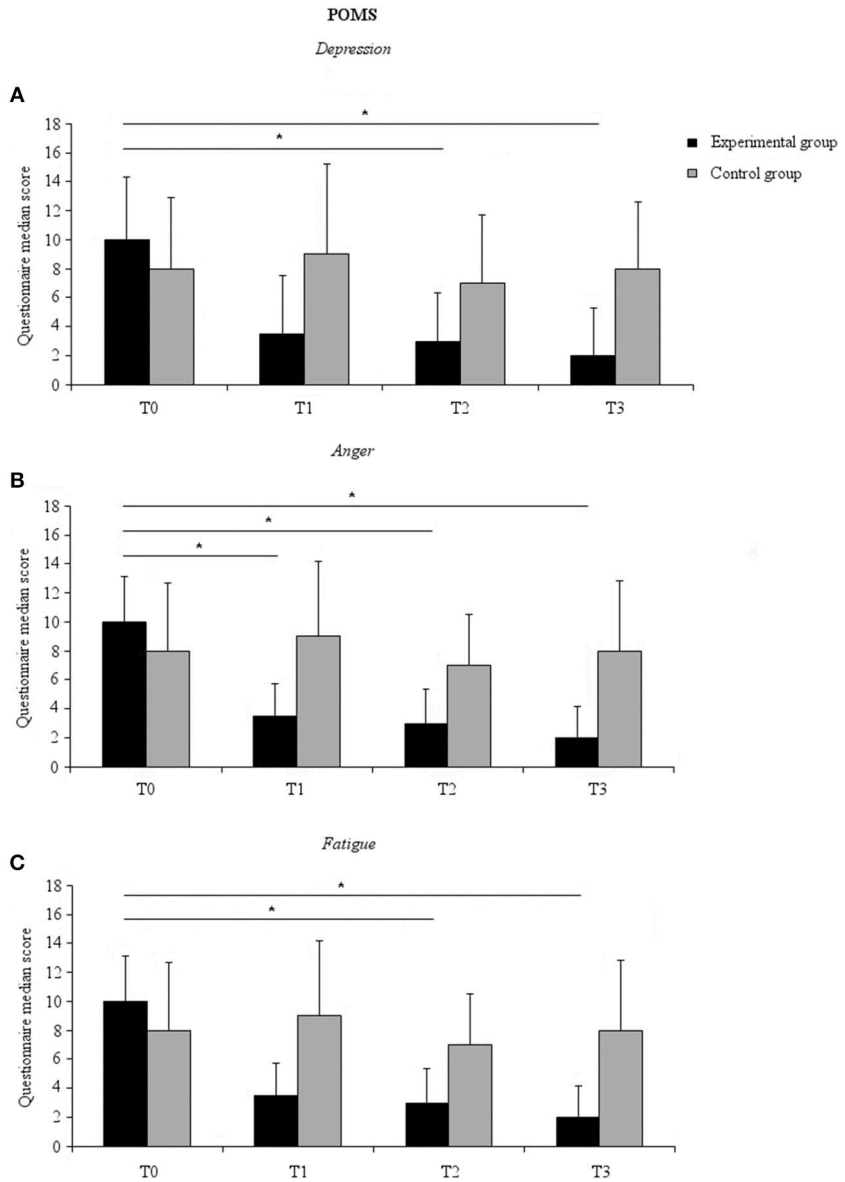

FIGURE 2 | Median POMS subscale score for the experimental (black columns) and the control (gray columns) groups at all-time points. **(A)** Depression subscale; **(B)** Anger subscale; **(C)** Fatigue subscale. Error bars represent 95% confidence interval. Asterisks indicate within-groups significant differences (Bonferroni corrected $p < 0.017$).

that probiotics intake did not influence the level of optimism in the experimental group.

DISCUSSION

With this exploratory study we investigated the effect of probiotics intake on different aspects of mood and dimensions of personality in healthy individuals. Overall, probiotics intake was noted to exert a positive effect on depressive mood state and sleep quality. This effect was specific for the experimental group, thus ruling out confounding factors like learning, expectations or maturation. We suggest, with caution, that these findings provide new support to the notion that probiotics may exert a beneficial psychological influence.

Effect of Probiotics on Mood-Related Aspects

Previous studies in non-clinical samples have demonstrated that multispecies probiotics have positive effects on mood (12, 36, 37). These studies focused mainly on depression and anxiety, whereas we extend previous findings with a more comprehensive assessment of these functions during and after 6 weeks of probiotics intake.

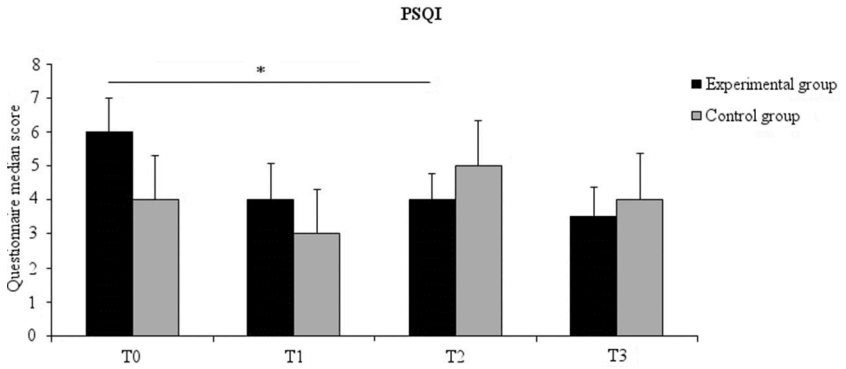

FIGURE 3 | Median PSQI score for the experimental (black columns) and the control (gray columns) groups at all time points. Error bars represent 95% confidence interval. Asterisks indicate within-groups significant differences (Bonferroni corrected $p < 0.017$).

Among the different indexes of cognitive reactivity to sad mood assessed by means of the LEIDS-R, the scores for *acceptance* were found to be higher in the experimental group than the control group after 6 weeks of probiotics intake. Acceptance is an emotion regulation strategy that facilitates recovery from depression in clinical populations (38). We speculate that increasing acceptance might protect healthy individuals from developing depressive mood.

Like Steenbergen et al. (12), we found no significant differences between-groups or across time points for depression scores as assessed by the BDI. This was not surprising since our participants all demonstrated being below the clinically relevant score for depression, suggesting that they did not have depressive symptoms. Nonetheless, using the POMS we were able to detect specific changes in positive and negative mood in healthy individuals. In line with previous studies (12, 36, 37), we found a reduction in depressive mood state in the group that received the probiotics. The *depression* subscale score was lower after 6 weeks of probiotics intake, suggesting that the experimental group benefited from probiotics intake. Interestingly, this positive effect was maintained after 3 weeks of washout, suggesting a long-term effect. Moreover, we found a reduction in anger as measured by the *anger* subscale of the POMS. This reduction appeared at the 3-week assessment and was consistent across other time points. Hence, the scores for anger were lower in the experimental group not only during the 6-week period of probiotics intake but also after 3 weeks of washout. The sense of *fatigue* was also lower in the experimental group at 6 weeks of probiotics intake and continued after the 3 weeks of washout. Since no between-group differences were detected, caution is needed in interpreting these findings. Nonetheless, we suggest that, overall, these findings hint at a beneficial effect of probiotics intake in the experimental group.

No significant differences were found for STAI scores, thus suggesting no changes in state and trait anxiety as assessed by STAI-Y1 and STAI-Y2. Of note, the STAY-Y1 measures the perceived anxiety level at a precise time point. In our study, this time point corresponded to the assessment sessions. The lack of differences between-groups and across time points may indicate that the study participants were relaxed and did not feel they were under pressure while completing the questionnaires, thus excluding potential biases due to anxiety.

The STAI-Y2, instead, measures a more stable dimension of anxiety, the trait anxiety, i.e., an individual's propensity to habitually give anxious responses. The lack of effect of probiotics on this trait could be explained by the fact that healthy individuals already have low anxiety scores that cannot be further lowered by probiotics intake.

Effect of Probiotics on Sleep Quality

Although we did not find significant differences between the experimental and control group at the PSQI, the former but not the latter reported an improvement in sleep quality. More precisely, the experimental group participants reported that their sleep quality improved after 6 weeks of probiotics intake. The conclusions that can be drawn from these findings are limited by the lack of between-group differences. At any rate, we suggest that probiotics intake had beneficial effects on sleep quality in experimental group. Recent studies have demonstrated that probiotics ameliorate sleep in patients with chronic fatigue syndrome (39), chronic pain (40), and in stressed medical students (41). Our finding extends previous observations, suggesting that the probiotics mixture we used was effective in improving sleep quality also in a healthy population. Moreover, the improvement in sleep quality fits well with the reduction in depressive mood state, anger, and fatigue we observed in the experimental group. Previous studies demonstrated a strong relationship between sleep quality and mood (15). This was also the case of our study. Correlation analysis indeed, showed that sleep quality correlated with different aspects of mood, like anxiety, depressive symptoms, fatigue, anger, confusion and vigor, and additionally, in the experimental group, with some aspects of cognitive reactivity to sad mood (e.g., aggression, risk aversion, acceptance and hopelessness). Probiotics might have positively influenced mood not only by influencing emotional processes, but also other related aspects such as sleep quality as well.

Effect of Probiotics on Aspects Related to Personality and its Relationship With Mood

We found no differences in personality traits across time points, suggesting that the two groups remained stable throughout the study. This suggests that personality dimensions are complex and consolidated features that cannot be easily modified over time. Whether the lack of effect was due to the duration of the study (too short) or to the dose of the probiotics (too small) will need to be investigated in a future study.

At certain time points and for specific TCI subscales, however, we found significant between-group differences. For instance, *novelty seeking* scores (i.e., exhilaration in response to novel stimuli) were higher for the experimental than the control group at T3, i.e., after 3 weeks of washout. Caution is warranted when interpreting these findings, however, since the between-group difference in novelty seeking was not consistent across time points. Nonetheless, we suggest that the improvement in mood induced by the probiotics could have facilitated novelty seeking in the experimental group. Support for this hypothesis derives from the evidence that positive emotions trigger exploratory behavior [for a review, see (42)]. Similarly, *self-directedness* and *cooperativeness* subscale scores were significantly different between the two groups only at T3 and at T2, respectively. Once again, because these differences were present only at single time points, it is difficult to draw strong associations with probiotics intake.

Two subscales in the COPE inventory, the *avoidance strategies* and *the positive attitude* subscales, revealed differences between the two groups at more than one time point. We found higher scores on the *avoidance strategies* subscale for the experimental group compared to the control group at T2 (after 6 weeks of probiotics intake) and at T3 (after 3 weeks of washout). This means that the experimental group participants were more likely to adopt strategies based on avoidance (e.g., through denial of stressful situations) when they experienced problems. Taking into account the findings on mood, we speculate that because the experimental group participants felt better, as shown by the reduced depressive mood state, anger and fatigue, they were also more likely to avoid negative thoughts or situations, which induced a positive bias in their responses. In this regard, it has been demonstrated that people who feel in a positive mood are motivated to maintain their positive state (43). For instance, studies on risk-taking behavior demonstrated that positive feelings can accentuate an aversion toward risky options related to a higher probability of loss (43). Of note, avoidance strategies allow to deny problems and related emotions that alter positive mood. In this sense, they might represent the "less risky option" to temporarily prevent loss of a positive state. Following this line of reasoning, we believe that the experimental group participants probably had a higher propensity to adopt avoidance strategies in order to preserve their acquired positive state. This is only speculative and cannot be completely supported by our data; nonetheless, it deserves further investigation.

Also, the *positive attitude* subscale scores were lower for the experimental compared to the control group at T1 (at 3 weeks into the study). Positive attitude is an adaptive coping strategy that allows individuals to positively reinterpret negative situations (44). Hence, a lower score for this subscale suggests that the experimental group participants were temporarily less prone than the controls to positively reinterpret a negative situation. How does this result fit with the amelioration of mood observed in the experimental group? It has been widely demonstrated that positive feelings can bias attention toward mood-congruent stimuli (45, 46). In virtue of this congruency effect, people who feel in a positive mood are apt to attend to positive rather than negative events (46). We speculate that, in virtue of a general positive mood, the experimental group participants subjects did not need to reinterpret negative situations probably because they tended to focus on positive events congruent with their mood rather than on negative events.

Limitations of the Study

Some limitations of this study should be acknowledged. For instance, the small sample size and the potential pre-existing group differences with regard to some personality traits (e.g., *persistence* subscale of the TCI) may limit generalizability of the findings. Future studies with larger sample will allow to apply a randomization method that allows to take into account more than one covariate (21). Moreover, due to time constraints, we used only dimensional questionnaires to assess personality, thus limiting our findings. Future investigations with categorical diagnostic tools (e.g., Structured Clinical Interview for DSM-IV, SCID-II) will allow to achieve a more comprehensive view by assessing personality disorders. Despite these limitations, we think that our study indicates that probiotics might help to promote psychological well-being. As one of the possible underlying mechanisms, we speculate that probiotics, by interacting with intestinal microbiota, facilitated the production of precursors of neuroactive substances involved in modulating emotional processing, sleep, and other brain functions (5, 6). Since the current study did not focus on changes in intestinal microbiota following probiotic intake, this is only a speculation based on previous findings (5, 6). Future studies on larger samples are needed to verify this hypothesis and to uncover the biological mechanisms at the basis of these effects by investigating the changes in the intestinal microbiota related to probiotics intake. Moreover, it would be interesting to extend these investigations to clinical populations and verify whether the positive effects of probiotics intake can be observed in such patients. If so, this would suggest the use of probiotics as adjunctive therapy for conditions characterized by altered mood and/or sleep disturbances.

CONCLUDING REMARKS

We did not find significant differences between the experimental and control group neither at mood-related questionnaires, nor at the questionnaire assessing the quality of sleep. Nonetheless, we found changes in mood state and sleep quality across sessions in the experimental and not in the control group. More precisely, our exploratory study shows an improvement

across time in different aspects of the profile of mood state, like sad mood, anger, and fatigue only in healthy individuals which took probiotics. Sleep quality also reportedly improved after probiotics intake. Of note, sleep quality strongly relates to mood. More precisely, as suggested by the significant correlations between sleep quality and mood-related questionnaires, the higher the quality of sleep, the better the mood state in the experimental and in the control group. Finally, significant differences between-groups have been observed for some personality-related questionnaires. In this regard, our findings suggest that improving mood by means of probiotics intake might additionally determine changes in cognitive strategies to deal with problems by reducing sensitivity to negative situations, as well as the need to deal with them. Moreover, we speculate that ameliorating mood can differentially affect an individual's predisposition, for instance, by facilitating novelty seeking.

AUTHOR CONTRIBUTIONS

MF, GF, and AD conception and design of the research project. MF, GF, AD, and AM organization of the research project. AM and ES data acquisition. AM and MF data analysis. AM, MF, GF, and AD interpretation of the data. AM writing the first draft. MF, GF, ES, MP, AA, and AD revision and comments on the first draft. AM, ES, AD, MP, AA, LM, GF, and MF final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00164/full#supplementary-material

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ORIGINAL RESEARCH
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The Experience of Sleep Problems and Their Treatment in Young People at Ultra-High Risk of Psychosis: A Thematic Analysis

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We view sleep disruption as a contributory causal factor in the development of psychotic experiences. Clinical trials indicate that psychological interventions targeting insomnia result in improvements in both sleep and psychotic experiences. The aim of this study was to gain the perspective of young people at ultra-high risk of psychosis on their sleep problems and associated psychological treatment. Interviews were conducted with 11 patients, aged 15–22 years, at ultra-high risk of psychosis who had received a psychological sleep intervention. Responses were analyzed using thematic analysis. Disrupted sleep timing and a lack of routine were the characteristic hallmarks of participants' sleep problems. Sleep disturbance, psychological wellbeing, and functioning had a reciprocal relationship. There were negative expectations prior to therapy, however meaningful improvements occurred in sleep, mood, and functioning. The active implementation of therapy techniques was highlighted as important. These findings indicate that the treatment of sleep problems is highly valued and has a meaningful impact on wellbeing in young people at ultra-high risk of psychosis.

Keywords: at-risk-mental-state, ARMS, CBT, intervention, qualitative, schizophrenia

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INTRODUCTION

Sleep disturbance has been identified as a potential causal factor in a range of severe mental health problems (1), including psychotic experiences (2, 3). In adolescents, sleep disruption and psychotic experiences overlap in genetic and environmental causes (4). Sleep problems are common during adolescence and have a significant impact on functioning (5, 6). In young people at high risk of serious mental health problems, sleep disturbance and circadian rhythm disruption are associated with poor outcomes and persistence of psychotic experiences (7–9). A consensus is emerging that "early treatment of sleep problems might reduce the risk of developing mental health problems and can be considered a helpful preventive strategy" (10). Sleep problems are important to be treated in their own right but also, if successfully reduced, have the potential for broad health benefits.

Cognitive Behavioral Therapy for insomnia (CBTi) has demonstrated treatment effects in adults and is the recommended first line treatment in clinical guidance (11). Importantly, improving sleep has been shown to result in additional benefits on mental health outcomes including anxiety, depression, psychotic experiences, and psychological wellbeing (12–14). However, CBTi has not been adequately tested in young people, either for its effects on sleep disturbance or potential wider effects on mental health outcomes.

Our group have conducted the first investigation of psychological interventions to treat sleep problems in young people at ultra-high risk of psychosis (15). In this case series, we found that the intervention was acceptable and may be associated with clinical benefits: following treatment, we found improvements in sleep, negative affect, and psychotic experiences. The effect sizes were large and the changes were maintained at the 1 month follow up.

Throughout the treatment development process, it is essential to incorporate the patient perspective on the phenomenology of the problem and the experience of receiving treatment. Previous qualitative studies have explored sleep problems in the absence of other mental health problems (16), or specifically in patients with sleep disturbance in the context of severe and enduring psychosis (17, 18). However, these accounts do not explore the specific developmental context of adolescence and early adulthood nor the novel target of addressing sleep as a preventative intervention for those at risk of serious mental health problems. The aim of the current study is to explore the experience of sleep problems and their treatment in young people at ultra-high risk of psychosis.

MATERIALS AND METHODS

Participants

Eleven patients, assessed as meeting criteria for ultra-high risk of psychosis based on attenuated psychosis [see (19) for full criteria] on the Comprehensive Assessment of At-Risk Mental States (CAARMS), took part in this qualitative study. All patients had recently received an adapted cognitive-behavioral intervention for sleep disturbance as part of a feasibility case series (15). Patients were identified based on their participation in the feasibility case series. All 11 patients approached consented to participate in the study. Participants were aged 15–22 years (mean = 18.27, $SD = 1.95$). Participants were employed full time ($n = 2$), part time ($n = 2$), or in education at school ($n = 4$) or university/higher education institution ($n = 3$). See **Table 1** for clinical and demographic details.

Intervention

The intervention is designed for young people to precisely target the key mechanisms which underpin sleep disturbance. It utilizes CBTi techniques, strategies to reduce hyperarousal, and circadian entrainment. The intervention is manualized in a modular format. All patients received 5 core modules:

(1) Psychoeducation, assessment, formulation, and goal setting,
(2) Establishing the environmental and lifestyle context for sleep (sleep hygiene),
(3) Stimulus control (re-associating bed with sleep) and strategies to reduce hyperarousal,
(4) Circadian entrainment (to regulate the timing of sleep by setting the sleep window, boosting zeitgebers for example meal and activity times, and increasing daytime activity),
(5) Relapse prevention.

Additional modules (addressing nightmares, voices, and motivation) were delivered according to the individualized formulation of the young person's sleep problems. Further details of the intervention are reported by (15).

Procedure

Ethical approval for this study was obtained from an NHS research ethics committee. The interviews were conducted at participants' homes or at their local clinic. The interviews were conducted and audio-recorded by EC, a research worker, and transcribed verbatim. The mean duration of the interviews was 23 min ($SD = 10.8$) with a range of 10–47 min.

Semi-structured Interview

A semi-structured interview was developed by FW and JB. It focused on participants' experience of sleep problems and their treatment. The interview schedule was used flexibly, with additional verbal and non-verbal cues given to encourage elaboration. The participants' own vocabulary was used in relation to psychotic-like experiences. The interview schedule included four core questions: (1) "Can you tell me a bit about how things are for you at the moment?" (2) "Have there been any changes?" (3) "What was it like for you taking part in this therapy?" (4) "Is there anything that we haven't asked that you feel may have been important to your experience?" All participants focused their answers on sleep and its improvement therefore additional targeted prompts were not necessary.

Analysis

Thematic analysis is a widely used method for organizing, encoding, and identifying patterns within qualitative data. Analysis of this data set was carried out following the guidance provided by Braun and Clarke (22). First, the transcripts were read whilst listening to the corresponding audiotape to ensure accuracy and familiarity with the data set. Initial codes were then applied manually to segments of data and collated. Candidate themes were identified by organizing codes manually into theme-piles and a draft thematic map was created. Candidate themes were reviewed and data extracts within the themes were checked to ensure coherence within the theme and, if necessary, themes were adjusted. A candidate thematic map was developed and reviewed to ensure it represented the data set. The map was adjusted where necessary to better fit the data set. Finally, the accepted themes were refined and a thematic map finalized for the report (see **Figure 1**). Initial codes and candidate themes were developed by JB. SR and JCB (who were independent of the therapy and interviews) then joined JB in reviewing and refining the themes through an iterative process until a consensus was reached on the final thematic map.

RESULTS

Three main themes were developed, each with sub-themes. The finalized thematic map is shown in **Figure 1**. The first theme centered on the experience of sleep problems; the second and third themes related to the experience and utility of the intervention.

TABLE 1 | Demographic and clinical details of the participants, including data from baseline assessment.

Participant number	Gender	Ethnicity	Number of treatment sessions	Insomnia (ISI)	Wellbeing (WEMSBS)	Unusual thought content (CAARMS)[a]	Non-bizarre ideas (CAARMS)[a]	Perceptual abnormalities (CAARMS)[a]
1	Female	White	7	18	33	No	Yes	Yes
2	Male	Asian	8	18	26	Yes	Yes	Yes
3	Female	White	7	18	30	Yes	Yes	Yes
4	Male	White	8	16	36	Yes	Yes	Yes
5	Male	White	8	20	21	No	No	Yes
6	Male	White	7	14	43	Yes	No	Yes
7	Female	White	8	14	38	Yes	No	Yes
8	Female	White	7	19	38	Yes	No	No
9	Female	White	8	18	41	No	Yes	Yes
10	Male	White	8	15	49	Yes	Yes	Yes
11	Female	White	8	19	34	No	No	Yes

Insomnia Severity Index (20); WEMWBS, Warwick and Edinburgh Mental Wellbeing Scale (21); CAARMS, Comprehensive Assessment of At Risk Mental States (19); [a] Score of 3+ on CAARMS subscale.

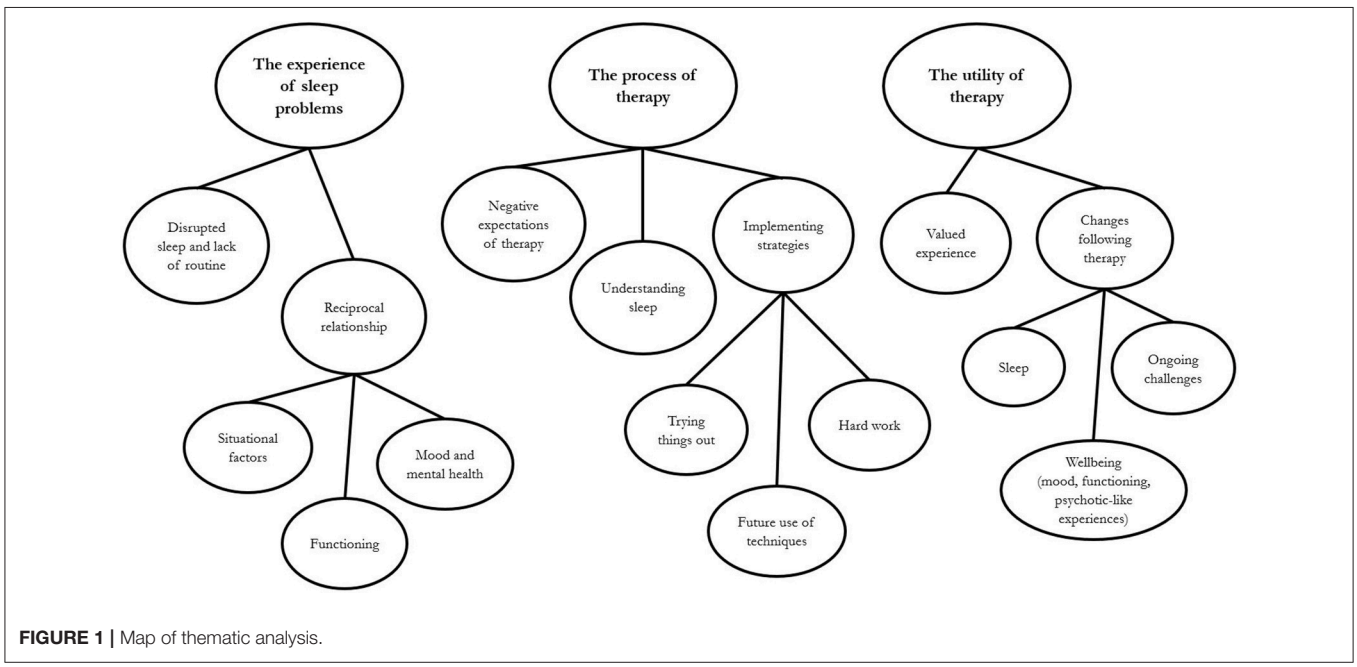

FIGURE 1 | Map of thematic analysis.

Theme 1: The Experience of Sleep Problems

Participants described a strong connection between disrupted sleep timing, lack of routine, and sleep problems. A reciprocal relationship between sleep disturbance, mental health problems, and daily functioning was also described.

"It Was a Lot of Just Feeling Tired at the Wrong Time" (P2) – Disrupted Sleep Timing and Lack of Routine

Participants frequently described their sleep problems as being characterized by delayed sleep phase and lack of routine: "I could be like staying up to about two, three o'clock in the morning and then going to sleep, and then I'd be napping for like an hour or two during the day, and then staying up all night because I'd slept during the day" (P1). Circadian rhythm disruption included day-night reversal: "I was staying up until about like four in the morning, awake, and then I'd sleep until about three in the afternoon" (P7); "basically, I was nocturnal" (P5). This delayed sleep phase was reinforced by occupation in other activities at night: "when I went to bed, I'd sit there for ages, just on my phone or listening to music or something, without trying to sleep" (P6); "I'm ready to clock off, but my brain's not, and then I'm thinking through things" (P10); "I used to use my bed for work and things like that" (P11). Others identified a general lack of structure or predictability to their sleep patterns: "I just wouldn't really have a lot of structure to, kind of like, my sleeping pattern" (P9); "I

never went to bed at the same time. I'd always be varying times, so that… Sometimes, it was even 3 or 4 h' difference" (P2).

"It Makes Everything a Lot Worse" (P2) – The Reciprocal Relationship

A complex interrelationship between sleep problems, mood, and functioning was described: "I would just sleep through the day and that like put a massive strain on like my social aspect and mood and my mental health, and I just think that it just turned my life like the other way around, so I would be up at night and then, because I was up at night, I wouldn't be up in the day and I wouldn't go out and see people because I was sleeping, and it was just… I just think it was very unhealthy" (P7). It was noted that poor sleep lowered mood, whether directly due to symptoms of insomnia, "not being able to get to sleep, not being able to stay asleep, and then being too tired during the day to actually do anything, which was really, really affecting my mood" (P3), or because of the social and functional consequences "It wasn't good for like my mental state, just like being by myself like not really talking to anyone" (P7). Others identified effects on anxiety, "it will pick up when I'm tired" (P11) or irritability "I'd just want to go home [and want to] go to sleep, and then, during the night, [I'd get] grouchy because I'd be like "I've got to go to sleep and I can't!" (P1). Participants also noticed the reverse effect, where low mood or anxiety disrupted sleep: "I'm generally feeling quite low, so that very much affects my sleep" (P2); "I'm thinking about so much that I can't relax, and that will last for like a good hour or so every night" (P10). Participants described the reciprocal relationship between sleep disruption and everyday functioning: "I just would have been in bed, doing nothing, nothing like proactive or anything" (P7); "The more I get up in the night, the more I will just stay in bed for longer" (P1).

Other situational factors were identified in the onset or maintenance of sleep problems: "when I started, I wasn't sure whether we were moving out of the area, we were staying, we were kind of up in arms and everything" (P11); "like you have hormone cycles that affect your sleep as well" (P3); "I'm traveling 3 h a day by bus and things like that, which is always quite grueling" (P10).

Theme 2: The Process of Therapy

A theme was identified on the process of treating sleep problems. There were negative expectations of the therapy and its potential efficacy. Participants described two phases of therapy: understanding sleep and enacting strategies to improve it.

"I Didn't Think It Would Work at First" (P8) – Negative Expectations

There were a range of negative expectations regarding therapy. These included concerns about the potential efficacy of the treatment especially in the limited timeframe of the intervention, "when I started it, I was like no one can do this in 10 weeks" (P11); "I just thought… I'd give it a go and it probably wouldn't work" (P8). Particular intervention techniques also raised doubts: "some people [I'd heard in class], they were just like, oh, just sleep late, just, you know, like hot chocolate, or just count some sheep, and I was like, "Oh, it's just going to be that all over again!" (P1); "little methods, such as like writing things down, and how actually when you think about that, that seems like it's not really going to do anything" (P2). There were negative expectations of the specific treatment model, "I never wanted to go through CBT, ever" (P11), and the style of therapy, "my worry was it was just going to be like some depressing… fest [laughing]" (P10). For some, there were concerns about judgment from the therapist: "I was scared that I was going to kind of be judged for like my sleep and stuff" (P9).

"I Learnt a Lot About Sleep" (P6) – Understanding Sleep

Participants' described the impact of monitoring sleep: "it sort of opened… well, not opened my eyes as such, but gave me a wider understanding of what actually affects my sleep" (P4); "with the sleep diaries, you thought more about your sleep and when you were sleeping" (P1); "I'd thought that maybe I wasn't getting enough sleep and I was tired during the day, but I didn't really think much more than that" (P6). For some participants, this revealed the scale of the sleep problem: "I didn't really realize how bad my sleep was" (P6); "I never would have imagined myself realizing how bad my sleep routine was" (P11). This detailed assessment allowed participants to gain awareness and knowledge regarding their sleep: "I learnt quite a lot, and it was just kind of… some obvious stuff, but it was said kind of in a way that I hadn't thought about before and I hadn't thought like how it was really affecting my sleep" (P9).

"I've Got a Repertoire of Skills Now" (P5) – Implementing Strategies

In developing a set of strategies to improve their sleep, participants identified a process of "trying things out": "I can just go, "Right, let's try this." If it doesn't work, I can try this. That works a bit. I can try this. That works even more" (P5); "It was just see what ones you can do, see what ones' work" (P9). This process included providing feedback on the strategy and then amending it or working on an alternative: "So, [my therapist] would give me a technique and then I'd come back and say 'This worked for me; this didn't work for me,' and then we could kind of work around that" (P3); "all the other things that we'd done before I felt they hadn't worked as much, and then we did the wind-down routine and it really helped" (P6).

Making changes to overcome sleep problems was challenging: "there's some days where I just want to like not move and just stay in my bed and just not do anything. It's hard to try and change that, to try and get myself motivated" (P7). Others identified specific strategies they found hard to implement: "the one thing I struggled with was kicking the laptop out my room, stop eating chocolate before bed, the amount of caffeine and things like that" (P11); "[my therapist] said if I get into bed and I don't fall asleep within 15 min, like to get back up again, like things like that, because once I'm in bed, I just don't really want to get back out of it [laughing]" (P8). For some, it was maintenance rather than implementation of strategies that was the challenge: "every time that I try to implement some of those strategies, there is a definite benefit, but it's quite difficult to maintain" (P10). However, implementation became easier over time: "it got easier,

because I got used to what I was doing" (P8); "I've tried my best to sort of keep some of the routines…to where I don't even really think about them now" (P10).

A number of participants also talked about continuing to use strategies after completing therapy. Some were still actively using techniques and working toward their sleep goals: "I'm still doing the sleep plan" (P4); "I'm using a lot of the techniques that I was given through this" (P10); "I've been using the quarter-hour rule" (P9). Others reflected that they knew they could draw on the techniques if they needed to in the future and that the manual may be helpful for this: "if you begin to lose your sleep again, it's nice to be able to read back and remind yourself of what you did the last time" (P1); "if I sort of felt like I was having sleep problems again, I can go back to this and go, well, here's things I can use" (P5).

Theme 3: The Utility of Therapy

Participants gave extensive feedback on the intervention and its outcomes. The reciprocal relationship between sleep disturbance, mental health problems, and daily functioning identified within the earlier theme was reinforced by participants' observations of the benefits when their sleep improved.

"I've Quite Enjoyed the Therapy I've Had" (P1) – Valued Experience

The majority of participants gave positive feedback on the overall experience of the intervention. "it was very good, very interesting as well" (P4); "I thought it was really, really helpful" (P3). The specific style of treatment sessions, for example home visits, contact between sessions and active engagement were noted as important: "if I was struggling during the week, I could just email and say, "Having a tough day–any advice?" sort of thing. That was really helpful" (P3); "you guys are going sort of fairly…above and beyond sort of…even coming to my house" (P10); "It was kind of very friendly. It wasn't like scary" (P9). The collaborative approach to setting the focus of the session was valued: "[my therapist] was very happy to work through any other problems that I was having at the same time" (P3); "It is based, like, what you do during the day, diet, social life, like taking all that into account along with your sleep" (P1).

Limitations of the intervention were identified. This includes the treatment outcomes: "they don't solve the situation, too much, but it does still help" (P10); "I would say just the stuff about the nightmares. For some, it does work, but for others, it doesn't, which I can understand but I would like to try and find something that would work for all of them [nightmares]" (P4). There were contrasting responses to the booklets used in therapy: "the booklet things, did confuse me a bit" (P8), "the booklets were a little over-simplified" (P3). Some elements of the intervention delivered as standard in every session (the sleep diary, insomnia questionnaire, and session summary) were described as "repetitive" (P3 and P5) or "tedious" (P9).

"Everything has Kind of all Eased up at the Same Time" (P11) – Changes Following Therapy

Participants described improvements in their sleep following the intervention. Specific changes included: realigning circadian rhythm: "I do sleep now [laughing], at like the proper time" (P7), enhancing sleep quality: "waking up no more than twice during the night and not feeling concerned when I wake up" (P3), improving sleep onset latency and total sleep time: "I've been falling asleep quicker and spending more time asleep" (P4). Participants highlighted the importance of their sleep: "If I get a decent night's sleep, I'm not tired during the day" (P11); "I had originally thought it was more down to stuff during the day, like how much energy you had used on this activity or this activity or, again, what you're eating, but I didn't realize how much was down to sleep" (P10). Participants described issues related to their sleep which they would need to continue addressing such as increasing total sleep time "I'd say it's enough sleep, compared to where it was. It's still not a great amount" (P11) or hypnogogic/hypnopompic experiences "There was one thing that's still quite an issue [my therapist] called it hypnogogic experiences" (P10).

A number of participants directly linked improvements in their sleep to changes in mental health outcomes. The impact of improving sleep on mood and anxiety was reported: "I suffer from depression so it's not going to be high all the time, but because it's so highly linked with sleep, when I sleep better, I tend to have a better day" (P3); "the depression has been the big step. It's really eased. It's nowhere near where it used to be" (P11); "I find it also has helped my anxiety a lot. I'm able to cope with situations a lot better and kind of stay in control, which I think has come from me gaining control of my sleep a bit" (P9). Of particular relevance to a group at ultra-high risk of psychosis, improvements in sleep were also tentatively linked to improvements in sub-threshold psychotic symptoms: "since I've been sleeping better, my, visual things have like stopped" (P8); "I used to hear things quite a lot, like walking down the street, and that's subsided, almost entirely. I don't know whether that's a consequence of the work I've been doing with the psychologist [from the clinical team] or the sleep intervention or like a combination" (P3).

Mirroring the theme of the reciprocal relationship between sleep problems and broader difficulties, one participant summarized the wide effects of improving sleep: "the stuff that I normally wouldn't have done because I was physically just too tired, I find I can now have the energy to do that, those things, which makes me feel happy because I'm getting stuff done and I'm not getting stressed out at the fact that I haven't done the things that I wanted to do. It makes me feel happier" (P9). These concurrent changes in energy, mood, and functioning were noted both by individuals and their social networks: "my boyfriend in particular and then a couple of my friends, they've noticed how much more energy I have and how I've been contributing more in conversations" (P3).

DISCUSSION

To our knowledge, this is the first study to report the experience of sleep problems and their treatment in young people at ultra-high risk of psychosis. Participants gave vivid accounts about the importance of good sleep for mental health and

day-to-day functioning. The experience of a delayed sleep phase, characteristic of the changes in sleep architecture in adolescence, was clearly described by participants. A lack of routine was identified as a key feature of sleep problems and thus a target for treatment.

A link between poor sleep, mood, sub-threshold psychotic experiences, and functioning was described. This is consistent with findings from a qualitative study of insomnia in adolescents with depression in which the negative impact of sleep disturbance on functioning was highlighted (23). The description of the reciprocal nature of sleep disturbance and mental health problems is aligned with accounts from patients with severe and enduring psychotic experiences (18). This supports theoretical models of sleep disruption as a causal factor in mental health problems (1). Importantly, in the current study, improvements in sleep were linked with improvements in mood, functioning, and psychological wellbeing.

Despite high treatment uptake rates there were negative expectations of therapy prior to taking part. It may be the case that some participants viewed their sleep problems as so intractable as to be untreatable – this attitude has been reported in patients with sleep problems in the context of established psychosis (17). Faulkner and Bee found that patients had pessimistic or neutral views on the likely effectiveness of "talking therapy" as an intervention for sleep problems, although individual components (e.g., stimulus control, increasing daytime activity) were seen as far more likely to be effective. What was notable, in the current study, was the spirit of experimentation, a willingness to try the intervention in spite of doubts about its efficacy. "Willingness to change" has been identified as a theme in other qualitative accounts of young people with sleep problems (24). It is unclear whether this disparity between expectation and engagement is specific to this age group (that is, whether adolescents are more willing to try strategies than other age groups) or whether it merely reflects the attitudes of those who express interest in research and so might be more willing to try the intervention in spite of reservations. Nevertheless, this finding may have specific implications for how this therapy may best be advertised and delivered in this group.

Two distinct phases of treatment were described: improving understanding of sleep and taking action to improve sleep. Prior to implementing new techniques, participants described the process of improving their understanding of sleep. Increasing knowledge of both good-quality and poor-quality sleep has been highlighted as an important target for identifying and treating sleep problems in adolescents (25). The current study indicates that young people at ultra-high risk of psychosis are keen to learn about sleep and value this information. In particular, participants described monitoring sleep as a route to increasing understanding. However, a limitation of the feasibility case series was the low rates of sleep diary completion (15). This reluctance to complete sleep diaries is consistent with findings from other studies, for example adolescents with depression identified sleep diaries as a barrier to treatment, regardless of the mode of delivery (23). Future research will need to addresses these discrepancies between desire to increase knowledge and the current tools for monitoring sleep to ensure treatment is both engaging and effective.

Previous research has described how young people at ultra-high risk of psychosis have concerns regarding discussing unusual experiences and thus delayed help seeking (26). It is possible that sleep problems carry less stigma than other mental health problems. In the current study, participants described gaining control of sleep as a route to increasing control of their mental health and overall wellbeing. This may indicate that sleep problems could be an accessible first treatment target. This is an important consideration in the context of the current clinical guidance to improve timely access to services for early psychosis (27).

There were limitations to the present study. This was a selected sample in the context of a feasibility case series. Therefore, there is potential bias in their experiences. For example, themes identified on the experience of sleep problems may reflect the content of the intervention. The most likely bias is in the enthusiasm for the intervention. However, the findings of the present study fit both with the established evidence base in adults that psychological treatments for sleep problems are effective and the emerging literature indicating wider benefits to mental health. Clearly the findings of this small qualitative study are not generalizable. For example, the current study is not intended to reflect the experiences of sleep problems in early adolescence: given the changing developmental markers in sleep architecture, social demands, and cognitive development the current findings are limited to the late adolescent period (the peak age of onset for psychotic experiences). However, the aim of this study was to use first person accounts to inform theoretical and clinical developments. We believe the findings presented provide a resource to achieve this aim.

CONCLUSION

This study highlights the importance of addressing sleep problems in young people at ultra-high risk of psychosis, and provides insight on the motivations and reservations they have toward treatment. A number of key themes emerged related to treatment: negative expectations prior to treatment, two phases of therapy (understanding and action), and the importance of treatment style. These can be used to further develop the treatment and to optimize engagement. The findings support the promise of sleep interventions in young people, as reported in the feasibility study (15). Namely that, following therapy, participants reported improvements in their sleep, psychological wellbeing, and everyday functioning. The findings suggest that sleep interventions in this group should be given higher clinical and research priority.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethical Principles of Psychologists

and Code of Conduct (28). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the National Health Service South Central–Oxford A Research Ethics Committee (15/SC/0378).

AUTHOR CONTRIBUTIONS

FW and JB developed the interview for data collection. JB and EC recruited participants for the study. JB provided the intervention. FW provided clinical supervision. EC conducted the interviews for data collection. JB, SR, and JCB conducted the analysis. DF and FW provided overall supervision. FW took the main responsibility for drafting of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Moderating Effect of Mindfulness on the Relationships Between Perceived Stress and Mental Health Outcomes Among Chinese Intensive Care Nurses

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This study aimed to explore the potential moderating effect of mindfulness and its facets on the relationships among perceived stress and mental health outcomes (burnout, depression, anxiety, and subjective well-being) among Chinese intensive care nurses. A total of 500 Chinese intensive care nurses completed self-report measures of mindfulness, burnout syndromes, perceived stress, depression, anxiety, and subjective well-being. Correlation and hierarchical multiple regressions were applied for data analysis. Mindfulness moderated the effects of perceived stress on emotional exhaustion (the core component of burnout syndrome), depression, anxiety, positive affect, and negative affect but not on the other two dimensions of burnout and life satisfaction. Further analyses indicated that the ability to act with awareness was particularly crucial in improving the effects of perceived stress on depression. These results further broaden our understanding of the relationships between perceived stress and burnout, depression, anxiety, and subjective well-being by demonstrating that mindfulness may serve as a protective factor that alleviates or eliminates the negative effects of perceived stress on depression, anxiety, burnout syndrome, and subjective well-being and may instigate further research into targeted mindfulness interventions for Chinese intensive care nurses.

Keywords: mindfulness, perceived stress, burnout syndrome, depressive symptom, anxiety symptom, subjective well-being, intensive care nurses

INTRODUCTION

The intensive care unit (ICU) is a fast-paced, demanding, and tension-charged environment. Nurses working in the ICU are predisposed to workplace stress owing to direct and indirect exposure to traumatic and critical events, excessive workload (1), high patient care demands (2), long shift work, close contact with death and severe illness (3), and even medical violence (4); however, nurses working in the ICU have limited authority (2). Highly stressful daily events may lead to a heightened stress response combined with negative emotions (5). A growing number of studies have examined mental health among intensive care nursing, but studies on this topic are still rare. Previous studies have produced concordant results demonstrating that ICU nurses show high rates of stress that have

resulted in epidemic levels of some work-related mental health problems (6).

The most commonly explored outcome of high-level work-related stress in health care providers is burnout syndrome (7, 8). An increasing number of studies have shown that ICU nurses have an increased prevalence of burnout syndrome (9–11). Burnout is often described as a three-dimensional syndrome that is characterized by emotional exhaustion (EE), depersonalization (DP), and lack of personal accomplishment (PA) (12), which are experienced by 73%, 48%, and 60% of critical care nurses, respectively (10). Compared to nurses in other units, nurses in the ICU treat patients with specific characteristics. Triggers of stress that are different from those experienced in other units include high patient mortality and morbidity, a challenging work environment, and frequent encounters with the critical and traumatic events mentioned above.

The current data show that the prevalence of burnout among critical care staff in different countries has reached alarming levels of approximately 30% in France (11), 16% of nursing staff and 10% of nursing assistants in Spain (13), 56% in a group of pediatric intensive care unit (PICU) staff in Spain (80.9% of nurses and nursing assistants), 84.4% in Argentina (14), and from 25% to 33% in the United States, with up to 86% of the critical care staff experiencing at least one of the three dimensions of burnout. In China, one study indicated that the prevalence of burnout was 83.7% among nurses in the ICU and emergency department (15). Burnout syndrome has been reported to have many negative consequences. It was found that burnout reduces the quality of care (16), lowers patient satisfaction, increases medical error, and leads to interpersonal conflicts, negative emotions, physical symptoms, compulsive behaviors, intention to leave, a higher turnover rate, and absenteeism (9, 10, 12, 17–19).

Perceived stress, depression, and anxiety are strongly and positively related, suggesting a close link between stress and psychopathological symptoms and well-being (20). According to the WHO, over the past two decades, the number of people suffering from anxiety and/or depression worldwide has increased by nearly 50%. Mental illnesses are common among nurses from different countries. Studies have shown that 61.7% of nurses working in the Northeast China Hospital have depressive symptoms (21). The influencing factors and effects of anxiety and/or depression in nurses have been studied. Depressive symptoms among nurses have been linked to stressful work environments, job demand, effort–reward imbalance, etc., which may adversely result in sickness-related absences and affect quality of life and quality of care (21). Well-being is essential for quality of care and productivity. However, prolonged or excessive stress places increasing strain on individuals and has deleterious effects on well-being (22).

Since it is apparent that nursing in the ICU is associated with unique sets of stressors, it is imperative to study the influencing factors and strategies to prevent burnout syndrome, depression, and anxiety, and to promote well-being, and it is crucial for ICU nurses to find ways to manage their stress and prevent the development of these mental health outcomes. According to Folkman et al.'s stress and coping theory (23), stress occurs when one appraises the stressor as exceeding his or her coping resources. The theory suggests that whether perceived stress can predict negative psychological outcomes may depend on the characteristics of the stressors, as well as the individual's assessment of these stressors and his or her access to coping resources.

Mindfulness may be a potential coping strategy that moderates the negative effects of appraised stress. Mindfulness can be conceptualized as both a trait-like quality (a psychological trait that refers to the tendency to be mindful in everyday life) and a state-like quality (a receptive attention to internal and external experiences) (24). Research of mindfulness interventions in nursing staff has revealed that mindfulness was associated with lower levels of reported stress (25, 26), improved coping with stress and diminished burnout (27–29), decreased EE and anxiety (30), and increased life satisfaction (31). According to Baer et al., mindfulness has five components—observation, description, acting with awareness, nonjudgment of inner experience, and nonreactivity to inner experience (32)—and each facet of mindfulness has specific effects. For example, mindfulness provides individuals the ability to detect the signs of stress by improving awareness (33). Research showed that high dispositional mindfulness may increase awareness of low-level stress symptoms, which, in turn, increases access to coping resources and helps alleviate the negative effects of stress (34). In addition, the ability to observe the effect of the buffer against stress on reduced life satisfaction and depression has been proposed (35). Therefore, it has been suggested that mindful individuals have greater abilities to handle with a set of stressors, which could help moderate the relationship between stress and adverse mental health outcomes (34, 36).

Recently, researchers have shown increasing interest in the stress buffering role of mindfulness. Bergin and Pakenham studied a sample of 481 Australian law school students and found that dispositional mindfulness moderated the effect of perceived stress on anxiety and depression (35). In another student sample, Bodenlos et al. (37) found that the mindfulness facet of nonjudgment acted as a buffer of well-being. By studying 292 patients with gastrointestinal cancer, Zhong et al. (38) concluded that the relationship between psychological symptoms and perceived stress was notable in patients with low dispositional mindfulness. Ciesla et al. (36) conducted a prospective study of 78 high school students and found that nonjudgment and nonreactivity mitigated the effects of daily stress on the daily changes in dysphoric affect. In a sample of 382 Swedish adults, Bränström et al. (34) found that dispositional mindfulness buffered the negative impact of perceived stress on mental health. However, most of the studies mentioned above were carried out in Western societies, and whether mindfulness also constitutes a health resource for ICU nurses working in Chinese societies is insufficiently explored.

Given the high rate of stress in ICU professionals found in previous studies combined with the lack of information focused on both the negative and positive indicators of mental health outcomes, this study pursues two specific goals: first, to test how stress, mindfulness, depressive and anxiety symptoms, and subjective well-being (SWB) are interrelated in Chinese ICU nurses and, second, to detect whether mindfulness moderates

the relationship between perceived stress and the related mental health outcomes mentioned previously. Moreover, out of the studies on the moderating role of mindfulness, there have been few studies examining the stress-moderating role of all five mindfulness facets illustrated by Baer et al. (39). Therefore, this study will explore the moderating effects of observation, description, acting with awareness, nonjudgment of inner experience, and nonreactivity to inner experience on perceived stress and other variables. We hypothesized that

1) High levels of mindfulness would be associated with better mental health outcomes for ICU nurses, and mindfulness would moderate the relationship between perceived stress and mental health outcomes.
2) Compared to ICU nurses with lower levels of mindfulness, the association between higher perceived stress and worse mental health outcomes would be weaker and better health outcomes would be more prevalent in nurses with higher levels of mindfulness.

MATERIALS AND METHODS

Participants and Procedure

From March 2016 to April 2017, a total of 500 intensive care nurses were recruited from hospitals in Xinjiang, Ningxia, Beijing, Shandong, Heilongjiang, Fujian, Chongqing, Sichuan, Guizhou, Yunnan, and Hubei provinces through purposive sampling methods. The nurses were recruited from local hospitals, military hospitals, first-class hospitals, and second-senior class hospitals in the northwestern, northern, northeastern, southeastern, southwestern, and central regions of China. The ages of the 500 participants ranged from 20 to 52 years (mean = 27.68 years, SD = 4.275). Among the participants, 41 were male and 459 were female, and 246 were unmarried and 256 were married. None of the participants had meditation experience or practiced meditation before.

The research design of this cross-sectional study was previously approved by the Ethics Committee of Army Medical University. Informed consent forms were obtained from participants who completed questionnaires, including the Five Facet Mindfulness Questionnaire (FFMQ), the Positive and Negative Affect Schedule (PANAS), the Perceived Stress Scale (PSS), the Maslach Burnout Inventory–Human Services Survey (MBI-HSS), the Satisfaction with Life Scale (SWSL), the Center for Epidemiological Studies Depression Scale (CES-D), and the Self-Rating Anxiety Scale (SAS). The uniform instructions were used for the test.

Measures

Demographic information. Participants provided demographic information including age, gender, marital status, and meditation experience.

Burnout. The Maslach Burnout Inventory–Human Services Survey (MBI-HSS) was used to assess the burnout syndrome of the human service professionals. The MBI-HSS includes 22 items in three job-related dimensions: emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA), and the 22 items were rated on a seven-point Likert scale, ranging from 0 = "never" to 6 = "every day" (40). Samantha Mei-Che Peng from The Hong Kong Polytechnic University translated the Chinese version of the MBI-HSS, which demonstrated good validity and reliability in China (41). There were nine items in the EE dimension, five items in the DP dimension, and eight items in the PA dimension. The Cronbach's alpha values were 0.86 for EE, 0.76 for DP, and 0.76 for PA. Based on previous studies, medical professionals with scores >26 on the EE subscale, >9 on the DP subscale, or <34 on the PA subscale are defined as having high burnout in that field.

Mindfulness. Translated from the FFMQ (39), the Chinese version of the Five Facet Mindfulness Questionnaire (Ch-FFMQ) is a questionnaire that measures dispositional mindfulness with 39 items (42). These items are rated on a five-point Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true), focusing on five facets of mindfulness: Observation, Description, Acting with awareness, Nonjudgment of inner experience, and Nonreactivity to inner experience (32). The Observation facet evaluates a tendency to observe or focus on external and internal experiences, such as emotions, thoughts, and sensations. Description assesses the propensity to describe and categorize these experiences with words. The Acting with awareness facet measures a sense of bringing full awareness and constant attention to the present experience or activity. The Nonjudging of inner experience facet measures a nonevaluative perspective toward inner experiences and cognition. Nonreactivity to inner experience assesses the tendency to allow feelings and thoughts to surface then leave, without becoming stuck on them or becoming overwhelmed by them. It has been shown that the FFMQ has good internal consistency (39), and the Cronbach's alpha values for the Ch-FFMQ are acceptable (42).

Depression. The Chinese version of the Center for Epidemiological Studies Depression Scale (CES-D) (43) was used to assess depressive symptoms. The CES-D consists of 20 items and is widely used to measure the epidemiology of depressive symptoms, with a focus on emotional components and depression. Participants in this study rated the frequency of occurrence of depressive symptoms on a four-point Likert scale: 0 = "never," 1 = "sometimes," 2 = "frequently," or 3 = "always." The Chinese version of the CES-D has good reliability and validity ($\alpha = 0.89$) (44). Individuals with a total CES-D score 16 or higher were defined as having "depressive symptoms" (45), which was further defined as mild for CES-D scores between 16 and 26 or moderate to severe for scores 27 or higher, which was based on the established criteria (46, 47).

Anxiety. Zung's Self-Rating Anxiety Scale (SAS) (48) served as an assessment tool to reflect the severity of anxiety symptoms reported by participants during the 7 days prior to completing the questionnaire. The SAS contains 20 items rated on a four-point Likert scale from 1 = "never" to 4 = "always," with a total raw score ranging from 20 to 80 and index score ranging from 25–100,respectively. The SAS and the cutoff point defined have been used extensively in studies of anxiety in China, and the Chinese translation of the survey has been previously validated

(49). In terms of an investigation of Chinese National Normative Scores, Chinese researchers defined SAS scores >50 as the cutoff point for symptom severity associated with anxiety disorders (50). The score is positively related to the severity of anxiety. Cronbach's alpha coefficient for the scale was 0.849 in the present study.

Perceived stress. The Perceived Stress Scale (PSS) is extensively used to measure the extent to which an individual considers his or her life to be stressful and to assess how controllable and unpredictable the stress has been over the past month (51). This scale has 14 items, with 7 items negatively stated and 7 items positively stated, which are rated on a five-point Likert scale from 1 = "not at all" to 5 = "always." Higher scores indicated a higher level of perceived stress. The total score for all 14 items ranges from 14 to 70. The Chinese version of the Perceived Stress Scale (CPSS) was developed by Yang and Huang (52) to assess perceived stress with good reliability and validity. The alpha coefficient values for the positive and negative subscales were 0.86 and 0.77, respectively (53).

Subjective well-being. Subjective well-being (SWB) is a composite concept that includes a high level of satisfaction with life, more positive emotions, and fewer negative emotions (54). Greater life satisfaction, high positive affect, and low negative affect are often considered as indices of greater SWB (55). Thus, the measure of SWB was shown to be consistent with the Positive Affect and Negative Affect Schedule (PANAS) (56) and with the Satisfaction with Life Scale (SWLS) (57). The PANAS are 20 adjectives that indicate positive affect, such as enthusiasm and activity, and negative affect, such as hatred, contempt, and feelings of guilt. Participants are asked to rate each mood state listed on a five-point Likert scale ranging from 1 = "very lightly or not at all" to 5 = "very much." The internal consistency coefficients in our sample for the positive and negative affect subscales were 0.86 and 0.83, respectively. The SWLS is a five-item scale used to measure global life satisfaction. Participants were asked to describe the extent to which they agree or disagree with each item on a seven-point Likert scale from 1 = "totally disagree" to 7 = "totally agree." Higher scores indicate greater perceived life satisfaction. The internal consistency coefficient of SWLS in the present study was 0.89.

Analyses

Descriptive analyses were based on the mean (M), standard deviation (SD), and range. Preliminary analyses were carried out to test the relationships between demographic variables (age, gender, and marital status), predictors, and outcome variables to identify demographic variables that must be controlled for in further analyses. Through independent-samples *T* test, we found that unmarried ICU nurses perceived more stress and reported higher DP than married ICU nurses. Therefore, age and marital status were controlled for in further analyses.

Hierarchical multiple regression analyses were performed to determine whether stress interacts with mindfulness, as well as the five facets individually, in the prediction of burnout (including three dimensions), depression, anxiety, and SWB (including three components). To increase the interpretability of the moderation model and to control for multicollinearity, all continuous variables were centered, and then the product terms were calculated, which represent the two-way interactions among stress, depression, anxiety, well-being, and mindfulness (58). The variables were entered in the following steps: a) the controlled demographic variables, b) the total perceived stress by ICU nurses, c) the total mindfulness, and d) the interaction term of stress × total mindfulness. Mindfulness was entered after perceived stress to explore the unique differences in mindfulness in the test results. **Table 1** shows a summary of all the separate hierarchical multiple regression models. To explore the potential main and moderate effects of the five mindfulness facets, regression analyses were conducted repeatedly using the five facets to replace total mindfulness at step 3a, and five interactions between each facet and the total perceived stress were input in step 4b. Simple slope analyses were conducted to illustrate the significant interactions among all the moderating models. According to Jaccard et al. (59), the unstandardized regression coefficients (B) of the regression lines for ICU nurses for low (1 SD below mean) and high (1 SD above mean) effects of the moderating variable were adopted. SPSS 19.0 was applied for data analyses.

RESULTS

Descriptive Statistics

The descriptive statistics and internal reliability coefficients for each measure are shown in **Table 2**.

According to the cutoff of dimensions of burnout, depression, and anxiety mentioned in measures, the prevalence of these psychological symptoms was common. Of the 500 Chinese ICU nurses, 56% (280/500) were positive for symptoms of depression and 35.2% (176/500) were positive for symptoms of anxiety. There is a prevalence of burnout syndrome, with 84% (420/500) of nurses having positive symptoms in at least one of the three individual dimensions: 23% (115/500) were positive for EE, 27% (135/500) were positive for DP, and 77.8% (389/500) were positive for lack of PA.

Table 3 confirms that perceived stress was significantly positively associated with EE, DP (two negative dimensions of burnout), depressive and anxiety symptoms, and negative affect and was negatively associated with personal achievements (the positive dimension of burnout) and SWB. On the other hand, total mindfulness was negatively correlated with EE, DP, depression, and anxiety and was positively correlated with personal achievements and SWB (all $p < 0.01$). The mindfulness facets of description and acting with awareness were significantly negatively associated with EE, DP, anxiety, and depression and were significantly positively correlated with personal achievements and SWB. Observation was significantly positively correlated with DP, personal achievement, and depression; nonjudgment was significantly negatively correlated with EE, DP, personal achievement, and depression; and nonreactivity was significantly positively correlated with DP and personal achievement.

As hypothesized, after controlling for the demographic variables of age and marital status, the entry of perceived stress

TABLE 1 | Hierarchical multiple regression analyses of perceived stress and mindfulness on burnout, depression, anxiety, and subjective well-being.

Steps and independent variables	Dependent variables											
	Emotional exhaustion			Depersonalization			Personal achievement			Depression		
	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2
Step 1												
Age	0.05			−0.01			0.08			−0.03		
Marital status	−0.05	0.01	0.01	−0.10	0.01	0.01	0.03	0.01	0.01	0.07	0.01	0.01
Step 2												
Stress	0.42***	0.18	0.17***	0.28***	0.01	0.08***	−0.38***	0.14	0.14***	0.55***	0.31	0.30***
Step 3a												
Total FFMQ	−0.78***	0.64	0.46***	−0.41***	0.21	0.12***	0.02	0.14	0.00	−0.23***	0.34	0.04***
Step 4a												
Stress × Total FFMQ	−0.09**	0.65	0.01**	−0.01	0.21	0.00	−0.01	0.13	0.00	−0.13**	0.36	0.02**
Step 3b												
Observing	−0.04			0.04			−0.00			0.05		
Describing	−0.09			−0.02			0.14**			−0.04		
Awareness	−0.25***			−0.25***			0.09			−0.31***		
Nonjudging	−0.06			0.06			−0.11*			−0.02		
Nonreactivity	−0.08	0.23	0.05***	0.11*	0.17	0.09***	0. 07	0.19	0.05***	−0.07	0.38	0.08***
Step 4b												
Stress × Observing	0.08			0.09			−0.03			0.02		
Stress × Describing	−0.05			−0.03			−0.02			0.03		
Stress × Awareness	0.01			0.02			0.04			−0.14**		
Stress × Nonjudging	0.06			0.07			−0.03			−0.03		
Stress × Nonreactivity	−0.01	0.24	0.01	0.10	0.19	0.02	0.08	0.20	0.01	−0.06	0.40	0.02*

Steps and independent variables	Dependent variables											
	Life satisfaction			Positive affect			Negative affect			Anxiety		
	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2	β	Total R^2	ΔR^2
Step 1												
Age	0.02			0.06			0.07			0.09		
Marital status	−0.20***	0.05	0.05***	−0.01	0.00	0.00	0.03	0.00	0.00	−0.01	0.01	0.01
Step 2												
Stress	−0.43***	0.22	0.18***	−0.37***	0.14	0.13***	0.49***	0.24	0.23***	0.50***	0.26	0.25***
Step 3a												
Total FFMQ	0.13**	0.24	0.01**	0.16**	0.16	0.00**	−0.25***	0.28	0.05***	−0.65***	0.57	0.32***
Step 4a												
Stress × Total FFMQ	0.01	0.24	0.00	−0.11**	0.16	0.01**	−0.08*	0.29	0.01*	−0.10**	0.58	0.01**
Step 3b												
Observing	0.12*			0.19***			0.02			−0.01		
Describing	0.07			0.15**			−0.03			−0.08		
Awareness	0.02			0.03			−0.25***			−0.22***		
Nonjudging	−0.03			−0.01			−0.00			0.03		
Nonreactivity	0.09	0.27	0.05***	0.12*	0.24	0.10***	−0.04	0.28	0.05***	−0.07	0.30	0.04***
Step 4b												
Stress × Observing	0.02			−0.01			−0.08			0.03		
Stress × Describing	−0.02			−0.01			0.07			0.00		
Stress × Awareness	0.03			−0.07			−0.06			−0.01		
Stress × Nonjudging	−0.02			−0.04			−0.08			0.01		
Stress × Nonreactivity	0.05	0.27	0.00	−0.02	0.25	0.01	−0.06	0.28	0.01	−0.04	0.30	0.00

TABLE 2 | Descriptive statistics and psychometric properties of the major study variables (n = 500).

Main study variables	M	SD	Internal reliability α	Range
Total perceived stress (PSS)	40.33	6.10	0.762	19–61
Total mindfulness (FFMQ)	117.98	10.21	0.890	77–160
Observing (O)	21.72	4.68	0.727	8–37
Describing (D)	24.51	4.34	0.768	8–40
Acting with awareness (AWA)	28.42	4.83	0.828	8–40
Nonjudging (NJ)	24.44	4.57	0.780	9–39
Nonreactivity (NR)	18.96	3.19	0.605	10–30
Emotional exhaustion (MBI_EE)	20.87	9.89	0.853	0–53
Depersonalization (MBI_DP)	7.88	5.33	0.803	0–30
Personal achievement (MBI_PA)	26.96	8.46	0.819	3–48
Depressive symptoms (CES-D)	19. 90	6.49	0.945	9–46
Anxiety symptoms (SAS)	46.82	11.20	0.849	25–85
Life satisfaction (SWLS)	19.69	6.23	0.885	5–35
Positive affect (PA)	27.39	6.07	0.873	11–45
Negative affect (NA)	21.12	6.70	0.902	10–50

PSS, Perceived Stress Scale; FFMQ, Five Facet Mindfulness Questionnaire; CES-D, The Center for Epidemiological Studies Depression Scale; SAS, Self-Rating Anxiety Scale; MBI, Maslach Burnout Inventory–Human Service; SWB, PA + SWLS-NA.

in step 2 indicated that perceived stress was positively associated with all negative outcome variables, such as EE, DP, depressive and anxiety symptoms, and negative affect. Moreover, as expected, perceived stress was negatively associated with all positive outcome variables, such as personal achievements, life satisfaction, and positive affect. After the entry of total mindfulness in step 3a, the results revealed a unique variance in all outcomes, except personal achievement, after controlling for perceived stress, age, and marital status. The entry of the five mindfulness facets in step 3b showed a set of significant effects on all outcome variables after controlling for perceived stress, age, and marital status. Observation was positively correlated with life satisfaction and positive affect; description was positively associated with personal achievement and positive affect; awareness was significantly correlated with all negative outcome variables and none of the positive outcome variables; nonjudgment was negatively correlated with personal achievement, which contrasted with our expectation; and nonreactivity had a positive main effect on positive affect and on DP.

The entry of the interaction term stress × total mindfulness in step 4a resulted in significant results related to EE, depression, anxiety, positive affect, and negative affect. This indicated that mindfulness alleviated the effect of perceived stress on EE, depression, anxiety, positive affect, and negative affect. A simple slopes analysis showed that perceived stress predicted EE at both low (B = 0.20, t = 1.51, $p < 0.05$) and high levels of mindfulness ($B = 0.15$, $t = 0.57$, $p < 0.05$), but the association between perceived stress and EE was weaker when the mindfulness level was high (see **Figure 1A**). As shown in **Figure 1B** through **E**, similar results were observed for depression (low level of mindfulness: B = 0.52, t = 3.12, $p < 0.01$; high level of mindfulness: B = 0.42, t = 5.60, $p < 0.01$), anxiety (low level of mindfulness: B = 0.36, t = 1.38, $p < 0.01$; high level of mindfulness: B = 0.29, t = 2.54, $p < 0.01$), positive affect (low level of mindfulness: B = −0.19, t = −1.45, $p < 0.01$; high level of mindfulness: B = −0.39, t = −3.89, $p < 0.01$), and negative affect (low level of mindfulness: B = 0.47, t = 4.67, $p < 0.01$; high level of mindfulness: B = 0.33, t = 2.32, $p <$ 0.05). While the overall mitigating effect of mindfulness on EE, depression, anxiety, and negative affect and the promoting effect of total mindfulness on positive emotion existed at both high and low levels of perceived stress, the effects were more significant when perceived stress levels were high.

After the entry of the five two-way interactions between perceived stress and mindfulness facets in step 4b, only one moderating effect was found. Acting with awareness moderated the relationship between perceived stress and depression. The simple slopes analysis indicated that ICU nurses with higher levels of acting with awareness had a weaker positive effect of perceived stress on depression (B = 0.71, t = 4.97, $p < 0.01$) than nurses with lower levels of acting with awareness (B = 0.34, t = 5.40, $p < 0.01$), and the mitigating effect of acting with awareness was pronounced when perceived stress levels were high (see **Figure 2**).

DISCUSSION

This study aimed to explore the potential moderating effect of mindfulness on the relationships among perceived stress and both positive and negative mental health indicators in Chinese intensive care nurses. This study found that the prevalence of psychological disorders such as burnout syndrome, anxiety, and depressive symptoms is common in Chinese ICU nurses, which is consistent with the previous studies (10, 18), and there was a higher prevalence of job-related burnout syndrome among ICU nurses than among general medical/surgical nurses (10). Although several studies have reported the effects of mindfulness on nurses (31, 60, 61), to our knowledge, no published studies have examined the moderating effect of mindfulness on stress-related mental health outcomes, especially burnout syndrome, in ICU nurses. After controlling for the effects of perceived stress and demographic variables of age and marital status, the present research confirmed that a higher level of mindfulness was associated with better psychological indicators in all outcome variables, except for personal achievement. These findings are in accordance with existing literature showing that higher levels of mindfulness may serve as a buffer for negative stress responses and consequently negative emotions such as burnout (28), depression (62, 63), and anxiety (62) and may also serve as a promoter for SWB (32, 64, 65).

The facet of observation could positively predict two positive indicators: life satisfaction and positive affect. Individuals who have a higher observation ability may be attuned to internal and external positive experiences and may be associated with the absence of ruminating thoughts during periods of high stress (35). Moreover, description was also significantly positively associated with two positive indicators, positive affect and personal achievement. Higher description ability may be important for effective communication and self-control (66), which may enable individuals to receive social support or facilitate successful task completion, thereby promoting positive affect and personal achievement. The facet of acting with awareness was significantly

TABLE 3 | Summary of bivariate correlations among the main study variables ($n = 500$).

Main study variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Total stress	–														
2. Total mindfulness	−0.49**	–													
3. Observing	−0.04	0.17**	–												
4. Describing	−0.46**	0.52**	0.24**	–											
5. Acting with awareness	−0.45**	0.45**	−0.33**	0.29**	–										
6. Non-judging	−0.16**	0.12**	−0.49**	−0.17**	0.34**	–									
7. Non-reactivity	0.01	0.09*	0.45**	0.10*	−0.38**	−0.52**	–								
8. Emotional exhaustion	0.40**	−0.80**	−0.01	−0.29**	−0.35**	−0.10*	0.02	–							
9. Depersonalization	0.26**	−0.48**	0.13**	−0.16**	−0.36**	−0.13**	0.19**	0.61**	–						
10. Personal achievement	−0.37**	0.20**	0.01*	0.32**	0.20**	−0.09*	0.10*	−0.17**	−0.18**	–					
11. Depressive	0.55**	−0.44**	0.01*	−0.30**	−0.49**	−0.16**	0.08	0.45**	0.35**	−0.27**	–				
12. Anxiety	0.48**	−0.74**	−0.02	−0.32**	−0.36**	−0.05	−0.01	0.82**	0.54**	−0.24**	0.55**	–			
13. Subjective well-being	−0.56**	0.80**	0.09	0.41**	0.36**	0.02	0.07	−0.82**	−0.51**	0.29**	−0.53**	−0.82**	–		
14. Life satisfaction	−0.44**	0.30**	0.20**	0.30**	0.14**	−0.08	0.15**	−0.26**	−0.10*	0.27**	−0.33**	−0.28**	0.52**	–	
15. Positive affect	−0.37**	0.30**	0.29**	0.35**	0.09	−0.14**	0.22**	−0.24**	−0.13**	0.39**	−0.20**	−0.25**	0.44**	0.36**	–
16. Negative affect	0.47**	−0.43**	0.06	−0.26**	−0.41**	−0.13**	0.07	0.43**	0.42**	−0.20**	0.54**	0.54**	−0.56**	−0.19**	0.05

*$p < 0.05$; **$p < 0.01$.

inversely correlated with all the negative indicators, including EE, DP, depression, anxiety, and negative affect. Several studies provide support for this prediction. Awareness is associated with a set of psychological benefits, such as reduced anxiety and depressive symptoms (24) and reduced EE (67). Using a single-item measure adapted from the facet of the acting with awareness subscale of the FFMQ (68), Donald et al. found that higher levels of awareness predicted greater perceived self-efficacy in dealing with stressful daily events, as increased awareness widens the range of available response options. Moreover, awareness exists independently of an individual's level of perceived threat associated with the stressor and the degree of general negative affect the person experiences on a given day, thus facilitating more effective coping with daily stressors (68). Awareness was also proposed to improve an individual's executive control (69), therefore mitigating the effect of perceived stress on mental health. Interestingly, in contrast to our predictions, non-judgment was negatively associated with personal achievement. Moreover, although non-reactivity to inner experience was positively correlated with positive affect, it was also positively correlated with DP. Only two studies were found to directly examine the interaction effects of facets of mindfulness and dimensions of burnout. Using a sample of 381 employees, Taylor et al. (70) found that all five facets of mindfulness were significantly and inversely correlated with the three components of burnout tested by the Maslach Burnout Inventory–General Survey (MBI-GS), with the exception of observation and EE. In a longitudinal cohort study of 27 clinicians who were offered a Mindfulness-Based Stress Reduction (MBSR) course, Dobkin et al. (71) found that the decrease in EE was correlated with acting with awareness and less-judgmental attitudes. Based on these results, we could posit that nonreactivity to inner experience refers to allowing thoughts and feelings to come and go without fixating on them, which may tend to detach ICU nurses' responses to workplace stressors. Nonjudgment of inner experience refers to the ability to take a nonevaluative stance toward thoughts, which may reduce the motivation to pursue personal achievement. In their most recent research, Hafenbrack and Vohs (72) found that participants in the mindfulness group reported less motivation than did the participants in the comparison group. Another possible explanation for these findings is that different individuals interpret the meaning of the items in different ways, which might be due to different cultural values. As Maslach et al. (73) noted, the concept and measures of MBI had been established based on the culture in the United States. In China, sentiments of group solidarity play a more significant role, whereas individualism plays a major role in the North American society. Therefore, public expression of some dimensions of burnout syndrome, notably cynicism or DP, may be more widely acceptable in the United States than in China. As Rudkin et al. (74) found in their most recent reliable and valid research, the absence of certain items in the FFMQ may explain the novel function of some facets of FFMQ. The author then noted that their findings have implications for the development of multidimensional measures for mindfulness assessment. It has also been proposed that a bifactor structure might provide a better assessment than the existing five facets (75). Nevertheless,

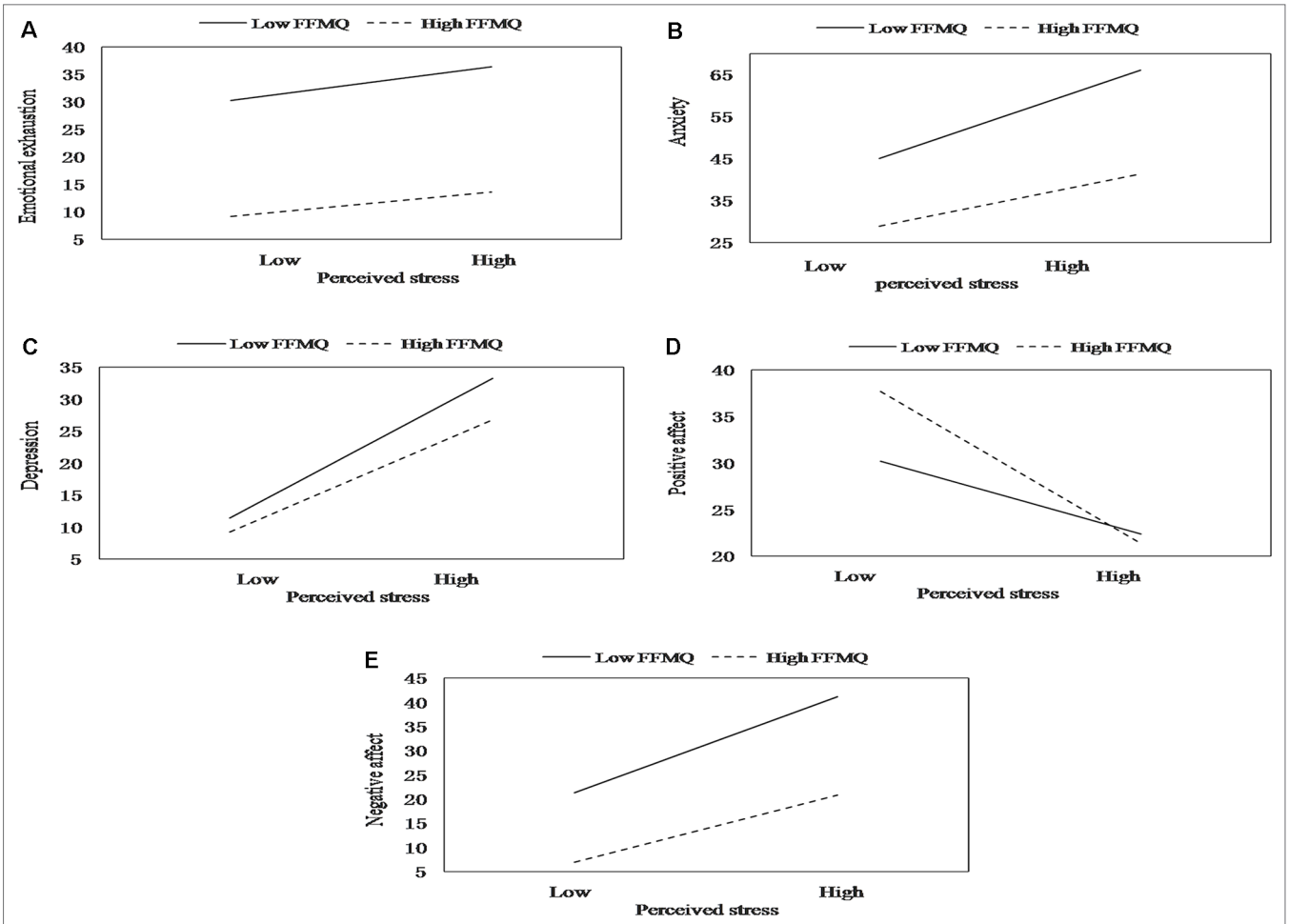

FIGURE 1 | The moderating effect of mindfulness on the relation between stress and emotional exhaustion **(A)**, depression **(B)**, anxiety **(C)**, positive affect **(D)**, and negative affect **(E)**.

these novel findings may be interpreted to mean a number of things that are potentially important for the future research and understanding of mindfulness–burnout relations.

According to the results, the total level of mindfulness moderated the relationships among perceived stress and EE, depression, anxiety, positive affect, and negative affect. Feelings of EE are generally viewed as having the strongest correlation with the burnout variable (76); thus, EE is considered a core symptom of the burnout syndrome (77). The regression model results indicated that for ICU nurses with higher levels of mindfulness, the positive relationship between perceived stress and EE was weakened. However, for those with lower mindfulness levels, the relationship between perceived stress and EE was augmented. Therefore, we conclude that mindfulness may serve as a minimizer between perceived stress and EE. This finding is in accordance with a study conducted in Italy, which also suggested that dispositional mindfulness is important for protecting against the onset of burnout in healthcare professionals (78). Mindfulness might facilitate better self-regulation of emotional and cognitive activities and reduce reactions to potentially emotional and stressful stimuli (79). These improvements in appraising and reacting to potentially stressful events in ICU working environments help ICU nurses avoid EE (67).

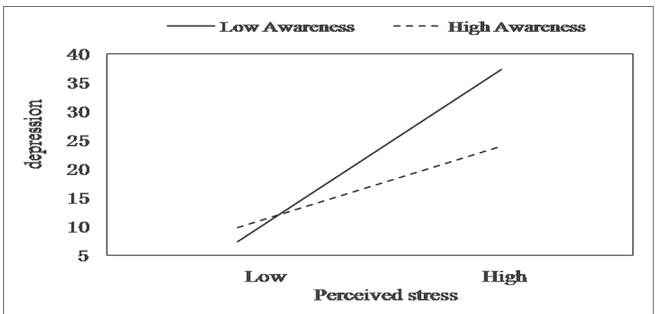

FIGURE 2 | The moderating effect of acting with awareness on the relation between stress and depression.

Moreover, higher mindfulness levels are significantly correlated with lower perceived stress and lower rates of depression and

anxiety. For ICU nurses with higher mindfulness levels, the positive relationship is weaker between perceived stress and depressive and anxiety symptoms. Within individuals with lower levels of mindfulness, this relationship is exactly the opposite. That is, the relationship between perceived stress and depressive and anxiety symptoms is weaker when levels of mindfulness are higher and vice versa. Therefore, mindfulness can be used as a buffer to reduce the tendency to experience more anxiety and depressive symptoms. Mindfulness moderated the relationship between perceived stress and depressive and anxiety symptoms in the sense that perceived stress was associated with fewer depressive and anxiety symptoms in ICU nurses with higher mindfulness scores. This is consistent with the results of many other studies including a large range of samples. In a group of law students, previous research found that total levels of mindfulness buffer the effects of perceived stress on depression and anxiety (35). A Swedish study tested the buffering role of mindfulness and found that the relationship between perceived stress and depression was attenuated for those with a higher level of mindfulness (34). Mindfulness has also been shown to improve anxiety and depression in cancer patients (80). Mindfulness, which focuses on being in the very present with a nonjudgmental and nonreactive mindset, may thereby alleviate the suffering that often accompanies depression and anxiety. This highlights the importance of taking a mindful approach toward internal cues to decrease depressive and anxiety symptoms.

Although mindfulness did not moderate the negative effects of stress on overall SWB or the component of life satisfaction, the results showed that mindfulness moderated the relationships of stress with positive affect and negative affect. These findings are particularly interesting, and somewhat ironic, as mindfulness is nonjudgmental, nonpreferential (neither toward or away from positive affect or negative affect), and nondisputational (81) but may, nevertheless, paradoxically strengthen the experience of positive affect or negative affect. An alternative explanation for our research result might be that the development of dispositional mindfulness may act as a buffer against stressors that result in reduced levels of positive affect across time and contexts (82). A very recent study also verified that mindfulness predicts greater improvements in positive affect and greater reductions in negative affect (83). ICU nurses who are naturally more mindful may have a decentered perspective of the mind or self and experience greater improvements in positive affect. Moreover, ICU nurses with higher, not lower, levels of mindfulness would be mindfully aware of and accept their internal experience, which may result in more benefits in light of negative affect reductions.

Further analyses focusing on particular mindfulness skills indicated that acting with awareness moderated the relationship between perceived stress and depression. This is the only facet of mindfulness buffering effect that emerged. This finding is consistent with the results of several other studies. By studying a sample of 520 Spanish adolescents and a subsample of 461 adolescents, Royuela-Colomer and Calvete (63) found that acting with awareness correlated negatively with depressive symptoms and predicted a reduction in depression over time. Pereira et al. (84) reported that acting with awareness had a protective effect against antenatal depressive symptoms in 427 pregnant women. In an exploratory factor analysis, Rudkin et al. (74) found that all meditator and nonmeditator participants identified the emotional awareness factor as the only factor that correlated with psychological symptoms. Caluyong et al. (85) also found that acting with awareness was a significant predictor of lower depression scores. This may be because the acting with awareness facet of mindfulness enables the detection of signs of stress and increases the ability of self-regulation and facilitates adaptive reactivity to negative and distressing situations. Thus, those with a higher ability to act with awareness have more potential to increase the awareness of low-level stress-related symptoms, which may potentiate access to coping resources and buffer against the negative effects of stress, such as depressive symptoms.

Based on these findings, interventions designed to encourage adaptive stress management, improve mindfulness levels, and provide the necessary skills to deal with stressful situations are likely to reduce or eliminate burnout syndromes and depressive and anxiety symptoms and improve the well-being of nurses working in the ICU. The results of the present study may help explain the relationships among perceived stress and mindfulness, burnout, anxiety, depression, and SWB. In addition, our results verified that mindfulness was a protective factor for alleviating or eliminating the negative effects of perceived stress on burnout, depression, anxiety, and SWB. In addition to its strengths, this study also has several limitations. First, we acknowledge that the data are based on ICU nurses' self-reports. Current self-reported measurements of mindfulness may not accurately capture the constructs of the variables. A semistructured interview or longitudinal study may produce different results from those of the self-reported questionnaire used in our study. Second, as a cross-sectional study, this study failed to draw conclusions about the cause and effect relationships among the variables. For instance, whereas it seems that ICU nurses perceive less stress when they are more mindful, it might be possible that exposure to daily stressors results in decreased levels of mindfulness. Further longitudinal studies must be conducted.

CONCLUSION

The high prevalence of prolonged stress, burnout syndromes, and depressive and anxiety symptoms in Chinese ICU nurses deserves immediate attention. The findings of the present study show that mindfulness is associated with lower levels of stress and fewer mental health complaints among Chinese ICU nurses. This study also indicates that mindfulness has the potential to act as a stress-coping resource. As a result, our findings suggest that mindfulness may be a target variable for health interventionists working with ICU nurses. Given the popularity of mindfulness, it might be a useful component of preventive health interventions and may allow for more targeted interventions.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of Army Medical University 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 Ethics Committee of Army Medical University.

AUTHOR CONTRIBUTIONS

FL, YX, and ML designed the research. FL, TWa, JX, BL, and SX recruited the participants and conducted the assessments. FL, YY, and TWu analyzed the data. FL wrote the manuscript, and YX and YY assisted with the statistical interpretations. YX, YY, LP, and TWa critically reviewed the manuscript. All of the authors contributed to the revision of the initial manuscript and approved the submission.

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REVIEW
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Harnessing the Four Elements for Mental Health

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Humans are intimately connected to nature, and our physical and mental health is influenced strongly by our environment. The "elements," classically described in humoral theory as Fire, Water, Earth, and Air, all may impact our mental health. In a contemporary sense, these elements reflect a range of modifiable factors: UV light or heat therapy (Fire); sauna, hydrotherapy, and balneotherapy (Water); nature-based exposure therapy and horticulture (Earth); oxygen-rich/clean air exposure; and breathing techniques (Air). This theoretical scoping review paper details the emerging evidence for a range of these elements, covering epidemiological and interventional data, and provides information on how we can engage in "biophilic" activities to harness their potential benefits. Interventional examples with emerging evidentiary support include "forest-bathing," heat therapy, sauna, light therapy, "greenspace" and "bluespace" exercise, horticulture, clay art therapy activities, and pranayamic yoga breathing exercises. Further robust research is however required to firmly validate many of these interventions, and to establish their therapeutic applications for the benefit of specific mental health disorders.

Keywords: lifestyle, mental health, mood, anxiety, psychological, well-being, nature, lifestyle medicine

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INTRODUCTION

Humans have an intimate connection to nature, and by our very being, we are part of nature (1). Several distinguished clinicians and historians in centuries past have posited that primordial elements construct a person and that imbalances are the cause of ill health. While scientific advancement has moved well beyond such rudimentary medical theory, there may still be merit in considering some of the basic tenets of the philosophy underpinning the humors for potential application in maintaining or enhancing mental health. At the very least, it should be recognized that some aspects of modernity have had a deleterious effect on mental health (2, 3). While a range of medications have been invented, these have had only modest effects for most psychiatric disorders, and concerns have increased over the impact of negative psychosocial changes such as the breakdown of family units, stressful jobs and a challenging work–life balance, a more sedentary life, poorer nutrition, declining air quality, and a decreased connection with nature. In respect to the diminishing interface with our biosphere than was evident with our ancestors, this is also affecting our microbiome, which is modified by exposure to nature (4).

The classical understanding of the elements and their relationship with human health was advanced by physicians such as Hippocrates and Galen (5). This was characterized as the "four humors," which each pertained to an element with distinct qualities: Melancholic [Earth (dry)], Sanguine [Air (cold)], Choleric [Fire (hot)], and Phlegmatic [Water (moist)]. An imbalance of these

elements internally was considered to be responsible for disease. There was also appreciation that external exposure to these elements could modify health *via* redressing imbalance. For example, if a person had signs of melancholia (dry skin, feeling cold, emotionally withdrawn, reduced mobility, and depressed mood), then exposure to warmth, moisture, and activity may be considered to be of assistance. Traditional medicine models including Unani, Ayurveda, and Traditional Chinese Medicine also embodied similar elemental constructs and are still practiced in modern times, with health conditions treated by addressing elemental imbalances and deficiencies (6).

Firstly, *we are not proposing that therapeutic use of "the elements" should replace mainstream pharmacotherapy or psychological techniques*. We are, however, suggesting that enhanced contemporary understanding (and requisite robust research) of this interplay may inform a potential use within an integrative treatment model for mental disorders. This may provide an additional avenue to enhance general mental health and perceived well-being. In the most basic form, as humans, to survive (and indeed thrive) we need clean air, fresh water, a regulated body temperature, and the nutrients that are ultimately derived from the earth. As our understanding of the importance of these aspects on mental health is advancing, so is the consideration of harnessing their benefits for use as potential health-enhancing interventions.

To our knowledge, no academic paper to date has covered a review of the evidence for the mental health applications of all "the elements" in this classic sense; thus, we conducted a broad scoping review of the area. We reviewed pertinent literature from Medline, EBSCO, and Web of Science databases, and selected key literature that best fitted thematically within the domains of "Earth," "Fire," "Water," and "Air." **Figure 1** details the therapeutic interventions covered under these domains. We specifically cover the key literature on 1) the relationship between these elements and mental health (in respect to underlying epidemiological data) and 2) any clinical trials utilizing interventions that fitted thematically under one of the four elements.

EARTH

We categorized this domain to encapsulate aspects pertaining to the influence of direct exposure to earth/soil and flora, time spent in nature (in particular wilderness environments) and the application of "greenspace exercise," interactions with animals, and novel interventions such as clay art therapy.

Adequate exposure to nature (greenspace) may provide benefits for general health, and data support that increased urbanization and exposure to excessive industrialization may negatively impact health (7). The benefits of spending time in nature for mental

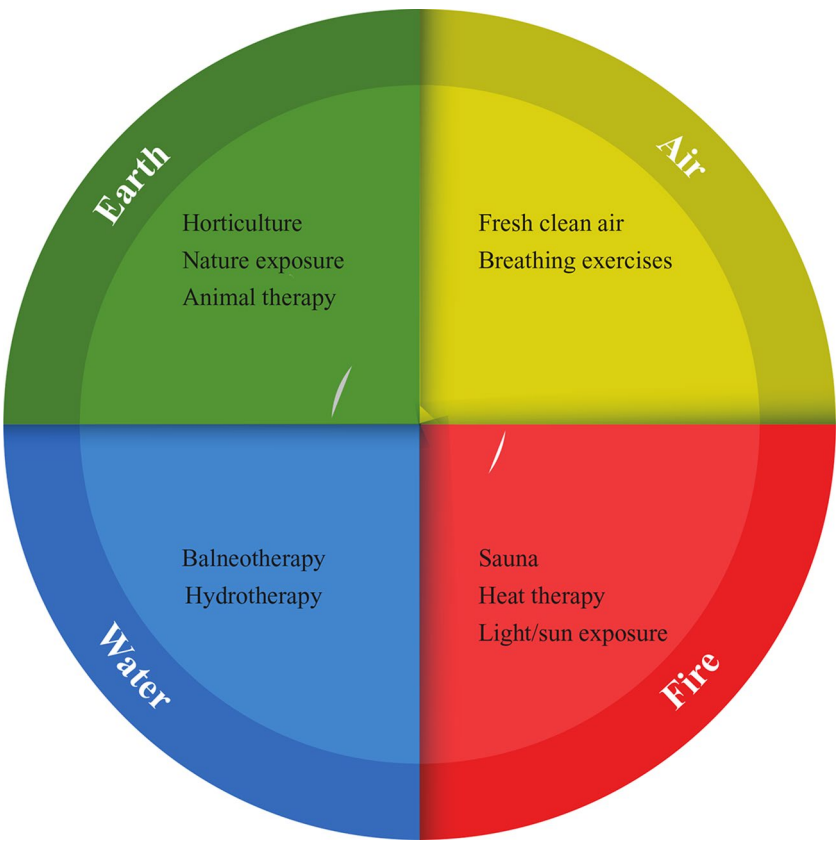

FIGURE 1 | Four elements (humors) and mental health applications.

health are evident (8), including increased exposure to sunlight and fresh air, in addition to a range of beneficial psychosocial elements in some situations. Aside from these benefits, direct interaction with nature (and biodiversity) also impacts the development of the microbiome, which may also have mental health influences (9, 10). While this may be beneficial, when interacting with soil, some caution is needed in terms of potential contaminants (e.g., chemicals and harmful pathogens).

In respect to interventions within this domain, a novel study involving "clay art" therapy conducted a short-term intervention (six 2.5-h sessions) assessing its effects on a range of mental health outcomes for 106 depressed individuals (11). Compared to the visual art group control, depressive symptoms decreased, in addition to improvements in general health and perceived well-being. The therapeutic effects of sufficient greenspace may involve a range of factors, and it is of note that, in children, it also stimulates cognitive development *via* increased scope for risk-taking, imagination, and self-discovery (12).

Actively engaging in horticulture may also improve mental health. A nature-assisted rehabilitation program in a group of general patients (n = 118) with noted severe stress levels and/or mild to moderate depression was assessed for changes in sick-leave status and healthcare consumption (13). These patients were compared to matched controls (n = 678). Results showed that there were benefits in reduced healthcare consumption for those participating in the rehabilitation garden compared to the control, but no change in sick-leave status.

In respect to being a potential adjunctive intervention in people with a range of psychiatric disorders, a Serbian study was conducted involving 30 patients who participated in a horticultural therapy (HT) program or a control group (occupational art therapy) (14). The results indicated that HT had a positive influence on the mental health and well-being of the participants. Furthermore, a difference was revealed in the test results of the stress subscale before and after the intervention, with a stronger effect for anxious males. Another HT project involving 49 participants undergoing a Veterans Affairs substance abuse treatment program showed that 5 h/day of HT for 3 weeks had a reduction in cortisol levels and a trend for improvement in depressed mood and quality of life compared to usual occupational therapy (15). Other uncontrolled research involving a 12-week HT program (n = 46) for people with clinical depression confirmed significant beneficial change in mental health variables during the intervention (16). A reduction in depression severity persisted at 3-months follow-up, and most interesting, an increase in social activity and social cohesion was reported after the intervention. An 8-week indoor gardening program has also revealed beneficial social connectedness and a reduction in loneliness in the elderly confined to nursing homes (17). Further research has shown that compared to a sedentary activity, such as reading, it can even have acute stress-reducing effects, as seen in salivary cortisol reductions (18).

To increase a mental health benefit from exposure to nature, physical activity may also be coupled with this (e.g., nature walks). Such exercise may synergistically increase well-being beyond physical activity in an urban setting (19). While the evidence of specific health benefits from nature-assisted therapy (e.g., wilderness treks) is unclear due to a current lack of rigorous studies, overall the evidence is supportive of a therapeutic effect. A meta-analytic analysis of 10 UK studies involving a clinical population of participants (n = 1,252) with a range of mental disorders found moderate effect sizes for green exercise in improving mood and self-esteem in healthy samples (19). This result also mirrored a systematic review by Annerstedt and Wahrborg (20) who found that for studies of moderate to low evidence grade, health improvements were reported in 26 out of 29 studies. Finally, a systematic review of 11 studies (n = 833) on participation in physical activity and exercise in natural environments (versus indoor activity) revealed that 9 out of 11 trials showed some improvement in mental well-being (21). Compared to exercising indoors, exercising in natural environments was associated with decreases in tension, confusion, anger, and depression, and a perceived increase in energy and feelings of positive engagement. Specific examples of nature-based physical activity, with a direct connection to soil or flora, that have shown to enhance mental health outcomes include sailing, gardening, horse-riding, wilderness hiking, and running in nature (19). Green exercise has also been found to be an effective way to reduce the stress of workers, showing an improvement on positive affect and blood pressure beyond urban indoor exercise, in a small-scale acute pilot study (n = 14) (22).

One interesting public health application found to occur in Japan (23) is the prescriptive recommendation of "forest bathing," known as "*Shinrin-yoku*." In simple terms, this involves advising people to spend time in forests. Preliminary evidence reveals that such exposure (compared to time spent in urban settings) can improve general mental health while altering physiological stress and immune biomarkers. Studies have, for example, revealed that short-term exposure to forests reduces levels of malondialdehyde, interleukin-6, tumor necrosis factor alpha, and cortisol, and enhances mental health indices (24). The same research group found a similar beneficial effect in elderly people with chronic heart failure (25). Forest-based therapy has also been found to be beneficial for treating depression and anxiety symptoms in patients with chronic stroke (26). One study involving 55 patients with chronic stroke were randomly assigned to either a stay at a recreational forest site or at an urban hotel. The results revealed lower depression, anxiety, and stress scores in favor of the forest stay group.

Humans commonly have close relationships with animals, and they can provide physical affection and a feeling of unconditional love, assist in the maintenance of a routine, and also provide responsibility and an additional sense of life purpose. Formalized animal-assisted therapy may involve horses (equine therapy), dogs, or even interactions with mammals such as dolphins. Time spent with farm animals by people with a range of psychiatric disorders may reduce depression and state anxiety and increase a sense of self-efficacy (27).

FIRE

We categorized this domain to encapsulate aspects pertaining to the influence of direct exposure to light (sunlight or artificial light) or heat (*via* vectors including sauna, or heated objects applied to the body, e.g., hot rocks).

It is a commonly held transcultural anecdotal belief that one's mood improves when the sun is out, and inclement weather is at bay. While acute exposure to sunshine (and a pleasant temperature according to the individual) may enhance mood, there is an inconsistent relationship with seasonal variations with the prevalence of mood disorders (28, 29). The effects of sunshine exposure on mental health may in part be mediated by vitamin D. However, while low levels of vitamin D appear to be associated with depression risk, there is conflicting evidence as to the effects of supplementation on improving mood (30–32). In fact, one study involving 198 participants with multiple sclerosis who were followed prospectively for an average of 2.3 years revealed that reported sun exposure was inversely associated with depression and fatigue scores (33). Interestingly, only high levels of vitamin D (> 80 nm) were inversely associated with depression scores, but this was not significant after adjustment for reported sun exposure. In other words, the sun exposure, not the vitamin D levels, reflected improvement in mood and energy.

Another facet of "light-based therapy" for mood modulation is in the application of simulating dawn in order to stimulate serotonin and cortisol secretion and to regulate circadian rhythm (34, 35). Several clinical trials have shown that this may be particularly beneficial for seasonal affective disorder (SAD). Randomised controlled trials (RCTs) of 2 to 8 weeks in duration have assessed the differential effectiveness between simulating dawn (half an hour prior to waking between 100 and 300 lux) versus high 1,500–10,000 lux bright light therapy (36–38). Results are conflicting, and both may be potentially effective in SAD, with stronger support for general bright light therapy.

One of the most common health interventions involving the targeted use of heat is sauna, which includes the traditional variety (using radiant heat and hot rocks to create moisture) and the modern infrared variety (which typically uses far-infrared light). To date, significantly more research exists with regard to traditional sauna (39), although emerging evidence suggests that infrared sauna promotes similar physiological benefits (40). While evidence remains preliminary with only a very small number of controlled studies having been conducted on the health effects of regular sauna bathing (40), the basic physiological effects have been known for some time (41).

More recently, the first longitudinal studies have been conducted on a large Finnish cohort ($n = 2315$), with results that show positive outcomes in a range of health domains, such a cardiovascular disease (42), hypertension (43), respiratory illness (44), and even dementia (45). The authors of these studies outline how the physiological response to sauna bathing corresponds to low- and moderate-intensity physical exercise and suggest that "these proposed functional improvements associated with sauna bathing correspond to similar benefits seen with regular physical exercise" (p. 546) (42). Although a current breadth of research is lacking (especially for mental health applications), because the general benefits appear to be associated with increasing activity of the thermoregulatory system, it is reasonable to assume that similar benefits are obtained from other modalities of atmosthermic bathing from different cultural traditions. These include the Islamic "hammam," the Native American "sweat lodge," and the Japanese "onsen," all of which enjoy long-held reputations for their regenerative capacity (46).

One particular aspect of classic sauna practice that requires further interrogation for general and mental health effects is the common adoption of cold exposure after heat exposure (cold showers/air/snow after the sauna). A 2015 study involving 3,018 participants (aged 18–65 years) without severe comorbidity and no routine experience of cold showering were randomized to hot and cold shower cycles (or a control group) during 30 consecutive days followed by 60 days of showering cold at their own discretion for the intervention groups (47). The primary outcome was illness days and related sickness absence from work. Results revealed a 29% reduction in sickness absence for hot to cold showers compared to the control group, but not illness days in adults without severe comorbidity. These results suggest that further investigation into cold exposure and sauna bathing is an important area of research, especially considering the prevalence of the practice at a global level.

At least one small study exists ($n = 9$), but this examined acute body temperatures rather than longer-term effects and did not investigate qualitative differences in perception of sauna enjoyment as a result of cold exposure (48). Another study from 2016 ($n = 37$) found that cold water immersion after sauna may be safe for patients with chronic heart failure, but that the practice should be conducted with caution (49). The study likewise did not consider qualitative aspects of cold exposure, which has been described as eliciting perceived regeneration in recent ethnographic literature (50). While outside the focus of this review (and in direct contrast to heat based therapies), there is also a recognized potential use of cold therapy alone (cryotherapy) for a range of health applications.

In respect to specific effects on mental health outcomes from sauna, there is overwhelming anecdotal evidence from traditional folklore (46), but minimal scientific or sociological evidence. In the same Finnish cohort discussed above, there was found to be a strong association between frequent sauna bathing and a reduction of psychotic disorders after a median follow-up of 25 years (51), but this is the only longitudinal evidence currently available. Other studies have suggested a positive effect of mood from a Korean "jjimjilbang" sauna (52, 53), as well as reduction of pain intensity in chronic conditions such as hypertension headaches (54). Given the prevalence of anecdotal reports about the relationship between sauna and improved mental health, this is another promising line of investigation that requires sustained attention from the global scientific community, especially in light of recent positive results concerning the use of whole body hyperthermic (WBH) therapy to alleviate major depressive disorder (55). WBH involves the use of sustained heat for 1–2 h to raise core body temperature (sometimes *via* a device that heats the inside of a tent that covers the body).

A prior uncontrolled study found that a single session of WBH reduced depressive symptoms in people experiencing depression, and thus researchers sought to test whether this effect would outperform a sham control condition (a matched procedure but with no heat). They assessed a single acute treatment in a 6-week, randomized, double-blind study involving 34 adults with major depressive disorder (MDD) (55). Results revealed that compared with the sham group (mimicking all attributes accept the intense heat), just one WBH therapy treatment showed significantly reduced depression scores maintained across the 6-week post-intervention study period.

WATER

We categorized this domain to encapsulate aspects pertaining to the influence of direct consumption of water, and the exposure to water, including the use of general hydrotherapy, balneotherapy (treatment of disease *via* bathing in natural mineral springs), and water-based physical activity (56).

Mammalian life requires water for existence, with the human body being composed of approximately 60% water (57). Aside from the importance of adequate hydration for the proper electrolyte balance, intracellular function, and extracellular communication, there may be mood and cognitive consequences of dehydration (58). In respect to mental health effects, a novel study assessing mild dehydration (produced by intermittent moderate exercise) was conducted on 25 healthy females. Participants undertook three 8-h, placebo-controlled experiments involving different hydration states (based on exercise or diuretic-induced states) (59). While most aspects of cognition were not affected, significant adverse effects of 1.36% dehydration showed a degradation in mood, increased perception of task difficulty, lower concentration, and more headache symptoms. This equates to a moderate level of dehydration (many studies will not push the body past 1.50% dehydration due to an increasing range of negative consequences).

The therapeutic application of water is evident in many cultures, especially in respect to natural mineral spa bathing (commonly in hot springs). One study (n = 237) comparing balneotherapy in spa resorts with paroxetine in treating generalized anxiety disorder showed a significant advantage of the spa treatment as assessed on anxiety scales, with remission and sustained response rates also significantly higher in those treated with balneotherapy (60). When compared to progressive muscle relaxation for stress-relief, short-term balneotherapy provided higher subjective ratings of relaxation with healthy participants (n = 49) and was similarly beneficial in decreasing salivary cortisol (61).

Balneotherapy has also been shown to improve quality of life and symptoms of chronic pain in fibromyalgia patients. A study conducted at the Dead Sea for 10 days (n = 48) demonstrated significant improvements on all well-being measures (62). Further evidence from Ozkurt et al. (63) supported these positive effects for fibromyalgia sufferers (n = 50), with their 2-week treatment producing significant improvements on all outcome measures, including pain, fibromyalgia impact, depression, and quality of life. In both studies, follow-up assessments showed physical improvements lasting 3 months on average, while psychological improvements were shorter-lasting, suggesting the benefits of regular balneotherapy in managing fibromyalgia. The classical use of contemporary steam rooms also provides an ambient therapeutic interface with both heat and water.

While in-depth exploration of water-based physical activities are outside the auspices of this review, a couple of novel applications of immersive water-based activities are worth noting. A recent study evaluated Deptherapy, a UK-based charity that provides a scuba diving intervention as support to military veterans who experienced life-changing injuries from combat (64). A total of 15 male veterans were assessed in an uncontrolled format both prospectively and retrospectively on a range of quantitative measures of mental well-being and functional ability outcomes. Participants reported enhancement on a range of psychosocial well-being measures. The researchers posit that scuba diving has the potential in part to benefit injured veterans due to the requirement of complete focus and the feeling of weightlessness when underwater. Another water-based application is in the use of "surf therapy," which has shown to improve participants' well-being (65, 66). It is however recognized that this offers a range of other ancillary benefits (beyond direct effects from the immersion in water), including increased mindfulness and atelic skill development, exposure to fresh air and sunlight, and general physical activity.

AIR

We categorized this domain to encapsulate aspects pertaining to the influence of direct exposure to fresh clean air, conscious and more effective breathing, and specific breathing exercises (such as utilized in yoga, known as *pranayama*). This may be achieved *via* regulated breathing-focused biofeedback techniques (67), which may reduce anxiety and perceived stress. For instance, regulation of natural breathing synchronizes electrical activity in human piriform (olfactory) cortex, as well as modulating limbic-related brain areas (which includes amygdala and hippocampus; key brain areas affecting anxiety/stress, and memory) (68).

One key environmental factor that is recognized to influence physical health involves the increased exposure to particulate air pollution, which is one common issue of modernity (69). This has been found to have a potential profound effect on the central nervous system. Exposure to air pollution, for example, has been found in a longitudinal study of 537 elderly Koreans to be associated with an increase in depressive symptoms (70). Additionally, evidence from a cross-sectional study indicates that secondhand cigarette smoke is positively associated with increased depressive symptoms in smoking-naive people (even after adjustment for a range of demographic factors and comorbidities) (71, 72).

Emerging preclinical evidence suggests that air pollution may induce oxidative stress, neuroinflammation, microglial activation, and cerebrovascular dysfunction, while potentially altering the blood–brain barrier (73). For example, a mouse model study investigated whether long-term (10 months) exposure to ambient fine airborne particulate matter compared to filtered air affected depression-related animal behavior and cognitive responses (74). The data revealed that mice exposed to long-term air pollution displayed more depressive-like responses and impairments in spatial learning and memory as compared with mice exposed to filtered air.

As well as the quality of the air that we breathe, the way that we breathe is also associated with our health and well-being. While functional and dysfunctional breathing are difficult to define, dysfunctional breathing, including restricted, shallow, rapid, or irregular breathing, is implicated in a range of physical and psychological health conditions (67). In particular, dysfunctional breathing is recognized as symptomatic of depression and anxiety,

and there is a corresponding high prevalence of depression and anxiety among people with chronic breathing disorders (75).

Mindful breath awareness (MBA) and breath regulation techniques (BRTs) have been reported as the most commonly used mind–body therapy by adults with medical conditions in the United States (76) and the second most commonly used of all complementary health approaches (second only after all natural dietary supplements combined) (77). MBA and BRTs are commonly used as components of psychological and complementary treatments for mental health conditions, including cognitive behavior therapy (CBT), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR), and mind–body practices in general, including yoga, taichi, qigong, relaxation training, and mindfulness and other forms of meditation (78). Each of these has been studied in clinical research and included in numerous reviews (78–82).

Clinical studies that have focused on BRTs as a primary intervention for general mental health are mostly yoga-based breathing exercises. MBA and BRTs are integral to several aspects of yoga practice. For example, yoga postures are ideally done with MBA and coordination of breath with movements; specific yoga BRTs (known as *pranayama*), relaxation, and meditation techniques often use the breath as a means to relax and focus the mind. Several clinical studies have found that yoga BRTs were effective in reducing severity of depressive symptoms (83–87). One RCT using a yoga BRT technique, known as Sudarshan Kriya Yoga (SKY), found that the technique was equally as effective as both electroconvulsive therapy (ECT) and a commonly prescribed pharmacological antidepressant (imipramine) for clinical depression over a 4-week period (85). Later studies using the same yoga BRT also found reductions in depressive symptoms among alcohol-dependent participants following a detox program (87) and reductions in posttraumatic stress (PTS) and depressive symptoms among survivors of the 2004 Southeast Asia Tsunami (84). More recent studies that incorporate MBA into multi-component yoga interventions have also found benefits for reducing symptoms of depression and anxiety and improving well-being (83, 86). Streeter and colleagues have also found preliminary evidence that suggests that breath-centered yoga practices increase gamma amino-butyric acid (GABA) levels in the brain, which is associated with improvements in depression (88).

Several researchers have postulated neuro-physiological models to explain the benefits of breath-centered yoga practices in diverse, frequently comorbid medical conditions, including mental health disorders, based on the concept and evidence that yoga practices reduce allostatic load in stress response systems and restore homeostasis and balance in the human system (88, 89). They hypothesize that breath-centered yoga-based practices 1) correct underactivity of the parasympathetic nervous system (PNS), in part through stimulation of the vagus nerves, the main peripheral pathway of the PNS; 2) increase low levels of GABA; and 3) reduce the allostatic load of stress. Depression, anxiety, PTS, and chronic pain exemplify medical and mental health conditions that are exacerbated by stress, have low heart rate variability (HRV) and impaired GABAergic activity, respond to pharmacologic agents that increase activity of the GABA system, and show symptom improvement in response to breath-centered yoga-based interventions (88, 89).

DISCUSSION

As detailed above, the "elements" in both a classical and a contemporary sense have effects on our mental health and are potentially modifiable aspects that can be harnessed as therapeutic interventions. The most robust interventional evidence currently available shows tentative support for several use of the elements *via* horticultural and nature-exposure therapy, green exercise/physical activity, sauna and heat therapy, balneotherapy, and breathing exercises. It should be noted that, in many cases, these interventions were not studied in definitive diagnosed psychiatric disorders and thus it is premature to consider these therapies to be gold standard treatments. Regardless, the evidence does reveal many positive general mental health benefits. The mechanisms of action underpinning these lifestyle medicine approaches are varied (due to the breadth of interventions covered). More attention is required to tease out the direct health effect of the elements, as many interventions will have other confounding aspects such as physical activity, mindfulness, or attention-based activity, they may also have a social interface component, and finally commonly will have a range of nature-based environmental influences (involving increased exposure to sunlight, fresh air, etc). As detailed above, known health effects for example include early morning light increasing serotonin and cortisol production, modulation of core temperature boosting circulation and the immune response, breathing regulation affecting a range of neurochemical effects and HRV and blood flow dynamics, and exposure to flora and fauna altering the microbiome.

While it is understood that this paper does not follow a strict reductive analysis of specific techniques for specified psychiatric disorders, it is intended to provide a paradigm to be able to expand a different way of thinking, particularly for the consideration of novel interventions that may work alongside conventional treatments to enhance mental health. It is clearly accepted that many of the interventions do not currently possess firm evidentiary support, and further research employing randomized and controlled designs (ideally within mixed-methods designs) is required. Promising areas of future inquiry concern further research into the impact of the elements on mental health, in particular interventions such as sauna and heat therapy, hydrotherapy, and nature-exposure therapies.

There are many potential benefits of "harnessing the four elements" for health purposes. This approach can be recognized as being considered part of the emerging field of "lifestyle medicine." Aside from providing the fundamentals of sustaining life, and the potential mental health benefits detailed above, there are a range of ancillary advantages. Such approaches may enhance social connectivity, improve physical health, may enhance brain health and cognition, and increase "self-efficacy" or mastery (90). These approaches are generally very low-cost, although choices may be limited in developing countries and those with overindustrialized, polluted environments. In respect to clinical considerations for more mainstream lifestyle medicine implementation, recent data from Sweden suggest that there are a range of barriers still persisting (91). Major factors for why lifestyle modifications are not being more commonly implemented in clinical practice include a lack of

knowledge and roles, lack of organizational support and resources, a low perceived importance of these measures, and a deficit of time to provide the needed attention. Overcoming these barriers within the mental health sphere also presents with more challenges in respect to increased comorbidity, potential motivational issues, lower socioeconomic status in those with more severe mental illness, and a deficit in most jurisdictions of qualified clinical staff with lifestyle medicine-focused skills and training. While there is no easy solution at present, the increased academic emphasis on the emerging lifestyle medicine field should increase awareness and, with an evolving evidentiary base, be able to interface more profoundly with policy makers and clinical bodies.

One further "element" that may be considered within the elemental paradigm is the philosophical consideration of a fifth element, which has been termed as "void," "space," or "ether." This element is generally not present in the Hippocratic–Western framework, yet it is found in other traditional systems such as Ayurveda. A more abstract-related connection to this concept is that of our understanding of space and the quantum physics field. Quantum theorists postulate the importance of quantum physics for cognitive neuroscience and psychiatry, and suggest that the laws of quantum mechanics may have an influence on the dynamics of consciousness and the nature of mind (92). A further curious factor relating to space and mental health is a well-documented phenomenon known as the "overview effect," experienced by astronauts travelling into space (93, 94). Viewing the Earth from space has often prompted astronauts to report overwhelming emotion and feelings of identification with humankind and the planet as a whole. Psychological constructs, such as awe and self-transcendence, appear to contribute to a psychological understanding of the experience of vast open spaces. While such experiences may be associated with well-being and increased altruism and other prosocial behavior, in some cases they can also be associated with increased fear and anxiety (94). There are many factors associated with mental health, open spaces, and space travel, and they warrant further investigation for mental health implications, including for the majority of us who do not leave the planet.

At the heart of this paper is encouragement for the psychiatric field (and the broader medical field) to consider going back to basics in terms of understanding the importance and the potential utilization of the elements for mental health. Of course, we are not diminishing the importance of pharmacotherapy and psychological techniques for psychiatric disorders. We are however saying that nature still holds a key to addressing many of the woes that currently plague society. We are becoming increasingly more socially isolated and hyperstimulated, and connecting more intimately to the biosphere and our fellow humans will always provide mental health sustenance.

AUTHOR CONTRIBUTIONS

JS: lead author and contributor to the earth section. MdM: contribution to section on air. FH: contribution to section on water, referencing, and editing. JT: contribution to section on fire.

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Use of the Pittsburgh Sleep Quality Index in People With Schizophrenia Spectrum Disorders: A Mixed Methods Study

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The Pittsburgh Sleep Quality Index (PSQI) is a measure of self-reported sleep quality and sleep disturbance. Though the PSQI is widely used, it is unclear if it adequately assesses self-reported sleep disturbance in people with schizophrenia spectrum disorders. We used mixed methods to examine the relationship between scores on the PSQI and qualitative self-report during in-depth interview in a group of participants diagnosed with schizophrenia spectrum disorders (N = 15). Although the PSQI appears to accurately capture issues related to sleep initiation, average duration, and interruption by physical complaints, it did not adequately assess other salient issues including irregularity in sleep duration and timing, shallow unrefreshing sleep, prolonged sleep inertia, hypersomnia, and sleep interrupted by mental or psychological complaints. In interview by contrast these types of problems were readily reported and described as important by participants. Our findings suggest that using the PSQI summary score as a measurement of general sleep disturbance in this population may be misleading, as this failed to capture some of the types of sleep problems that are particularly common in this group.

Keywords: screening, outcome measure, psychometric, interview, qualitative, psychosis, circadian rhythm disorder, insomnia

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INTRODUCTION

The Pittsburgh Sleep Quality Index (PSQI) is a widely used self-reported questionnaire measure of sleep (1). The PSQI is practical and brief, returning a single score representing overall sleep quality, which incorporates qualitative and quantitative aspects of sleep; scores above 5 are suggested as indicative of a potential sleep problem. The PSQI includes open-ended questions that can be used to identify the nature and possible causes of sleep problems to help direct treatment (2), and gives subscale scores that can indicate the type of sleep problems (sleep duration, latency, disturbances, quality, efficiency, daytime dysfunction, and use of sleep medication), as well as some questions on indicators of sleep apnea.

The PSQI was initially developed with a sample of people with depression, healthy sleepers, and people with sleep disorders (2). Many authors, including those who developed the PSQI, have subsequently developed new measures; some of which utilize more modern standards for patient involvement and psychometric analysis (1, 3). The widespread adoption of the PSQI has led to a

large literature that appears to facilitate comparison between samples, and now acts as a motivating factor for researchers and clinicians to continue to use the PSQI in preference of other measures. This includes some populations for which it has not been validated (4).

The PSQI is often used as a global measure of self-reported sleep disturbance in people with schizophrenia spectrum disorders, but the validity of the PSQI (English version) as a global measure of sleep disturbance in this population has, to our knowledge, not been evaluated. We explored the content validity of the PSQI for assessing patient-reported sleep quality and sleep disturbance in people with schizophrenia spectrum disorders.

METHODS

We recruited 15 adults with schizophrenia spectrum disorders, who were in contact with specialist mental health services in the United Kingdom, and had a self-reported problem with sleep initiation, maintenance, quality, timing, or refreshingness. People whose predominant complaint was of parasomnia or sleep apnea were not included, in order to focus on insomnia and circadian rhythm problems. All participants' data are included in the current analysis. Written informed consent was obtained after participants reviewed the participant information sheet and had sufficient opportunity for further explanation or questions. Ethical approval was obtained through the NHS Research Ethics Committee Proportionate Review Service (14/NS/1085).

Demographic data were collected, and symptoms and functioning were rated using the Global Assessment of Functioning (GAF) split version (GAF-F and GAF-S). Participants completed the PSQI and were invited to report their experience as they went through the questionnaire; this was followed by an in-depth interview that further explored their sleep experiences and complaints (see **Supplementary File S1**). In addition to the planned questions, the interviewer used continuers and active listening techniques; interview questions later went on to cover other research aims including exploring acceptability of potential treatments, and barriers to improving sleep; these results are reported elsewhere (5). The use of in-depth interview is an additional complementary approach to quantitative psychometrics in evaluating the validity of standardized self-report questionnaires, and it has been used informatively to examine interpretation of other self-reported health measures (6).

Transcription noted long pauses and we made field notes on nonverbal expressions (e.g., frowning, and nonlexical utterances such as "Errrr…"). Analysis was facilitated by Nvivo (qualitative analysis software), creating an audit trail, and ensuring themes were linked back to the data. Transcript content was coded in relation to the PSQI question each section related to, and in relation to emergent themes and subthemes from in-depth analysis of participant interviews. The qualitative analysis used a framework approach, and samples of the data were independently analyzed by a second researcher to enhance reliability. The mixing of methods was approached through qualitization of individual PSQI component scores, and summarizing and classification of the sleep problems described in interviews, to facilitate comparison of component and total PSQI scores, with the clinical presentation as described in each participant's qualitative account (7).

RESULTS

Fifteen participants were recruited, including acute inpatients (n = 2), outpatients receiving intensive (daily) support (n = 3), those under Community Mental Health Teams (n = 8), and under outpatient clinic only (n = 2); none were currently in paid employment. There were 10 males and 5 females, with a mean age of 45.9 (SD = 10.55), diagnosed with schizophrenia (n = 8), schizoaffective disorder (n = 6), and delusional disorder (n = 1). All were prescribed either one (n = 8) or two antipsychotics (n = 7); dosages as a fraction of defined daily doses (8) ranged from 0.36 to 5.5 (mean 2.19, SD 1.28). GAF-F and GAF-S scores ranged from 38 to 85, and from 21 to 80, respectively (mean 62.3, SD 12.16 and mean 47.7, SD 19.40, respectively). For itemized PSQI component scores and raw values, see **Table 1**. Overall, the areas in which these participants scored higher (indicating worse problems) were sleep latency, sleep quality, and daytime dysfunction, while sleep duration scored very low (which should suggest minimal problems). **Table 2** shows summary statements describing the nature of sleep complaints described in interview, and a breakdown of participants endorsing various types of problems.

Acceptability

Most participants reported no problem completing the measure and felt it asked relevant questions. Although some noted a preference for open questions, this is not an issue specific to the PSQI. A minority of participants suggested there should be more questions relating to psychological or mental health-related causes of sleep disruption.

Sleep Duration

Nine participants scored 0 for sleep duration; however, four of these participants were sleeping 11 to 14.5 h, and expressed concerns about this:

> "I've looked it up on Google and it says things like, a higher risk of heart attack, diabetes or early death [laughs]. […] I do feel guilty, quite a lot, yeah. I would like to be able to … I would love to be able to just be a morning person" (r05, reported sleep duration = 14.5 h, score on this item = 0)

Hypersomnia was seen as a potential health concern, and a cause for negative self-concept:

> "you're lazy … you're wasting your life away" (r12).

Participants who described a large amount of nightly variation found average sleep duration difficult to calculate accurately:

TABLE 1 | Participant itemized PSQI scores, hours of sleep, and minutes sleep latency.

Respondent	Hours of actual sleep: h/score[1]	Sleep latency: min/score[1]	Sleep disturbances[1]	Daytime dysfunction[1]	Habitual sleep efficiency[1]	Self-reported quality[1]	Use of sleeping medication[1]	Total PSQI score[2]
r01	11/0	60/3	0	0	0	0	0	**3**
r02	4.5/3	3/0	1	2	1	2	3	**12**
r03	12/0	10/0	1	2	0	0	3	**6**
r04	6/1	60/1	0	0	0	0	0	**2**
r05	14.5/0	180/3	1	3	0	1	0	**8**
r06	6.5/1	60/3	1	3	1	1	0	**10**
r07	4/3	120/3	1	1	2	2	3	**15**
r08	8.5/0	20/1	1	1	0	1	3	**7**
r09	11/0	30/2	2	1	1	1	0	**7**
r10	4.5/3	30/2	1	3	3	3	3	**18**
r11	8/0	30/1	1	0	1	1	0	**4**
r12	3/3	180/3	1	2	3	1	0	**13**
r13	8/0	60/3	1	0	0	2	3	**9**
r14	9/0	10/2	1	0	0	0	0	**3**
r15	7/0	60/3	2	2	1	2	3	**13**
Averages	7.83/0.9	61/2.0	1.0	1.3	0.9	1.1	1.4	**8.7**
Number of participants PSQI indicates have poor sleep quality = 11								

[1]Minimum score = 0 (better), maximum score = 3 (worse). [2]Minimum score = 0 (better), maximum score = 21 (worse), Total >5 associated with poor sleep quality. PSQI, Pittsburgh Sleep Quality Index.

TABLE 2 | Qualitative summaries of participant's description of their sleep problems.

Self-report regarding sleep	r01	r02	r03	r04	r05	r06	r07	r08	r09	r10	r11	r12	r13	r14	r15
Frequent problem with long sleep latency[1]				x			x					x	x		x
Occasional severe problem with long sleep latency[1]	x	x									x				
Problem maintaining sleep or excessively early rising[1]		x			x	x	x			x		x	x		
Problem with difficulty rising or waking[1]	x			x	x				x					x	x
Problem with too long sleep duration[1]			x		x					x				x	
Unusually long sleep, not a problem at present[2]	x								x						
Usually regularly naps[2]	x				x	x			x	x	x	x			x
Problem with prolonged sleep inertia[1]		x	x	x	x	x			x					x	
Significantly troubled by bad dreams[1]		x						x		x		x	x		x

[1]Items are selected where this was a major and consistent aspect of the participant's self-reported complaint; items are only selected where the participant subjectively perceived this as a problem.

[2]Items are selected where this was a frequent occurrence, may not subjectively be a problem.

> "sometimes [waking up] will be 6 o'clock for like three weeks, but very rarely it's 11 o'clock […] if I'm feeling too enthusiastic I'll be awake all night because of the excitement from the day […] yeah so it asks for a fixed time, but it's quite hard to estimate, it varies a lot" (r02, reported average sleep duration = 4.5 h, score on this item = 3)

Seven of the 15 participants tried to give ranges, which were sometimes several hours apart; three participants described nights of getting almost no sleep at all, followed by very long sleep when they did eventually sleep. These participants' mean total sleep time did not capture this issue as the very long and very short sleep times were averaged to a normal duration. Some distinguished "actual sleep" from light sleep/partial sleep, so were unsure how best to respond. Some answers weren't internally consistent (e.g., time to bed till time to wake, minus sleep latency and sleep interruptions, was inconsistent with reported total sleep time). It should be acknowledged that the latter of these issues could affect many retrospective self-report measures.

It is important also to note that daytime naps are not included within the sleep duration total, and for over half in this sample (eight participants), naps were a significant source of sleep:

> "Respondent: […] I always go to sleep in the afternoon
>
> Interviewer: Most days?
>
> Respondent: Yeah I'd say every day.
>
> Interviewer: How long for?
>
> Respondent: One and a half to two hours" (r10, reported sleep duration = 4.5 h, score on this item = 3)

Other participants described 3- or 4-h naps; hence, the PSQI total sleep time question missed roughly half of their actual total sleep for that day.

Sleep Timing

Average sleep timings are measured by the PSQI, but do not contribute directly to the score. The times recorded give useful information for clinicians on circadian preference or social commitments when sleep timing is regular; in this group, however, times varied and averages may be less meaningful. This variability may have been missed altogether if times were averaged by participants without comment. Dissatisfaction with sleep timing, and unpredictability of sleep timing, were significant sources of dysfunction and distress in participant accounts; participants described the impact on their ability to take on work, education, or social commitments. Satisfaction with or regularity of sleep timing is not part of the PSQI scoring so a problem with sleep timing does not directly impact the score.

Sleep Latency

Sleep latencies reported in answering the PSQI and in interview were similar. While it is interesting that some participants had long sleep latency (60 min, score 3 = worst) and were untroubled by this, this constitutes a quantitative aspect of their sleep disturbance, which is accurately summarized by the PSQI.

Sleep Disturbance

It is not clear how decisions were made regarding what are considered normal frequencies for some of the listed types of sleep disturbance, resulting in floor and ceiling effects. Participants who described "problems" with going to the bathroom at night went several times per night, the highest option to select being ×3 per week. Someone who woke to use the toilet twice a week explained that they felt this was probably less than most people. With regards to the impact of bad dreams, it seemed that frequency of bad dreams bore limited relation to the distress caused; in this sample, no one endorsed 3× per week, but some described less frequent but intense bad dreams causing significant distress, which was not well captured:

> "Oh jeeze I'm always having bad dreams … I'd say maybe twice a week." (r12)

Significantly, in interview the vast majority of the sample complained of problems with poor sleep maintenance and depth, in terms of "broken" sleep, sleep that was "not deep," or was not "proper sleep"; however, the average score for sleep disturbance was 1.0 (0 = best, 3 = worse). This can largely be attributed to the aggregation of scores from physical and psychological causes of sleep disturbance where there are more physical causes listed. It was noted that sleep, which was disturbed by a wide range of causes, scored higher than sleep very often disturbed, but generally by the same cause. Comparison of individual accounts and sleep disturbance scores showed that sleep that felt broken, but without a complete awakening, did not readily translate to a high score for "sleep disturbance."

"Another Reason…"

Although perhaps a trivial matter, the phrasing of this question proved problematic for well over half of participants, causing a pause in completion and questions regarding either the first part or both parts of this question:

> "…but what does that mean, how often during the past month have you had trouble sleeping because of this, because of what?" (r10)

It was also noted that this question rarely elicited information, as participants brought up many "other reasons" in interview (e.g., hypnopompic hallucinations), but wrote "N/A" on the PSQI. This may contribute to the unusually low scores for sleep disturbance, as these "other reasons" were not scored.

Daytime Dysfunction

The PSQI asks about trouble staying awake "while driving, eating meals, or engaging in social activity"; this question appeared not to be sensitive to sleepiness in those who did not drive and socialized infrequently:

> "My sleep's a bit spontaneous, my body don't plan it […] I'm always falling asleep watching films […] but no, I'm trying to think now how often I do a social activity, it's less than once a week isn't it. So it's less than once a week isn't it falling asleep." (r15, score on this item = 0)

Many asked if falling asleep in front of the television counted, and some then answered yes for this question.

The other question concerns "enthusiasm to get things done"; some noted they had difficulty with enthusiasm due to mood or psychotic symptoms, rather than their sleep. Daytime dysfunction questions did not pick up on the impact on daytime

functioning, where participants were napping or sleeping for excessive periods to counter tiredness:

> "I'm really fed up because I'd like to get out and do things instead of sleeping the days away" (r01, daytime dysfunction score = 0)

> "It can be as short as half an hour or as long as two hours […] I go to sleep because I'm tired in the day time, not because I'm bored." (r14, daytime dysfunction score = 0)

Sleep inertia and difficulty waking were also major complaints discussed by participants within the current study (n = 6 of 15). These should be detected as a form of daytime dysfunction; however, half of those expressing this complaint scored 0 for daytime dysfunction (see **Tables 1** and **2**).

Sleep Efficiency

Sleep efficiency has been found to be lower on average in groups with schizophrenia (9); in this sample, average sleep efficiency score does not suggest that this was a particular difficulty (average = 0.9). Interview accounts described difficulties initiating sleep, or maintaining sleep, suggesting poor sleep efficiency. Of those who reported one or more of these difficulties (n = 11), the average sleep efficiency score was 1.09; only four reporting such complaints scored 0. This suggests that the sleep efficiency score detected relevant problems to some extent in most cases.

Quality

Interestingly, over half of participants rated quality as very good (0) or fairly good (1), but went on to state significant concerns with their sleep and its impact on their life, including that their sleep was not restorative, that their poor sleep pattern was a barrier to getting a job, or that their sleep was "medicated sleep" and therefore substandard:

> "[If I wasn't on medication] That I'd actually sleep, yeah. And I think I'd be able to do more things as well, you know, in the day, if I wasn't on the medication, sometimes, if I managed to get natural sleep." (r03, sleep quality rated "very good" = 0)

For some, there seemed to be a direct contradiction between self-reported "sleep quality" on the PSQI and their view of their sleep during interview:

> "Interviewer: …how would you describe your sleep, if you were sort of telling someone about it?
>
> Respondent: Umm, not very good.
>
> Interviewer: No?
>
> Respondent: No. Not like other people … go on like sleep's supposed to be, you know?
>
> Interviewer: What?
>
> Respondent: Like, when they say have a nice sleep and you'll feel refreshed and all this nonsense.
>
> Interviewer: They say that.
>
> Respondent: Yes, and I don't feel like that.
>
> Interviewer: No.
>
> Respondent: I feel like, jeez, what's happened?" (r12, sleep quality rated "fairly good" = 1)

In the context of the rest of the analysis (5), this can be attributed to lowered expectations, so "fairly good" could mean good—when all is considered, good—compared to others with the same condition. It is also possible that participants responded regarding sleep quality by evaluating individual periods of sleep obtained, in contrast to the adequateness of their day-to-day sleep as a whole. Potentially also more rapport was built during the in-depth interview and participants felt more open and prepared to describe problems.

Sleeping Medication

The present sample's highest scoring domain was use of sleeping medication. This did not, however, represent high levels of hypnotic use in this sample; in six out of seven of those scoring 3 (highest), their answer related to their oral antipsychotic being "sleeping medication" (although some felt this was an ineffective sleeping medication). Some described in interview using their antipsychotic to control their sleep onset, but answered "never" to this question on the PSQI, and some raised the dilemma of whether their antipsychotic counted or not. Answers were therefore dictated by semantic interpretation rather than any meaningful differences between perceptions or behaviors.

Sleep Disordered Breathing

The PSQI includes questions regarding snoring or breathing among its sleep disturbance questions, and also a section for completion by the person's bed partner/roommate to screen for sleep disordered breathing, in acknowledgement of people's reduced awareness of their own breathing during sleep. Participants in this study did endorse snoring, but rarely endorsed "cannot breathe comfortably," rather clarifying that they breathed heavily, not had *difficulty* breathing:

> "…cause I'm a big lad as well so when I'm lying down … I'd say not it's hard to breathe but I breathe heavily." (r15, cannot breathe comfortably = 1, cough or snore loudly = 3, circled 'loudly' for emphasis).

It was never designed as such, and it is important that the PSQI is not considered to be an effective screening for sleep disordered breathing, particularly without the bed partner/roommate questions being completed.

Total Scores

The total PSQI scores indicated that seven participants were either good sleepers or had only mild sleep problems (n = 4 score <5, n = 3, score 6–7). Of these seven, four described significant and severe concerns during interview, while the other three described milder but definite problems. Of those whose PSQI scores suggested moderate or severe problems (score 8–18), the global impression from the interview was also of moderate or severe problems.

DISCUSSION

The sample reported multiple and complex problems with sleep initiation, continuity, quality, and timing, with attendant daytime dysfunction; the PSQI was capable to assess some, but not all, of these issues. The PSQI appeared to be suitable for identifying self-reported short sleep, long sleep latency, or complete awakenings during the night, but poorly represented some other problems such as variable and inconsistent sleep length, poor sleep depth or quality, increased sleep inertia, hypersomnia, and inappropriate or inconsistent sleep timing. While issues with sleep timing are beyond the intended scope of the PSQI, sleep duration, quality, and daytime dysfunction are within its scope and were poorly captured. Furthermore, it is common for total PSQI scores to be treated as a global measure of sleep disturbance, which these findings suggest is not valid. Reliance on total PSQI score as a measure of sleep dysfunction is particularly inappropriate for those with schizophrenia spectrum disorders whose sleep problems include more circadian dysregulation than other groups (10), and who as a result experience more inconsistent and variable sleep, and more difficulties timing sleep patterns to fit with life expectations (5, 11, 12). Some of the measurement issues highlighted also have potential implications for interpretation of PSQI scores in other populations.

Measuring Sleep Duration, Variability, and Depth

As some participants feared, both excessively short and excessively long sleep are indeed associated with increased mortality (13), and it has previously been recommended that the relationship of sleep duration to assumed sleep quality on the PSQI should be U-shaped and not linear (14). Our findings support this suggestion, concurring that unusually long sleep, as well as too short sleep, caused concerns for participants. It is also important to note that in people taking significant naps, as was common in this sample, the PSQI can mischaracterize (underestimate) a person's total sleep time, as might also occur in regional populations in whom biphasic sleep is common. These issues with calculation and scoring of sleep duration of course affect the use of the PSQI in many other clinical and nonclinical samples, not just in those with schizophrenia spectrum disorders.

Participant PSQI scores were similar to those from research with the Japanese version of this instrument in a similar sample (14), where sleep latency, sleep quality, and daytime dysfunction received higher scores on the PSQI, while sleep duration scored very low [which should suggest minimal problems; Doi et al. (14) also noted hypersomnia was not captured]. In contrast to our study, the subgroup of the Japanese sample with schizophrenia (n = 24) scored low regarding sleeping medication, perhaps owing to different phrasing in the translation (14).

Insufficient detection of problems with sleep depth is significant particularly for this population, for whom levels of shallow sleep (stage 1) are often elevated, and deeper sleep (Stage 2 and Stage 3 non-REM sleep) is often reduced (9). Although objective assessment of sleep depth requires polysomnography or spectral analysis, the experience of deep sleep was important to participants. Even apart from importance to individuals, subjective evaluations of sleep have often been found to be equally if not more predictive of health and functioning outcomes than some more objective measures (15, 16), suggesting even "inaccurate" experiences may be equally important to capture.

Our findings are consistent with those of Waters et al. (12) who found only small and statistically nonsignificant differences in PSQI scores between people with schizophrenia and healthy controls, but found increased variability in sleep latency, efficiency, and duration in schizophrenia when using actigraphy. Actigraphy or sleep diaries can be recommended to assess variability. However, retrospective self-report is less burdensome and has the potential to offer some insight; a future measure might include questions that assess how frequently various sleep values deviate from the average, by more than a certain amount (e.g., "How many times in the last month? was it 2 h more or less than this?"). Appropriate phrasing, format, and content would require development and testing.

Clinical Assessment of Sleep

For current clinical practice, supplementary questions or additional measures should be used when using the PSQI as a screening for sleep problems. For instance, the PSQI should not be relied upon to screen for sleep disordered breathing; a ready alternative is the STOP-Bang questionnaire, which has been found to be reasonably accurate in detection (17) and is freely available and brief (18). Measures of circadian preference might be added (19, 20); however, these do not measure regularity of rhythm. It is possible to measure and quantify regularity of rest-activity rhythms through actigraphy, describing both amplitude (relative amplitude) and regularity of rhythm (interday stability) (21), as has been more extensively utilized in samples with dementia (22) who also experience circadian dysregulation. At least one retrospective self-report measure of regularity is available [e.g., (23)], although none has yet been tested in schizophrenia spectrum disorders. During clinical interview, therefore, additional questions are recommended regarding regularity of sleep timing, and the match between sleep timing and individual lifestyle choices and requirements.

Outcome Measurement

Whether for research or clinical outcome measurement for quality improvement, the findings of the present study caution against relying on the PSQI total score alone, as improvements in sleep timing or regularity (often accompanied by improved quality of life and functioning) may go undetected. There are more recently developed tools, including the PROMIS sleep dysfunction item bank (1), and the Glasgow Sleep Impact Scale (3), which have been specifically designed to act as a barometer of the patient's perceived standard of sleep. Both tools were developed with patient involvement and

have undergone validation in healthy controls and those with sleep disorders, or in insomnia, respectively. These measures are very promising and may offer a useful adjunct to clinical assessments of sleep issues for people with schizophrenia spectrum disorders, and, by virtue of their use of modern psychometric methods, may also offer a reliable means of comparison across diagnostic groups.

These tools, however, are designed to measure change for research or clinical outcome measurement; they do not simultaneously help to characterize the sleep problem—as might be desired by a clinician. And in this respect, they do not replace the PSQI. Asking the patient to specify sleep latency, sleep times, and causes of sleep disturbance, as the PSQI does, can help identify the problem and therefore direct treatment. Unfortunately, the PSQI alone is likely to give an incomplete and sometimes misleading picture, in the case of people with schizophrenia spectrum disorders, and possibly many other groups.

Limitations and Future Directions

The generalizability of the findings from a small sample might be questioned, although as the types of problems described are similar to those found in larger samples studied using quantitative methodologies, we believe these findings are transferable. Although the diversity in the type and extent of problems is potentially representative of the diverse problems experienced in this group, it also limits the number of cases with each particular type of problem (e.g., with short sleep, or with hypersomnia). Furthermore, diversity in the environmental context of the participants, particularly the inclusion of both inpatients and outpatients, complicates interpretation. It would also have been useful to find out the approximate length of time since diagnosis, and length of time on antipsychotic medication, to better describe the sample and facilitate comparison with other studies. In hindsight, it would also have been useful if participants had been asked to comment on the recommended interpretation of their component or total PSQI scores (for instance, "This score suggests overall you have good/slightly disturbed/severely disturbed sleep. Do you agree?"), which might have provided a further point of reference.

This study did not set out to make statistical analysis of sensitivity or specificity, but these findings suggest a hypothesis of too low sensitivity, and missed cases, but no issues with overdetection. Future studies comparing PSQI to other measures such as actigraphy or polysomnography might confirm or quantify this, and could further examine which types of problem are underdetected in a larger sample. More detailed description of the weaknesses this study has highlighted would support improved interpretation of the considerable body of important work, which has used the PSQI to describe their sample or to measure change.

Our analysis demonstrates that the PSQI is insensitive to some sleep issues, which are described as important to people with schizophrenia spectrum disorders. This disparity between the range of issues highlighted in our interviews and those covered by the PSQI may suggest a need for a disease-specific measure to achieve high sensitivity to the particular problems of this group. Another possibility is the development of a measure of sleep disturbance, which can equally measure sleep problems of circadian, insomniac, or combined cause and nature, which could be used trans-diagnostically. A future measure could attempt also to take into account different environmental contexts; for instance, in many institutional settings, patients may more commonly go "to bed" far in advance of intending to sleep, as their bedroom may be the only private space in which to wind down for sleep. This can lead to underestimation of sleep efficiency, as has previously been noted in relation to sleep diaries (24); and alternative phrasing around "into bed" has been recommended. There may also be utility in a measure that examines or considers the impact of a mismatch between environment, occupational routine, and the individual, upon sleep, as well as factors that are more inherent to the person.

Self-Report Items versus Self-Evaluated Items

The PSQI is of course not unique among self-report measures in being affected by participants calibrating some of their responses in relation to their own context and peer group, as we found here regarding rating of sleep quality. Similar findings of peer group-dependent evaluations were presented by Adamson et al. (6) regarding the evaluation of general health:

> "Mrs K: Oh, I suppose for my age my health is excellent., I mean to say, it wasn't until I went up for the assessment I knew there was anything wrong with my heart" [(6), p142]

This context-dependent evaluation may equally measure a difference in a person's perceived peer group, as much as based on a change in self-perceived sleep, and makes it difficult to use exclusively self-evaluated items to compare between populations. It may therefore be desirable to include some quantitative self-report elements, which are more influenced by the individual's perception of their sleep than contextual factors.

CONCLUSION

Future research should develop a valid and reliable tool, with a similar shared utility for both clinicians and researchers as the PSQI has uniquely offered; this shared utility no doubt facilitates understanding between clinicians and researchers, and accounts for its enduring popularity. The authors suggest the development of a new measure that can act as a clinical screening and initial interview, and as an outcome measure in research.

ETHICS STATEMENT

Ethical approval was obtained through the NHS Research Ethics Committee Proportionate Review Service (14/NS/1085), North of Scotland Research Ethics Committee 1. Written informed consent was obtained after participants reviewed the participant information sheet and had sufficient opportunity for further explanation or questions. A disclosure or risk protocol and a distress

protocol were followed during data collection, and information sharing with care providers was discussed with participants in advance (information was shared on participant's request, or if any immediate risks necessitated information sharing).

AUTHOR CONTRIBUTIONS

SF designed and conducted the study, collected and analyzed the data, and wrote the first draft of the manuscript. SF and CS-G were involved in editing, conceptual formulation, and discussion of the findings and implications of the study.

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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.2019.00284/full#supplementary-material

FILE S1 | Question schedule and optional prompts.

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SYSTEMATIC REVIEW
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Depression in Somatic Disorders: Is There a Beneficial Effect of Exercise?

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Background: The beneficial effects of exercise training on depressive symptoms are well-established. In the past years, more research attention has been drawn to the specific effects of exercise training on depressive symptoms in somatically ill patients. This reviews aims at providing a comprehensive overview of the current findings and evidence of exercise interventions in somatic disorders to improve depressive symptoms.

Methods: We systematically searched PubMed and Cochrane databases and extracted meta-analyses from somatically ill patients that underwent exercise interventions and provided information about the outcome of depressive symptoms.

Results: Of the 4123 detected publications, 39 were selected for final analysis. Various diseases were included (breast-cancer, prostate cancer, mixed-cancer, cardiovascular disease, coronary heart disease, hemodialysis, fibromyalgia syndrome, acute leukemia, other hematological malignancies, heart failure, HIV, multiple sclerosis, mixed neurological disorders, Parkinson's disease, stroke, ankylosing spondylitis, traumatic brain injury, lupus erythematodes). Most meta-analyses (33/39) found beneficial effects on depressive symptoms, but quality of the included studies as well as duration, intensity, frequency, and type of exercise varied widely.

Conclusion: Exercise training has the potential to improve depressive symptoms in patients with somatic disorders. For specific training recommendations, more high quality studies with structured exercise programs and better comparability are needed.

Keywords: depressive symptoms, training, aerobic, somatic disease, comorbidity

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INTRODUCTION

Depression alone and comorbid with other chronic somatic diseases accounts for significant disease burden worldwide (1, 2). By 2030, depression is in addition to HIV/AIDS and ischemic heart disease assumed to be one of the three leading causes of burden of disease (3). Exercise therapy in depressive patients, as an independent intervention and as an adjunct intervention to antidepressant medication or psychotherapy, has been discussed to improve clinical outcomes in somatic diseases (4, 5). Compared to pharmacological treatment, the beneficial effects of exercise seem to be similar and are present at short-term and during follow-up periods of up to one year (6, 7). Especially for somatically unstable patient, this offers new treatment perspectives without the common side-effects of psychopharmacological medication. Usually both the depressive symptoms and the underlying somatic condition improve as a consequence of exercise therapy.

In a large World Health Survey of 245 404 participants from 60 countries, an average between 9.3 and 23.0% of participants with one or more chronic physical diseases had comorbid depressive symptoms (2). For numerous somatic diseases, an association with depression is well-established. For example, patients with multiple sclerosis (8), stroke (9), parkinson's disease (10), diabetes mellitus (11), breast cancer (12) or heart failure (13) have an elevated risk for developing a major depressive disorder (MDD). From a psychiatric perspective, it is important to note that a recently published study with 1,237,194 participants showed that individuals who exercised (various types of disciplines) had 1.49 (43.2%) fewer days of poor mental health in the past month than non-exercising individuals (14).

As the comorbid physical diseases often complicate the pharmacological treatment of depressive symptoms, further research approaches with a focus on alternative therapy options are urgently needed. Based on the beneficial effects of physical exercise in MDD (15), prior studies investigated the effects of exercise in patients with somatic disorders and comorbid depressive symptoms. A meta-analysis of different chronic illnesses including stroke, ischemic heart attack, fibromyalgia, dementia, and other psychiatric diseases, revealed a significant overall reduction of depressive symptoms. The majority of effects were derived from cardiovascular diseases, chronic pain and fibromyalgia (16). The results lead to the conclusion that physical exercise seems to have positive effects on depressive symptoms in patients with various somatic diseases without subdividing the different diseases with specific recommendations. However, a comprehensive overview of the available evidence of how exercise may improve depressive symptoms in patients with somatic diseases is lacking.

In this systematic meta-review, we will provide a detailed overview of recent meta-analyses evaluating different somatic diseases with comorbid depressive symptoms. The efficacy and the types and durations of exercise will be analyzed. Up to date, meta-analyses of specific diseases or disease groups (e.g., cardiovascular diseases) have been published as well as meta-analyses comprising different somatic diseases with an emphasis on cardiovascular diseases, fibromyalgia and pain (16). With our review, we aim to close this gap and point to limitations of prior studies as well as possible future research strategies.

METHODS

We systematically searched PubMed and Cochrane databases with all combinations of the following search terms: depressive disorder OR depression AND exercise, depressive disorder OR depression AND physical activity, depressive disorder OR depression AND endurance training, depressive disorder OR depression AND training, depressive disorder OR depression AND resistance training, depressive disorder OR depression AND aerobic, depression OR depressive disorder AND somatic AND exercise, depression OR depressive disorder AND physical illness. The database search was last updated on 31th July 2018. All citations were screened for relevance by title in a first step, by abstract in a second step and by full-text in a last step. In all included meta-analyses, the citations were screened manually for further relevant meta-analyses that may have not been detected by the systematic search. The systematic literature search and selection was performed by AR, the selection was afterwards reviewed independently by SK.

Both AR and SK retrieved the relevant information and the results were compared. In case of disagreement, a third author (AH) was consulted. Inclusion criteria were: meta-analysis investigating the effects of exercise on depressive symptoms in patients with comorbid physical illness based on interventional trials, published within the past 10 years. Exclusion criteria contained meta-analyses published earlier than within the past 10 years, systematic reviews without meta-analyses, meta-analyses in non-English language, meta-analyses only investigating depressive patients with no somatic comorbidities, lack of data post-intervention. No limitations were defined for the type or duration of exercise and the type of somatic illness.

RESULTS

Study Selection

The initial search without further restrictions resulted in 103,468 citations. After limiting the citations for the past 10 years, 60,430 citations remained. When only considering the meta-analyses, 4,123 citations remained and after eliminating duplicates, 981 citations were included for further analysis. The screening on title-level eliminated 869 citations (112 remaining), the screening on abstract-level another 63 citations (49 remaining). After full-text screening, 39 citations remained for final analysis (see **Figure 1**).

Study Characteristics

Table 1 provides an overview of the included somatic diseases. The duration of the single studies varied between three (46) to 52 (21) weeks, the intensity between one time (51) and seven times (37) per week and the duration of the sessions between 30 and 122 min (16). Adherence rate was solely reported in two meta-analyses (21, 22) and intensity of the training with heart rate controlled exertion in one meta-analysis (37). The interventions consisted of aerobic exercise, resistance training, balance training, yoga, moderate cycling, walking, nordic walking, running, swimming, tai chi chuan, qigong, Bobath exercises, jogging, calisthenics. Across all trials, the mean sample size was 658 with a minimum of 39 (28) and a maximum of 3.425 (36). Depressive symptoms were rated with different questionnaires (observer or self-assessment): BDI (Beck Depression Inventory), CDI (Children Depression Inventory), CES-D (Center for Epidemiological Studies Depression Scale), DASS (Depression Anxiety Stress Scales), GDS (Geriatric Depression Scale), HAD (Hospital Anxiety and Depression Scale), HAM-D (Hamilton Rating Scale for Depression), SCL-90 (Symptom Checklist-90), TAS (Toronto Attitude Scale), POMS (Profile of Mood States), SAS (Symptom Assessment Scale), CSDD (Cornell Scale for Depression in Dementia), IDS-SR (Inventory of Depressive Symptomatology Self Report), LPD (Levine-Pilowsky Depression Questionnaire), MADRS

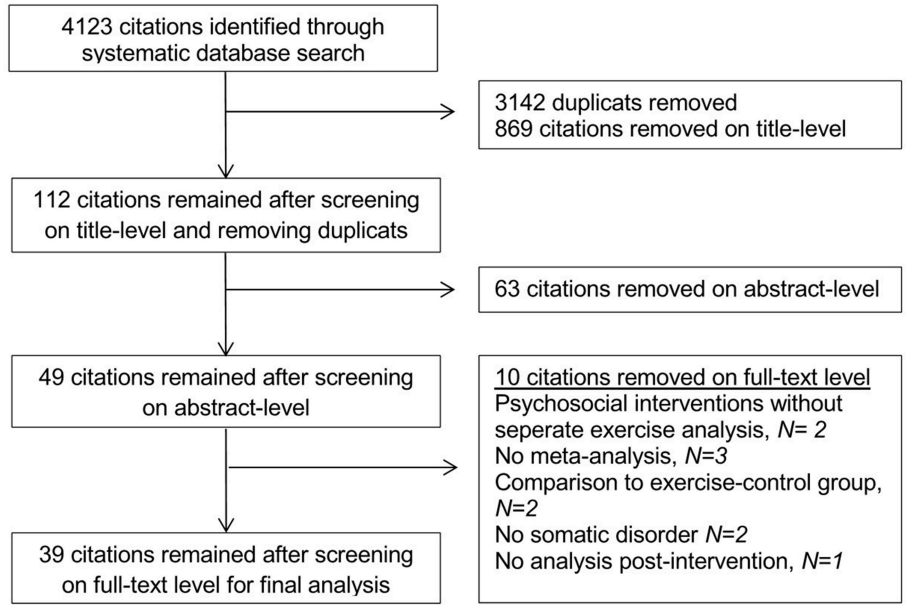

FIGURE 1 | Flow-chart of included citations.

TABLE 1 | Included somatic diseases.

Somatic disease in meta-analysis	No. of meta-analyses	References
Breast cancer	7	(17–23)
Mixed cancer types	7	(24–30)
Prostate cancer	3	(31–33)
Cardiovascular disease	1	(34)
Coronary Heart disease	1	(35)
Heart failure	2	(36, 37)
Intradialytic patients	2	(38, 39)
Hemodialysis patients	1	(40)
Fibromyalgia	2	(41, 42)
Ankylosing spondylitis	1	(43)
Lupus erythematodes	1	(44)
Acute leukemia	1	(45)
Hematological malignancies	1	(46)
HIV	1	(47)
Multiple sclerosis	3	(16, 48, 49)
Mixed neurological disorders	1	(50)
Parkinson disease	1	(51)
Stroke	2	(52, 53)
Traumatic brain injury	1	(54)
Total	39	

HIV, human immunodeficiency virus.

(Montgomery-Asberg Depression Rating Scale), MDI (Major Depression Inventory), POMS (Profile of Mood States), QOL (Quality of Life), DASS (Depression Anxiety Stress Scales), TAS (Toronto Attitude Scale), MAACL (Multiple Affect Adjective Checklist), HDCDS (Hare-Davis Cardiac Depression Scale), SDS (Self-rating Depression Scale), BSI-18 (Brief Symptom Inventory). Thus, in the different meta-analyses, various different questionnaires were used, most often self-rating questionnaires: the BDI I/II in 26, the HADS in 18 and the CES-D in 17 meta-analyses. The majority of meta-analyses included more than three different questionnaires. As observer-rating scales, HAMD was used in four and MADRS in three meta-analyses.

Risk of Bias Within and Across Studies

Most meta-analyses (51) reported about different cancer-type patients followed by neurological disorders (7). For other diseases, such as HIV, only one meta-analysis could be identified. The variety of exercise modalities and the different durations of interventions lead to a reduced general transferability of the conclusions. Recommendations regarding effects of specific interventions on depressive symptoms in specific somatic conditions can hardly be drawn. None of the trials included in the respective meta-analyses could be declared double-blind as this is challenging to fulfill with exercise interventions. The application of various different rating-scales is another potential risk of bias. Moreover, most of the included studies in the respective meta-analyses did not define depressive symptoms as primary outcome parameter.

Results of Individual Studies

A detailed summary of the included studies with inclusion/exclusion criteria, study population, intervention summary and outcomes is provided in **Tables 2**, **3**.

Exercise Interventions in Cancer Patients

Exercise interventions in breast cancer patients

Our search resulted in seven meta-analyses that met the inclusion criteria. The majority found positive effects of

TABLE 2 | Methods and Limitations of the included meta-analyses.

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
Adamson et al. (50)	23 studies, $N = 1.324$ participants	1) Adults aged >18 years 2) Any diagnosed neurologic disorder (ad or dementia, migraine, ms, parkinson disease, spinal cord injury, and traumatic brain injury) Excluded: fibromyalgia, rheumatoid arthritis	Aerobic exercise, resistance training, balance training, yoga, and others involving a combination of these exercises. No limits concerning frequency, intensity, or duration of the exercise intervention.	BDI, BDI-II, CES-D, CSDD, GDS, HAD, IDS-SR, MADRS, LPD, MDI, POMS	123/26 studies evaluated depression. 13 of the 26 studies Received a score >6 on the PEDro scale. 3 trials identified depression as primary endpoint.
Bergenthal et al. (46)	3 RCTs, $N = 249$	1) RCTs comparing an aerobic physical exercise intervention, intending to improve the oxygen system, in addition to standard care with standard care 2) Only for adults suffering from hematological malignancies.	Studies that evaluated aerobic exercise (such as moderate cycling, walking, Nordic walking, running, swimming and other related forms of sport) or aerobic exercise in addition to strength training were included. Studies that investigated the effect of training programs that were composed of yoga, tai chi chuan, qigong or similar types of exercise were excluded. Duration of the intervention between 3 and 12 weeks with 3–5 sessions per week.	NR	3/9 studies could be included in the meta-analysis for depression (secondary endpoint). Low quality of evidence.
Brown et al. (24)	37 RCTs, $N = 2.929$	1) RCT comparing an exercise intervention with a control group 2) Report of depression outcomes 3) Adults diagnosed with any type of cancer, regardless of stage of diagnosis or type or stage of treatment At baseline, the standardized metric of depressive symptoms was 34.2 and ranged from 3.49 to 81.5. 65% Breast Cancer, 5% Prostate cancer, 5% Leukemia, 5% Lymphoma, 20% diverse groups of cancer	Exercise interventions occurring in any setting, with or without supervision. Mean length of the exercise interventions was 13.2 weeks with an average of 3.0 sessions per week lasting 49.1 min/session.	CES-D, POMS, BDI, HAS, SAS	The mean PEDro score of the exercise interventions was 7.061 suggesting relatively high methodological quality.
Buffart et al. (25)	8 RCTs, $N = 471$	1) Design: RCT 2) Population: adults with any cancer diagnosis either during or post treatment 3) Intervention: yoga including physical postures (asanas) 4) Control group: non-exercise or wait-list 5) Outcome: physical and psychosocial outcomes Average age of the participants ranged from 44 to 63 years. 1 study with lymphoma patients, the rest with breast cancer patients.	All included a supervised yoga program with physical poses (yoga asanas), combined with breathing techniques (pranayama) and relaxation or meditation (savasana or dhanya). Median program duration was 7 weeks with a range of 6 weeks to 6 months. In general, the number of classes per week ranged from one to three, and home practice was encouraged in nine studies, supported by audio or videotapes. Session duration ranged from 30 to 120 min; three studies did not report the session duration.	HADS-D, BDI, CES-D, POMS	The median quality score was 67% (range: 22–89%). All but one study were of high quality. 8 of 16 studies evaluated depression.
Carayol et al. (17)	9 RCTs, $N = 801$	1) Participants were adult women diagnosed with breast cancer, 2) Presented a randomized, controlled experimental design 3) Included an intervention program involving physical activity (yoga-based interventions were included whereas relaxation-based were not) 4) Intervention program was scheduled during adjuvant cancer therapy (chemotherapy and/or radiotherapy), (v) assessed at least one psychological outcome among fatigue, anxiety, depression, and QoL 5) Provided pre and post-intervention data to calculate standardized mean differences(SMDs) The median age of included patients was 50.5 years old. All patients with breast cancer have been diagnosed with non-metastatic cancer and were undergoing adjuvant therapy, i.e., chemotherapy and/or radiotherapy during exercise intervention.	Exercise duration between 5 and 26 weeks, 2–6 sessions per week of 30–60 min. Interventions consisted of aerobic exercise and/or resistance training or Yoga.	CES-D, HADS-D, BDI, POMS	Regarding methodological quality, median score was 7, ranging from 2 to 9. 9/17 studies evaluated depression.

(Continued)

TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
Chung et al. (38)	4 RCTs, $N = 212$	1) This review included randomized controlled trials (RCTs) published in the English or Chinese language 2) participants aged >18 years diagnosed with end stage renal disease (ESRD) requiring maintenance hemodialysis (HD) as renal replacement therapy 3) participants undergoing HD for more than 3 months who received exercise training during HD sessions (intradialytic)	Exercise interventions included aerobic cycling alone, resistance training, cycling or resistance training and aerobic cycling combined with strength training or range of motion. Each exercise session lasted 10–90 min. The exercise program lasted between 8 and 48 weeks.	Zung Depression Scale, BDI	In over half of the studies, there was a low or unclear risk of detection bias. 4/17 studies evaluated depression.
Craft et al. (26)	14 RCTs, $N = 1.371$ participants	1) RCTs of adults diagnosed with cancer 2) Comparison of an exercise program with usual care 3) The exercise program was chronic in nature (i.e., at least 4 weeks in duration) 4) Reported depressive symptoms pre- and post-intervention 5) Utilized a depression inventory or a clinician interview to quantify depressive symptoms 6) published in English Average age of participants was 51.6 years. 9 (60%) breast cancer, 1 colorectal cancer, 1 lymphoma, 2 prostate cancer and 2 diverse groups of cancer	All studies included an aerobic exercise component, with several also including a strength training component.	CES-D, BDI, HADS, QOL	Only 1 trial identified depression as primary endpoint. 11 RCTs with PEDro "high" quality. Potential moderators: exercise location, Supervised and partially supervised exercise, exercise bout durations of >30 min.
Cramer et al. (19)	6 RCTs, $N = 161$	1) RCTs 2) Studies of adult (older than 18 years) patients with a history of breast cancer 3) Studies that compared yoga with no treatment or any active treatment 4) No restrictions were made regarding yoga tradition, length, frequency or duration of the program. Co-interventions were allowed. 5) Studies that assessed health-related quality of life or well-being and/or psychological health.	Yoga interventions were heterogeneous. Program length and intensity varied, ranging from daily interventions over 1 week to one intervention per week over 6 months.	CES-D, HADS, BDI	Generally, risk of selection bias was high. 6/10 studies evaluated depression.
Cramer et al. (18)	11 RCTs, $N = 496$ (7 RCTs yoga vs. No therapy) $+ N = 226$ (4 RCTs, yoga vs. Psychosocial intervention)	1) RCT 2) Compared yoga interventions vs. no therapy or vs. any other active therapy in women with a diagnosis of non-metastatic or metastatic breast cancer 3) Assessed at least one of the primary outcomes on patient-reported instruments, including health-related quality of life, depression, anxiety, fatigue or sleep disturbances	Of the 24 included studies: the duration of yoga programs ranged from 2 weeks to 6 months, with a median duration of 8 weeks; the frequency of yoga interventions ranged from one to 10 (median: two) weekly yoga sessions of 20 to 120 (median: 67.5) min in length.	HADS, BDI, CES-D, POMS	11/24 studies evaluated depression.
Dalgas et al. (48)	12 RCTs, $N = 476$	1) RCT design 2) Enrollment of participants with definite MS according to the McDonald criteria 3) Evaluate an exercise intervention that was compared with either non-training controls, active controls or another exercise intervention 4) Inclusion of a primary validated measure of depressive symptoms available in English	resistance training, endurance training, combined training (i.e., resistance training + endurance training) or as other exercise modalities	BDI, MDI, IDS-SR, HADS, POMS, CES-D	Only one of the RCT studies applied depressive symptoms As the primary outcome. Average PEDro score was 5.6 ± 1.3 points.
Eng and Reime (52)	13 RCTs, $N = 1.022$	1) Confirmed diagnosis of stroke by medical records, imaging, or clinical examination 2) Adult patients over 18 years of age 3) Intervention and control group treatments clearly defined 4) Baseline and follow-up of at least 4 weeks available for depressive symptoms The time since stroke ranged from 30 days to 6 years and the patients' age ranged from 21 to 93 years.	Progressive resistance training, functional, aerobic exercises, treadmill exercises, Bobath exercises, individualized exercises with education, community-based rehabilitation services including physical therapy and occupational therapy. Eleven of the 13 studies had a frequency of at least two sessions per week for a minimal duration of 4 weeks. The length of the intervention ranged from 4 weeks to 12 weeks.	HAD, GDS, BDI, CES-D	PEDro scale ranged from three to eight.

(Continued)

TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
		The mean baseline depressive symptoms of the study samples were below established thresholds for clinically relevant depressive symptoms in the majority of studies (12/13).			
Ensari et al. (49)	13 RCTs, $N = 477$	1) Studies that compared exercise training vs. no-treatment control Reliable and valid measures of depressive symptoms (e.g., HADS, CES-D) as an outcome assessment pre/post intervention in patients with MS 2) Only samples in 2 of the studies had mean scores above the threshold for moderate depressive symptomatology.	Aerobic and an-aerobic. 7 of the 13 studies had a frequency of at least 3 sessions per week.	BDI, IDS, MDI, HADS, CES-D, POMS	9 of the 13 studies received a score of 6 or higher on the PEDro scale. Exploratory analyses only identified depression symptom scale as a potential moderator variable ($p = 0.04$).
Fong et al. (27)	4 RCTs, $N = 168$ 4 RCTs with different outcome measurements, $N = 533$	Adult patients (aged ≥18) Patients diagnosed with cancer 3) Patients who had completed their main treatment for cancer but might be still undergoing hormonal treatment 4) And assessed the effect of physical activity on health indicators ¾ included studies evaluated breast cancer, 1 endometrial cancer.	All 4 studies used aerobic exercise.	BDI, HADS, POMS	4/34 studies evaluated depression via BDI and were included in the meta-analysis. 2 studies used the HADS and 2 the POMS. No overall analysis was performed.
Furmaniak et al. (20)	5 RCTs, $N = 674$	1) RCTs of exercise training during adjuvant (including neoadjuvant) treatment (radiotherapy chemotherapy) for women with non-metastatic breast cancer 2) Exercise training during adjuvant (including neoadjuvant) treatment (radiotherapy, chemotherapy) for women with non-metastatic breast cancer. 3) Studies that assessed the effects of all forms of repeatedly performed aerobic or resistance exercise or both with program duration of at least 6 weeks	Aerobic or resistance training.	BDI, CES-D	Cochranes risk of bias tool. 1 study evaluated depression via HADS and was not included in the meta-analysis. 5/32 studies evaluated depression.
Gomes Neto et al. (39)	3 RCTs, $N = 88$	1) Studies that included hemodialysis patients randomized to two different intra-dialytic exercise training modalities or to a group of specific exercise modality and group of usual care without exercise training. 2) Studies that enrolled patients with cardiac or respiratory diseases were excluded	Combined aerobic and resistance training.	BDI	3/56 studies evaluated depression with the BDI.
Graven et al. (53)	54 RCTs, 10 with exercise and 2 for meta-analysis, $N = 137$	1) Patients with a primary diagnosis of cerebrovascular accident 2) Participants who were community-dwelling 3) RCTs 4) Trial outcomes that measured at least one of the domains of participation, the mood disorder of depression and HRQoL (using validated scales that are commonly applied) 5) Interventions conducted in the community setting by predominantly nursing or allied health practitioners 6) The availability of an English full text version	All the studies incorporated an experimental exercise regime that was of an intensity of two to three sessions per week over a 6–12-week duration (average 9.8 weeks).	CES-D, GDS-15	PEDro methodological rating of at least four points was an inclusion criterion.
Herring et al. (16)	14 RCTs, $N = 624$	1) English-language peer-reviewed publications 2) Adults aged >18 years with a formal diagnosis of MS 3) Randomized allocation to either an exercise intervention or a non-active control condition that lacked exercise training 4) A measure of depressive symptoms measured at baseline and at mid- and/or post-intervention The mean age was 44.0 years. The mean percentage of women was 75%. Mean reported disease duration was 9.8 years, and mean baseline Expanded Disability Status Scale (EDSS) score was 3.4.	Aerobic, Resistance Aerobic+, Resistance+, Yoga Exercise training consisted of three sessions per week, 51 min per session, and 11 weeks in duration. Based on reported methods, PwMS were prescribed 122 ($SD = 38$) min of exercise per week. The mean exercise training adherence rate was 85%.	BDI, CES-D, HADS-D, IDS-SR, POMS-D, MDI	Mean PEDro score was 5.86. Depressive symptoms were not the primary outcome in any of the included trials.

(Continued)

TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
Langhorst et al. (41)	6 RCTs, $N = 306$	1) RCTs 2) Studies with meditative movement therapies 3) Patients diagnosed with FMS on recognized criteria, of any age 4) Studies should assess at least one key domain of FMS (pain, sleep, fatigue), health-related quality of life (HRQOL) and depression	Tai Chi and/or Yoga, and/or Qi Gong. In the whole review (7 studies), the number of sessions was 12 (8–24). The total treatment time was 18 (6–48) h.	BDI, CES-D, CDI	Publication bias was assessed by Egger's intercept test and Begg's rank correlation test at the significance level $p < 0.05$. 6/7 studies evaluated depression.
Liang et al. (43)	3 RCTs/quasi-RCTs, $N = 121$	1) Adults diagnosed by a rheumatologist as having AS (ankylosing spondylitis) 2) Participants > 18 years 3) Quasi-randomized and randomized controlled trials (RCT), in which at least one of the groups received home-based exercise therapy	Home-based exercise program including muscle relaxation, flexibility exercises for cervical, thoracic and lumbar spine, range of motion exercises of coxofemoral joints, stretching exercises for the major muscle groups, muscular strengthening, straight posture, and respiratory exercises.	BDI	3/6 trials investigated depression. The research team performed an analysis of all included studies (6), using a funnel plot to determine publication bias in all the literature. The outcome from the funnel shows asymmetry, thereby indicating that publication bias possibly exists in the included studies.
Lin et al. (29)	8 RCTs, $N = 519$	1) Randomized control trial design 2) Examination of yoga or MBSR (mindfulness based stress reduction) on psychological health, quality of life, and physical health of cancer patients 6 studies assessed the effects of yoga for patients with breast cancer, 1 for patients with lymphoma, and 1 for mixed cancer population.	The style of yoga used and the duration and frequency of the yoga sessions varied among all studies. Intervention duration ranged from 6 to 24 weeks.	HADS, CES-D, POMS SCL-90-R	8/10 studies evaluated depressive symptoms. Of the 10 studies, the PEDro scores ranged from 4 to 7.
Lin et al. (28)	2 RCTs, $N = 39$	1) Randomized controlled trials (RCTs) published in a peer-reviewed journal 2) Patients of any age, diagnosed with any type of gynecological cancer (i.e., cancers of the vulva, vagina, cervix, uterus, ovary, fallopian tube and placenta), at any stage of their illness 3) studies including an intervention with any type of exercise component (i.e., aerobic training, muscle strengthening, stretching exercises or education regarding exercise) The mean age of the participants across all studies (7) ranged from 52.1 to 63.9 years.	The length of interventions ranged from 5 days to 6 months. Participants were coached to meet the physical activity guidelines of at least 30 min of physical activity on 5 days per week.	BDI, BDI-II	The mean PEDro score was 5.3 (standard deviation 1.5) out of 10 for the whole analysis (7 studies). 2 of the 7 studies assessed depressive symptoms.
Liu et al. (35)	2 RCTs/CCTs, $N = 84$	1) Patients with CHD (coronary heart disease), regardless of disease stage and severity. Eligible CHD diagnoses included myocardial infarction (MI), angina or a revascularization procedure (coronary artery bypass grafting or percutaneous coronary intervention) 2) Thai Chi Intervention, no limits were imposed on type, duration, frequency, length or intensity of the Tai Chi intervention. 3) RCTs, non-randomized controlled clinical trials (CCTs) 4) Articles published in English or Chinese	Thai Chi groups, duration of 3 months and 2–5 sessions per week.	SDS	2/11 studies evaluated depressive symptoms. The two studies were rated as 'moderate' regarding global quality.
Newby et al. (31)	4 RCTs, $N = 466$	1) RCTs 2) Comparison of any intervention to treat depression in patients with prostate cancer 3) Entry criteria for depressive scores did not have to be severe enough to be considered a case of Diagnostic and Statistical Manual major depressive disorder (clinical depression)	For most studies, the intervention was 6–9 weeks. Precise exercise regimen was not stated.	CES-D, HADS, GDS, BDI	4/9 studies evaluated depression. Overall quality was fair (3 studies) to poor (1 study).

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TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
O'Brien et al. (47)	2 RCTs, $N = 65$	1) RCTs with human participants who were HIV positive 2) adults 18 years of age or older 3) aerobic exercise intervention performed at least three times/week, at least 20 min per session for at least 4 weeks 4) a randomized controlled comparison group	Aerobic exercise was defined as a regimen containing aerobic interventions performed at least three times per week for at least 4 weeks. Aerobic interventions included but were not limited to walking, jogging, cycling, rowing, stair stepping, and swimming. Interventions may or may not have been supervised.	POMS	2/10 studies evaluated depression via POMS and were included in the meta-analysis.
O'Dwyer et al. (44)	3 RCTs, $N = 75$	1) Quasi-randomized and randomized controlled trials in SLE (systemic lupus erythematodes) comparing at least one exercise group to controls 2) Studies evaluating adults diagnosed with SLE by established criteria 3) studies with participants under 18 years of age were excluded 4) studies comparing exercise to no intervention controls, studies comparing different exercise or physical activity protocols (e.g., aerobic exercise vs. strengthening exercise), and studies comparing an exercise-based intervention to another treatment approach (e.g., relaxation)	Exercise-based interventions comprised one or more of the following components: range of motion (stretching), resistance training, or aerobic exercise. 3–6 weeks of duration and 2–3 sessions/week.	BDI	Overall risk of bias of these studies was unclear.
Patsou et al. (21)	14 RCTs, $N = 1.701$	1) Written in English 2) Published in 2011 and beyond 3) Participants were adult women diagnosed with breast cancer based on mammography and biopsy 4) Included an intervention program involving physical activity 5) Randomized controlled trial (experimental) design 5) Results for depression outcomes The median age of the included breast cancer survivors was 52 years. In all studies, women had been diagnosed with 0–IIIc stage breast cancer.	Aerobic, resistance, aerobic and resistance, yoga exercises The length of the interventions ranged from 6 to 52 weeks. The reported exercise frequency was 2–3 sessions per week for the majority of the studies, while duration varied from 30 to 90 min per session and weekly exercise duration ranged from 90 to 270 min. All studies had over 80% up to as high as 99% retention rates, while adherence rates, when reported, varied from 70 to 92.7%.	HADS, CES-D, BDI-II, POMS	The mean PEDro score of the studies was 6.1 ± 2, indicating High quality. Depression was the sole primary outcome measure in only one study, while in three more studies, depression was included either as primary or not as psychosocial/psychological outcome.
Perry et al. (54)	2 RCTs/7 non-RCTs, $N = 188$	1) Participants aged 18 or older and have sustained a TBI (traumatic brain injury) 2) Interventions must utilize physical exercise 3) Depression-related outcome measure	Eight out of the nine studies had an aerobic intervention including treadmill, exercise bike and swimming, one study used a walking intervention. The intervention length was between 8 and 12 weeks, apart from one study which had just two sessions, 1 week apart	BDI, HAM-D, POMS, BRUMS, CES-D, HADS	Majority of included trials was non-randomized, no PEDro scores provided.
Samartzis et al. (36)	9 RCTs (+ 4 RCTs with SSRI comparison), $N = 3.425$	1) An experimental CHF patient group, and a CHF patient group as controls that received standard care 2) Patients were randomly allocated 3) Both groups were evaluated for depression before and after the intervention, by using psychometric instruments 4) data were published	Home and hospital exercise training interventions.	HAM-D,BDI-II, BDI, MADRS, GDS, MAACL	No PEDro scores provided. A trend for superiority of hospital-based exercise training for depression was noted.
Singh et al. (22)	14 RCTs, $N = 1005$	1) RCTs in which at least 50% of the sample was diagnosed with Stage II+ breast cancer 2) Exercise trials 3) Trials were eligible regardless of the level of supervision provided, mode of intervention delivery, intervention duration or intensity. Median recruitment rate was 56% (1–96%), 15 withdrawal rate was 10% (0–41%) and adherence rate was 82% (44–99%).	Aerobic exercise, resistance exercise, combined,	POMS, HADS, CES-D, Greene Climacteric Scale, BDI, Functional Living Index of Cancer	14/61 trials evaluated depression. 38/61 trials were rated as "high quality" according to the PEDro score.

(Continued)

TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
Song et al. (51)	4 RCTs, *N* = 148	1) RCTs and prospective non-randomized controlled and observational studies published in English 2) Parkinson's disease was the primary disease and Tai Chi and/or Qigong were the primary interventions were included. 3) RCTs	3 studies used Thai Chi, 1 study used Qigong. The duration of interventions ranged from 7 to 16 weeks. Individual intervention sessions ranged from 45 to 90 min, and the frequency of classes varied between 1 and 3 times per week.	BDI, GDS, MADRS	5/21 studies (4 RCTs) evaluated depression.
Song et al. (40)	8 RCTs, *N* = 368	1) RCTs 2) patients with ESRD (end-stage renal disease) undergoing HD (hemodialysis) for more than 3 months 3) 18 years and older 4) exercise training compared to routine HD treatment or exercise training with pharmacological treatment compared to the same pharmacological treatment	Aerobic exercise, resistance training, flexibility training, Yoga, Pilates. The duration of one intervention and the total interventions ranged from 15 min to 90 min and 4 weeks to 48 weeks (12 months).	BDI, HADS, Zung Depression Scale	8/15 trials evaluated depression. Cochrane risk of bias tool was applied.
Sosa-Reina et al. (42)	11 RCTs, *N* = 641	1) RCTs comparing types of therapeutic exercise or comparing therapeutic exercise with a control group receiving another intervention or standard care 2) Studies with participants older than 18 years, diagnosed with FMS (fibromyalgia syndrome) in the absence of significant comorbidity 3) Studies using aerobic, strengthening, or stretching exercises or a combination of these were considered. Studies of exercise interventions based on activities such as yoga or tai-chi were excluded. Almost all the participants were women (97.90%). The average age of participants was 42.36 years.	Aerobic exercise, combined exercise, muscle strengthening, flexibility, stretching.	BDI, HAD, and VAS	11/14 studies evaluated depression. It was concluded that all the studies included in this meta-analysis exceeded minimum thresholds for methodological and scientific quality.
Tu et al. (37)	16 RCTs, *N* = 3.226	1) RCTs 2) Included patients (>18 years old) with either systolic HF or HF with a preserved EF of any etiology in the control and in the intervention group (diagnosis based on LVEF or clinical findings) 3) Patients received exercise training either alone or as part of a comprehensive cardiac rehabilitation program (i.e., included components such as psychological intervention or health education) 4) compared with a standard medical treatment or education placebo control group 5) reported the effect of exercise training on depression or depressive Symptoms The median age of the populations ranged between 54 and 81 years.	Walking, bicycle, treadmill, games, jogging, calisthenics, Tai Chi Chuan, and strength training. Frequency 2–7 days/week; duration 20–60 min per session; intensity 40–80% of maximum heart rate, 60–70% of maximal heart rate reserve, or maximum oxygen uptake; and overall length of the programme 6 weeks to 1.5 years.	BDI, CES-D, GDS, HADS, HAM-D, HDCDS	Jadad scale between 2 and 7. Antidepressant effect was not influenced by age, duration of the exercise intervention, or exercise setting, but rather by LVEF and the exercise mode; HF patients with LVEFs of <50%, as well as aerobic exercise intervention, demonstrated consistent benefits on depressive symptoms.
Vashistha et al. (32)	3 RCTs, *N* = NR	1) RCTs published in English 2) The population of interest was men with clinically diagnosed prostate cancer and participation in a prescribed exercise program 3) Acceptable exercise interventions included Pilates, yoga, mind-body stress reduction, tai chi, walking alone or in combination with cycling, cycling, resistance training, strength training, qigong, aerobic exercise, anaerobic exercise, and/or stretching. 4) Included studies had to contain one of the following primary outcome measures: cancer-specific QOL, overall QOL, fatigue, depression, and/or anxiety. No limit was placed on the duration of exercise intervention or length of follow-up.	Walking, stretching, and light resistance exercises, aerobic exercise, QiGong. Study duration varied from 4 weeks to 6 months (whole study, *N* = 13).	BSI-18	5/13 studies evaluated depression, 3 used the BSI-18 and were enrolled in the meta-analysis. Using the Cochrane Collaboration tool for risk of bias assessment for all 13 RCTs included in our systematic review, we found that 10 studies had high risk of bias, two had unclear risk of bias, and one had low risk of bias.

(Continued)

TABLE 2 | Continued

References	Included trials, sample size	Included population/inclusion criteria	Intervention	Rating Scales	Quality and possible moderators
Wang et al. (34)	4 RCTs, $N = 245$	1) Published RCTs 2) Patients with CVD including ischemic heart disease or coronary artery disease, cerebrovascular disease, diseases of the aorta and arteries, and peripheral vascular disease 3) Articles that compared an intervention group (e.g., tai chi, qigong, baduanjin) with a control group that performed other exercises (egg, strength exercises), that received usual care, or that did not undergo any intervention.	Thai Chi, aerobic exercise. Duration of the intervention between 5 and 12 weeks.	HAMD, POMS	4/35 studies evaluated depression. A low risk of incomplete outcome bias was reported in 31 articles (88.5%), whereas a low risk of selective reporting bias was reported in most articles ($n = 28$, 73.6%).
Wayne et al. (30)	7 RCTs, $N = 783$	1) Randomized controlled trials (RCTs), prospective non-randomized controlled studies, and prospective non-controlled studies published in English 2) cancer was the primary disease and Tai Chi and/or Qigong were the primary interventions Most studies evaluated breast cancer patients. Other cancers included ovary, lung, gastrointestinal and colorectal cancer.	Intervention duration between 6 and 12 weeks.	POMS, CES-D, BDI, HADS, BSI-18, DASS-21	7/15 studies evaluated depression. Quality of RCTs indicated an overall low to high risk of bias For the 7 RCTs.
Ying et al. (33)	2 RCTs, $N = 124$	1) All participants were adult men and the diagnoses of prostate cancer were based on pathology reports and staging studies 2) The participants all underwent ADT (androgen deprivation therapy) for at least 3 months 3) Lifestyle interventions contain dietary advices, aerobic and resistance exercises, and physical activity 4) The patients had minimum lifestyle intervention duration of 6 weeks Exclusion criteria: Men with diabetes, uncontrolled hypertension, cardiovascular disease and unstable bony metastases.	Aerobic and resistance exercise. Duration between 12 and 24 weeks.	NR	Jadad scores between 3 and 5. 2/11 RCTs evaluated depression.
Zhu et al. (23)	8 RCTs, $N = 751$	1) English language 2) Adopted a randomized controlled trial design, comparing exercise intervention group with control group (usual care, maintain current activity level, or waitlist) 3) Included adults diagnosed with breast cancer 4) Evaluated the effects of exercise in breast cancer patients.	The main types of exercise interventions reported in this meta-analysis were aerobic, resistance, and stretching exercises. Duration in the whole study ($n = 33$) between 5 weeks and 6 months.	NR	8/33 studies evaluated depression. Delphi criteria were used for assessment of quality, the studies were heterogenous in the level of quality.
Zhou et al. (45)	3 RCTs, $N = 128$	1) participants with a diagnosis of AL [either acute myelocytic leukemia (AML) or acute lymphoblastic leukemia (ALL)] undergoing induction therapy or post-remission therapy 2) Intervention: an exercise component, regardless of the type of exercise 3) Comparison intervention: standard care with no exercise intervention or instruction 4) Outcome measures including depression 5) Study design: a randomized controlled trial (RCT) or a quasi-experimental design trial	Aerobic exercise, mixed-modality exercise. Duration was reported for 2 of the studies with 3–12 weeks.	HADS	3/9 studies evaluated depression. Risk of bias was heterogenous.

BDI, Beck Depression Inventory; CDI, Children Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; DASS, Depression Anxiety Stress Scales; GDS, Geriatric Depression Scale); HAD, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; SCL-90, Symptom Checklist-90; TAS, Toronto Attitude Scale; POMS, Profile of Mood States; SAS, Symptom Assessment Scale; CSDD, Cornell Scale for Depression in Dementia; IDS-SR, Inventory of Depressive Symptomatology Self Report; LPD, Levine-Pilowsky Depression; MADRS, Montgomery-Asberg Depression Rating Scale; MDI, Major Depression Inventory; POMS, Profile of Mood States; QOL, Quality of Life; DASS, Depression Anxiety Stress Scales; TAS, Toronto Attitude Scale; MAACL, Multiple Affect Adjective Checklist; HDCDS, Hare-Davis Cardiac Depression Scale; SDS, Self-rating Depression Scale; BSI-18, Brief Symptom Inventory; BRUMS, Brunel Mood Scale; NR, not reported.

TABLE 3 | Outcomes of the included meta-analyses.

References	Results/Main Outcomes
Adamson et al. (50)	Results from the meta-analysis yielded a small but statistically significant effect of 0.28 for depression reduction overall (SE = 0.07; 95% CI: 0.15 to 0.41; $p = 0.00$). The effect of exercise on depression is slightly larger (0.36) in the MS studies compared with the other studies (0.20), but this difference was not statistically significant.
Bergenthal et al. (46)	The pooled result of three trials ($N = 249$) for depression shows a statistically significant benefit for the exercise arm (SMD = 0.25; 95% CI:−0.00 to 0.50; $p = 0.05$).
Brown et al. (24)	Exercise provided a small overall reduction in depressive symptoms compared to standard care among all types of cancer ds = −0.13, 95% CI: −0.26 to −0.01). Collectively, the 40 effect sizes lacked homogeneity $I^2 = 55\%$, 95% CI: 35 to 68, $p < 0.001$. Subgroup analysis by cancer type revealed significant reductions in depressive symptoms among breast cancer survivors $d = -0.17$, 95% CI: −0.32 to −0.02, but no significant difference in depressive symptoms among prostate, leukemia, lymphoma, and colorectal cancer survivors.
Buffart et al. (25)	After excluding outliers, yoga resulted in significant large reductions in depression ($d = -0.69$; 95% CI: 1.02 to −0.37).
Carayol et al. (17)	Exercise resulted in an improvement of depressive symptoms ($d = -0.275$, 95% CI: −0.457 to −0.094, $p = 0.003$). $I^2 = 39\%$ ($p = 0.09$).
Chung et al. (38)	Exercise improved depressive symptoms ($d = -1.233$, SE = 0.482, 95% CI: −2.177 to −0.289, $p = 0.010$). Heterogeneity: $\chi^2 = 23.80$,$p < 0.001$; $I^2 = 87.40\%$
Craft et al. (26)	Mean ES of (−0.22, 95% CI: −0.43 to −0.009; $p = 0.04$) under a random effects model, when comparing exercise interventions to control groups.
Cramer et al. (19)	Evidence for large short-term effects were found for depression (SMD = −1.59, 95% CI: −2.68 to −0.51; $p < 0.01$). Heterogeneity: Chi² = 84.03, df = 5 ($p < 0.00001$); $I^2 = 94\%$ Long-term effects (2 studies, $N = 43$) of up to 24 weeks did not show significant results.
Cramer et al. (18)	Comparison of yoga vs. no therapy: Yoga did not appear to reduce depression (pooled SMD = −0.13, 95% CI −0.31 to 0.05; seven studies, 496 participants; low-quality evidence). Comparison of yoga vs. psychosocial/educational interventions provided moderate-quality evidence indicating that yoga can reduce depression (pooled SMD = −2.29, 95% CI: −3.97 to −0.61; 4 studies, 226 participants).
Dalgas et al. (48)	In summary the meta-analysis indicated a small beneficial effect of exercise on depressive symptoms in people with MS. The SMD across studies was($g = -0.37$, 95% CI: −0.56 to −0.17).
Eng and Reime (52)	Overall, physical exercise resulted in less depressive symptoms over 13 studies involving 1022 patients (SMD = −0.13, 95% CI: −0.26 to −0.01, $I^2 = 6\%$, $p = 0.03$) with low heterogeneity. Ten studies evaluated the effect on depressive symptoms after a period of time had elapsed following the exercise sessions (range from 10 weeks to 9 months). Physical exercise did not change depressive symptoms over these 10 follow-up studies involving 889 patients (SMD = −0.04, 95% CI: −0.17 to 0.09, $I^2 = 1\%$, $p = 0.53$).
Ensari et al. (49)	The weighted mean ES was small, but statistically significant ($g = 0.36$, SE = 0.09, 95% CI: 0.18 to 0.54, $Z = 3.92$, $p < 0.001$), indicating the exercise training resulted in an improvement in depressive symptoms compared to control.
Fong et al. (27)	Measured by the Beck depression inventory, physical activity was associated with reduced depression (−4.1, 95% CI: −6.5 to −1.8; $p <$ 0.01) in survivors of mixed types of cancer. Four other studies in the sample used the HADS (two) or POMS (two). The results for HADS were (−0.5, 95%CI: −2.8 to 1.7, $p = 0.64$ and for POMS −7.5, 95 CI:−16.0 to 1.0, $p = 0.09$).
Furmaniak et al. (20)	Exercise may lead to little or no improvement in depression (SMD = −0.15, 95% CI: −0.30 to 0.01, test for overall effect: $Z = 1.86$; $p = 0.062$). Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.73$, df = 5; $p = 0.59$; $I^2 = 0.0\%$.
Gomes Neto et al. (39)	Exercise lead to a reduction in depression symptoms (−7.32; 95% CI: −9.31 to −5.33). Test for overall effect size $Z = 7.21$, $p < 0.00001$.
Graven et al. (53)	When the data from the two studies was pooled; (SMD = −2.03, 95% CI: −3.22 to −0.85) immediately after the intervention phase (note, different time points were used in the two studies for the follow-up assessment).
Herring et al. (16)	Exercise training significantly reduced depressive symptoms by a heterogeneous mean effect of 0.55 (95% CI: 0.31 to 0.78, $p < 0.001$). A significant improvement in fatigue ($\beta = 0.37$, Z = 2.21, $p \leq 0.03$) accounted for significant variation in the overall effect of exercise on depressive symptoms.
Langhorst et al. (41)	Meditative movement therapies improved depressive symptoms (SMD = −0.49, 95% CI: −0.76 to −0.22, $p = 0.0004$ Heterogeneity $I^2 = 27\%$; $Tau^2 = 0.03$). 2 studies evaluated the follow-up ($N = 132$), with no significant improvement of depressive symptoms. In subgroup analyses, only Yoga yielded significant effects on depression at final treatment.
Liang et al. (43)	A statistically significant difference was observed (MD = −2.31, 95% CI: −3.33 to −1.30, p = 0.001), which indicated that home-based exercise interventionsreduced the depression scores, compared to the control groups. No significant heterogeneity between home-based exercise groups and control groups ($p = 0.24$, $I^2 = 30\%$).
Lin et al. (29)	Improvement of depressive symptoms (−0.95, 95% CI: −1.55 to −0.36, test for overall effect: $Z = 3.15$, $p = 0.002$). Heterogeneity: $\tau^2 = 0.63$, $\chi^2 = 66.81$, df = 7, $p < 0.00001$); $I^2 = 90\%$.
Lin et al. (28)	No significant effects were found for depression and health-related quality of life. (No SMD or CI provided)

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TABLE 3 | Continued

References	Results/Main Outcomes
Liu et al. (35)	The Thai Chi group had a significantly lower level of depression (SMD 9.42, 95% CI: 13.59 to 5.26, $p < 0.001$, $I^2 = 81\%$, $N = 168$) compared with the non-active control groups.
Newby et al. (31)	Exercise interventions significantly reduced depressive symptoms (Point estimate −0.961, SE = 0.319, CI 95% −1.585 to −0.337, $Z = -3.017$, $p = 0.003$).
O'Brien et al. (47)	One meta-analysis was performed and demonstrated a significant improvement in the depression-dejection subscale of the Profile of Mood States Scale (POMS) by a reduction of 7.68 points for participants in the aerobic exercise intervention group compared with the non-exercising control group (95% CI: −13.47 to −1.90, $p = 0.009$, $I^2 = 94\%$, $p < 0.0001$).
O'Dwyer et al. (44)	A meta-analysis including three studies found significantly lower depression scores in the exercise groups compared to controls (SMD = −0.40 SD; 95% CI: −0.71 to −0.09, test for overall effect size $Z = 2.54$, $p = 0.01$).
Patsou et al. (21)	Reduction in depressive symptoms showed a small to moderate effect of depressive symptoms in favor of the exercise $g = -0.38$ (95% CI −0.89 to 0.13, $p = 0.14$). With regard to the type of the exercise intervention, aerobic interventions yielded a large and significant effect on depression at the last follow-up (3–6 months) measurement compared with the control groups ($g = -1.23$, 95% CI: −1.97 to −0.49, $p = 0.001$).
Perry et al. (54)	This represents a statistically significant, positive small to medium overall effect size of physical exercise to reduce depressive symptoms in people following TBI (SMC = 0.48, 95% CI = 0.16 to 0.81). Tests of heterogeneity were significant ($p < 0.01$), confirming that heterogeneity was present amongst the studies included in the analysis.
Samartzis et al. (36)	Interventions using exercise training appeared more effective compared to usual care (SMD = 0.391, 95% CI: 0.213 to 0.569). There was a trend for SSRI superiority compared to exercise training for improving depression ($Q = 3.257$, df = 1, $p = 0.071$).
Singh et al. (22)	Large effect in favor of exercise SMD = 0.66, 95%, CI: 0.52 to 0.80, $p < 0.01$, $I^2 = 90\%$; high heterogeneity. Intervention duration had an effect on depression ($\chi^2 = 7.93$, df = 1, $p < 0.01$), with interventions lasting longer than 12 weeks producing a large effect (SMD = 0 .84, 95% CI: 0.65 to 1.03, $p < 0.01$) and interventions lasting 12 weeks or less having a moderate effect (SMD = 0.44, 95% CI: 0.23 to 0.65, $p < 0.01$).
Song et al. (51)	A fixed-effect model indicated that TCQ significantly reduced depression scores compared to control groups, with an overall medium effect size ($g = -0.457$, 95% CI: −0.795 to −0.118, $p = 0.008$). Q- value ($p = 0.739$) and I^2 (0%) indicated limited heterogeneity.
Song et al. (40)	Exercise training was able to reduce depression in HD patients (SMD =-0.95, 95% CI: −1.18 to −0.73; $Z = 8.33$, $p < 0.00001$).
Sosa-Reina et al. (42)	There is strong evidence from intention-to-treat and per protocol analysis that exercise reduces symptoms of depression (−0.40, 95% CI: −0.55 to −0.24; $p < 0.001$). Values of Cohen's g suggested that exercise had a small effect on symptoms of depression.
Tu et al. (37)	Strong evidence of a decrease in the symptoms of depression with exercise (SMD −0.38, 95% CI: −0.55 to −0.21, $p < 0.00001$) in 3–6 months follow-up.
Vashistha et al. (32)	The pooled data did not reveal a significant improvement in depression (−3.02, 95%CI: −7.83 to 1.79, test for overall effect: $Z = 1.23$, $p = 0.22$). Heterogeneity: $Tau^2 = 9.80$; $Chi^2 = 4.64$, df = 1, $p = 0.03$; $I^2 = 78\%$.
Wang et al. (34)	The HAMD scores of patients performing TCEs improved (MD −3.97, 95% CI: −5.05 to −2.89, $p < 0.001$; $I^2 = 0$, $p = 0.91$) compared with those of patients in the control group, based on a random-effects model. The POMS depression scale scores of the patients performing TCEs significantly improved (MD −3.02, 95% CI: −3.50 to −2.53, $p < 0.001$; $I^2 = 0\%$, $p = 0.76$) compared with those of patients in the control group, based on a random-effects model.
Wayne et al. (30)	The overall effect size based on a random-effects model favors TCQ on depression in cancer patients ($g = -0.27$, 95% CI: −0.44 to −0.11, $p = 0.001$). A subgroup meta-analysis limited to five RCTs using an active control group showed a statistically non-significant trend toward TCQ improving depression ($g = -0.22$, 95% CI:−0.47 to 0.02, $p = 0.080$). A subgroup meta-analysis limited to the three RCTs with a no-treatment control group showed a statistically positive effect of TCQ.
Ying et al. (33)	No obvious difference in mitigating depression (SMD = −0.18, 95% CI: −0.54 to 0.17, $p = 0.31$).
Zhu et al. (23)	Exercise intervention reduced depression, (SMD = −2.08, 95% CI: −3.36 to −0.80, $p = 0.001$, $I^2 = 2\%$, $p = 0.41$).
Zhou et al. (45)	Based on the data for depression, there were no significant differences in these parameters between the exercise and control groups (SMD = −0.15, 95% CI: −0.51 to 0.22, $p = 0.28$, p for heterogeneity = 0.57, $I^2 = 0\%$).

exercise on depressive symptoms in these cohorts (17, 21–23, 55). Different types of interventions were summarized (aerobic, resistance, aerobic and resistance, yoga exercises), with one meta-analysis providing more detailed information about differences between the exercise types: aerobic interventions yielded a large and significant effect on depression at the last follow-up measurement compared with the non-exercising control group (21). Another meta-analysis pointed toward the beneficial effects of an intervention duration of longer than 12 weeks (22).

One meta-analysis only showed little improvement in depression after exercise intervention (20). The two remaining meta-analyses with overlapping populations of Cramer et al. (18, 19) were heterogeneous. In the 2012 analysis, large short-term effects were shown (19), in the 2017 analysis these results could not be reproduced (18).

Exercise interventions in mixed cancer-samples

Most of these meta-analyses included a majority of breast-cancer patients.

Yoga intervention Buffart et al. showed significant large reductions in depressive symptoms of yoga interventions, one of the included RCTs included lymphoma patients, the other 6 trials breast cancer (25). Lin et al. (29) summarized 6/8 RCTs with breast cancer and different forms of yoga interventions and

showed that depressive symptoms improved significantly in the intervention groups (29).

In the cohort of Wayne et al. breast cancer was also the main disease. The overall effect size favored Thai Chi and QiGong interventions on depressive symptoms (30).

Aerobic or mixed intervention Brown et al. (24) (65% of patients with breast cancer) found a small overall reduction in depressive symptoms of aerobic and yoga interventions compared to standard care among all types of cancer. Subgroup analysis by cancer type revealed significant reductions in depressive symptoms among breast cancer survivors, but no significant difference in depressive symptoms among prostate, leukemia, lymphoma, and colorectal cancer survivors.

Another meta-analysis by Craft et al. revealed modest beneficial effects of exercise (26). Fong et al. evaluated 75% breast cancer patients and showed different outcomes with regard to different depression scales: measured by the BDI, physical activity (aerobic) was associated with reduced depression. Subgroups of four RCTs used the HAMD and POMS scales, the outcomes in this cohort were not significant (27).

In another meta-analysis by Lin et al. (28) with various gynecological cancer-types and various types of activity (i.e., aerobic training, muscle strengthening, stretching exercises or education regarding exercise) no statistically significant improvement could be shown. None of the included RCTs appeared in both analyses (28).

Exercise interventions in Patients with Prostate Cancer

Three meta-analyses were found eligible for this review with regard to prostate cancer. All of them included various types of exercise and one meta-analysis included lifestyle interventions consisting of exercise and other interventions (e.g., dietary advice) (33). The largest meta-analysis with four RCTs found significantly reduced depressive symptoms, while the two smaller ones with 3 RCTs and 2 RCTs found no statistically significant differences (31–33).

Exercise Interventions in Patients With Cardiovascular Disease and Coronary Heart Disease

For cardiovascular diseases, one meta-analysis could be included in our meta- review (34). 4 RCTs summarizing patients with ischemic heart disease or coronary artery disease, cerebrovascular disease, diseases of the aorta and arteries, and peripheral vascular disease compared Thai Chi, qigong, baduanjin interventions to control interventions (e.g., strength training or no intervention). Both outcome measures (HAMD and POMS) showed significant improvements in the intervention groups. One meta-analysis with 2 RCTs/CCTs analyzed the effects of 3-months of Thai Chi Interventions and found positive effects in the intervention group concerning the depressive symptoms (35).

Exercise Interventions in Patients With Heart Failure

The two included meta-analyses showed an improvement in depressive symptoms compared to standard care in large cohorts (36, 37).

Intradialytic Exercise Interventions and Exercise Interventions in Hemodialysis Patients

We could include two meta-analyses for the cohort of intradialytic exercise (38, 39). Exercise interventions included aerobic training, resistance training, or a combination with strength training or range of motion. Both publications showed significant improvements of depressive symptoms (38, 39).

One meta-analysis included intradialytic exercise patients and exercise interventions in hemodialysis patients on non-dialytic days (40). Beneficial effects of exercise were reported.

Exercise Interventions in Patients With Fibromyalgia, Ankylosing Spondylitis and Lupus Erythematodes (LE)

The two cited meta-analyses for fibromyalgia (41, 42) were able to present improved depressive symptoms. The interventions were heterogeneous with Tai Chi and/or Yoga, and/or Qi Gong (41) and aerobic exercise, combined exercise, muscle strengthening, flexibility, stretching (42).

Our search resulted in one meta-analysis that revealed a statistically significant beneficial effect of home-based stretching exercise in reducing depressive symptoms in patients with ankylosing spondylitis (43).

In a meta-analysis of patients with LE, significantly lower depression scores were found in the exercise groups (stretching or aerobic exercise) compared to controls (44).

Exercise Interventions in Patients With Acute Leukemia and Other Hematological Malignancies

Our systematic search resulted in two meta-analyses, one including solely acute leukemia (45) and one including various hematological malignancies (46). Zhou et al. found no significant differences between the exercise (aerobic exercise, mixed-modality exercise) and control groups, whereas Bergenthal showed a statistically significant benefit for the exercise group with aerobic exercise or combined aerobic/strength exercise in a larger cohort.

Exercise Interventions in Patients With HIV

We were able to identify one meta-analysis with a small sample size and various forms of exercise interventions (e.g., walking, jogging, cycling, rowing, stair stepping, and swimming). A significant improvement could be displayed in the depression-dejection sub scale of the POMS d (47).

Exercise Interventions in Patients With Neurological Diseases

Three meta-analyses revealed small but significantly positive effects of exercise on depressive symptoms in multiple sclerosis (16, 48, 49). Different forms of exercise were allowed (Aerobic, Resistance Aerobic+, Yoga).

In Parkinson's disease, exercise interventions (Tai Chi and/or Qigong) led to significantly improved depressive symptoms (51).

Overall, physical exercise resulted in less depressive symptoms in the two suitable meta-analyses of stroke patients (52, 53).

After 10 weeks of follow-up, this beneficial effect could not be maintained (52).

One meta-analysis included various neurological disorders and various exercise interventions. Depressive symptoms were significantly reduced. The effect of exercise on depression was slightly larger in the MS studies compared with the other studies. In addition to the above mentioned neurological disorders (with overlapping single studies), other diseases like Alzheimer's disease, were included (50).

Exercise Interventions in Patients With Traumatic Brain Injury

In one meta-analysis, two RCTs and seven non-RCTs were included and found statistically significant, positive effects of exercise on depressive symptoms (54).

DISCUSSION

We were able to include 39 meta-analyses confirming that the application of exercise as an add-on treatment in patients with somatic disorders is a frequently studied intervention. As stated above, different reasons for this observation can be discussed: the positive effects in depression alone (15), the principle lack of side-effects and the overall improvement of fitness and mortality. In our meta-review, most meta-analyses showed these (expected) beneficial effects of exercise on depressive symptoms (33/39). The six meta-analyses without these effects evaluated different exercise modalities in different types of diseases (18, 20, 28, 32, 33, 45). One of these meta-analyses provided data of breast cancer patients receiving yoga therapy and found no significant effect on depressive symptoms of yoga when comparing to no therapy, but did find significant improvements of depressive symptoms when comparing yoga to psychosocial intervention (7 and 4 included trials) (18). Another meta-analysis with breast-cancer patients found no significant results (20). The smallest of the included meta-analyses with 39 participants (2 trials) also evaluated depressive symptoms in any type of gynecological cancer and found no significant effects (28). Neither of the two meta-analyses with prostate cancer patients nor the meta-analyses with acute lymphoblastic leukemia (ALL) patients found significant reductions in depressive symptoms (32, 33, 45).

Five meta-analyses reported long-term effects with follow-up periods from 3 to 9 months of the exercise interventions (19, 21, 37, 41, 52). The results were heterogeneous with two meta-analyses showing no significant effects in a 3 to 9 months period (19, 52). One meta-analysis only found positive long-term effects during 3 to 6 months for one of the possible exercise interventions in subgroup analyses (41). The two remaining meta-analyses pointed to positive long-term effects in a 3–6 months period (21, 37). In all of these studies except one (37) the follow-up cohort was much smaller compared to the overall sample size. The small sample sizes on the one hand and the small number of meta-analyses in total restrict the generalizability of these results. Future studies should include a follow-up period of at least 3 months (preferably three and 3 months assessments) to accumulate data for meaningful statements.

Following the American College of Sports Medicine (ACSM) guidelines, healthy adults should engage in moderate aerobic exercise training for $\geq$30 min per day on $\geq$5 days per week, vigorous aerobic exercise training for $\geq$20 min per day on $\geq$3 days per week, or a combination of both moderate and vigorous aerobic training. On another 2–3 days, healthy adults should perform resistance exercises for each of the major muscle groups and flexibility exercises for each major muscle-tendon groups on $\geq$2 days per week (56). Future studies should lean on these recommendations to help homogenize the results.

In literature, many different rating scales (self- and observer-rating) have been introduced to assess depressive symptoms, reflecting the variety of questionnaires used in the original trials and the consecutive meta-analyses. For example, the practice guidelines for the treatment of depression in Germany (57) list nine possible questionnaires as valid tools. In specific somatic disorders, validation studies of the most often used scales were performed: HAMD for multiple sclerosis patient (58) and for stroke patients (59). BDI for cancer patients (60) and heart failure patients (61). In a mixed cancer population, a review recommended the CES-D as most precise instrument if depression is the sole focus (62). It has been stated that discrepancies between BDI and HAMD scores (self- and observer rating scales) could be due to different personality traits (e.g., high neuroticism is associated with higher BDI scores) and that therefore both should be regarded separately (63). To date, valid recommendations for all included somatic disorders or general recommendations for specific questionnaires to access depressive symptoms could not be identified. For future studies, similar outcome measured should be implemented to ensure comparability and both self- and observer rating scales should be combined.

The possible reasons for the varying observations regarding the different intervention types and the measuring time points could be the same reasons that complicate meta-analyses of the existing exercise trials. As stated above, in none of the meta-analyses, the included trials had matching exercise protocols regarding type, duration and frequency of the intervention. Most often no data was provided about the attendance rate of the participants and about the aerobic capacity before/after the intervention as a controlling variable. The quality of the trials ranged from very low to good quality (also with regard to the exercise-specific difficulty of blinding the intervention). In none of the meta-analyses the depressive symptoms after the exercise intervention were the primary endpoint in all of the included trials, so moreover the validity of the conclusions has to be discussed cautiously.

In summary, we were able to identify a large interest in this field of research for the above demonstrated reasons. In most of the meta-analyses, regardless of the underlying somatic disease, beneficial effects of exercise on depressive symptoms could be observed—keeping in mind that depressive symptoms were mainly secondary outcomes in the included studies. Some of the somatic diseases, especially cancer and in this field breast cancer, were overrepresented compared to others like heart failure.

More standardized trials with better comparability are required to draw specific conclusions about the recommended

type and duration of exercise in different diseases. The current findings point to beneficial effects of various forms of exercise, but the implementation in guidelines and for example in therapy strategies that are supported more extensively is still difficult because of the lack of clarity of specific outcomes. Especially the diversity of outcome parameters impedes the comparability of interventions within and between somatic disorders. Moreover, most meta-analyses did not report types of other antidepressant interventions like medication or psychotherapy. Thus, it is difficult to answer the question whether exercise therapy is efficient as an add-on treatment to an ongoing pharmaco- or psychotherapy or whether it should be offered as a single intervention in patients with somatic disorders and depression. Finally, information is sparse regarding whether patients continue to exercise after the intervention (e.g., in sport clubs) or whether their overall activity level (e.g., measured by pedometers or more accurately by accelerometers) increases and how this is related to outcome.

CONCLUSION

In this meta-review, we provide an overview of existing evidence for the effects of exercise on depressive symptoms in various somatic disorders. The results are promising, but meaningful recommendations are lacking because of heterogeneous study protocols. For better comparability, we would recommend to implement the following standards in future studies: homogeneous outcome measures, one self-rating scale (e.g., BDI) and one observer-rating scale (e.g., HAMD or MADRS). Moreover, specific information of other antidepressant treatments (especially medication and psychotherapy) should be consistently reported. State and duration of the somatic disease should be provided. Future studies should lean on recommendation of the ACSM regarding type and intensity of the intervention (e.g., moderate aerobic exercise training for $\geq$30 min per day on $\geq$5 days per week or vigorous aerobic exercise training for $\geq$20 min per day on $\geq$3 days per week; on another 2–3 days, resistance exercises for each of the major muscle groups and flexibility exercises for each major muscle-tendon groups on $\geq$2 days per week) (56). For aerobic training, bicycle ergometers are a widely-used and practical possibility (also for e.g., patients with arthrosis). The duration of the intervention should last at least 12 weeks. Attendance rates, setting (e.g., group activity, with/without supervision) and training intensity should be monitored, preferably with spiroergometric examinations at the start and the end of the study. Follow-up examinations of 3 and 6 months should be performed, and also in this period, information about antidepressant medication should be provided. On these occasions, information about the overall fitness level (e.g., via pedometer/accelerometer measurements over at least 3 days or via activity questionnaires like IPAQ) should be documented.

AUTHOR CONTRIBUTIONS

AR and AH conceived the study. AR and SK performed the qualitative analyses. AR, SK, IM, and AH wrote the first draft. AS and PF supervised the project. BM provided methodological advice; and all authors were involved in the reviewing the manuscript and approved the final version of the manuscript.

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REVIEW
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Exercise Intervention in PTSD: A Narrative Review and Rationale for Implementation

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Posttraumatic stress disorder (PTSD) is a prominent mental health problem in veteran and community populations. There is accumulating evidence to suggest that aerobic exercise may serve as an effective treatment option for individuals with PTSD. The purpose of this review is to summarize the existing literature exploring aerobic exercise and PTSD and briefly discuss potential mechanisms of PTSD symptom reduction. A search of electronic databases and reference sections of relevant articles published through October 1, 2018 revealed 19 relevant studies that examined aerobic exercise and PTSD symptomatology. A narrative review of extant studies provides encouraging evidence that aerobic exercise interventions alone or as an adjunct to standard treatment may positively impact PTSD symptoms. Potential mechanisms by which aerobic exercise could exert a positive impact in PTSD include exposure and desensitization to internal arousal cues, enhanced cognitive function, exercise-induced neuroplasticity, normalization of hypothalamic pituitary axis (HPA) function, and reductions in inflammatory markers. Randomized clinical trials and translational neuroscience approaches are required to clarify the efficacy of exercise intervention for PTSD and elucidate potential mechanisms of exercise-induced PTSD symptom reduction.

Keywords: aerobic exercise, physical activity, fitness, emotion regulation, cognition, MRI, fMRI, PTSD

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INTRODUCTION

Posttraumatic stress disorder (PTSD) can develop after exposure to life-threatening and highly distressing events such as military combat, accidents, assault, or natural, or human-caused disasters. PTSD is a prominent mental health problem in veteran and community populations, affecting 7.6% of OEF/OIF veterans (1) and 3.5% of adult Americans (2). According to the DSM-5, the diagnosis of PTSD is characterized by four broad symptom clusters that include intense reliving of the traumatic event through disruptive memories and nightmares, avoidance of reminders of the event, negative cognitions and mood, and hyperarousal. The impact of PTSD is multi-faceted. In addition to the characteristic symptoms of PTSD, impaired cognitive performance (3, 4) and alterations in brain structure and function (5, 6) are well-documented. Further, individuals with PTSD have increased rates of health-care utilization, loss of productivity, and major chronic diseases (7, 8). For instance, individuals with PTSD have higher rates of diabetes, obesity, and metabolic syndrome (9–12). Moreover, individuals with PTSD exhibit reduced participation in regular physical activity relative to pre-PTSD time periods (13), which likely contributes to the medical, cognitive, and neural comorbidities associated with sedentary behavior (14–16).

Although there are evidence-based psychological and pharmacological (17) treatments that have proven to be effective in treating the characteristic symptoms of PTSD, there are often barriers to treatment initiation among those suffering from PTSD, including stigma, motivation, cost, and access to care (18). While exercise is not without its barriers, such as limited motivation, self-efficacy, or time, it is one intervention that is broadly accessible, low-cost, and could avoid the negative connotations associated with traditional mental health treatment approaches (19). Given the constellation of psychiatric, cognitive, and general health issues associated with PTSD, it is important to consider the case for aerobic exercise for the treatment of PTSD, which may have the potential to enhance functioning in each of these areas. Indeed, aerobic exercise has the potential to exert a positive impact on PTSD via both psychological and neurophysiological mechanisms, such as exposure and desensitization to internal arousal cues, enhanced cognitive function, exercise-induced neuroplasticity, normalization of hypothalamic pituitary axis (HPA) function, and reductions in inflammatory markers.

The notion that physical activity and exercise are viable treatments for PTSD has been gaining momentum in the research community (20–25). The terms are often used interchangeably but are distinct from one another. Physical activity is "any bodily movement produced by skeletal muscles that results in energy expenditure" [(26), p 126]. Physical activity can be in the form of walking, cycling, sport, household or occupational activities, and can vary widely in the amount of energy expenditure (see **Table 1** for description of exercise intensities). Regular physical activity often results in improved balance, coordination, musculoskeletal strength, and/or aerobic fitness, depending on the type. The term exercise is commonly used in the literature and refers to a subcategory of physical activity that is planned, structured, repetitive, and intended to improve or maintain physical fitness (26). Cardiorespiratory fitness is one type of physical fitness that refers to the ability to perform large-muscle, dynamic, moderate to high-intensity physical activity for a prolonged period, and depends on the cardiovascular, respiratory, and skeletal muscle systems. Regular physical activity and/or exercise that is tailored to improve cardiorespiratory fitness, such as walking, dancing, or cycling, has significant health benefits such as reducing the risk of cardiovascular disease, diabetes, and obesity (28). Benefits of regular physical activity and/or exercise also extend to mental health (29–31). In fact, research suggests aerobic exercise, which improves cardiorespiratory fitness, is an effective treatment for depression, anxiety, and schizophrenia (32–36) through both physiological and psychological mechanisms, and may be comparable or superior to other common treatments, such as psychotherapy and pharmacology (37–39). Although PTSD shares some symptomatic overlap with depression and anxiety disorders, there is consensus that PTSD is a distinct disorder, in terms of etiology, symptomatology, and neurobiological correlates. Treatments that are highly efficacious for the treatment of depression may be less effective in PTSD treatment. Therefore, the purpose of this review is to provide a summary of the extant literature examining the impact of exercise on PTSD specifically. We discuss possible mechanisms underlying the potential link between aerobic exercise and PTSD symptoms, and conclude with future directions for aerobic exercise studies in PTSD.

TABLE 1 | Exercise intensities.

Intensity	Percentage of Maximal HR*	Oxygen Consumption*	Examples
Light	57–63%	<3 METs	Slow walk, household chores
Moderate	64–76%	3–6 METs	Brisk walk, slow jog, easy bike riding, tennis
Vigorous	77–95%	>6 METs	Running, hard bike riding, fast swimming, basketball, soccer

Values from Garber et al. (27). HR, heart rate; MET, metabolic equivalent.

METHODS

For this narrative review, we focused on aerobic exercise studies targeting enhancement of cardiorespiratory fitness. To identify studies examining the impact of aerobic exercise on PTSD symptoms, we completed a search of electronic databases (PubMed, Google Scholar, PsycINFO) for relevant studies published through October 1, 2018 using the search terms "PTSD" and "exercise' or "physical activity" or "walking" or "cycling" or "high intensity interval training" or "aerobic fitness" or "cardiorespiratory fitness." We also searched the reference section of relevant articles. To be included in the review, studies had to include an assessment of PTSD symptomatology (in trauma-exposed community or clinical samples) and metrics of aerobic physical activity or exercise or implement an aerobically based exercise intervention in patients with PTSD (or assess PTSD symptoms). If the intervention was combined with an aerobic component (e.g., aerobic + resistance training), we included it in our review. We excluded other exercise interventions that have been explored in the context of PTSD, such as yoga (40), which typically elicits smaller changes in cardiorespiratory fitness than aerobic-focused exercise programs or have a dearth of studies to draw upon for review (e.g., resistance training alone). Our search revealed 19 relevant studies (nine observational and 10 intervention) that examine aerobic exercise and PTSD symptomatology in community and clinical samples of trauma-exposed individuals with methodology exploring correlational, preventative, and treatment effects.

RESULTS AND DISCUSSION

Observational Research

An aggregate of correlational studies suggests that exercise reduces PTSD symptoms (see **Table 2**). Of note, the majority of studies assessed PTSD using DSM-IV criteria or using PTSD questionnaires that assess the three broad symptom clusters defined in the DSM-IV (re-experiencing, avoidance/numbing, and hyperarousal). In one prospective study of 38,883 randomly selected U.S. veterans (77% male), 96% of which did not have PTSD at baseline, participants who reported engaging in

TABLE 2 | Observational studies of exercise and PTSD.

Study	*N*	Age	Gender	Ethnicity	Population/ Dx criteria	Study Design	EX Type/ Measure	Outcome Measure	Results	Significance
Arnson et al. (41)	55	Mean: 49.7 ± 7.5 Range: 19–60	0% female	NR	Israeli veterans/ DSM-IV PTSD	CS	Self-reported EX/ (single item: regular, infrequent, or none)	CAPS	Severity of PTSD did not differ across EX groups	$p = 0.52$
Bosch et al. (42)	76	Mean: 36.4 ± 9.9 Range: NR	18% female	58% white	OEF/OIF/OND veterans/ DSM-IV-TR full or subthreshold PTSD	Longitudinal	Self-reported EX/ (dichotomous variable: engaging in exercise or not)	PCL-M 1 year FU	Baseline EX not significantly related to PTSD sxs at FU	$p = 0.57$
Bourn et al. (43)	239	Mean: 50 ± 15.3 Range: 21–83	9% female	88% white	U.S. Veterans/ CAPS full or subthreshold PTSD	CS	Self-reported EX/GLTEQ	CAPS	Among those reporting high levels of pain severity and interference, individuals who reported being active reported fewer PTSD sxs than those who reported being inactive	*
Davidson et al. (44)	346	Mean: 45.5 ± 14.27 Range: NR	19% female	60% white	U.S. veterans/ residential treatment for PTSD	CS	Self-reported EX/ (single item: days of EX per week)	PCL-M	EX not correlated with PTSD sxs	n.s.
Harte et al. (45)	108	Mean: 23.9 ± 10.22 Range: 18–62	42% female	92% white	Trauma-exposed community/ DSM-IV Criterion A	CS	Self-reported EX/ EHQ-R	PDS	Vigorous, but not light- or moderate-intensity EX, was significantly and inversely related to hyperarousal PTSD sxs	*
LeardMann et al. (46)	38,883	Mean: NR Range: NR	23% female	83% white	U.S. Veterans/ PCL-C	Longitudinal	Self-reported EX/ 2001 National Health Interview Survey	PCL-C	Engaging in vigorous EX (≥20 min, 2 + times/wk) resulted in: Decreased odds of developing sxs; Decreased odds of having persistent PTSD sxs at follow up	 OR = 0.58 [0.049–0.70] OR = 0.59 [0.42–0.83]
Rosenbaum et al. (47)	76	Mean: 47.6 ± 11.9 Range: NR	17% female	NR	Inpatient/ DSM-IV PTSD	CS	Self-reported EX/ IPAQ-SF	PCL-C	Total walking time negatively associated with PTSD sxs; moderate and vigorous EX not significantly correlated with PTSD sxs	*** n.s.
Vujanovic et al. (48)	86	Mean: 24.3 ± 10.54 Range: NR	58% female	89.5% white	Trauma-exposed community/ DSM-IV Criterion A	CS	Self-reported EX/ EHQ-R	PDS	Regular smokers who also endorsed a high level of weekly EX had fewer PTSD sxs than low-level exercisers	*
Whitworth et al. (49)	182	Mean: 34.6 ± 13.3 Range: 18–69	72% female; 1% other	63.2% white	Adults/ PTSD per PCL-C	Longitudinal	Self-reported EX/ GLTEQ	PCL-C 3 month FU	Total EX: - Directly related to avoid/numbing at FU Indirectly associated with total PTSD sxs through alcohol use at FU Strenuous EX: - Directly related to avoid/numbing and hyperarousal sxs at FU - Indirectly related to total PTSD, avoid/numbing, and hyperarousal sxs through sleep at FU	* 95% CI [0.18–1.42] * 95% CI [−2.43 to −0.05] 95% CI [−1.88 to −0.07]

*CAPS, Clinician-Administered PTSD Scale; CS, cross-sectional; Dx, diagnostic; EHQ-R, Exercise Habits Questionnaire- Revised; EX, exercise; FU, follow-up; GLTEQ, Godin Leisure-Time Exercise Questionnaire; IPAQ-SF, International Physical Activity Questionnaire- Short Form; NA, not applicable; NR, not reported; n.s., not significant; PCL-C, Posttraumatic Stress Disorder Checklist–Civilian Version; PCL-M, Posttraumatic Stress Disorder Checklist–Military Version; PDS, Posttraumatic Diagnostic Scale; sxs, symptoms; +, sample deemed too small to conduct traditional significance tests. No observational studies assessed cardiorespiratory fitness. *$p < 0.05$; ***$p < 0.001$.*

vigorous exercise (≥ 20 min, two or more times per week), but not combined light or moderate intensity, had significantly decreased odds of developing new PTSD symptoms (odds ratio [OR] 50.58, 95% confidence interval [CI] 0.49, 0.70) or having persistent symptoms (OR 50.59, 95% CI 0.42, 0.83) at 3–5 year follow-up (46). Similarly, Harte et al. (45) found in a cross-sectional analysis of community recruited trauma-exposed adults ($N = 108$; mean age = 23.9; 58% male; 81.7% white) that self-reported vigorous-intensity exercise, but not light- or moderate-intensity exercise, was significantly and inversely associated with PTSD hyperarousal symptom severity on a self-report questionnaire (Posttraumatic Diagnostic Scale [PDS]; $\beta = -0.22$, $p = 0.04$). One caveat was that the participants in the study endorsed relatively low levels of PTSD symptomatology (PDS total score: $M = 7.6$, $SD = 8.75$) and did not suffer from other psychopathology, suggesting the findings may not be reflective of associations in clinical samples with greater severity of PTSD or other co-morbid conditions.

The link between vigorous-intensity exercise and PTSD was further supported by Whitworth et al. (49) who longitudinally assessed 182 community-recruited adults with PTSD (mean age: 34.6 ± 13.3, 72% female, 63% white) at baseline and 3 month follow-up. Findings suggested that those who reported engaging in vigorous-intensity exercise (vigorous running or cycling) but not moderate intensity exercise (non-exhaustive sports) on the Godin Leisure-Time Questionnaire (GLTEQ) had fewer avoidance/numbing ($\beta = -2.18$, $p = 0.05$) and hyperarousal ($\beta = -1.87$, $p = 0.03$) symptoms at follow-up, assessed with the PTSD Checklist-Civilian screening (PCL-C). For those participants reporting both moderate- and vigorous-intensity exercise, the longitudinal association between total exercise and PTSD was observed only for avoidance/numbing symptoms ($\beta = -1.76$, $p = 0.05$). Moderate-intensity activity alone was not associated with total PTSD symptoms or any of the symptom clusters at follow-up. Taken together, the findings suggest that those with low levels of PTSD who engage in vigorous-intensity activity may see the most profound effects on hyperarousal symptoms, whereas there may be more widespread symptom effects as PTSD severity increases.

In contrast to the evidence supporting the link between vigorous-intensity exercise and PTSD, a cross-sectional study found that light-intensity exercise (time spent walking) endorsed on a self-report questionnaire (International Physical Activity Questionnaire- Short Form; IPAQ-SF) was significantly and negatively correlated with PTSD symptoms ($\beta = -0.4$; $t = -3.4$; $p < 0.001$) in an inpatient clinical sample ($N = 76$; mean age = 47.6; 83% male), but moderate- and vigorous-intensity exercise were not (47). There are also studies that have failed to establish a significant association between exercise and PTSD symptomatology (41, 42, 44). However, methodological limitations may explain these inconsistencies. For example, studies that failed to detect a significant association measured exercise with a single-item questionnaire or variable (e.g., assessing engagement in exercise or not, or number of days per week of exercise), whereas studies that have found significant effects used validated, multiple-item exercise assessment measures. A single-item measure does not capture frequency, intensity, and time (duration) and type of exercise, and therefore may not be adequate to assess behaviors that promote alterations in cardiorespiratory fitness or the effectiveness of aerobic exercise.

Additional cross-sectional studies highlight co-morbid health concerns as moderators of the association between exercise and PTSD symptoms. For instance, it has been shown that exercise moderates the association between regular smoking and PTSD symptoms in a non-clinical sample of trauma-exposed individuals ($N = 86$; mean age = 24.3; 42.9% male, 89.5% white), such that regular smokers who also endorsed high levels of weekly exercise had fewer hyperarousal ($\beta = -0.33$, $p = 0.05$), and avoidance ($\beta = -0.38$, $p = 0.04$) symptoms of PTSD than their low-level exercise counterparts (48). Moderating effects have also been observed in clinical samples with PTSD. Despite no main effect of exercise on PTSD severity in PTSD treatment-seeking veterans ($N = 239$; mean age = 50; 91.1% male; 87.5% white), among veterans who endorsed high levels of pain severity ($\beta = -0.031$, $p = 0.031$) and pain interference ($\beta = -0.142$, $p = 0.025$), those who reported being physically active reported fewer PTSD symptoms than those who reported being inactive (43).

The observational research provides promising support for the association between exercise and PTSD along with indications of some variables that could influence this association. These studies suggest that the effect of exercise may vary by disorder severity and/or co-morbid health concerns, which might also serve as a marker for disorder severity. Further, findings suggest that exercise might target different symptoms based on intensity (i.e., vigorous-intensity and hyperarousal symptoms), which may provide insight into potential mechanisms of action. For instance, it may be that vigorous-intensity exercise allows for exposure and desensitization to arousal cues, thereby reducing the heightened response to these cues often seen in hyperarousal. These observational studies, however, are not without their limitations. Many of the studies rely on retrospective self-report measures of exercise, which may be prone to bias, inaccuracies, and misunderstanding of questions [e.g., (50–52)]. Several studies did not report time since the traumatic event, and thus the extent to which chronicity of PTSD symptoms relates to the benefits of exercise is unknown. Moreover, given the cross-sectional nature of many of these studies, the directionality of the relationship between exercise and PTSD symptoms is unknown. That is, an association between exercise and PTSD symptoms might suggest that exercise leads to a reduction in PTSD symptoms, but it does not rule out the possibility that those individuals with lower levels of PTSD tend to exercise more.

Intervention Research

We identified 10 published studies that explored the impact of exercise interventions on PTSD symptoms, using a randomized clinical trial (RCT), quasi-RCT, or single-group intervention design. These studies suggest that exercise may be effective as a stand-alone treatment or as an augmentation to traditional PTSD treatment (see **Table 3**).

TABLE 3 | Exercise intervention studies and PTSD.

Study	*N*	Age	Gender	Ethnicity	Population/ Dx criteria	EX Type/ Measure	Fitness indices	Control	Outcome Measure	Results	*p*
Babson et al. (53)	217	Mean: 52.2 ± 7.06 Range: 24–70	0% female	NR	U.S. veterans/ residential treatment for PTSD	Cycling while in group cycling program/ cyclometer on road bike; no specifications about frequency, intensity or duration	NA	None	PCL-M	For those reporting poor baseline sleep quality, time spend cycling improved hyperarousal PTSD sxs	*
Diaz and Motta (54)	12	Mean: 15.42 ± 0.79 Range: 14–17	100% female	17% white	Residential treatment center/ DSM-IV PTSD	5 week aerobic EX program (25 min moderate walking 60–90% HR at completion, 3x/wk)	NA	None	CPSS; TSCC	Reduced PTSD sxs and trauma severity; 1 month follow up mixed for 3 participants remaining at facility	* *
Fetzner and Asmundson (55)	33	Mean: 36.9 ± 11.2 Range: NR	76% female	79% white	Community sample/ DSM-IV-TR full or subthreshold PTSD	2 week aerobic EX program (20 min EX at 60-80% HR, 6x/intervention) with attentional focus (distraction or somatic sensations)	YMCA ergometer bike test at baseline	EX program without attentional focus	PCL-C	Reduced PTSD symptoms regardless of attentional focus	**
Goldstein et al. (56)	47	Mean: 46.8 ± 14.93 Range: 24–69	19% female	40% white	U.S. veterans/ DSM-IV full or subthreshold PTSD	12 week EX program (3, 1hr exercise sessions combining aerobic and resistance exercise and yoga movements)	NA	Waitlist	CAPS	Those participating in EX program reported greater reduction in PTSD sx severity compared to waitlist controls	*
LeBouthillier et al. (57)	32	Mean: 36.75 ± 11.3 Range: NR	75% female	78% white	Community sample/ DSM-IV-TR full or subthreshold PTSD	2 week aerobic EX program (20 min EX at 60–80% HR, 6x/intervention)	Baseline YMCA ergometer bike test (VO_2 max)	None	PCL-C	Those with lower baseline fitness reported a greater reduction in avoidance and hyperarousal PTSD sxs, compared to those with higher baseline fitness	**
Manger and Motta (58)	9	Mean: 48.1 Range: NR	NR	NR	Community sample/ CAPS ≥ 20	10 week aerobic EX program (2–3x/wk, 30 min walk or jog at moderate intensity (60–80% max HR), 10 min cool down ≥12x/intervention)	NA	None	PDS	Reduced PTSD sxs after intervention and at 1-month follow-up	*
Newman and Motta (59)	11	Mean: 15.7 Range: 14–17	100% female	36% white	Residential treatment center/ DSM-IV PTSD	8-week aerobic EX program (40 min with 20 min at 60–80% max HR, 3x/wk)	NA	None	CPTSDI; PTSD-RI	Reduced PTSD sxs compared to baseline; fewer individuals met criteria for PTSD	*** ***
Powers et al. (60)	9	Mean: 34 ± 11.82	89% female	89% white	Community sample/ DSM-IV PTSD	12 session moderate aerobic EX (stationary cycling at 70% age predicted HR) plus PE	NA	PE	PSSI	Greater reduction in PTSD sxs	+ $d = 2.65$
Rosenbaum et al. (61)	81	Mean: 48 ± 12.1 Range: 23–73	16% female	NR	Inpatient population/ DSM-IV-TR PTSD	12 week EX program (progressive resistance training 30 min, 3x/wk and walking 10,000 steps/day) + inpatient care as usual	6-min walk test, resting HR, blood pressure	Inpatient care as usual	PCL-C	Greater reduction in PTSD sxs; groups did not differ in fitness level post intervention (no pre- to post-intervention fitness analyses)	*
Shivakumar et al. (62)	16	Median: 34	100% female	14% white	U.S. veterans/ CAPS ≥ 45	12 week aerobic EX program (brisk walking at 3 mi/hr for 30–40 min, 4x/wk)	NA	None	CAPS; PCL	Improved overall PTSD symptoms	*

*CAPS, Clinician-Administered PTSD Scale; CPSS, Child PTSD Symptom Scale; CPTSDI, Child PTSD Inventory; Dx, diagnostic; EHQ-R, Exercise Habits Questionnaire- Revised; EX, exercise; GLTEQ, Godin Leisure-Time Exercise Questionnaire; IPAQ-SF, International Physical Activity Questionnaire- Short Form; NA, not applicable; NR, not reported; n.s., not significant; PCL-C, Posttraumatic Stress Disorder Checklist–Civilian Version; PCL-M, Posttraumatic Stress Disorder Checklist–Military Version; PDS, Posttraumatic Diagnostic Scale; PE, prolonged exposure therapy; PSSI, PTSD Symptom Scale-Interview; PTSD-RI, UCLA PTSD Reaction Index for DSM-IV; sxs, symptoms; TSCC, Trauma Symptom Checklist for Children; +, sample deemed too small to conduct traditional significance tests. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.*

Exercise Only

One of the first studies in this area (58) assessed the impact of a 10 week aerobic exercise program with multiple baselines on PTSD, anxiety, and depression in 9 non-exercising community members who reported severe PTSD symptomatology in response to a trauma occurring at least 3 months prior during a structured interview [Clinician-Administered PTSD Scale [CAPS]: $M = 63.67 \pm 25.95$ (63)]. After the intervention, which included at least 12, 30-min moderate intensity (60–80% max HR) exercise sessions over 10 weeks, and at one-month follow up (participants refrained from exercising between intervention and follow up), participants who completed the exercise intervention reported significant reductions in PTSD [$t_{(8)} = 3.49$, $p = 0.008$ and $t_{(8)} = 3.30$, $p = 0.011$, respectively], as well as depression symptomatology [$t_{(8)} = 4.26$, $p = 0.003$ and $t_{(8)} = 3.05$, $p = 0.016$, respectively] and trait anxiety [$t_{(8)} = 3.07$, $p = 0.002$ and $t_{(8)} = 2.31$, $p = 0.050$, respectively]. The researchers followed up this initial study with another multiple baseline intervention in a sample of institutionalized female adolescents ($N = 11$; age: range 14–17 years; 36% white) who met DSM-IV criteria for PTSD based on a clinical administered scale [Children's PTSD Inventory [CPTSDI]; (64)]. Results from the study showed that, compared to baseline, participants who engaged in an 8 week aerobic exercise program (three times per week, 40 min with 20 min at 60–80% maximum heart rate) at an average of 3 years following the experienced trauma reported reduced PTSD symptomatology after the intervention [$t_{(10)} = 23.56$, $p < 0.001$] such that fewer individuals met full criteria for PTSD (59). Further, at 1 month follow-up, PTSD symptomatology increased but did not revert to baseline level, suggesting that reductions may have been at least partly dependent on the exercise intervention. Similarly, another study (54) of 12 institutionalized female adolescents (age range: 14–17 years; 100% female; 17% white) who met criteria for PTSD based on self-report [≥11; Child PTSD Symptom Scale [CPSS]; (65)], with no clear duration since experiencing trauma, showed that a shorter, 5 week aerobic exercise intervention (three times per week, 25 min of moderate-intensity walking: 60–90% maximum heart rate at completion) also resulted in significant reductions in self-reported PTSD symptoms (CPSS) and trauma symptom severity [Trauma Symptom Checklist for Children [TSCC]; (66)]. Only three participants remained at the facility at 1 month follow up and all continued to report significantly less PTSD symptoms and trauma symptom severity compared to baseline.

A more recent study conducted by Shivakumar et al. (62) resulted in similar findings. A small convenience sample of female veterans who reported PTSD symptomatology on the CAPS (≥45; $N = 16$; median age = 34; 14% white, 50% military sexual trauma) and completed a 12 week moderate-intensity exercise program (30–40 min of brisk walking at 3 mph, four times per week) reported significant reductions in overall PTSD symptomatology based on two separate assessments of symptoms (CAPS & PCL; $z = -2.395$, $p = 0.017$ and $F_{(2, 12)} = 9.42$, $p = 0.03$, respectively). In a larger study of male veterans in a 60- to 90-day residential treatment program ($N = 217$; mean age = 52 years), time spent cycling in a non-standardized group bicycling program reduced hyperarousal symptoms at discharge ($\beta = 0.24$, $p = 0.002$), but only for those who reported poor baseline sleep quality (53). Findings suggest that only select individuals might benefit from unstandardized exercise with no clear frequency, intensity, or duration. Authors did not report when the interventions occurred in relation to the participants' experienced trauma(s) in either of these two studies.

Studies with larger sample sizes and randomized conditions show further promise for the beneficial effects of aerobic exercise on PTSD. Fetzner and Asmundson (55) examined the influence of aerobic training and attentional focus to somatic sensations on PTSD symptoms in a community sample ($N = 33$; mean age = 37, 75% female). The exercise program consisted of six, 20-min moderate-intensity aerobic exercise sessions (60–80% heart rate) over 2 weeks. It was implemented, on average, 8 years following the participants' experienced trauma with most occurring 1–4 years prior to intervention. The results indicated that the aerobic exercise training, regardless of attentional focus, reduced total self-reported PTSD symptoms on a questionnaire (PCL-C; $p < 0.01$), which was driven by reductions in avoidance symptoms ($p < 0.01$). Another article published from these data (57) suggested that participants with lower fitness at baseline, measured using the YMCA ergometer bike test which assesses submaximal VO_2 maximum, reported a greater reduction in PTSD symptoms compared to their higher-fit peers ($\beta = 0.10$, $p < 0.10$). These results suggest that individuals with low fitness may preferentially benefit from the effects of aerobic exercise on PTSD. Finally, a randomized study conducted in a veteran population ($N = 47$; mean age = 46.8; 19% female) explored the impact of a 12 week aerobic exercise program (at least three, 1 hour sessions per week of moderate-intensity aerobic and anaerobic exercise), compared to waitlist control, on self-reported symptoms of PTSD [CAPS; (56)]. There was no indication when intervention took place in relation to experienced trauma. Results revealed that participants who completed the exercise program reported greater reduction in PTSD symptom severity compared to waitlist controls [$F_{(1, 35.3)} = 4.64$, $p = 0.038$]. Further, hyperarousal symptoms were the only cluster that benefitted significantly from the exercise intervention [$F_{(1, 35.2)} = 4.40$, $p = 0.044$]. Additional findings from the same sample suggest that the exercise program was also associated with increased self-reported mindfulness and interoceptive awareness (67).

Exercise Plus Standard PTSD Treatment

Two additional studies examined the effect of aerobic exercise training on PTSD symptoms in conjunction with other forms of treatment. A study conducted by Powers et al. (60) compared PTSD symptom changes in community adults with PTSD ($N = 9$; mean age = 34; 89% female) who were assigned to moderate-intensity aerobic exercise (stationary cycling; 70% age predicted heart rate max) prior to 12 prolonged exposure therapy sessions (an evidence-based treatment for PTSD) or to prolonged exposure therapy only ($d = 2.65$, $SE = 0.92$). The results indicated that the group who exercised prior to therapy showed greater improvement in PTSD symptoms relative to the group only participating in therapy.

In another study, inpatients with PTSD ($N = 81$; mean age: 48; 84% male; BMI = 30.1 obese) were assigned to either a 12 week exercise program that included three, 30-min sessions per week of progressive resistance training, walking (daily step count goal = 10,000 steps), and "care as usual" to "care as usual" alone (68). Individuals in the exercise group had significantly greater symptom reduction on a self-report measure of PTSD (PCL-C; *mean difference* = −5.4, 95% CI −10.5 to −0.3, $p = 0.04$), as well as greater reductions on measures of depression, anxiety, stress, weight, percent body fat, and weight circumference compared to the "care as usual" group. The reductions in PTSD symptomatology occurred despite the finding that there were no between-group differences in indicators of cardiorespiratory fitness as measured by the 6-min walk test, resting heart rate, and blood pressure. Pre-to post-intervention within-group differences in cardiorespiratory fitness were not measured. Results from these two studies converge to suggest that exercise combined with other forms of treatment may reduce symptoms above and beyond symptom reduction with standard treatments alone.

The intervention studies to date suggest that exercise may in fact lead to reduction in symptoms among individuals with PTSD. While the existing studies are promising in this regard, many of the studies have small sample sizes. In addition, six of the ten intervention studies lack control groups, and thus do not account for other variables that may contribute to symptom improvement. This is important to note given that in some cases symptoms of PTSD resolve without intervention and only a percentage of the population requires treatment for PTSD symptom resolution. However, half of these studies were conducted in the context of residential treatment programs suggesting the participants were likely constituents that would, in fact, benefit from treatment to promote symptom reduction.

General Discussion

To summarize, both observational and intervention studies provide support for the notion that aerobic exercise, either alone or in combination with standard treatments, exerts positive mental health benefits among individuals with PTSD. The results are encouraging as positive effects were observed in both civilian and military populations, as well as in both predominately female and male study samples. Based on the pattern of findings across studies and other existing areas of research we briefly review potential mechanisms by which aerobic exercise may exert a positive impact in PTSD symptoms, followed by the limitations of the current studies and potential future directions.

Exposure and Desensitization to Internal Arousal Cues

One of the core features of PTSD symptomatology is hyperarousal, which results in sensitivity to physiological arousal cues. Research suggests that repeated exposure to these physiological cues, such as rapid heartbeat, in the context of exercise may increase tolerance of and facilitate desensitization to the physiological sensations (32, 69, 70). However, existing research has focused on this mechanism in anxiety disorders and this effect has been largely unexplored in individuals with PTSD. Nevertheless, the possibility that exercise could result in desensitization to physiological arousal cues in a clinical PTSD sample is consistent with the findings reviewed that suggest that those who engage in vigorous-intensity exercise have fewer hyperarousal symptoms of PTSD (45, 49, 53). In other words, it may be that the vigorous activity, which by definition elicits the greatest increase in physiological arousal cues, is a means of exposure, and reduces the individuals' subjective heightened response to these cues in other (non-exercising) contexts. While we are not aware of quantitative evidence of this exercise-related exposure effect in PTSD populations, a recent case study suggested that this type of exposure might contribute to the therapeutic effects of exercise on PTSD. More specifically, the case study revealed that an individual with PTSD who participated in a 3 month exercise program (2x/week for a total of 90 min) became more aware that his bodily sensations, like pain or fast heartbeat, were not necessarily catastrophic or related to a traumatic event (71). Taken together, it is reasonable to hypothesize that exposure to arousal cues may partly explain the beneficial effect of exercise on PTSD symptomatology.

Improved Cognitive Function

A well-replicated finding in the PTSD literature is that of disrupted cognitive control in individuals with PTSD, evidenced by greater distractibility from task irrelevant stimuli and difficulty inhibiting responses to task irrelevant stimuli (72–74). At the center of the cognitive control disturbance is difficulty disengaging attention from salient stimuli that may be interpreted as potentially threatening, even if neutral or positively valenced (75, 76). This impairment in cognitive control may contribute to the maintenance of PTSD symptoms, such as hypervigilance and avoidance (77). In addition to impairments in cognitive control, PTSD is also associated with reduced learning and memory. In particular, individuals with PTSD show reduced encoding of specific episodic details, including autobiographical memories, as well as increased false memory and reduced extinction learning, which also has implications for the maintenance of PTSD symptoms.

To date, we are not aware of any aerobic exercise studies in PTSD that used cognitive outcome measures. Nevertheless, PTSD-related cognitive impairment and the maintenance of PTSD symptoms may be alleviated by improvements in cognition that are often associated with aerobic exercise. To date, the majority of studies on aerobic exercise and cognition have focused on older adults. For instance, extant research among healthy older adults suggests that cardiorespiratory fitness and aerobic exercise positively affect executive function (78, 79) and episodic memory (80–83)—the same cognitive functions negatively impacted by PTSD. Although speculative, it may be the case that aerobic exercise improves executive function and episodic memory function in PTSD, which are deficits that contribute to the core psychiatric symptoms of PTSD, such as re-experiencing, avoidance, and hyperarousal.

Alterations in Brain Structure and Function

The presence and severity of PTSD symptoms have been linked to structural gray and white matter abnormalities in

the medial temporal lobes and fronto-parietal regions, which underpin executive function and episodic memory. For instance, gray matter changes associated with PTSD include reduced volume in the hippocampus and the anterior cingulate (84–86), reduced volume or cortical thickness in the precuneus, insula, and ventromedial and lateral prefrontal cortex (87, 88). A preliminary quantitative meta-analysis of seven adult onset PTSD studies (89) revealed white matter abnormalities in the cingulum bundle, a white matter tract that links the anterior medial prefrontal cortex to the medial temporal lobes, and the superior longitudinal fasciculus, which connects the frontal and parietal lobes (90). These structural alterations co-occur with functional brain alterations in PTSD, which include alterations in activation and connectivity in amygdala, hippocampal, orbitofrontal cortex and dorsal anterior cingulate cortex (3, 6, 91, 92).

We are not aware of any exercise intervention studies in PTSD that assess brain structure or function. However, there is overlap among the neural correlates of PTSD and the brain regions impacted by aerobic exercise (93), suggesting that exercise-induced brain changes may be a mechanism by which aerobic exercise positively impacts PTSD symptomatology. For instance, aerobic training studies in older adults have revealed increased volume of prefrontal regions, including anterior cingulate cortex, during aerobic training (exercising at up to 70% of their heart rate reserve; HRR) relative to a non-aerobic stretching control group (94). Another study found that increases in physical activity resulting from exercise training were associated with gray matter volume increases in the cingulate gyrus (including both anterior and posterior cingulate cortex), left superior frontal gyrus, left medial parietal cortex, among others (95). After participation in an aerobic exercise program in another study, older adults demonstrated an approximately 2% increase in hippocampal volume, whereas a *decrease* of roughly 1.4% was observed in the stretching control group (96). Increased hippocampal volume may in part be explained by exercise associated increases in neurogenesis in the dentate gyrus subfield of the hippocampus (97, 98), which is negatively impacted in PTSD (84). Cardiorespiratory fitness and aerobic exercise have been positively associated with fronto-parietal and medial temporal lobe white matter tracts including the fornix, cingulum bundle and superior longitudinal fasciculus (99–102). Functional brain alterations have also been associated with aerobic fitness (103–105), and aerobic exercise has been shown to impact activation in many of the same regions implicated in PTSD (93, 106, 107).

Normalization of Hypothalamic Pituitary Axis (HPA) Axis Function

The HPA axis is a neuroendocrine system that regulates reactions to stress and physiological processes. In the context of stress, the hypothalamus releases corticotrophin releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). Ultimately, cortisol is released by the adrenal cortex, which regulates the system by providing negative feedback to the hypothalamus and pituitary gland. Alterations in the HPA axis are a relatively reliable finding in the PTSD literature. More specifically, a recent review of the neuroendocrine characteristics of PTSD indicated that individuals with PTSD tend to express low basal cortisol levels, which is associated with increased levels of CRH, and an exaggerated HPA axis negative feedback loop, while peripheral and central catecholamine levels are increased (108). Further, a review of studies that assess the acute response to laboratory stressors suggests that the HPA axis response among those with PTSD is characterized by an exaggerated cortisol response (109).

Normalization of the HPA axis may be a therapeutic target for PTSD based on its association with PTSD symptom improvement (110, 111). In fact, acute and regular aerobic exercise exert positive effects on the HPA axis, which may promote normalization and reduction in PTSD symptoms. For instance, an early review suggests that acute exercise induces the secretion of ACTH which stimulates the release of cortisol (112). Findings from more recent intervention studies suggest that acute moderate- and vigorous-intensity, but not low-intensity, exercise result in increased levels of cortisol (113, 114), which might target the low basal cortisol levels seen in PTSD populations. Additional research conducted in healthy or other clinical populations provides evidence that acute and regular exercise regulate or improve one's stress-related activation of the HPA axis, including a blunted cortisol response (115–118). The extent to which these findings translate to the PTSD-related HPA axis alterations is unclear because to our knowledge, this effect has only been explored in healthy populations or clinical populations with HPA axis alterations that differ from those observed in PTSD.

Activation of the Immune System and Reduced Inflammation

The activation of the HPA axis has pro-inflammatory implications for the immune system (119). While the understanding of the role of inflammation in the etiology and maintenance of PTSD is limited, there is evidence to suggest that PTSD is characterized by increased inflammatory activity. More specifically, a meta-analysis comparing individuals with PTSD and healthy controls, found that PTSD was associated with elevations in pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma [INF-γ; (120)]. There is also evidence to suggest that there is increased c-reactive protein (CRP), decreased anti-inflammatory markers (e.g., interleukin-8 [IL-8], interleukin-2 [IL-2]) as well as alterations in cell function and genes related to inflammation in populations with PTSD (119, 121–123).

Interestingly, exercise has been shown to influence these same inflammatory pathways in a manner that could possibly counteract some of the augmentations documented in PTSD. For example, regular aerobic exercise can increase factors involved in immunomodulatory function and diminish pro-inflammatory signaling, through downstream anti-inflammatory effects of acute production of IL-6 (124–127). There is also evidence to suggest that inflammatory alterations might partly explain the effect of exercise on sleep quality (128), which has shown to both moderate and mediate the association between aerobic exercise and PTSD (49, 53). Pro-inflammatory cytokines that are

modulated by exercise play a crucial role in sleep regulation, with low concentrations of IL-1 and TNF-α associated with enhanced non-REM sleep (128–130), and high levels linked to sleep disorders. Taken together, the favorable effects of exercise on inflammation and the role of inflammation in sleep regulation support the notion that exercise may be an effective tool for improving PTSD symptoms but requires additional study to directly test this assertion.

Limitations

Although the current review of the literature is encouraging, the extant studies have limitations. For instance, many of the studies had small sample sizes, restricted age ranges and/or ethnicities (many predominantly white samples), focused on either females or males, and/or relied on convenience sampling for recruitment. In addition, the populations from these studies are quite variable in terms of severity of PTSD symptoms (ranging from inpatient to trauma-exposed without PTSD), veteran status, and whether they are seeking treatment. While these factors limit the generalizability of each study to dissimilar populations, the positive association between exercise and PTSD across these variable samples provides some evidence for the generalizability of the findings. There are also considerable limitations related to the heterogeneity in research methodology. In terms of measurement, PTSD was assessed using many different self-report measures of PTSD symptoms and only select studies reported on time since traumatic event, which could impact the benefits of exercise on PTSD. There is substantial variability in the exercise measures and protocols administered across studies. First, single-item measures of exercise may hinder the detection of significant findings due to the oversimplification of exercise. Second, many of the studies rely on retrospective self-report measures of exercise, which may be prone to bias, inaccuracies, and misunderstanding of questions [e.g., (50–52)], rather than objective measures of exercise or fitness levels. In addition, the majority of the existing intervention studies failed to implement rigorous pre- and post- intervention fitness assessments and few included a control group. Therefore, some of these early studies are not able to demonstrate that alterations in PTSD were specific to alterations in fitness (as opposed to common factors). As more randomized clinical trials of exercise and PTSD appear in the literature, it will be possible to complete a quantitative meta-analysis of the effects of aerobic exercise on PTSD symptoms. However, given the heterogeneity in the study methods outlined above, and in particular the lack of an adequate number of studies that included a control group, we felt a quantitative analysis of the literature was not appropriate at this time. Nevertheless, these early and promising findings as well as the consideration of some of the potential mechanisms by which exercise could exert a positive impact in PTSD provide motivation for further investigation.

Future Directions

While there is evidence that aerobic exercise may positively impact PTSD symptoms, appropriately powered randomized clinical trials are required to more firmly establish the relationship between exercise and PTSD. At a minimum, aerobic exercise interventions should adhere to CDC's recommended guidelines for cardiovascular fitness-improving activity (i.e., 150 min of moderate-intensity or 75 min of vigorous-intensity exercise per week). Future studies should implement gold standard pre- and post-intervention diagnostic interviews to determine the presence and severity of PTSD symptomatology, such as the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and a progressive, graded exercise test to assess cardiorespiratory fitness. Objective assessment of exercise adherence could be assessed through the use of accelerometers paired with chest-strap heart rate monitors (shown to be superior to wrist-based heart rate monitors), which would allow researchers to objectively assess the frequency, intensity, and time (duration) of exercise during the intervention. Moreover, use of accelerometers would also provide insight about non-exercise related physical activity, such as occupational, domestic, or travel-related physical activity, which could potentially moderate treatment effects. Given the constellation of psychiatric, cognitive, neural, and general health markers of PTSD, it is also important to consider the use of cognitive, neuroimaging, and neurobiological outcome measures. These data may elucidate the mechanisms of exercise-induced symptom reduction in PTSD, and once clarified, may provide insight as to the dosage of exercise required to attenuate PTSD symptoms. Moreover, given the current state of the literature, we have focused exclusively on aerobic fitness. Other exercise interventions, which have yet to be thoroughly explored, including resistance training or combined aerobic and resistance training, could also elicit significant reductions in PTSD symptoms. Further research on exercise and PTSD using some of these suggestions would help to better understand the effects of exercise on PTSD and might shed light on the possible mechanisms by which exercise improves PTSD and its sequelae.

Conclusion

Aerobic exercise is a low-cost, widely accessible activity known to provide multiple health benefits, including cardiovascular health and musculoskeletal health, as well as reduced rates of co-morbidity and mortality (28). Moreover, aerobic exercise is not associated with the stigma of standard mental health treatment (19). There is growing evidence of the beneficial effects of exercise on mental health disorders, including depression and anxiety (32, 33, 35, 36). Our review of the literature suggests aerobic exercise may also reduce PTSD symptomatology across a variety of populations providing evidence for the clinical utility of exercise as a form of treatment. Additional RCTs are required to provide more definitive evidence of a causal relationship between exercise and PTSD. Nevertheless, we are not aware of any negative effects of exercise on PTSD symptoms. Thus, in the absence of medical contraindications for exercise, providers for patients with PTSD may consider prescribing aerobic exercise. To date, the precise mechanisms by which the beneficial effects of exercise may influence PTSD are unknown. However, there are multiple psychological, cognitive, and neurobiological routes that may underpin exercise-induced improvements in PTSD. Methodologically-rigorous research is required to provide more

definitive evidence of a positive effect of aerobic exercise on PTSD and identify the mechanisms of exercise-induced alterations in PTSD.

AUTHOR CONTRIBUTIONS

SH generated the idea and outline for the project. NH completed the literature search and wrote the review, with JH and SH contributing conceptual guidance and writing.

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Low Physical Activity and Cardiorespiratory Fitness in People With Schizophrenia: A Comparison With Matched Healthy Controls and Associations With Mental and Physical Health

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Introduction: The aim of this study was to objectively assess time spent in physical activity (PA) and sedentary behavior (SB) in patients with schizophrenia compared to healthy controls matched for age, gender and socioeconomic status. Associations between both PA and cardiorespiratory fitness (CRF) and mental and physical health parameters in patients with schizophrenia were examined.

Materials and Methods: Moderate and vigorous PA (MVPA), moderate PA, vigorous PA, total and active energy expenditure (TEE and AEE), number of steps, lying down and sleeping time was assessed with SenseWear Pro-2 body monitoring system for three 24-h bouts in patients with schizophrenia ($n = 63$) and matched healthy controls ($n = 55$). Severity of symptoms (Positive and Negative Syndrome Scale and Montgomery and Åsberg Depression Rating Scale), CRF (peak oxygen uptake, VO_{2peak}), body mass index (BMI), and metabolic syndrome were assessed.

Results: Patients with schizophrenia performed less MVPA and moderate activity had lower TEE and AEE, spent more time per day lying down and sleeping, and had poorer CRF compared to healthy controls. The amount of MVPA, but especially CRF was associated with severity of negative symptoms in patients with schizophrenia. Only CRF was associated with BMI.

Discussion: The current data offer further evidence for interventions aiming to increase physical activity and decrease sedentary behavior. Given strong associations of CRF with both negative symptoms and BMI, treatment aimed at CRF-improvement may prove to be effective.

Keywords: physical activity, sedentary behavior, cardiorespiratory fitness, schizophrenia, matched healthy controls

INTRODUCTION

The premature mortality risk in patients with schizophrenia is two to three times higher compared to the general population leading to a 7–20 year reduction in life expectancy (1–3), mainly due to cardiovascular disease (4, 5). The increased cardio-metabolic risk is partly attributable to side effects of antipsychotic medication such as weight gain, dyslipidemia, and diabetes mellitus (4, 6).

Three recent meta-analyses show patients with schizophrenia engage in less physical activity (PA) (7), have high levels of sedentary behavior (SB) in their waking day (8), and have low cardiorespiratory fitness (CRF)-levels (9). The majority of the included studies used self-report to assess PA (7) which, due to recall errors and social desirability bias, has limited validity (10, 11). Illustrative, whereas no difference in PA was found using self-report measurement, accelerometry showed a large reduction of PA in patients with schizophrenia compared to healthy controls (12). As for SB, a meta-analysis demonstrated that patients with psychosis spend 11 h of their waking day being sedentary. Again, objective measurement of SB demonstrated significantly higher levels of SB compared to self-report measurements (8).

In patients with psychosis, a limited number of studies have suggested that high levels of SB and low levels of PA are associated with an increased cardio-metabolic risk [e.g., (13, 14)]. These studies did not take CRF into account, and most of these studies assessed SB and PA using self-report (10, 11). One study examined independent associations of objectively measured SB and PA with cardio-metabolic risk in inpatients with schizophrenia as well as in age/sex/body mass index-matched healthy controls (15), but failed to take CRF into account. As far as we know, only one study (16) did include CRF when investigating associations between SB and PA with cardio-metabolic risk factors in patients with psychosis. This study showed that SB is, independently of PA and CRF, associated with the individual risk factors waist and fasting blood glucose. Strikingly, CRF, even when controlled for SB and PA, remained significantly associated with clustered cardio-metabolic risk and the individual risk factor waist. The study by Bueno-Antequera et al. (16) is mildly hampered by some limitations. For instance, they did not include healthy controls, measured CRF with a submaximal test instead of a "gold standard" cardiopulmonary exercise testing (CPET), thus limiting the validity of its results (17), and had a small sample of size of outpatients, predominantly men. Therefore, they call for more research, as well as the use of (gold standard) objective measures.

The aim of this study, therefore, is to compare objectively assessed SB and PA, as well as CRF measured by CPET, in patients with schizophrenia with matched, physically inactive, but otherwise healthy controls using data from the "The Outcome of Psychosis and Fitness Therapy" study (TOPFIT).

The second aim was to determine whether SB, PA, and CRF were associated with mental and physical health parameters in both patients with schizophrenia and matched healthy controls.

MATERIALS AND METHODS

Participants and Setting

This study included data of 63 patients with a schizophrenia spectrum disorder and 55 healthy controls, matched for gender, age, and socioeconomic status (expressed as the highest educational level of one of the parents). Patients were recruited at the University Medical Center Utrecht (Netherlands) ($n = 26$) and regional mental health care institutes (Altrecht; GGZ Duin- en Bollenstreek; GGZ Friesland) ($n = 37$). Healthy controls ($n = 55$) were recruited from the local population via advertisements. Participants were enrolled in the study between May 2007 and May 2010 and written informed consent was obtained after the procedures, and possible side effects were explained. This study was part of the TOPFIT project ("The Outcome of Psychosis and Fitness Therapy") and registered in the ISRCTN register (http://www.controlled-trials.com/ISRCTN46241817). Patients had a diagnosis of schizophrenia ($n = 45$), schizoaffective ($n = 15$), or schizophreniform disorder ($n = 3$) according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Diagnosis was confirmed by psychiatrists using the Comprehensive Assessment of Schizophrenia and History (CASH) (18). Patients were stable on antipsychotic medication, i.e., using the same dosage for at least 4 weeks prior to inclusion. They showed no evidence for significant cardiovascular, neuromuscular, endocrine or other somatic disorders that prevented safe participation in the study (19). Patients had no primary diagnosis of alcohol or substance abuse and had an IQ $\geq$ 70, as measured with the Wechsler Adult Intelligence Scale Short Form (WAIS-III SF) (20).

The inclusion criteria for the healthy controls were no diagnosis of psychiatric disorders according to DSM-IV lifetime, no first-degree relative with a psychotic or depressive disorder, and being physically inactive before inclusion (i.e., undertaking $<$1 h of moderate PA weekly; based on self-report). The study was approved by the Human Ethics Committee of the University Medical Center Utrecht and research committees of participating centers.

Assessments

All measurements were assessed by a research assistant and a sports physician. Participants were asked to wear the SenseWear Pro-2 (BodyMedia, Inc., Pittsburgh, PA), body monitoring system during three 24-h time bouts (2 weekdays and 1 weekend day) except during water-based activities. This device objectively measures PA and estimates energy expenditure (21–23). The SenseWear was worn over the right arm triceps muscle and assesses minute-to-minute data through multiple sensors, namely a two-axis accelerometer and sensors measuring heat flux, galvanic skin and near body-temperature. Data are combined with gender, age, body weight, and height, to measures physical (in)activity and estimate energy expenditure using algorithms developed by the manufacturer (SenseWear Professional software, version 5.1.0.1289).

Several variables were calculated from the SenseWear data. PA was expressed in average metabolic equivalents (MET; in

kcal/kg/h), an indicator of daily energy expenditure. The unit MET was used to estimate the amount of oxygen used by the body during SB and PA. Daily average time spend in total SB (<3 MET), moderate and vigorous PA (MVPA) (≥3MET), moderate (3–6 MET), vigorous (≥6 MET) were calculated from all minutes with a MET-value. Total energy expenditure (TEE; in kcals), active energy expenditure (AEE; in kcals: ≥3 MET), number of steps, lying down and sleeping time were also estimated. Data was accepted when the average on-body measuring time was at least 1,368 min per day (95% of a 24-h bout).

CRF, defined as the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity, was assessed with a cardiopulmonary exercise test (CPET), performed using a 20 watt per minute (W/min) step wise incremental protocol to exhaustion on a cycle ergometer (Lode Excalibur, Lode BV, Groningen, the Netherlands) (24). CRF was defined as the highest oxygen uptake during any 30-s interval during the test (VO2peak $ml \cdot kg^{-1} \cdot min^{-1}$) (25). Waist circumference (in cm) and anthropometric measurements (height in cm and weight in kg), using the same calibrated equipment in all participants, and metabolic syndrome (MetS), assessed according to the International Diabetes Foundation criteria (26), were obtained by the sports physician prior to the CPET.

To evaluate the severity of schizophrenia symptoms, the Positive and Negative Syndrome Scale (PANSS) total, positive, negative, and general (sub)scores were assessed (27). The Montgomery Åsberg Depression Rating Scale (MADRS) assessed co-morbid depressive symptoms (28). Detailed information on the amount and type of prescribed antipsychotic and other medication were gathered. Current antipsychotic medication prescribed was described in cumulative dosage and converted into haloperidol equivalents, conformable to a table from the Dutch National Health Service (29).

Statistical Analyses

SPSS 25.0 was used to analyze the data (Armonk, NY: IBM Corp). All statistical tests were performed two-tailed and a $p < 0.05$ was considered significant. Data were examined for outliers. All analyses were performed with and without extreme outliers to examine their influence on results. In case of non-normal distribution logarithmic transformation was applied.

Multiple analyses of variance for non-categorical variables and χ^2 analyses for categorical variables were used to examine differences between patients with schizophrenia and matched healthy controls in demographic and clinical variables. Univariate analyses were used to examine differences in SB, MVPA, moderate PA, vigorous PA, TEE, and AEE, number of steps, lying down and sleeping time, and CRF between patients and healthy controls. Gender, age, WAIS IQ-score, marital status, employment status, and Body Mass Index (BMI) were included in analyses as possible confounding factors. To investigate if differences exist between day of measurement (weekdays vs. weekend) within and between groups (patients vs. controls), repeated measures analysis of variance were performed comparing the average weekday vs. weekend day SB, MVPA, moderate PA, vigorous PA, TEE and AEE, number of steps, lying down, and sleeping time. Correction for multiple testing was applied according to the Bonferroni-correction procedure.

In patients, backward linear regression analysis (criterion: probability of F-to-remove ≥0.10) was used to assess whether the independent variables gender, age, PANSS positive, PANSS negative, PANSS general, employment status, and MADRS-score were associated with the level of SB, MVPA, and CRF (VO_{2peak} $ml \cdot kg^{-1} \cdot min^{-1}$). Similarly, we examined the association between physical health parameters (gender, age, employment status, BMI, haloperidol equivalent of antipsychotic medication prescribed, and number met criteria for the MetS) and SB, MVPA, and CRF (VO_{2peak} $ml \cdot kg^{-1} \cdot min^{-1}$). We repeated the latter regression analyses in healthy controls, examining the association between physical health parameters (gender, age, employment status, BMI, number of met criteria for MetS) and SB, MVPA, and CRF.

RESULTS

Descriptive Statistics

Demographic and illness characteristics are shown in **Table 1**. Healthy controls had lower BMI ($p = 0.01$), waist circumference ($p = 0.002$), triglycerides ($p < 0.001$), and LDL-cholesterol ($p = 0.02$). Healthy controls were less likely to have MetS ($p = 0.04$), met on average less MetS criteria ($p = 0.003$), and smoked less cigarettes per day ($p \leq 0.001$). Healthy controls were more likely married ($p \leq 0.001$), had a higher IQ ($p \leq 0.001$), and higher HDL-cholesterol levels ($p < 0.001$). No significant differences in demographic and illness characteristics, except higher diastolic blood pressure ($p = 0.02$) and lower HDL-cholesterol ($p = 0.007$), were found between male and female patients. There were no differences in type [$\chi^2_{(9)} = 5.68; p = 0.77$] and dose [$F_{(1,58)} = 1.24; p = 0.27$] of antipsychotic medication used between genders in patients.

Differences in SB, PA, and CRF

All variables, except SB, moderate PA, vigorous PA, and active energy expenditure data, complied with normality and homogeneity of variance demands. After logarithmic transformation of these variables, all data were analyzed parametrically. Average on-body percentage was below 95 percent in one patient with schizophrenia and three healthy controls. In total, 62 patients and 52 healthy controls, with an average on-body time of 98.3 (SD: 1.4) and 98.0 (SD: 1.2) percent, respectively, were thus included in further analyses. Results are presented in **Table 2**. Compared to physically inactive but otherwise healthy matched controls, patients showed significantly higher SB ($p = 0.005$), less MVPA ($p = 0.005$), and less moderate PA ($p \leq 0.001$), but equal vigorous PA ($p = 0.15$). Patients with schizophrenia had significantly lower total ($p = 0.001$) and active ($p = 0.002$) energy expenditure compared to controls. Though the average daily number of steps taken was lower in patients with schizophrenia (mean: 8040; SD: 3072) than in controls (mean: 8884; SD: 2837), this difference did not reach significance ($p = 0.16$). Patients spent significantly more time lying down ($p \leq 0.001$) and sleeping ($p < 0.001$) (expressed as minutes per day) than

TABLE 1 | Demographic and clinical characteristics for patients with schizophrenia and matched healthy controls.

Characteristic	Patients ($n = 63$)	Controls ($n = 55$)		
	***N* (%)**	***N* (%)**	***F***	***p***
Gender (male)	46 (73)	36 (65)	0.79	0.37
CASH: Schizophrenia	45 (71)			
Schizo-affective disorder	15 (24)			
Schizophreniform disorder	3 (5)			
Marital status (single/married/divorced)	56/4/3	30/24/1	22.71	**<0.001**
Employment status (welfare/ working/ student/ unemployed/ unknown)	51/8/1/3/0	1/27/24/2/1	81.38	**<0.001**
Treatment (inpatient/ day hospital/ out-patients/ unknown)	9/20/33/1			
Parental education level[a]:			6.79	0.34
Primary school or less	3(5)	1 (2)		
Secondary school	37 (59)	24 (44)		
College or university degree	21 (33)	30 (54)		
Unknown	2 (3)	0		
MetS (yes)[b]	22 (35)	9 (16)	5.22	**0.04**
	Mean ***SD***	**Mean** ***SD***	***F***	***p***
Age (year)	29.6 7.4	29.3 7.7	0.07	0.80
Height (cm)	177.9 9.2	178.2 10.1	0.03	0.86
Weight (kg)	83.0 19.2	76.3 14.3	4.51	**0.04**
BMI (kg/m^2)	26.3 6.0	23.9 3.3	6.60	**0.01**
VO_{2peak} (ml/min/kg)	31.6 9.9	35.9 5.5	7.92	**<0.01**
WAIS Total IQ	87.2 15.6	108.1 13.8	58.13	**<0.001**
Nr. of MetS-criteria met[b]	2.3 1.4	1.5 1.2	9.55	**0.003**
Waist circumference (cm)	93.4 16.0	85.4 11.2	9.60	**0.002**
Systolic blood pressure (mm/hg)	125.4 12.6	122.8 12.2	1.33	0.25
Diastolic blood pressure (mm/hg)	76.2 9.1	74.6 9.1	0.99	0.32
Tryglicerides (mmol/L)	1.5 1.0	0.9 0.5	16.91	**<0.001**
HDL-cholesterol (mmol/L)	1.0 0.3	1.3 0.3	24.44	**<0.001**
LDL-cholesterol (mmol/L)	3.3 1.0	2.9 0.8	6.06	**0.02**
Smoking (cigarettes/day)	11.8 10.5	0.9 4.3	52.03	**<0.001**
Alcohol usage (glasses/week)	3.6 6.9	5.0 5.2	1.50	0.23
PANSS total score	62.6 10.7			
PANSS positive factor score	15.52 4.0			
PANSS negative factor score	17.46 5.8			
MADRS total score	15.16 8.4			
Duration of illness (years)	6.6 5.8			
Hospitalization until measurement (days)	193.7 265.3			
HEQ dose (mg/day)	8.1 5.2			

[a] *Socioeconomic status, expressed as highest level of education of one of both parents according to Roick et al. (30).*

[b] *Assessed according to the International Diabetes Foundation criteria (26). CASH, Comprehensive Assessment of Schizophrenia and History; MetS, Metabolic Syndrome; BMI, Body Mass Index; VO2peak, maximum rate of oxygen consumption; WAIS, Wechsler Adult Intelligence Scale; HDL, High-density lipoproteins; LDL, Low-density lipoproteins; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery and Åsberg Depression Rating Scale; HEQ, haloperidol equivalent. Significant differences at < 0.05 level are presented in bold.*

controls. Patients had significantly poorer CRF than healthy controls ($p < 0.01$). Controlling for gender, age, BMI, and marital status did not change results. Controlling for WAIS IQ led to non-significance for TEE only. However, controlling for employment status led to non-significant differences in SB, PA, and TEE and AEE, but not in lying down and sleeping time. Bonferroni-correction for multiple testing did not influence the conclusions.

Differences in SB and PA on Weekdays vs. Weekend Days

Except for vigorous PA, patients and controls demonstrated significantly more SB, significantly less time on MVPA and moderate PA, had lower TEE and AEE, took fewer steps, and spent more time lying down and sleeping during the weekend compared to weekdays (Monday through Friday) (see **Table 3**). After Bonferroni-correction for multiple testing participants still

TABLE 2 | SB and PA in patients with schizophrenia and matched healthy controls, controlled for gender, age, and BMI influences.

Characteristic	Group		Test statistic	
	Patients ($n = 62$)	Controls ($n = 52$)		
	Mean ± SD	Mean ± SD	*F*	*p*
SB (<3 MET; min/day)	1303.6 ± 70.2	1254.1 ± 68.1	8.39	**0.005***
MVPA (≥3 MET; min/day)[1]	136.4 ± 70.2	185.2 ± 68.6	8.39	**0.005***
Moderate (3-6 MET; min/day)[1,a]	105.3 ± 72.1	152.1 ± 63.3	12.98	**< 0.001***
Vigorous (>6 MET; min/day)[1,a]	10.5 ± 20.3	16.1 ± 26.6	2.10	0.15
Total energy expenditure (kcal/day)[1]	2897 ± 582	3036 ± 455	10.74	**0.001***
Active energy expenditure (kcal/day)[1,a]	718 ± 595	965 ± 421	9.62	**0.002***
Steps (steps/day)[1]	8040 ± 3072	8884 ± 2837	1.97	0.16
Lying down (hours/day)[2]	11.4 ± 2.1	8.6 ± 1.2	65.95	**<0.0001***
Sleeping time (hours/day)[2]	9.2 ± 1.9	6.5 ± 1.0	68.63	**<0.0001***

[1]*Higher score indicates superior physical activity.*
[2]*Lower score indicates superior physical activity.*
[a]*EXP-values of logarithmically transformed and analyzed data are presented. Significant results are presented in bold, *significant after Bonferoni correction for multiple testing.*
SB, sedentary behavior; PA, physical activity; BMI, body mass index; MET, metabolic equivalent; MVPA, moderate to vigorous physical activity.

took significantly fewer steps and spent more time lying down and sleeping. No significant differences between the two 24-h weekday assessments were found in either patients or controls for any of the SB or PA variables (all $p > 0.20$). Whereas, no differences in PA or energy expenditure were found between Saturdays or Sundays in healthy controls, patients had less MVPA ($p = 0.04$) and lower TEE ($p = 0.005$), and AEE ($p = 0.009$) on Saturdays compared to Sundays.

Associations of SB, MVPA, and CRF With Mental and Physical Health

In patients, for mental health, a significant final model for SB emerged [$F_{(1,59)} = 4.46$; $p = 0.039$; $R^2 = 0.069$] in which PANSS negative score (beta = 0.263; $p = 0.039$) was significantly associated with SB. In the final model, gender, age, employment status, WAIS IQ, PANSS positive, PANSS general, and MADRS-score were not significantly associated with SB. This means that increasing severity of negative symptoms was associated with more SB. An identical but inversed model emerged for MVPA which means that increasing severity of negative symptoms was associated with fewer MVPA. For mental health, a significant model for CRF emerged also [$F_{(4,56)} = 17.195$; $p < 0.00000001$; $R^2 = 0.551$] in which gender (female vs. male; beta = −0.398; $p < 0.0001$), age (beta = −0.417; $p < 0.0001$), and PANSS negative score (beta = −0.502; $p < 0.00001$) MADRS score (beta = 0.198; $p = 0.040$) were significantly associated with CRF level indicating female gender, higher age, and more severe depressive and particularly negative symptoms were associated with poorer CRF.

In patients, for physical health, no significant final model for either SB nor MVPA emerged since none of the variables (gender, age, employment status, BMI, haloperidol equivalent of antipsychotic medication prescribed, and number met criteria for the MetS) were significantly associated with SB or MVPA, respectively. For physical health, a significant model for CRF did emerge [$F_{(4,54)} = 17.566$; $p < 0.00000001$; $R^2 = 0.570$] in which gender (female vs. male; beta = −0.255; $p = 0.011$), age (beta = −0.214; $p = 0.032$), employment status (beta = −2.04; $p = 0.032$), and BMI (beta = −0.489; $p < 0.00001$) were significantly associated with CRF level. This means female gender, higher age, being unemployed or on welfare, and higher BMI were associated with poorer CRF. When negative symptoms and BMI were combined in one regression model with CRF, both factors were equally related.

In healthy controls, a significant model emerged for MVPA [$F_{(7,10)} = 7.095$; $p = 0.002$; $R^2 = 0.225$] in which gender (female vs. male, beta = 0.307; $p = 0.02$) and BMI (beta = −0.31, $p = 0.02$) were significantly associated with MVPA. The same holds for SB [$F_{(7,19)} = 7.095$; $p = 0.002$; $R^2 = 0.225$; with gender −0.307, $p = 0.02$ and BMI 0.32, $p = 0.02$ being significantly associated] and CRF [$F_{(3,48)} = 18.101$; $p < 0.00000001$; $R^2 = 0.531$, with again gender −0.638, $p < 0.0000001$, employment status (beta = −0.210; $p = 0.056$), and BMI −0.54, $p < 0.0001$ being significantly associated with CRF]. Noteworthy, females tended to have more MVPA and less SB, but poorer CRF. The latter corresponds with the model in patients, in which also female gender and higher BMI were associated with poorer CRF.

DISCUSSION

This study examined objectively measured PA and inactivity, SB and CRF in patients with schizophrenia compared to inactive healthy controls. Patients with schizophrenia performed significantly less MVPA, moderate PA, more SB, had lower total and active energy expenditure, spent more time per day lying down and sleeping, and had poorer CRF compared to healthy controls. The amount of MVPA, but more prominently CRF level, was associated with the severity of negative symptoms in patients with schizophrenia. Only CRF, and not SB or MVPA, was associated with BMI.

TABLE 3 | Differences between day of measurement (weekdays vs. weekend) within (day) and between groups (day × group; patients vs. controls).

Characteristic	Group							
	Patients ($n = 62$)		Controls ($n = 52$)		Test statistic			
	Weekday	Weekend	Weekday	Weekend	Day		Day × Group	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*p*	*F*	*p*
SB (<3 MET; min/day)	1296 ± 82	1318 ± 74	1249 ± 84	1263 ± 70	5.3	**0.02**	0.3	0.60
MVPA (≥3 MET; min/day)[1]	143.8 ± 82.2	121.6 ± 74.7	190.6 ± 84.0	174.6 ± 74.7	5.8	**0.02**	0.2	0.70
Moderate (3-6 MET; min/day)[1]	126.4 ± 75.7	106.5 ± 61.9	165.7 ± 71.2	152.6 ± 60.4	5.3	**0.02**	0.2	0.63
Vigorous (>6 MET; min/day)[1]	17.5 ± 16.6	15.2 ± 26.4	24.9 ± 23.5	21.9 ± 27.7	1.1	0.29	0.02	0.89
Total energy expenditure (kcal/day)[1]	2943 ± 634	2805 ± 621	3069 ± 522	2970 ± 475	6.5	**0.01**	0.2	0.67
Active energy expenditure (kcal/day)[1]	896 ± 546	745 ± 525	1055 ± 471	979 ± 432	4.8	**0.03**	0.5	0.47
Steps (steps/day)[1]	8565 ± 3522	6990 ± 3522	9104 ± 3251	8443 ± 3669	9.8	**0.002***	1.6	0.20
Lying down (hours/day)[2]	11.1 ± 2.2	11.9 ± 3.3	8.1 ± 1.3	9.6 ± 2.3	17.0	**<0.0001***	1.7	0.19
Sleeping time (hours/day)[2]	8.8 ± 2.1	9.8 ± 2.7	6.1 ± 0.9	7.3 ± 1.9	25.1	**<0.0001***	0.2	0.62

[1] *Higher score indicates superior physical activity.*

[2] *Lower score indicates superior physical activity.*

*SB, sedentary behavior; MET, metabolic equivalent; MVPA, moderate to vigorous physical activity. Significant results are presented in bold, *significant after Bonferoni correction for multiple testing.*

This study adds to current knowledge by being one of the few to include CRF in studying the relationship between PA, SB and cardiovascular disease, and, more importantly, by being the only one to use the gold standard CPET in measuring CRF. CRF indeed appeared independently related to cardio-metabolic risk, more so than SB or PA. This has two implications; it stresses the importance of taking CRF into account when assessing patients' physical health status, and it implies that the implementation of interventions aiming to increase CRF is of utmost importance in tackling the alarming cardio-metabolic health of patients with schizophrenia (31). Two previous intervention studies showed this was feasible in patients with schizophrenia (32, 33). In the current study, we found an association between CRF and severity of negative symptoms, which is in line with previous research (34). The direction of this association is as of yet not exactly known; it may seem conspicuous to think negative symptoms lead to inactivity which in turn affects CRF levels. There is however emerging evidence that a bidirectional association may be possible as well. Two studies found evidence of a direct relationship of CRF (35) on cognition and PANSS symptomatology (36), respectively. In other areas, such as depression and bipolar disorder, the effect of physical activity on mood has been widely established, even though the mechanisms through which physical activity and brain functioning (mood, cognition and symptoms) affect each other are not completely understood yet. Nonetheless, this gives hope to the idea that interventions aiming to increase CRF may also reduce negative symptoms (37). This could, on its turn, have important functional benefits as well since negative symptoms evidently impact an individual's functional capacity in daily activities (38).

Our results are furthermore consistent with previous studies which reported lower levels of PA in patients with schizophrenia compared to healthy comparison subjects (30, 39–44). In line with earlier findings, we found patients with schizophrenia spend less time on moderate PA, but not on vigorous PA (43). In accordance with the only study that used doubly labeled water, the established criterion standard method for free-living energy expenditure assessment, we found reduced total and active energy expenditure in patients with schizophrenia (45).

Some limitations should be considered when interpreting present findings. First, SenseWear reliably assesses PA and energy expenditure in normal and overweight healthy adults (21–23, 46), yet has not been validated in patients with schizophrenia. SenseWear overestimated energy expenditure in obese subjects (46) and the current study included 15 obese patients and 2 obese healthy controls (BMI>30). Papazoglou et al. (46) used an older software version than the present study which was later shown to have an inferior accuracy (23). Second, as this is a cross-sectional study, only relationships between SB, PA, and CRF, and mental and physical health parameters could be examined, not causality. Third, we did not succeed in enrolling healthy controls fully matching the schizophrenia patient group, other than on age, socio-economic status and inactivity. In terms of cardiometabolic health, the patients were much worse off, which on the one hand stresses the seriousness of their health condition, but on the other hand impedes true comparison of the two groups. In addition, patients with schizophrenia and healthy subjects volunteered to engage in the study, which may have led to some selection bias because subjects motivated for PA and health improvement might have had greater interest in this study. Accordingly, this may have led to an overestimation of activity levels compared to the entire schizophrenia population. Also, the absence of a matched psychiatric control group is a limitation of our study. It would have been interesting to see whether activity patterns and CRF levels of patients with schizophrenia differ from patients with other psychiatric diagnoses. This might also shed light on the role of negative symptoms, which may be present in patients with other psychiatric disorders but are often more pronounced in patients with schizophrenia. Fourth, one could argue that the CPET is too strenuous for patients with schizophrenia. In our study, however, all controls and all but four patients with schizophrenia met maximal effort demand (RER peak ≥1.1),

albeit that patients with schizophrenia did reach significantly lower average RER peak values than controls. This could however in part be due to poorer CRF and the fact that they are not accustomed to perform high-intensity exercise. Last, others often define SB as <1.5 MET whereas we defined it as <3 MET. This may have led to a higher estimate of SB.

In conclusion, our study shows patients with schizophrenia perform less PA, expend less total and active energy, spend more time lying down and sleeping, and have poorer CRF compared to physically inactive matched, healthy controls. Given the remarkably strong associations of CRF with both negative symptoms and BMI, improvement of CRF should be a primary treatment aim, which may affect both mental and physical health in patients with schizophrenia.

DATA AVAILABILITY

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

AUTHOR CONTRIBUTIONS

TS, FB, TT, and WC conceived, designed, and amended the study and wrote the protocol. TS was responsible for the acquisition of the data. TS, FJ, and TT performed the statistical analyses. TS, FJ, and TT wrote the first draft of the manuscript. All authors provided critical review of the manuscript and approved the final version.

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Less Medication Use in Inpatients With Severe Mental Illness Receiving a Multidisciplinary Lifestyle Enhancing Treatment. The MULTI Study III

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Besides having an unhealthy lifestyle contributing to premature mortality, inpatients with severe mental illness (SMI) use high dosages of medication. Previous research has shown improved health after lifestyle improvements in SMI. In addition, we aimed to retrospectively study whether a multidisciplinary lifestyle enhancing treatment (MULTI) was associated with changes in medication use after 18 months, as compared with patients that continued treatment as usual (TAU) and explored mediation by a change in physical activity. We conducted an observational study within a cohort of inpatients with SMI, who received MULTI ($N = 65$) or continued TAU ($N = 49$). Data on their somatic and psychotropic medications were collected, converted into defined daily dose (DDD), and analyzed using linear multilevel regression, correcting for baseline value and differences between groups in age, diagnosis, and illness severity. Compared with TAU, the DDD for psychotropic medication significantly decreased with MULTI ($B = -0.55$, $P = 0.02$). Changes in total activity did not mediate this association, suggesting that multiple components of MULTI contributed. Corrected between-group analyses for subgroups of medication were not possible due to lack of power and skewed distributions. Within-group data showed a decreased proportion of users as well as median DDD in both groups for almost all medications. In addition to previously reported health improvements after 18 months of MULTI, we observed a significant decrease in dose of psychotropic medication in MULTI compared to TAU. This first study evaluating a wide range of medications indicates a possible effect of lifestyle improvements on medication use in inpatients with SMI. Findings need to be confirmed in future controlled studies, however.

Keywords: medication, antipsychotics, physical activity, hospitalization, severe mental illness, schizophrenia, lifestyle, side effects

INTRODUCTION

In patients with severe mental illness (SMI), a high prevalence of metabolic risk factors (1–3) contribute to their poor cardiovascular health, largely contributing to a reduced life expectancy of at least 7–20 years compared to the general population (4–6). Besides a sedentary lifestyle (7–10), side effects of psychotropic medication (such as weight gain, dyslipidemia, diabetes mellitus, and direct and indirect harm to the vascular system) are associated with these cardiovascular health issues (11–14). Polypharmacy, higher dosages, and longer-term use are associated with higher risk for most of these side effects and somatic diseases (11, 12, 15). A study in people diagnosed with schizophrenia showed that both no exposure as well as high exposure to antipsychotics were associated with higher cardiovascular mortality than either low or moderate exposure (16). Unfortunately, polypharmacy is very prevalent among people with SMI (15, 17) and the dosage of antipsychotic medication has only increased during the last decades for long-term hospitalized patients (18, 19). Alongside this psychotropic medication, patients use antihypertensive, lipid-lowering, antihyperglycemic and other additional drugs if cardiovascular health issues (whether or not caused by psychotropic medication) are too severe (20–24).

Nowadays, there is more focus on the lowest effective dose, on the avoidance of inappropriate polypharmacy to minimize the side effect of antipsychotics (25–28), and on supporting a healthy lifestyle (29–32). Despite an increased number of studies showing benefits of lifestyle interventions in people with SMI, there is a lack of evidence to support the long-term effectiveness of such interventions in hospitalized patients (33, 34). Moreover, to the best of our knowledge, studies evaluating lifestyle interventions in inpatients did not analyze changes in medication use. Recently, improved physical activity and metabolic health were shown after 18 months in this group of patients receiving a multidisciplinary lifestyle enhancing treatment for inpatients with SMI (MULTI) (35). MULTI was pragmatically implemented in a group of inpatients whose psychotropic medication was already critically reviewed prior to its implementation; hence, dose reduction was not a specific goal. The treatment focused on decreasing sedentary behavior, increasing physical activity, and improving dietary habits in the context of daily treatment.

Because the (side) effects of medications are associated with cardiometabolic health issues, we hypothesized that we might observe changes in medication use after lifestyle changes, in addition to improvements in physical health. Therefore, the present study aimed to retrospectively study whether 18 months of MULTI was associated with changes in medication use, as compared with patients that continued treatment as usual (TAU) and to explore whether changes were mediated by increased physical activity as an essential component of MULTI.

MATERIALS AND METHODS

Study Design

This observational cohort study was conducted at wards for long-term inpatient mental healthcare in a psychiatric hospital of GGz Centraal (The Netherlands). The current study is part of a comprehensive evaluation of MULTI, a treatment that was implemented pragmatically in February 2014 in three wards. MULTI was developed because of the identified need to address the comorbidity (e.g., sleep apnea and cardiovascular morbidity) in this population, in part due to a lack of physical activity, obesity, and dietary risks). The implementation of MULTI (described in the next paragraph) was conducted by psychiatrists, nurses and team leaders in collaboration with activity coordinators and a dietitian. During a previous MULTI study (35), data of baseline (Aug.–Dec. 2013) and one follow-up (Aug.–Dec. 2015) were collected from 114 patients (65 received MULTI and 49 continued TAU). Data on types and dose of medication were extracted from electronic patient records and compared between patients receiving MULTI and those receiving TAU. Because of the observational nature of this study, whereby MULTI was already implemented pragmatically in three wards before the start of this study, no randomization took place. Therefore, we analyzed potential differences between groups at baseline and, if significant, corrected for these differences in analyses as potential confounders. The study protocol was approved by the Medical Ethical Committee of the Isala Academy (case 14.0678). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Study Population

The cohort consisted of patients with SMI who had been hospitalized for at least 1 year. Patients were included in the MULTI study if they had not received any other intervention related to lifestyle within 18 months since the start of MULTI and if baseline accelerometer data was available. Exclusion criterion was a lack of data after 18 months due to being either discharged or deceased. Patients included for follow-up were dropped out for further analyses if they had insufficient accelerometer data (see Physical Activity below) or refused the repeated accelerometer measurement.

MULTI

The purpose of MULTI was a holistic lifestyle change with a focus on decreasing sedentary behavior, increasing physical activity, and improving dietary habits. Improving the daily structure formed the base of the treatment, by starting each day with getting up on time, having three joint meals per day, and an active day program consisting of sports-related activities (e.g., walking, running, yoga, biking, indoor team sports), work-related activities (e.g., gardening and helping out with daily jobs), psycho-education (e.g., about side effects, dietary habits), and skills training (e.g., making a grocery list, shopping, cooking). Also, existing policies were reviewed critically—e.g., the use of personal transport within walking distance around the hospital area for every patient was reduced to its use for immobile patients and in case of extreme weather only. Because of heterogeneity in illness severity and different capabilities and interests, the content and intensity of the day-to-day program were tailored to the particular ward and individual patients by the nurses and specific disciplines (see below). Therefore, the actual frequency, intensity, kind of activities and format (e.g., group or alone) could

vary between patients and wards. However, it was intended that all patients were doing some of the activities in the morning and afternoon, to prevent prolonged periods lying in bed or sitting at the ward. Also, the participation of nurses in the day-to-day program was an essential element, which contributed to the culture change within the institution and in the provision of support to patients. MULTI was based on a "change from within-principle" developed by current staff (psychiatrists, nurses, and team leader in collaboration with activity coordinators and a dietitian), working with regular context and resources in daily routine care. It was supervised and disseminated per ward by the head practitioner (a psychiatrist) as an innovative treatment method. Nurses received support from the psychiatrists (psycho-education), activity coordinators, and the dietitian. Adherence to and compliance with the treatment was discussed in the weekly multidisciplinary consultation. If a patient could not get along in the day-to-day program (e.g., getting out of bed or attending selected activities), it was agreed upon that specific action was to be taken to physically activate a particular patient, using extra individual motivational interviewing by their mentor (one of the nurses) or psychiatrist, who were trained in this, and by consulting an activity coordinator or dietitian if needed.

Patients who received TAU continued their treatment, which mainly concerned pharmacological treatment and a less structured day program and did not include any supported lifestyle interventions or adjustments.

Measurements

Medication

Medication use was classified by type of medication in the main groups and by converting doses to daily defined doses (DDD) according to the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization (36). Somatic medications included medications for the alimentary tract and metabolism (A), blood and blood-forming organs (B), cardiovascular system (C), and respiratory system (R). Psychotropic medications included the medications for the nervous system (N). Due to the differences in specific purpose, efficacy, and side effects of psycholeptics (N05), we distinguished antipsychotics (N05A) from anxiolytics, hypnotics, and sedatives (N05B & N05C). Likewise, we distinguished the category antipsychotics into three groups: (i) typical and (ii) atypical antipsychotics (occurring in different subgroups) and (iii) lithium (N05AN). For this study, we only used fixed prescriptions (i.e., not including medication to be given as needed). Physical activity.

Physical Activity

To test for potential mediation by a change in physical activity, we used accelerometer data (ActiGraph GT3X+) that was collected within the MULTI study. Detailed procedures and settings used in the baseline and follow-up measurement were described elsewhere (9, 35). Accelerometers were worn on the right hip; wear time of $\geq$6 h/day for $\geq$3 days was used as the criterion for sufficient measurement, and the same timeframe (9:00 a.m−10:00 p.m) was used for each dataset to be able to compare individual data. These were analyzed using the ActiGraph (*ActiGraph Corp., Pensacola FL, USA*) software ActiLife 6.8.0 and calculated into average total activity counts per hour (TAC/h) as a continuous and detailed outcome variable, where more counts indicate a higher level of activity. The GT3X+ showed a high inter- and intra-instrumental reliability and validity in healthy adults. Inter-instrument reliability in free-living conditions (hip worn) was high for overall activity (ICC = 0.97 and a 95% limit of agreement of $\pm$81.3 counts per minute for vector magnitude) (37, 38) and moderate-to-vigorous activity (ICC = 0.99) (39). The GT3X+ showed acceptable agreement between step counts observed in a laboratory setting (ICC = 0.61–0.99) and free-living situations (ICC = 0.90) (40).

Statistical Analysis

Data analyses were performed using SPSS 22.0 and interpreted at a two-tailed significance level of $p < 0.05$. Differences in patient and disease characteristics between patients who received MULTI and those receiving TAU were analyzed using independent *t*-test and chi-square statistics. Continuous variables were examined for linearity, normality, and homogeneity as assumptions for linear analysis by comparing means with medians and analyzing frequency histograms, normality plots, and plots of residuals vs. predicted values. If variables were not distributed linearly toward the dependent variables, they were added as tertiles in the analysis, with the first tertile as the reference category. If data was not distributed normally, analyses were performed using non-parametric tests.

Sum scores of changes in DDDs of somatic and psychotropic medications were distributed normally, after excluding two outliers ($z < -3$) from the DDD of somatic medication. We used linear multilevel regression to evaluate changes in these outcomes between MULTI and TAU, whereby possible clustering of data within wards was taken into account using a two-level structure, with the wards as the first level and the patients as the second. The change scores of the outcome variables were regressed on the treatment variable and adjusted for the baseline value to prevent potential regression to the mean (crude, model 1). We added patient and disease characteristics that significantly differed between patients receiving MULTI and TAU as covariates in models 2 and 3, respectively. We were not able to properly run corrected between-group analyses on subgroups of medication due to skewed distributions and insufficient power for non-parametric between-group analyses. Therefore, we analyzed the change in DDDs within subgroups of medication separately within MULTI and TAU, using Wilcoxon signed-rank tests.

Additionally, final significant models were analyzed for possible mediation by a change in total activity counts per hour (TAC/h), using the PROCESS tool in SPSS (41) (**Figure 1**). The mediation effect was calculated as the product of those coefficients (ab, not shown within the model) and was considered significant if the bias-corrected and accelerated (BCa) bootstrapped confidence intervals did not include zero.

RESULTS

Table 1 shows the baseline characteristics of patients receiving MULTI and TAU. None of the included 114 patients dropped out.

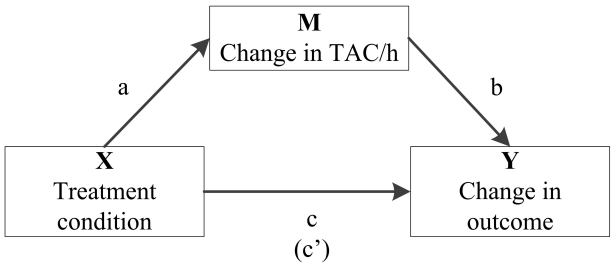

FIGURE 1 | Model summarizing how the role of change in average total activity counts per hour (TAC/h) as a potential mediator (M) in the association between treatment condition (X) and significant change in medication use (Y) is quantified in mediation analysis. It includes the associations between treatment condition and TAC/h (a), TAC/h and the particular outcome variable (b) and treatment condition on the particular outcome variable (c). The coefficient between the latter two, controlling for change in TAC/h, is in parentheses (c′).

TABLE 1 | Baseline characteristics of patients ($N = 114$).

Outcome (scale)	MULTI ($n = 65$)	TAU ($n = 49$)
Sex, *n* (%) male	43 (66.2)	27 (55.1)
Age, years, mean (*SD*)	**52.2(8.9)**	**58.7 (11.6)**
Diagnosis, *n* (%)		
Schizophrenia and other psychotic disorders	**61[a](93.8)**	**28[b](57.1)**
Other disorders	**4[c] (6.2)**	**21[d] (42.9)**
Illness severity, CGI-S scale 1-7, mean (*SD*)	**5.0 (1.2)**	**4.3(1.2)**
Years of hospitalization, mean (*SD*)	14.4 (10.9)	13.2 (12.7)

Significant differences between groups are shown in bold.
MULTI, MUltidisciplinary Lifestyle enhancing Treatment for Inpatients with severe mental illness; TAU, Treatment As Usual; CGI-S, Clinical Global Impression–Severity scale.
[a]*other: schizoaffective disorder (n = 4) and a psychotic disorder not otherwise specified (n = 1).*
[b]*other: schizoaffective disorder (n = 4) and psychotic disorder not otherwise specified (n =2).*
[c]*mood disorders (n = 2): a pervasive disorder not otherwise specified (n = 1) and an anxiety disorder (n = 1).*
[d]*mood disorders (n = 8): personality disorders (n = 4), alcohol-related disorders (n = 4), somatoform disorders (n = 2), delirium, dementia, and amnestic and other cognitive disorders (n = 2) and a pervasive disorder not otherwise specified (n = 1).*

On average, patients receiving MULTI were younger ($M = -6.45$ years, 95% CI: −10.27 to −2.64), had a higher baseline illness severity ($M = 0.63$, 95% CI: 0.17 to 1.08) and were more frequently diagnosed with schizophrenia or other psychotic disorders ($X^2 = 21.98$, $p < 0.001$) than patients receiving TAU.

Total Use of Somatic and Psychotropic Medication

Table 2 shows the number of patients using ≥1 medicine within the relevant groups at baseline and follow-up, including their median DDD and the result of analyzing dose changes within both groups. In both MULTI and TAU, there were fewer patients using somatic medication after 18 months, and their median DDD significantly decreased. The same was observed in the totals for psychotropic medication. **Table 3** shows the linear regression estimating the effect of MULTI on the change in DDD sum scores for both somatic and psychotropic medication. After adjusting for baseline sum scores, age, diagnosis, and baseline illness severity, the association with the change in the dose of psychotropic medication remained significant in favor of MULTI. This association was not mediated by a change in TAC/h, as no indirect effect was found (ab = 0.06, 95% BCa CI: −0.01–0.26).

Analyses on Medication Subgroups

The results of analyses of changes in subgroups of medication are shown in **Table 2**. For almost all somatic medications, a reduction in the percentage of users was shown in both MULTI and TAU, the largest being in the subgroup regarding the cardiovascular system. The DDD concerning the alimentary tract and metabolism significantly decreased within both groups. For MULTI and TAU this concerned significantly decreased doses of drugs for acid-related disorders (A02; $z = -4.22$, $p < 0.001$), constipation (A06; $z = -4.68$, $p < 0.001$), and diabetes (A10; $z = -2.97$, $p = 0.003$). For TAU, decreases in this main group were also reflected in dose reductions in drugs for acid-related disorders (A02; $z = -4.0$, $p < 0.001$) and constipation (A06; $z = -4.11$, $p < 0.001$), but not for diabetes. Although the median dose of cardiovascular system drugs increased within TAU, the percentage of users decreased. A significant decrease in dose was observed in beta-blocking agents in both MULTI (C07; $z = -4.00$, $p < 0.001$) and TAU (C07; $z = -3.54$, $p < 0.001$). Patients receiving MULTI also used a lower dose for disorders of the respiratory system, as shown by a significant decrease of medication for obstructive airway diseases (R03; $z = -2.56$, $p = 0.01$), while TAU showed a decreased use of medication of blood and blood-forming organs, as reflected by lower use of antithrombotic agents (B01; $z = -2.06$, $p = 0.04$).

For psychotropic medication, a reduction in the percentage of users was shown for almost all subgroups as well, the highest decrease being 40% in users of anxiolytics, hypnotics, and sedatives within MULTI. Both groups showed significant reductions in dose of medications such as antiepileptics, anti-Parkinson drugs, atypical antipsychotics, anxiolytics, hypnotics and sedatives, and psychoanaleptics. In contrast to TAU, MULTI also showed a decrease in the dose of typical antipsychotics.

DISCUSSION

In the current study, we observed a significant dose reduction in psychotropic medications after 18 months of MULTI, compared to TAU. Although the dose reduction in somatic medication was in favor of MULTI too, it was not significant. When these main groups were split into subgroups, there was a lack of power for corrected between-group analyses. However, the first steps in gaining more detailed insight into dose reductions by using within-group analyses showed interesting leads, for example, in the reduction of medication for diabetes and the respiratory system, which is in line with previously reported physical health improvements within MULTI (35). It also showed clearly the remarkable dose reductions in TAU. It is not likely that this is a time effect, as there was no change of policy in the organization regarding the dosage of medication during these 18 months. The reductions might, however, be a disruptive effect caused by

TABLE 2 | Number of patients using at least one medicine within main groups of medication at baseline and follow-up, their median daily defined dose, physical activity scores and the results of analyzing changes in dose and physical activity within both MULTI and TAU ($N = 114$).

Outcome	MULTI ($n = 65$)									TAU ($n = 49$)								
	Baseline				Follow-up					Baseline				Follow-up				
	n	(%)			*n*	(%)			*p*	*n*	(%)			*n*	(%)			*p*
Somatic medication[a]	60	(92)	**2.65**	**(1.51–5.13)**	54	(83)	**0.58**	**(0.50-1.69)**	**<0.01**	48	(98)	**2.35**	**(0.84–3.90)**	42	(86)	**1.00**	**(0.50–2.37)**	**<0.01**
Alimentary tract and metabolism (A)	53	(82)	**2.33**	**(1.38–3.61)**	53	(82)	**0.50**	**(0.50–1.05)**	**<0.01**	46	(94)	**1.83**	**(0.50–3.05)**	40	(82)	**0.50**	**(0.50–1.19)**	**<0.01**
Blood and blood forming organs (B)	2	(3)	3.00	(2.00–*)	2	(3)	1.62	(1.00–*)	0.72	10	(20)	**1.25**	**(1.00–2.25)**	6	(12)	**0.67**	**(0.30–1.20)**	**0.04**
Cardiovascular system (C)	34	(52)	**0.85**	**(0.36–1.67)**	13	(20)	**0.73**	**(0.33–1.17)**	**<0.01**	24	(49)	**0.42**	**(0.19–1.25)**	12	(25)	**0.83**	**(0.42–1.13)**	**0.02**
Respiratory system (R)	15	(23)	**1.00**	**(1.00–1.50)**	5	(8)	**0.50**	**(0.25–0.75)**	**<0.01**	6	(12)	1.10	(0.92–3.03)	5	(10)	1.00	(0.25–1.35)	0.16
Psychotropic medication[a]	65	(100)	**3.74**	**(2.32–5.87)**	49	(75)	**0.79**	**(0.43–1.50)**	**<0.01**	45	(92)	**2.61**	**(1.92–4.49)**	39	(80)	**0.95**	**(0.42–1.83)**	**<0.01**
Antiepileptics (N03)	20	(31)	**0.82**	**(0.38–1.30)**	9	(14)	**0.17**	**(0.08–0.33)**	**<0.01**	7	(14)	**1.00**	**(0.60–1.67)**	5	(10)	**0.20**	**(0.11–0.30)**	**0.02**
Anti–Parkinson (N04)	20	(31)	**0.40**	**(0.40–0.60)**	5	(8)	**0.20**[†]	[†]	**<0.01**	10	(20)	**0.40**	**(0.20–0.53)**	4	(8)	**0.20**[†]	[†]	**0.01**
Typical antipsychotics (N05A)	30	(46)	**1.25**	**(0.72–2.33)**	17	(26)	**0.83**	**(0.23–1.79)**	**<0.01**	20	(41)	0.73	(0.48–1.13)	13	(27)	0.36	(0.13–1.21)	0.07
Atypical antipsychotics (N05A)	53	(82)	**1.25**	**(1.00–1.85)**	37	(57)	**1.17**	**(0.88–1.70)**	**<0.01**	28	(57)	**1.27**	**(0.88–2.00)**	24	(49)	**1.00**	**(0.14–1.88)**	**<0.01**
Lithium (N05AN)	5	(8)	0.90	(0.56–0.90)	3	(5)	0.68	(0.45–*)	0.21	3	(6)	0.45	(0.45–*)	2	(4)	0.23[†]	[†]	0.10
Anxiolytics, hypnotics & sedatives (N05B+C)	39	(60)	**1.20**	**(0.70–1.80)**	13	(20)	**0.40**	**(0.40–0.80)**	**<0.01**	31	(63)	**1.20**	**(0.50–2.40)**	20	(41)	**0.40**	**(0.20–1.00)**	**<0.01**
Psychoanaleptics (N06)	28	(43)	**1.50**	**(1.00–2.00)**	9	(14)	**0.38**	**(0.29–0.75)**	**<0.01**	23	(47)	**1.00**	**(1.00–1.50)**	9	(18)	**1.00**	**(0.29–1.00)**	**<0.01**
Other nervous system drugs (N07)	2	(3)	0.88	(0.69–*)	2	(3)	0.71	(0.18–*)	1.00	1	(2)	0.36[†]	[†]	1	(2)	0.18[†]	[†]	0.32
Physical activity[b]																		
Wear time during measurement (hours)			55.9	(7.8)			53.6	(9.1)	0.07			55.1	(10.2)			53.3	(10.0)	0.29
Average total activity counts per hour			**29102**	**(12371)**			**33020**	**(14453)**	**0.01**			24636	(14210)			23793	(13151)	0.62

Significant differences within groups are shown in bold.

MULTI, MUltidisciplinary Lifestyle enhancing Treatment for Inpatients with severe mental illness; TAU, Treatment As Usual.

[a] *Median (IQR)*

[b] *Mean (SD)*

[*] *not available due to a low number of users and therefore a lack of dispersion.*

[†] *the daily dosages are constant.*

TABLE 3 | Linear regression estimating treatment effects of MULTI compared to treatment as usual on mean daily defined dose ($N = 114$).

Outcome (ATC code)	B	(95% CI)	*p*
Somatic medications (A, B, C, R)*			
Model 1	**−0.48**	**(−0.90– −0.06)**	**0.025**
Model 2	−0.44	(−0.88–0.01)	0.054
Model 3	−0.38	(−0.87–0.11)	0.130
Psychotropic medications (N)			
Model 1	**−0.47**	**(−0.86– −0.07)**	**0.022**
Model 2	**−0.48**	**(−0.90– −0.07)**	**0.023**
Model 3	**−0.55**	**(−1.00– −0.09)**	**0.020**

Significant results are shown in bold. MULTI, MUltidisciplinary Lifestyle enhancing Treatment for Inpatients with severe mental illness; ATC code, Anatomical Therapeutic Chemical code; A, Alimentary tract and metabolism; B, Blood and blood-forming organs; C, Cardiovascular system; R, Respiratory system; N, Nervous system.
Model 1: crude model, corrected for baseline measurement.
Model 2: adjusted model, corrected for baseline measurement and age.
Model 3: adjusted model, corrected for baseline measurement, age, diagnosis (schizophrenia and other psychotic disorders, yes/no) and illness severity at baseline.
**n = 112, as two outliers were excluded.*

a change in medical staff during the 18 months of this study. The psychiatrist responsible for the majority of the patients within TAU retired and was replaced by a younger colleague, who critically reviewed medication policies. Nevertheless, such a critical review had already been done on the wards receiving MULTI prior to its implementation, so dose reduction was not a specific goal within MULTI. Therefore, the significant decrease in the dose of psychotropic medication is even more striking. One explanation could be that this may be caused partly by decreased psychotic symptoms, but earlier results of the MULTI study showed no significant changes in these symptoms, as compared with TAU, after 18 months (35). Another explanation may be that the psychiatrists reduced the dose of medication based on observed improvements in psychosocial functioning in people who received MULTI (42). It is, however, challenging to clarify specific mechanisms with regard to dose reduction, as there are many variables involved (e.g., interactions between different medications; changes in and preferences of the staff; etc.).

Our findings are somewhat in line with the only other study known to us that evaluated medication use after a lifestyle focused program in patients with SMI (43). In that naturalistic study, Højlund et al. found a decrease in the use of antipsychotics in patients, although they found no specific association between these changes and the degree of participation in the intervention they delivered. However, their reported proportions of patients who used psychotropic co-medication (N categories except for N05) showed little change at follow-up, which is not in line with our observations. Differences may be caused by a different population, as their study was conducted in outpatients with a substantially shorter history of illness, who were relatively young and of whom only a minority used psychotropic co-medication. Also, the absence of a comparison group without lifestyle support makes it difficult to compare results. Indicating decreases in medication use after lifestyle improvement is however very relevant for clinical practice. The ideal situation would be to have medication that addresses the symptoms of psychosis with minimal side effects. However, due to a lack of fundamental innovation in psychopharmacology during recent decades, we still have to work with antipsychotics with a range of motor, metabolic, and cognitive side effects (28, 44). Moreover, as there is still an overall favorable benefit-to-risk ratio for the use of antipsychotics (45), addressing lifestyle is of importance to help minimize such side effects. Besides previously reported improvements in physical health (35), current results show that an integrated multidisciplinary approach is associated with a decrease in the dose of medication. Thereby, it potentially reduces (the risk for) those side effects, which are partly dose-dependent (11, 46). Additionally, because many but not all side effects are reversible, it suggests that lifestyle improvements could contribute to the prevention of irreversible effects, e.g., motor side effects. The reductions found are also promising from the patient's point of view, as side effects and negative attitudes toward medication use are associated with non-adherence, distress, and life impact (47–50).

Our explorative mediation analysis showed that the increase in physical activity observed in patients receiving MULTI after 18 months (35) did not mediate the association between MULTI and change in psychotropic medication use in this same period of time. This indicates that the decrease of psychotropic mediation was not a result of just increasing physical activity. We hypothesize that, with an organizational culture change as a base, multiple components that complement physical activity contribute to improvements, including focus on dietary habits, psycho-education, personal tailoring, and support by peers and qualified participating staff, in line with recent studies advocating the use of such elements (29, 30, 51–53). Such a holistic approach, in which patients are encouraged to do any activities instead of none (i.e., decreasing sedentary behavior), may be more feasible and beneficial in the longer term for inpatients with SMI. While previous studies have shown that structured exercise is feasible in those with SMI in general (31), sedentary behavior (as distinct from physical inactivity) is highly prevalent and associated with cardiometabolic risks that are largely independent of time spent in structured exercise (7, 8). Thus, controlled trials are needed to examine further the feasibility and effects of interventions targeting sedentary behavior.

Limitations in this study mainly arise from the naturalistic and observational design. In this design, we were not able to randomize patients (e.g., the TAU wards treated fewer patients with psychotic disorders) and control for treatment settings in advance (e.g., the continuity of psychiatrists). In addition, although dose reduction was not a specific goal of MULTI, psychiatrists were not blinded for patients' treatment condition (i.e., receiving MULTI or not), which might have affected observed dose reductions. Although this observational study seems the first indicating a possible effect of lifestyle improvements on medication use in inpatients with SMI, future well-designed trials are needed to study the efficacy of lifestyle changes on medication use. Regarding the participation of patients in MULTI, we have no specific data on (the degree of) their adherence. It was intended that all patients were doing some activities in the morning and afternoon, tailored to the particular

ward and patients' abilities and interests. However, data on adherence to these individualized day-to-day programs including more detailed data on participation (e.g., frequency and intensity of activities) would make it possible to study the association between the (degree of) adherence and treatment outcomes. Also, our analyses depended on the availability of data within the cohort. Nevertheless, by using multilevel analyses adjusting for differences between MULTI and TAU, we aimed for robust results. However, more data will be needed to have sufficient power for adequate between-group analyses within subgroups of medication, whereby we could gain more detailed insight into specific reductions as indicated by within-group analyses (e.g., drugs for diabetes or obstructive airway diseases). This would provide the opportunity to control for possible differences between groups such as age, which can affect the prescribed dosages of medication (54–56). Furthermore, we used a simple mediation model to explore the influence of a change in physical activity, as an essential element of MULTI, on the association between MULTI and change in medication use. However, the main limitation of this is that by measuring all variables within the mediation analyses nearly simultaneously, we assumed that the association between change in total activity and change in medication use between our pre (T1) and post measurement (T2) would be the same as we would have measured between T2 and a (theoretical) third time point. To study if physical activity mediates associations between lifestyle interventions and medication use, in general, it would be the best to measure physical activity as a middle time-point to study the effect of a change in physical activity over time. Finally, we did not include pro necessitate medication (i.e., to be given as needed) because we cannot specify if and to what extent patients took these medications. The strength of this study is that it is the first study to report detailed dose-specific data on changes in both somatic and psychotropic medication use in inpatients with SMI after lifestyle changes. Despite the limitations, first steps were taken to analyze associations between lifestyle improvements and medication use in these patients, who are suffering from severe physical health problems and receive high dosages of medication. The naturalistic setting of the study improves the generalizability of the results and meets the need for observational studies to supplement randomized controlled trials in order to improve the external validity, such that clinicians treating patients in real-world settings have relevant evidence on which to base their clinical decisions (57). Regarding the impact of critically reviewing medication use that was most likely observed in TAU, it is a strength in favor of MULTI that medication was already critically reviewed on these wards before its implementation, so dose reduction was not a specific goal within MULTI. This suggests that lifestyle improvement has added value with regard to decreasing the dose of medication in inpatients with SMI. Above all, this strengthens the fact that we compared it with TAU. Otherwise, we would only have observed the improvements in MULTI without any context. Moreover, by analyzing possible mediation by total activity, we took a first step to gaining more insight into the contribution of different elements of MULTI to the observed improvements. Finally, by including baseline measures in this analysis, our mediation analysis is mathematically in line with a covariance approach, which was the recommended method for mediation analyses (58, 59).

In summary, in addition to previously reported improvements in physical activity and metabolic health after 18 months of MULTI, we observed a significant decrease in dose of psychotropic medication as compared with TAU. We encourage further longitudinal controlled research to gain more insight into the relationship between lifestyle changes and possible dose reductions to improve health outcomes in inpatients with SMI.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author on reasonable request and with permission of GGz Centraal.

AUTHOR CONTRIBUTIONS

JD: obtaining funding, study design, retrieving, processing and analyzing data, drafting the manuscript; DT: study design, supporting retrieving, processing and analyzing data; HvD: retrieving, processing and supporting analyzing data; IH: supporting analyzing data; DT and PvH: supporting grant applications; All authors critically revised the manuscript and approved the final version.

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Why Do People With Schizophrenia Exercise? A Mixed Methods Analysis Among Community Dwelling Regular Exercisers

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Individuals with schizophrenia have reduced rates of physical activity, yet substantial proportions do engage in independent and regular exercise. Previous studies have shown improvement in symptoms and cognitive function in response to supervised exercise programs in people with schizophrenia. There is little data on motivations of individuals who exercise independently, or their chosen type, duration, or setting of exercise. This study explores motivational parameters and subjective experiences associated with sustained, independent exercise in outpatients with a diagnosis of schizophrenia or schizoaffective disorder. Participants completed a semi-structured interview and then were given a prospective survey containing visual analog scales of symptom severity and the Subjective Exercise Experiences Scales to complete immediately before and after three sessions of exercise. Results from the semi-structured interview were analyzed by modified content analysis. The most important reason for exercise was self-image, followed closely by psychological and physical health. Among psychological effects, participants reported exercise was most helpful for mood and cognitive symptoms. The prospective ratings demonstrated 10–15% average improvements in global well-being, energy, and negative, cognitive and mood symptoms, with almost no change in psychosis, after individual exercise sessions. This suggests that non-psychotic parameters are more susceptible to inter-session decay of exercise effects, which may reinforce continued exercise participation.

Keywords: schizophrenia, exercise, lifestyle psychiatry, psychiatry, community dwelling adults with schizophrenia, qualitative analysis

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INTRODUCTION

The benefits of exercise are well-established and include not only weight loss and improved cardiovascular fitness, but also a reduction in risk of early mortality and cognitive decline (1, 2). Exercise also has the potential to prevent or delay the onset of several mental health disorders (3, 4). More recent studies have shown that exercise can have therapeutic effects for patients with psychiatric disorders and can specifically help to control and reduce the symptoms of schizophrenia (4, 5). Randomized controlled trials (RCTs) have identified that exercise significantly improves negative symptoms (such as social withdrawal, anergia, or apathy) but few studies have shown an

improvement in positive symptoms (most notably delusions or hallucinations) of schizophrenia (6–8). A recent review of 10 RCTs found significant improvement in global cognition among those receiving an exercise intervention, with medium to large effect sizes for improvements in working memory, social cognition and attention (9). Recent designs have turned toward combining exercise with cognitive rehabilitation in an attempt to magnify effects (10). Some studies have identified release of neurotrophic factors, changes in regional or global brain volume and even preservation of telomere length and integrity as possible biological underpinnings of these benefits (11).

As noted by Farholm and Sorenson, physical activity may be quite challenging for those with severe mental illness due to several barriers such as medication side effects, symptoms of mental illness, lack of support and even motivation (12). While many studies have addressed the other barriers, relatively few studies address motivation. A recent systematic review and meta-analysis of patients with any severe mental illnesses (such as schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, etc.) found that 91% of the participants were motivated to exercise to "improve health" with the most common response being "losing weight." "Improving mood" and "reducing stress" were other common responses. These same patients also identified many barriers to participating in physical activity (13). When the motivations for exercise of people suffering specifically from "early psychosis" were examined, improving health also stood out as the main motivator for exercise. Interestingly, this subpopulation did not identify weight loss as the top motivator for exercise, as "increasing fitness/energy" was the top response followed by "taking your mind off things" and "being more confident in a gym." The author points out that weight loss may not be a realistic goal in the short term, and it is encouraging that there are other more important motivators for physical activity (14).

Existing study designs have typically evaluated the addition of a time-limited exercise regimen to the routines of patients with schizophrenia who live a sedentary lifestyle. A recent meta-analysis by Vancampfort found that half of patients with severe mental illness do not get more than 150 min of moderate aerobic exercise per week (15). Conversely, this analysis indicates that there is a substantial subset of patients with severe mental illness who do exercise regularly. To our knowledge, no research has been conducted on the subset of patients with schizophrenia who have independently and spontaneously incorporated exercise into their lifestyles.

There are several advantages of exercise over other modes of therapy. First, exercise can lead to improvement in both the individual's physical and mental health. Second, exercise is the only available intervention in schizophrenia, a disorder associated with atrophic brain changes, which has clear and sustained neurotrophic effects (16). Additionally it is available to individuals who are apprehensive about taking medications or have contraindications to medications. It requires no equipment or access to a provider. It can be done at any time convenient to the individual and can be varied to meet the individual's specific needs or tastes. It requires only time, and can provide structured activity to a daily schedule. Finally it can be used as an adjunctive therapy that may allow the individual to minimize the use of other modes of therapy such as medications or to combat side effects associated with anti-psychotic medications such as weight gain (17).

There is currently very little evidence to guide clinicians in methods to support individuals with schizophrenia engaging in regular exercise (18). Furthermore, most studies lack data on the subjective experience of participants or how an individual's motivation to exercise can be sustained beyond the end of the study intervention. This study used a semi-structured interview to explore factors motivating sustained, independent exercise in a population of individuals with a diagnosis of schizophrenia spectrum disorder and prospectively evaluated the mental health effects of individual sessions of exercise in these individuals.

METHODS

The project received approval from the university institutional review board. The investigators identified eligible participants from throughout the clinical care sites of a medical center in rural New Hampshire and Vermont. Participants were drawn from the authors' usual care clinics for people with schizophrenia spectrum disorders including a residential treatment program and a community mental health center. Encouragement of a healthy lifestyle was routinely incorporated into care, but treatment was otherwise typical for patients with schizophrenia. Inclusion criteria for participating were being of age 18 years or older, with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder, and exercising spontaneously for at least 30 min, three times a week, for at least a month. Participants could have co-morbid diagnoses, such as depression or substance use disorder. Participants were taking a range of commonly prescribed antipsychotic medications including risperidone, clozapine, olanzapine, and aripiprazole. Few were taking first generation agents. Exclusion criteria were irregular exercise or physical activity that did not meet definition of exercise (e.g., hyperactivity that is not planned or purposeful or whose objective is not improving physical fitness *per se*) and inability to read or write in English.

Informed consent was obtained from all potential participants prior to screening with the modified SCID. Once an eligible diagnosis was confirmed, participants completed a semi-structured interview following a template with one of the investigators (DND or DLN). The interview included demographic information, as well as, open-ended questions regarding the reasons for exercise, whether exercise helped manage symptoms, what participants do to motivate themselves to exercise, and information on exercise type, frequency, duration, and interruptions. The investigators then reviewed the instructions for participant self-rating before and after three future sessions of exercise. After reviewing how to complete the scales, participants were given 3 sets of pre- and post-exercise scales with a stamped envelope and offered a $10 gift card to return the study materials to investigators once completed. Laboratory and medication data were collected by chart review using the most recent available results.

In order to assess each patient's experience with exercise, we selected the Subjective Exercise Experience Scale (19) (SEES), a 12-item self-report scale assessing three general categories of subjective responses to exercise stimuli: positive well-being (e.g., great), psychological distress (e.g., miserable), and fatigue (e.g., tired). For each item on the SEES, participants rate how strongly they are experiencing each feeling state along a 7-point Likert scale, ranging from 1 (not at all) to 7 (very much so). The SEES has been shown to have high internal consistency across a variety of populations.

Given the lack of an existing psychosis self-report scale, we also created a simple scale using a visual analog format to capture each participant's experience of well-being and symptoms in their natural exercise environment, which we named the Noordsy-Dahle Subjective Experience Scale (NDSE). The NDSE asked participants to rate the present status of their symptoms and wellbeing on a 10 cm line. The NDSE was constructed with 2 items each for psychosis (hallucinations, delusions), negative symptoms (motivation, social interest), mood (depression, anxiety) and cognition (clarity of thought, concentration). Global well-being was measured with the well-validated Lehman Quality of Life (QOL) scale (20), and an additional item rating energy, a dimension identified by many patients as central to their well-being (21). A detailed description of each item was provided, as well as, anchors at each end of the visual analog line. For psychosis and mood items, 0 corresponded to "none," and 10 to "extreme." For motivation, social interest, cognition and energy items, 0 was low and 10 was high. On the global QOL item, 0 corresponded to "delighted," and 10 to "terrible." Mean pre-workout scores on the NDSE were calculated for each item to provide a reference baseline.

The data collected from the semi-structured interview was analyzed by modified content analysis. Participant answers were categorized using a priori categories included in the interview template (available on request) but were also searched for any emerging themes that were not hypothesized prior to the interview. Responses were coded and collated by theme and frequencies calculated. The data collected on the NDSE was converted into numerical values by measuring the point marked by the participant from 0 to 10 cm along the visual analog line. These values and the numerical values from the SEES were used to calculate the change from pre- to post-exercise for each item in each episode of exercise rated and then the mean change in each item across all exercise sessions was calculated.

RESULTS

Twenty-three participants were enrolled in the study and completed the semi-structured interview. Participants had a mean age of 37.6 years (standard deviation 13.5 years, range 18–67 years). Seventy percent were male, 30% were female and there was an average duration of illness of 15.4 years. Fourteen participants (61%) returned the pre-post NDSE and SEES ratings for three exercise episodes, resulting in 42 ratings of response to exercise.

TABLE 1 | Study participant characteristics.

Variable	*N* = 23	%
Completion of scales	14	60.8
Male	16	69.5
Diagnosis		
Schizophrenia	10	43.5
Schizoaffective	13	56.5
Schizophreniform	0	0
Antipsychotic Use		
Participants on 1	13	56.5
Participants on >1	10	43.5
Co-morbidities		
Diabetes	3	13
Hypertension	5	21.7
Hyperlipidemia	5	21.7
Tobacco use	3	13
Health parameters	**Mean**	
BMI	28.9 kg/m^2	
Total cholesterol	176.3 mg/dL	
HDL	57 mg/dL	
LDL	91.2 mg/dL	
Triglycerides	142.1 mg/dL	
Blood glucose	102 mg/dL	
Systolic BP	122 mmHg	
Diastolic BP	80 mmHg	
Heart rate	87 BPM	

Demographic, metabolic, and treatment characteristics are presented in **Table 1**. 56.5% of the participants were diagnosed with schizoaffective disorder and 43.5% with schizophrenia. 56.5% of the participants were taking one antipsychotic medication at the time of the study, and 43.5% were prescribed more than one. Thirteen percent of the study participants used tobacco products during the study, 13% carried a diagnosis of diabetes, 22% had hyperlipidemia, and 22% had hypertension. Mean BMI was 28.9 kg/m^2 (overweight) and most recent mean serum glucose was 102 mg/dL (borderline high). However, mean blood pressure, pulse and lipid values were all in normal range.

In terms of medication treatment, 13 patients (56.5%) were on one antipsychotic medication while the other 10 (43.5%) were taking two antipsychotic medications during the study. The most common antipsychotic medications were clozapine (12 participants taking), olanzapine (5 participants taking), and aripiprazole (5 participants taking). Other participants were taking risperidone, quetiapine, paliperidone, lurasidone, and haloperidol. Finally, 2 participants were taking long acting injectable versions of antipsychotic medications: one on olanzapine and the other on paliperidone. Information on dosage was not collected. Mean pre-workout NDSE ratings ranged between 1.6 and 2.7 on psychosis and mood symptoms; 5.4–6.7 on motivation, social interest, cognition and energy items, and 3.7 on global QOL (**Table 2**).

Participants reported an average of 4.2 exercise sessions a week with 43.5% working out for more than 60 min. Most participants

TABLE 2 | NDSE mean pre-workout baseline scores.

NDSE item	Mean pre-workout score (cm)	Standard deviation
Global QOL	3.7	2.2
Anxiety	2.2	2
Depression	2.7	2.6
Energy	5.4	2.1
Hallucinations	1.6	2.5
Delusions	1.9	2.6
Motivation	5.9	2.5
Clarity of thought	6.7	2.4
Concentration	6.4	2.5
Social interest	5.7	2.8

(63.5%) reported working out alone. Running, weight lifting, cycling and swimming were the most popular types of exercise, with smaller proportions engaging in more diverse forms of exercise.

Participants overwhelmingly reported (91%) that the reason that they exercise is for "myself" rather than for others. Most participants (61%) had learned to exercise early in life but noted at least one period of significant disruption, usually due to an exacerbation of their mental illness. The encouragement of a doctor was helpful in re-starting exercise for 35.5% of participants. Almost seventy percent (69.6%) of participants ranked the number one reason for exercising as "self-image." The same percentage of participants also reported psychological and physical health as very important reasons to exercise when allowed to choose more than one reason for why he or she exercised (**Table 3**).

On the SEES, study participants rated 0.6–0.2 point mean increases in feeling "Great," "Exhausted," "Positive," "Terrific," and "Strong" in response to exercise sessions (**Figure 2**). In addition, they rated 0.4–0.2 point mean reductions in feeling "Awful," "Crummy," and "Discouraged" (22).

A majority of participants (56.5%) identified depression and cognitive slowing to be improved by exercise and 43.5% reported that exercise improved their anxiety in the semi-structured interview. This is in contrast to 8.7% of participants who identified exercise as improving psychotic symptoms such as hallucinations or paranoia. This was consistent with the prospective NDSE ratings that showed 7–11% average decreases in anxiety and depression and 10–11% average increases in clarity of thought and concentration with almost no change on average in hallucinations and delusions in response to individual exercise sessions (**Figure 1**) (22). NDSE ratings also showed participants rated 9–15% average increases in global QOL, energy, motivation, and social interest with each exercise session (22).

TABLE 3 | Semi-structured interview participant responses.

Topic	Responses	Participants (%)
Who do you exercise for?	Myself	91
	Others	9.1
Why do you exercise?	Self-image[a]	69.6
	Psychological health	69.6
	Physical health	69.6
	Socialization	13
	Energy	13
What improves with exercise?	Depression	56.5
	Cognitive slowing	56.5
	Anxiety	43.5
	Amotivation	26.1
	Mindfulness	17.4
	Disorganization	11.5
	Hallucinations	8.7
	Paranoia	8.7
If you do not feel like exercising, what helps?	Reminding self of benefits	30.4
	Accountability partner	26
	Reminding self of goals	17.4
	Watch TV/YouTube	13
	Nothing	13
Exercise pattern throughout life	Started young with substantial interruptions[b]	61
	Regular since childhood	34.8
	Started as adult	4.3
If there was a substantial interruption, what motivated you to re-start?	Encouraged by doctor	35.3
	Did not feel as good	23.5
	Encouraged by family/friend	23.5
	Health reasons	11.8
Current types of exercise	Running/walking	91.3
	Weight Lifting	73.9
	Cycling	52.2
	Swimming	47.8
	Elliptical/Stair-climber	34.7
	Aerobics class, Pilates, dance	21.7
	Skiing/Snowboarding	21.7
	Organized sports	13
	Hiking	13
Duration of exercise (minutes)	30–44	30.4
	45–60	17.4
	More than 60	43.5
Who do you exercise with?	No one (workout alone)	63.5
	With one or more people	36.4

[a] *Participants ranked this as the most important reason when asked to rank choices if multiple answers were given.*

[b] *The most common reason for an interruption was acute exacerbation of mental illness.*

DISCUSSION

Evidence pertaining to the effects of exercise in individuals with schizophrenia-spectrum disorders is growing. Typical designs, however, evaluate the effect of a time-limited exercise intervention on individuals who are sedentary at baseline. This study examined factors motivating and sustaining exercise in a unique population of individuals with schizophrenia-spectrum disorders who were already independently and regularly exercising. This study also examined whether self-reported retrospective mental health effects of exercise were

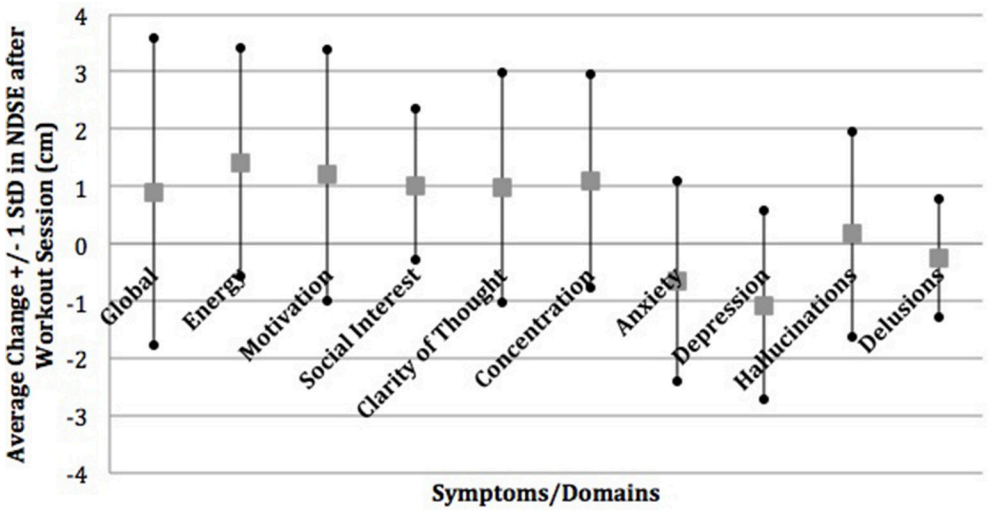

FIGURE 1 | Mean change in NDSE visual analog scales. Reprinted from Dahle and Noordsy (22) with permission from Elsevier.

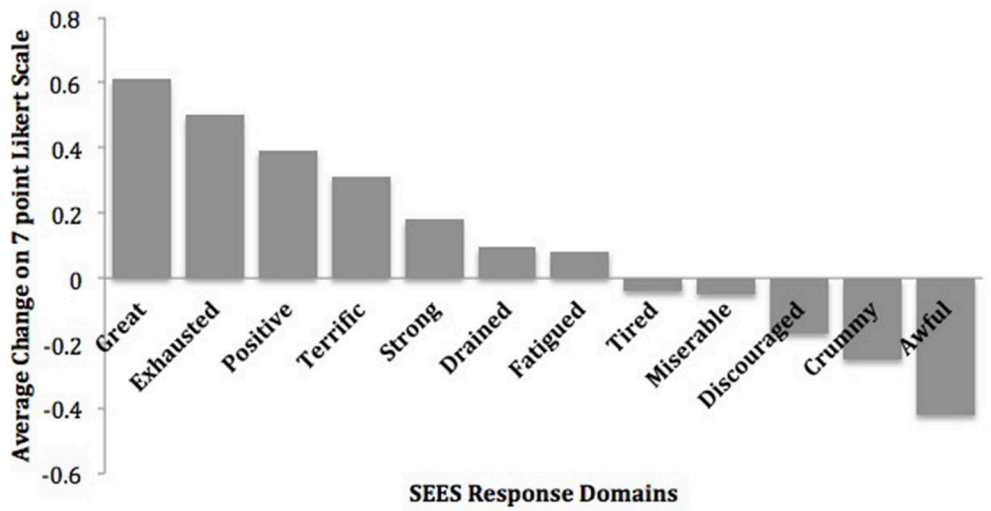

FIGURE 2 | Mean change in subjective exercise experiences scale. Reprinted from Dahle and Noordsy (22) with permission from Elsevier.

consistent with prospective ratings at the time of actual exercise sessions.

A recent systematic review found that people with schizophrenia engage in "significantly less" exercise than controls without schizophrenia, with about half of people with schizophrenia meeting a recommended 150 min of moderate physical activity per week (23). Our selected sample engaged in at least 90 min of exercise per week and reported an average of 4.2 sessions of running, weight lifting, cycling, swimming and other forms of exercise per week, with a majority reporting more than 45 min and nearly half reporting more than 60 min of exercise per session. Taken together, these findings indicate that while people with schizophrenia can stereotypically be considered inactive, some individuals engage in types and durations of exercise that would be considered exceptional in the general population.

Our study showed that individuals with schizophrenia-spectrum disorders were most commonly motivated to exercise for "self-image" or, as one participant stated, "to look good in jeans." This is noteworthy, as overemphasis by the medical community on the physical and mental health benefits when attempting to motivate patients to add a routine of physical exercise may be misguided. This motivation is consistent with past research on motivation for exercise in other populations. As noted by Brudzynski and Ebben in a study of body image and exercise in a midwestern university population, "appearance, was identified as the most common contributor to individual exercise behaviors" (24). While the patients in our study did identify physical and mental health reasons as motivators for exercising,

these were neither the primary nor the most important reasons. Furthermore, the finding that most of this unique population developed regular exercise habits during youth suggests the importance of culture and community in shaping healthy habits that can be sustained despite a diagnosis of major mental illness. It also shows the important role that physicians can play in encouraging patients to resume regular exercise after a disruption due to an acute exacerbation of their illness.

Our finding that people with schizophrenia report improved global well-being, depression, anxiety, energy, motivation, and cognition is consistent with prior research on mental health effects of exercise across multiple populations (25). Effects on subjective energy are mixed and may represent differences in impact on physical and mental energy. The finding of improved mood, negative, and cognitive symptoms with limited impact on positive symptoms is consistent specifically with prior research among people with schizophrenia (26). Although the effects were subjective and modest, these findings were consistent across both semi-structured interviews and structured prospective ratings.

Our sample reported low mean levels of psychosis and mood symptoms, moderate levels of motivation, social interest, cognition and energy and slightly favorable QOL immediately prior to their naturalistic exercise sessions. While population norms have not been established for the NDSE and there was substantial variability, these ratings suggest that our study participants were not highly symptomatic prior to exercise. This could mean that independent exercise represents a marker of high functioning, or be due to accrued benefits of their exercise activity. It is also possible that participants chose to exercise at times when they were less symptomatic or experienced anticipatory improvement in symptoms and well-being prior to exercising.

We found modest changes on the SEES and NDSE ratings of mental health parameters from immediately before to immediately after individual sessions of exercise. It is logical that single session effects would be smaller than cumulative effects over months of exercise. Given that respondents engaged in 30–60 + min of exercise per session, these effects are occurring quite rapidly. Participants were selected for sustained exercise, so they have likely accrued gains in their mental health prior to participation. These measures are targeting the time-limited effects of exercise that fade prior to the next exercise session. Therefore, the semi-structured interview provides evidence on the global effects of sustained exercise over individuals' moderate to long-term awareness, while the SEES and NDSE ratings hone in on the immediate reinforcing effects of individual exercise sessions. This suggests that benefits of exercise in non-psychotic symptom domains are subject to decay in the 1–2 day period between exercise sessions.

A meaningful subset of participants did report improvement in symptoms of psychosis in response to exercise in the interview, which was not reflected in the mean NDSE ratings. This suggests that the impact of exercise on the subjective experience of psychosis may be more gradual and sustained. It is also possible that the subset that reported improvement in psychosis were less likely to return completed NDSE ratings, or that low baseline levels of psychotic symptoms created floor effects.

The biological effects of vigorous sustained physical activity or exercise on the human body are numerous and include cardiovascular, pulmonary, metabolic, musculoskeletal, and immunologic regulation, as well as, changes in brain functioning and anatomy (27). In people with psychiatric disorders, no single mechanism has been found to account for the diverse range of health effects of exercise. Several have been suggested: (1). biochemical changes such as increased levels of neurotransmitters (e.g., endorphins or serotonin) or altered stress reactivity (hypothalamus-pituitary-adrenal axis), (2). physiological changes such as improved cardiovascular function or thermogenesis, and (3). psychological changes such as social support, sense of autonomy, experience of mastery, enhanced body image, self-efficacy, and improved coping skills (e.g., use of distraction) (25, 28, 29). One mechanism that has been proposed for people with schizophrenia is exercise-induced neurogenesis and synaptic proliferation. A study by Pajonk et al. found exercise-induced increases in hippocampal volume and decreases in positive and negative symptoms within 3 months, and another by Scheewe et al. found increases in gray matter volume and cortical thickness by 6 months (16, 30). While there is some evidence to suggest that neurogenic effects may develop relatively quickly in response to exercise, meaningful effects on mental and physical health will likely require sustained lifestyle changes (13).

Our study was limited by several factors. Our study relied on self-report and the use of less structured probes for the interview portion of the assessment. Interviewers may have elicited responses that participants might not have offered spontaneously. Validated measures of negative symptoms rely heavily on rater observation and it is not clear that people can accurately self-report this construct. Our study population was small, and recruited from a rural sample of patients. Although this convenience sample may not be representative of people with schizophrenia in other settings, all patients from the authors' usual care clinics who met criteria and consented to participate within the recruitment window were included. Another limitation is that the NDSE is not yet validated (a validation study is underway). Our participants, however, found the NDSE easy to use and demonstrated an expected degree of responsiveness to individual exercise sessions. Their responses on the NDSE closely paralleled their responses on the well-established SEES.

CONCLUSIONS

To our knowledge, this is the first study to examine a cohort of active and community dwelling individuals diagnosed with schizophrenia in order to describe their exercise patterns and subjective experiences. The granular detail on effects of individual exercise sessions provides a unique view into the experience of exercise for people living with schizophrenia. Our findings establish that some individuals with schizophrenia engage in regular physical exercise that stem from earlier life activities. These individuals identify primary motivations similar to those of people who do not have schizophrenia.

Duration and frequency of exercise rival those of community amateur athletes, and mean metabolic parameters are largely healthy despite BMI in overweight range. Individual sessions of exercise are rapidly reinforced by improvements in several areas including well-being, energy, and non-psychotic symptoms.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the institutional review board of Dartmouth-Hitchcock Medical Center 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 institutional review board of Dartmouth-Hitchcock Medical Center.

AUTHOR CONTRIBUTIONS

DD and DN contributed to study design and implementation. All authors contributed to manuscript preparation and approved the final draft.

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Pilot-Testing of "Healthy Body Healthy Mind": An Integrative Lifestyle Program for Patients With a Mental Illness and Co-morbid Metabolic Syndrome

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Background: Metabolic syndrome and co-morbid physical health conditions are highly prevalent in people with a mental illness. Modifiable lifestyle factors have been targeted to improve health outcomes. Healthy Body Healthy Mind (HBHM) program was developed to provide an integrated evidence-based program incorporating practical diet and exercise instruction; alongside meditation and mindfulness strategies, and comprehensive psychoeducation, to improve the physical and mental health of those with a mental illness.

Methods: We report on two data points: (1) Qualitative data derived from the first HBHM program (version 1) exploring its utility and acceptance according to patient feedback; (2) Biometric and mental health data collected on the modified and enhanced 12-week HBHM program (version 2) involving a pilot of 10 participants. Mental and physical health outcomes, weight, abdominal circumference, fasting glucose, cholesterol, and triglycerides were measured at program entry and completion.

Results: Qualitative data from HBHM version 1 provided valuable feedback to redevelop and enhance the program. At the end of the HBHM (version 2) 12-week program, a significant mean weight loss of 2 kg was achieved, $p = 0.023$. There was also a significant reduction in abdominal circumference (mean = 2.55 cm) and a decrease in BMI of almost one point (mean = 0.96 kg/m^2), $p = 0.046$ and $p = 0.019$, respectively. There were no significant changes in mental health measures or on any other biometrics.

Conclusion: Pilot data from the HBHM program found significant reductions in weight and abdominal obesity. The HBHM program could benefit from further modifications, and study replication is required using a controlled design in a larger sample.

Keywords: healthy lifestyles, lifestyle medicine, metabolic syndrome, depression, program development

INTRODUCTION

A highly complex relationship exists between physical and mental health. The rates of physical morbidity and mortality in people with mental illness is substantially higher than the general population (1, 2). Even in countries with adequate health care systems, the mortality gap is on the rise, up to a difference of 20 years (3). Obesity and related conditions such as cardiovascular disease, hyperlipidaemia, and diabetes mellitus are highly prevalent in people with mental illness (4).

The cluster of symptoms associated with these lifestyle diseases such as, excess visceral fat, along with hypertension, glucose intolerance/insulin resistance, and/or hyperlipidaemia has been labeled Metabolic Syndrome (MetS). In mental health populations, the rate of MetS is thought to be between 41 and 67% (5). A large proportion of the physical health burden in patients with a mental illness can be linked to side effects of second generation antipsychotics, lifestyle factors (e.g., higher rates of smoking, low levels of exercise), and factors associated with socioeconomic disadvantage (e.g., poverty and lack of access to nutritious foods) (6). Weight gain can result in lowered self-esteem, impaired body-image, and reduced social interactions, which can ultimately lead to poorer mental health (7). Furthermore, it is also a common cause of medication non-adherence, which can lead to illness relapse, hospitalization, and poorer outcomes (7, 8).

There is potential to modify lifestyle factors that contribute to MetS (e.g., caloric intake, physical activity levels, sleep hygiene) to improve the health and well-being of people with a mental illness. There are calls for an integrated response involving early diagnosis, treatment and management of physical and mental health via lifestyle modification (9). Several lifestyle-based programs have been developed to modify the lifestyle factors contributing to MetS (10). These programs typically focus on exercise and nutrition for metabolic issues and result in minimal weight loss and modest effects on well-being (10). In one review of lifestyle interventions in adults with a serious mental illness at risk of MetS, few programs incorporated behavioral components such as stress management and motivation alongside exercise and/or nutrition interventions (10). Thus, programs that target both mental and physical outcomes in patients who are taking psychotropic medication have not been adequately developed. Further, previous programs often do not provide a truly "integrative" model, tending to focus on nutrition and exercise without incorporating components that may improve general health and well-being (10).

To bridge the gap and provide an evidence-based integrated health approach, we developed the "Healthy Body, Healthy Mind Program (HBHM)." The aim was to assist people with a diagnosed mental illness and metabolic syndrome to improve mental and physical well-being. We presently report on: (1) Qualitative data derived from our first version of the HBHM program in 2011, exploring its utility and acceptance according to patient and clinician feedback; (2) Biometric data and mental health data collected on the modified and enhanced 12-week, second version of HBHM program involving a pilot of 10 participants.

TABLE 1 | Metabolic syndrome clinical diagnosis guidelines*.

Measure	Categorical cut point
Elevated waist circumference (European/North American)	≥ 102 cm for men, ≥ 88 cm for women
Elevated triglyceride levels (or drug treatment for elevated triglycerides)	≥1.7 mmol/L
Reduced HDL-C (or drug treatment for reduced HDL-C)	<1.0 mmol/L in men, <1.3 mmol/L in women
Elevated blood pressure (or drug treatment for hypertension)	≥130 systolic or ≥85 diastolic
Elevated fasting glucose (or drug treatment for elevated glucose)	>5.5 mmol/L

*For a diagnosis of Metabolic Syndrome, an individual must meet three of the five specified criteria. *As per the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart Lunch and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (11).*

MATERIALS AND METHODS

Setting And Overview

The Melbourne Clinic in Melbourne, Australia is a private psychiatric hospital with inpatient and outpatient services. The clinic had a longstanding weight management and lifestyle program, called Healthy Body Healthy Mind (HBHM), developed and facilitated by a general practitioner (GP), exercise physiologist and dietitian. HBHM program (version 1) provided weekly nutritional support from a dietitian, psychoeducation sessions on lifestyle modification and exercise practicals with an exercise physiologist. In late 2011, ethics approval was granted by The Melbourne Clinic Research Ethics Committee (HREC project number: 209) to collect qualitative data from participants to evaluate the perceived efficacy of the program's content, barriers in implementing the components, and feedback on how it could be improved. The qualitative data collected during 2011–2012 was used to redevelop and enhance the integrated lifestyle program which was pilot-tested at The Melbourne Clinic in 2016 (HREC project number: 249). This modified second program will henceforth be labeled as HBHM program (version 2).

Recruitment

Patients attending The Melbourne Clinic outpatient services were invited to attend the program via a doctor's referral. Patients with a diagnosed mental illness (e.g., Major Depressive Disorder, Bipolar Disorder; or with multiple diagnoses) taking stable psychotropic medication (same dose for at least 4 weeks) with co-morbid diagnosed metabolic syndrome (see **Table 1**) or obesity (defined as a BMI of >30 OR abdominal circumference of >80 cm for women and >94 cm for men) were the target participants for the program. Written informed consent was obtained from all participants to evaluate the two versions of the program.

HBHM Version 2 (2016) Measures

At week 0, a range of medical and demographic information was collected including, age, gender, employment status, medication information, psychiatric diagnosis and medical co-morbidity.

At week 0 and week 12, participants also had anthropometric measurements taken by an exercise physiologist (BP, height, weight, abdominal circumference) and completed self-report questionnaires on their mental health (Depression Anxiety Stress Scales—DASS-21). In addition at week 0, participants were asked to state their goals for the program and what they hoped to achieve. They were also asked to rate their readiness to change in order to achieve their listed goals on a scale of 1–10 with 1 being "not ready" and 10 being "ready." Participants were provided with a blood test request form to have fasting cholesterol, glucose and triglycerides measured at week 0 and week 12. The blood tests were conducted by Australian Clinical Labs.

Depression Anxiety Stress Scales—DASS-21

The DASS-21 is a self-reported screening instrument used to measure depression, anxiety and stress symptomatology (12). It consists of 21-items, across three scales, which measure symptoms of depression (7 items), anxiety (7 items), and stress (7 items). Individuals are asked to respond to each item on a four-point Likert scale (0 = *not at all* to 3 = *very much or most of the time*). Higher scores on each scale are indicative of greater symptom severity. Scores above 11 (depression), 8 (anxiety), and 13 (stress) are considered severe, as indicated by the recommended cut-offs (12).

Statistics

Qualitative data assessing the 2011 HBHM Program (version 1) was analyzed from written participant feedback forms. Comments were coded and grouped in categories by theme (beneficial/useful content, barriers to implementation and program improvements) and counted to obtain a frequency of mention by the 12 participants. For the quantitative data from the 2016 HBHM program (version 2), paired *t*-tests and Pearson's r correlations were used to compare the repeated measurements of the sample (week 0 vs. week 12). All data was analyzed in SPSS 24. An alpha level of <0.05 was used to determine significance.

RESULTS

HBHM Version 1 (2011)—Qualitative Data

Written qualitative data from 12 participants (83% female; mean age 43.4 years old) who participated in the first version of the HBHM program during 2011–2012 was thematically analyzed to aid the development of the 2016 HBHM program. **Table 2** summaries the qualitative data on the early program.

TABLE 2 | Qualitative feedback from HBHM (version 1).

Beneficial/useful content	• Cooking practicals
	  • Hands-on experience
	  • Meal planning with simple and practical recipes
	  • Templates for shopping/organizing pantry
	  • Providing alternative foods to swap out "bad" foods
	• Label reading and understanding ratios of good fats, proteins and hidden sugars
	• More understanding of the psychological underpinnings on "why I eat" and overeating
	• Exercise class
	  • Chair exercises
	  • Fresh air/park exercises
	  • Information about benefits of varying exercise
	• Further knowledge on
	  • Certain foods and their effects on the body (e.g., what sugar does to the body, proteins, good fats etc.)
	  • The harms of poor eating and no exercise on body mechanisms
	  • Cravings and how to beat them
	• Reminders of program schedule and encouragement to attend
	• Sharing experiences and "wins" with peers

Barriers	• Unable to concentrate/absorb content/participate fully because of low mood/anxiety • Injury/pain and physical health issues make exercise difficult or impossible • Poor motivation/discipline and difficulty getting started and maintaining momentum • Fear of change or not ready to make changes • Cooking for one person too hard or can't be bothered • Changing the eating patterns of the entire household
Program lessons	• Provide notes at each session rather than at the following week • Provide diagrams of exercises to do at home • Not enough practical cooking/exercise classes • Group size too big with new people coming in every week

The most beneficial/useful components of the program reported by the majority of participants were the cooking and exercise practicals ($n = 11$; 91%). One participant commented that he/she needed "*practical examples that can be implemented in day-to-day life*" and less theory in order to engage with the program. However, many participants ($n = 9$; 75%) commented that furthering their knowledge on how food effects the body and the harms of nutritionally poor food and no exercise on the body's functioning was useful as, "*understanding aids motivation to change, oversimplification does not.*" Poor motivation ($n = 4$; 33%), fear of change ($n = 3$; 25%) and difficulties engaging with the program due to low mood and anxiety ($n = 8$; 66.7%) were common among participants. Additionally, many participants found cooking for one person and/or maintaining momentum on their own difficult ($n = 4$; 33%). As one person stated, *"[the] desire to try a new recipe is high at time of session but then lost when at home."* Participants requested more diagram-based notes of exercises/recipes and program content to be accessible at home due to poor recall ($n = 3$; 25%). Injury and co-morbid physical health problems were some of the main barriers in adding exercise to their day-to-day lives ($n = 8$; 66.67%). At home chair-based exercises and information on how and why to vary exercise was deemed helpful ($n = 4$; 33.3%).

HBHM Version 2 (2016)—Program Development

Based on the qualitative data detailed above, the HBHM program in 2016 was remodeled and refined in consultation with a team of experts in the fields of psychiatry, endocrinology/cardiology, nutrition and dietetics, and exercise physiology. The program was designed to integrate five evidence-based components: lifestyle psychoeducation (13), exercise (theory and practicals) (14), diet and nutrition (theory and practical skills e.g., cooking

TABLE 3 | Example HBHM (version 2) practical components and education sessions.

	Diet and nutrition	Exercise	Motivation and goal setting	Meditation and mindfulness	Psychoeducation
Practical components	- Cooking demonstrations - Excursion to supermarket for healthy shopping tips - Food label reading	- Chair based exercises to increase strength - Pilates - Yoga and stretching - Body weight exercises - Interval, circuit and resistance training	- Goal setting - Ongoing review of personal goals throughout the program	- Meditation to improve sleep - Mindfulness for reducing and managing stress - Mindfulness for self-compassion	N.A
Education session topics	- Why diets don't work? - Sugar—myths and realities - Exploring macronutrients in foods—protein, fats and carbohydrates	- Benefits of physical exercise - The benefits of "greenexercise" (exercising in nature) - Incidental exercise strategies for everyday life	- Ways to plan realistic and attainable goals—SMART goal setting - Finding Motivation—the motivation matrix - Dealing with setbacks and the transtheoretical model of change	- What are the benefits of mindfulness meditation? - Mindful eating for weight loss and well-being	- What is the link between mental and cardiovascular health? - The "brain-gut" connection and its influence on mental & cardiovascular health The importance of sleep and how to improve sleep quality for our health & well-being

demonstrations and label reading exercises) (15), motivation and goal setting skills (16), and mindfulness techniques (17) (see **Table 3**). Each week, for 12 weeks, participants attended a 6-h session at TMC, where content and practical exercises from each of the five modules was delivered by an exercise physiologist, dietitian and/or a GP (see **Table 3** for examples). Participants were provided with a printed booklet each week outlining content for that session (e.g., psychoeducation theory, exercise diagrams, step by step recipes, label reading guidelines) with areas to take notes and complete tasks such as goal setting activities and shopping lists. **Table 4** provides an example program day.

HBHM Version 2 (2016)—Pilot Data

Characteristics

Fifteen patients were referred to the pilot program, five patients declined to participate and ten patients were willing to take part. All participants attended the week 0 and week 12 sessions. Some of the weekly follow-up sessions were missed due to illness or other personal commitments with an average attendance rate of 80%.

Most of the sample was female (n = 8; 80%) with a mean age of 51.8 years (SD = 12.9 years) (see **Table 5**). Over half the sample were unemployed/not working or on a disability pension (n = 6; 60%). The most common primary DSM-IV psychiatric diagnosis as reported in the treating psychiatrist referral to the program was Major Depressive Disorder (MDD) (n = 6; 60%) followed by Bipolar Affective Disorder (n = 2; 20%), Generalized Anxiety Disorder (GAD) (n = 1; 10%) and Alcohol Abuse (n = 1; 10%). Psychiatric co-morbidity was common with diagnoses of Generalized Anxiety Disorder (GAD) (n =3; 30%), Binge Eating Disorder (n = 1; 10%), Borderline Personality Disorder (n = 1; 10%) and Major Depressive Disorder (n = 1; 10%).

All participants were taking psychotropic medications defined as an antidepressant, mood stabilizer, second generation antipsychotic or benzodiazepine. The participant's primary medications were agomelatine (n = 2; 25–50 mg/day), desvenlafaxine (n = 2; 50–100 mg/day), fluvoxamine (n = 2; 200–300 mg/day), paroxetine (n = 1; 20 mg), venlafaxine (n= 1; 75 mg/day); escitalopram (n = 1; 40 mg/day); lamotrigine (n = 1; 50 mg). On average participants were taking 2.4 (SD = 1.17) psychotropic medications ranging from 1 to 4 psychotropic medications. The most common psychotropic medication taken alongside a primary psychotropic medication were second generation antipsychotics (e.g., quetiapine, lurasidone; n = 6; 60%) followed by mood stabilizers (n = 4; 40) (see **Table 5**).

The most common chronic medical conditions self-reported by participants or as listed in the referral to the program were hyperlipidaemia (n = 4; 40%), hypertension (n = 3; 30%), arthritis (n = 3; 30%), Type II Diabetes (n = 3; 20%), sleep apnoea (n = 2; 20%), and chronic pain/fibromyalgia (n = 2; 20%). Other conditions such as, fatty liver disease (n = 1; 10%), pancreatitis (n = 1; 10%), ulcerative colitis (n = 1; 10%), costochondritis (n = 1; 10%), fructose malabsorption syndrome (n = 1; 10%), endometriosis (n = 1; 10%), restless leg syndrome (n = 1; 10%) and hypothyroidism (n = 1; 10%) were self-reported.

Table 6 presents the anthropometrics of the participants at week 0 and week 12. The average BMI of the cohort at week 0 was 36.18 (SD = 4.67) which, according to the World Health Organization, classes the participants as Obese Class I. As a cohort, the participants also had impaired glucose tolerance as evidenced by a fasting glucose test average > 5.5 (mean = 5.57 ± 1.19). The participants' cholesterol and BP were normal, most likely due to their use of prescribed statins and hypertensive medications. According to DASS

TABLE 4 | An example HBHM (version 2) program day.

Time	Key component
9.30–10.00 a.m.	Greeting and brief overview of the session • Includes questions about the previous week or any updates
10.00–10.45 a.m.	Exercise theory and practice with an Exercise physiologist • Education session: Yoga theory and benefits • Practical component: Yoga
10.45–11.00 a.m.	Tea break
11.00–12.15 p.m.	Lifestyle psychoeducation with dietitian/GP • Education session: Cortisol—The "good" and "bad" of stress • Brainstorming strategies to manage stress
12.15–1.00 p.m.	Lunch • Practical component: Cooking demonstration with dietitian (example recipe: stuffed capsicums, roast vegetable and grain salad)
1.00–2.00 p.m.	Nutrition theory with dietitian • The evidence, benefits and "how to" of a Mediterranean diet
2.00–2.15 p.m.	Tea break
2.15–2.45 p.m.	Mindfulness meditation • Practical session: Mindfulness based stress reduction
2.45–3.30 p.m.	Motivation and goal setting – • Identify goal for the week using SMART guidelines

TABLE 5 | HBHM (version 2) Baseline characteristics ($n = 10$).

Characteristic	Mean ± SD/ *n* (%)
Age	51.80 ± 12.93
Female	8 (80%)
Primary psychiatric diagnosis	
Major Depressive Disorder	6 (60%)
Bipolar Affective Disorder	2 (20%)
Generalized Anxiety Disorder	1 (10%)
Alcohol Dependence	1 (10%)
Primary psychotropic medication*	
Antidepressant	9 (90%)
Mood stabilizer	1 (10%)
Other psychotropic medications*	
Second generation antipsychotic	6 (60%)
Mood stabilizer	4 (40%)
Antidepressant	2 (20%)
Benzodiazepine	2 (20%)

**Participants could be taking more than one psychotropic medication (mean = 2.4; SD = 1.17).*

measurement at week 0, participants had low to moderate levels of depression (mean = 8.30; SD = 4.69), anxiety (mean = 6.0; SD = 4.64), and stress (mean = 8.70; SD = 4.24) symptomatology (see **Table 6**).

Participant Goals

The most common goal was to increase exercise levels and fitness ($n = 5$; 50%) followed by eat healthier ($n = 4$; 40%), reduce sugar intake ($n = 3$; 30%) and lose weight ($n = 3$; 30%). On average the participants rated their readiness to change as 7.75 (SD = 2.12) with ratings ranging from 3 to 10. Thus, as a whole the participants were very ready to make change.

Outcome Data

The cohort had a significant weight loss over the 12 weeks with an average loss of 2 kg, $t_{(9)} = 2.75$, $p = 0.023$. Weight change ranged from a +1.4 kg weight gain to a −6 kg weight loss. Along with weight loss, there was also a significant reduction in abdominal circumference (mean = 2.55 cm) and a drop in BMI of almost one point (mean = 0.96 kg/m^2), $t_{(9)} = 2.32$, $p = 0.046$ and $t_{(9)} = 0.96$, $p = 0.019$. No significant changes in participant's blood levels or anthropometrics were found. Additionally, no significant changes in participant's mental health was found on the DASS when comparing week 0 to week 12 (see **Table 6**). Participant's readiness to change (mean = 7.75; SD = 2.12) was not correlated with change in BMI, abdominal circumference, or weight change at end of the program, $r = -0.615$, $p = 0.105$, $r = -0.205$, $p = 0.626$, and $r = -0.692$, $p = 0.057$, respectively.

DISCUSSION

This pilot study found that an integrated 12-week lifestyle program was associated with significant weight loss in patients with a mental illness. We found a mean 2 kg weight loss and a drop in BMI of almost one point across the course of 12 weeks. Our findings are in line with a recent meta-analysis which found lifestyle interventions were superior to treatment-as-usual in producing weight loss in patients with a serious mental illness (18). This improvement in anthropometric measures is clinically significant when considering the challenges experienced by patients with a mental illness in maintaining physical and mental wellness.

No beneficial effect on participant's mental health was found despite incorporating meditation, goal setting, mindfulness, and motivation modules, which was a distinguishing feature of the program. This finding was surprising given mindfulness-based therapies have been consistently related to improvements in mood and anxiety in clinical populations (17). However, a recent lifestyle intervention for residential patients with a serious mental illness also found no positive changes on psychosocial outcomes (19). This suggests that it is challenging to get a beneficial effect on psychosocial outcomes while attempting to improve physical and mental health outcomes simultaneously. The addition of individual psychotherapy alongside participation in the program might be warranted and the incorporation of other evidence-based psychotherapies such as, cognitive behavioral therapy should be considered in future versions of the program. Future iterations of the program should also incorporate quality of life assessments and measures of psychosocial functioning to more accurately assess the program's potential benefit.

Alternatively, the modest effect on participant's mental health during the program could be due to the low baseline levels of depression, anxiety, and stress (as captured on the DASS), and hence had less scope for improvement. Furthermore, when

TABLE 6 | HBHM (version 2) program ($n = 10$) outcome data (week-0 to week-12).

Outcome	Week 0	Week 12	Paired *t*-test
Weight (kgs)	100.3 ± 9.79	98.3 ± 9.72	$t = 2.75$ $p = 0.023$*
Abdominal circumference (cm)	119.95 ± 12.69	117.40 ± 12.47	$t = 2.32$ $p = 0.046$*
BMI	36.18 ± 4.67	35.22 ± 4.73	$t = 2.86$ $p = 0.019$*
Waist to hip ratio	0.96 ± 0.08	0.96 ± 0.07	$t = -0.362$ $p = 0.726$
Systolic blood pressure	122.67 ± 15.23	130.25 ± 14.82	$t = -1.12$ $p = 0.300$
Diastolic blood pressure	79.67 ± 11.59	80.88 ± 10.27	$t = 0.144$ $p = 0.890$
Fasting glucose[a]	5.57 ± 1.19	5.72 ± 1.03	$t = -0.44$, $p = 0.682$
HDL cholesterol[a]	1.21 ±.26	1.24 ±.21	$t = 0.500$, $p = 0.705$
LDL cholesterol[a]	2.61 ±.98	3.30 ± 1.20	$t = -2.00$, $p = 0.295$
Total fasting cholesterol[a]	5.34 ± 1.41	5.95 ± 1.20	$t = -2.61$, $p = 0.080$
Triglycerides[a]	2.30 ±.57	2.13 ±.30	$t = -0.33$, $p = 0.761$
DASS 21—Depression score	8.30 ± 4.69	9.70 ± 5.44	$t = -0.87$, $p = 0.408$
DASS 21—Anxiety score	6.00 ± 4.64	5.50 ± 5.10	$t = 0.75$, $p = 0.475$
DASS 21—Stress score	8.70 ± 4.24	8.50 ± 4.72	$t = 0.38$, $p = 0.716$

*$p < 0.05$.
[a]*Missing data on week 12 (n = 4).*

identifying goals of the program, not one participant mentioned they would like to improve their mental health. Rather the goals reported by participants were orientated toward improving their eating habits and losing weight. The incorporation of behavioral and psychological components (such as mindful eating and goal setting) is deemed to benefit the delivery and engagement of the program contents and helped to adhere to recommendations in order to achieve the weight loss results.

A major limitation to the current study was the small sample size and that it was uncontrolled. A larger sample with an appropriate control is required to assess the program effectiveness and allow for further feedback from participants to fine-tune the program. We also recognize that more work is needed to refine the delivery and format structure in respect to determining the best application of the program given costs and time constraints. In particular, the exercise component should aim to provide at least 90 min of moderate-to-vigorous exercise per week, as this intensity has been shown to improve psychiatric symptoms in patients with a serious mental illness (20). Furthermore, closer monitoring of physical activity outside of the program should be employed in order to assess the translational impact of the program to the home environment.

While the 12-week program was comprehensive, it also has its drawback in terms of time requirements, and a 6-h once per week delivery is quite intensive for people with a mental illness. A follow-up should also be employed to determine whether weight loss results are maintained, continued, or regained following the cessation of the program.

There is the potential to restructure the program to have a blend of face-to-face delivery with online components, and even the use of a mobile phone app. This would provide flexibility, less demands on time, and less financial burden for the participants. Weight loss in this population is extremely challenging as many patients have co-morbid medical conditions, and limited social and economic resources. Thus, facilitating weight loss using strategies that can be implemented into everyday life is paramount to success. In addition, implementing and assessing strategies which prevent the all too frequent "weight regain" phenomena is crucial (21).

As 60% of the sample were taking second generation antipsychotics, the results are encouraging for metabolically vulnerable patients. However, it is important to note, that the results cannot be generalized to participants with a serious mental illness as the current pilot did not include participants with schizophrenia who are at the most risk of developing MetS. It is unclear how this particular patient population would engage with this intervention. In conclusion, the pilot data of the HBHM program found significant benefits in reducing weight and abdominal obesity, with the potential to achieve substantial health benefits for patients with a mental illness and co-morbid metabolic syndrome. Study replication is required using a controlled design in a larger sample over a longer time period.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of The National Statement on Ethical Conduct in Human Research 2007 and The Melbourne Clinic Ethics Committee. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The projects were approved by the Melbourne Clinic Ethics Committee (Project 209 and 249).

AUTHOR CONTRIBUTIONS

All authors contributed to the drafting and editing of the manuscript. JAM and JS is responsible for the data analysis and manuscript preparation. JM, GO, CW, RO, and AB were involved in designing the program, running the program and collecting data. CN and JS contributed to the design of the program and provided oversight of the program.

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CASE REPORT
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The Impact of Hypomania on Aerobic Capacity and Cardiopulmonary Functioning—A Case Report

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Background: Hypomanic episodes are characterized by increased goal-directed behavior and psychomotor agitation. While the affective, cognitive, and behavioral manifestations of such episodes are well-documented, their physiological influence on aerobic capacity and cardiopulmonary functioning are unknown.

Methods: We describe a case report of an individual with schizophrenia who experienced a hypomanic episode while serving as a control participant (wait list) in a single-blind, randomized clinical trial examining the impact of aerobic exercise (AE) on neurocognition in people schizophrenia. As part of the trial, participants completed two scheduled clinical assessments and cardiopulmonary exercise tests (VO_2max) at baseline and 12 weeks later at end of study. All participants received standard psychiatric care during the trial. Following a baseline assessment in which he displayed no evidence of mood lability, the subject returned on Week-12 for his scheduled follow-up assessment displaying symptoms of hypomania. He was able to complete the follow-up assessment, as well as third assessment 2 weeks later (Week-14) when his hypomanic symptoms ebbed.

Results: While not engaging in AE, the subject's aerobic capacity, as indexed by VO_2max, increased by 33% from baseline to Week-12. In comparison, participants engaged in the aerobic exercise training increased their aerobic capacity on average by 18%. In contrast, participants in the control group displayed a small decline (−0.5%) in their VO_2max scores. Moreover, the subject's aerobic capacity increased even further by Week-14 (49% increase from baseline), despite the ebbing of his hypomania symptoms at that time. These changes were accompanied by increases in markers of aerobic fitness including peak heart rate, respiratory exchange rate, peak minute ventilation, watts, and peak systolic blood pressure. Resting systolic and diastolic blood pressure, and peak diastolic blood pressure remained unchanged.

Conclusions: Our findings suggest that hypomania produce substantial increase in aerobic capacity and that such elevations may remain sustained following the ebbing of hypomanic symptoms. Such elevations may be attributed to increased mobility and goal-directed behavior associated with hypomania, as individuals in hypomanic states

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may ambulate more frequently, for longer duration, and/or at higher intensity. Our results provide a first and unique view into the impact of hypomania on aerobic capacity and cardiopulmonary functioning.

Keywords: Schizophrenia, hypomania, aerobic fitness (VO_2max), cardiopulmonary, mania and bipolar disorder, cardiopulmonar exercise testing, cardiopulmonary activity

BACKGROUND

Hypomanic episodes are characterized by increased goal-directed behavior and psychomotor agitation manifested by more frequent pacing, fidgeting, and hand-wringing. While the cognitive, affective, and behavioral manifestations of such episodes have been documented extensively (1, 2), their influence on the physiological functioning of afflicted individuals is unknown. Specifically, the impact of hypomania on aerobic capacity and cardiopulmonary functioning is undetermined.

To address this issue, we describe a case report of an individual with schizophrenia, subject AA, who experienced a hypomanic episode while serving as a control participant in a single-blind, randomized clinical trial examining the impact of aerobic exercise (AE) on neurocognition in individuals with schizophrenia. As part of this study, participants were randomized to receive 12 weeks of regular psychiatric care (Treatment as Usual; TAU) or AE training in addition to TAU (3, 4). In this article, we report on subject AA's aerobic capacity and cardiopulmonary functioning before the trial (baseline), during the hypomanic episode (week 12), as well as 2 weeks later (week 14) when his hypomania symptoms ebbed. We characterized his performance and reviewed and contrasted it with the other study participants.

METHODS

The study was approved by the Columbia University's New York State Psychiatric Institute Institutional Review Board (NYSPI-IRB) and all participants signed a consent form. A written informed consent was obtained from the participant (subject AA) for the publication of this case report. All participants completed scheduled clinical, cognitive, and cardiopulmonary exercise tests (CPET) at baseline and follow-up (12 Weeks). Following approval by the NYSPI-IRB, subject AA completed a third CPET 2 weeks later (week 14).

Measures

Detailed descriptions of the study rationale and procedures have been reported elsewhere (4–7). Briefly, aerobic capacity was determined by CPET to establish VO_2max, considered the "gold standard" index of aerobic capacity. VO_2max is an index of the maximum capacity of an individual's body to transport and use oxygen during incremental aerobic exercise, reflecting the individual's aerobic capacity level. All tests were completed on weekdays at ∼10 a.m. and were performed on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics Inc., Yorba Linda, CA) with a Viasys Encore metabolic cart (Viasys Corporation, Loma Linda, CA). Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, TX). Participants completed measurements of a 5-min resting baseline, 3-min of no-resistance warm-up, ramping exercise protocol of 10–15 watts to peak exercise with a target of exercise for 8–12 min. Exercise was terminated when the subject reached maximum capacity (VO_2 plateau; 85% of maximal heart rate (HRmax; 220-age) (8); respiratory quotient $\geq$1.1; or self-reported exhaustion) (9). A 3-min active recovery period completed the test. We used VO_2peak (ml/kg/min) scores in all analyses.

Additional cardiopulmonary variables were collected including heart rate (HR), respiratory exchange ratio (RER), resting and peak systolic and diastolic blood pressure (SBP, DBP), peak minute ventilation (VE), peak tidal volume (Vt), end tidal carbon dioxide pressure ($PetCO_2$), rate of carbon dioxide production at peak (VCO_2 L/min), and peak work rate (Watts). The clinical raters and technicians administering the CPET were blinded to the subjects intervention assignment and clinical status.

RESULTS

Subject AA is a slender 20-year-old, never married, male of Asian descent with a DSM-IV diagnosis of schizophrenia (onset at age 19). At the time of the study, he lived with relatives and had no family history of psychosis. At study entry his body mass index was 21.8 and he was prescribed Proloxin 37.5 mg injection every other week, lamotrigine 100 mg twice a day, hydroxyzine 50 mg twice a day, and benztropine 1 mg twice a day. He denied smoking. Subject AA endorsed moderately severe auditory hallucinations and religious delusions, but was clinically stable and reported to function well, just completing his freshman year in a local community college. Subject AA completed his baseline CPET, clinical, and cognitive assessments with no difficulties and was randomized to receive TAU. He displayed no mood lability during his baseline assessment. On week 12, upon arriving for the scheduled follow-up CPET, he displayed symptoms consistent with hypomania including elevated mood, flight of ideas, psychomotor agitation, and poor impulse control. Despite his condition, he completed his CPET, but given his clinical status, he was tested again 2 weeks later (Week 14), at which point his hypomanic symptoms were no longer present and he returned to his clinical baseline. His urine toxicology tests at baseline, Week 12, and Week 14 were all negative.

Examination of changes in aerobic capacity from baseline to follow-up (Week 12) among all participants indicated the AE group increased their VO_2max on average by 18%, compared to

TABLE 1 | Subject AA cardiopulmonary functioning before, during, and post-hypomania.

	Baseline (before hypomania)	Week 12 (during hypomania)	Week 14 (post-hypomania)
VO_2 Peak (ml/kg/min)	26.1	34.8	39.1
Resting heart rate (RHR)	77	86	70
Peak heart rate (PHR)	122	170	161
Respiratory exchange ratio (RER)	0.9	1.1	1.0
Peak minute ventilation (L/min)	42.6	65.8	73.4
Peak end tidal carbon dioxide pressure ($PetCO_2$)	43.3	42.4	41.4
Peak wattage (watts)	100	154	155
Resting systolic blood pressure (RSBP)	115	118	121
Peak systolic blood pressure (PSBP)	157	198	183
Resting diastolic blood pressure (RDBP)	72	86	74
Peak diastolic blood pressure (PDBP)	75	78	80

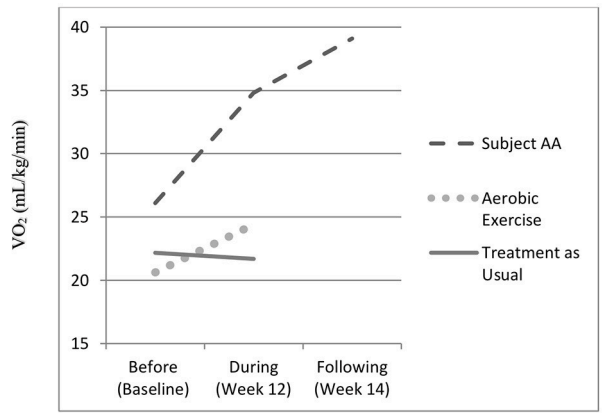

FIGURE 1 | Aerobic capacity before, during, and post-hypomania.

a small decline in the TAU group (−0.5%) (4). In comparison, Subject AA's VO_2max increased by 33% during this period, although he denied engaging in any aerobic exercises in the preceding weeks. At Week 14, his aerobic capacity was elevated even further (49% increase from baseline), despite the ebbing of hypomania symptoms at that point (see **Table 1** and **Figure 1**). His resting heart rate increased from 77 to 86 beats/min during hypomania and then went down to 70 beats/min following the hypomanic episode. A number of other cardiopulmonary variables increased from baseline to hypomania and post-hypomania periods including peak HR, respiratory exchange rate, peak minute ventilation, watts, and peak systolic blood pressure. PetCO2 decreased. These trends are all consistent with markers of increased aerobic fitness. In contrast, other parameters including resting systolic and diastolic blood pressure, as well as peak diastolic blood pressure remained unchanged.

To ensure that Subject AA's increase in VO_2max was not related to higher workload, we examined his VO_2 at the same workload (100 watts) to control for potential effort-related variability across sessions. His VO_2 at 100 watts was lowest prior to the hypomanic episode (1.66 L/min), higher during (1.75 L/min), and highest following the episode (2.03 L/min). Examination of the performance at the same workload (100 watts) show that for Peak VO_2, there was a larger component of volitional effect on conditioning. This view is corroborated by the similar trend in VO_2max showing the lowest prior (26.1 kg L/min), higher during (34.8 kg L/min), and highest following the hypomanic episode (39.1 L/min). Likewise, VE also rose in a similar fashion and peak HR were elevated more at both follow up evaluations (Weeks 12 and 14).

DISCUSSION

To the best of our knowledge, the present report is the first characterization of the impact of hypomania on aerobic capacity and cardiopulmonary functioning. Our results suggest that episodes of hypomania produce substantial increases in aerobic capacity and that such elevations may be present even following the ebbing of hypomanic symptoms. Such increases may be attributed to heightened mobility and goal-directed behavior associated with hypomania, as individuals in hypomanic states may ambulate more frequently, for longer durations, and/or at higher intensity, resulting in increased VO_2, peak wattage, as well as higher anaerobic threshold. Such episodes may also be associated with a greater ability to push harder on CPET, as indicated by higher workload (watts) with higher peak HR and VE in the latter tests. Thus, volitional aspects may also play a greater role in performance, necessitation careful review of CPET results of patients assessed during hypomanic states.

Overall, the improvement in subject AA's aerobic capacity, while not engaging in aerobic exercise, surpassed study participants engaging in a formal AE training program with a trainer (3 60-min sessions per week over 12 weeks). The improvement in other parameters such as workload and peak HR, support the view of hypomanic state-related increases in aerobic capacity, with the caveat that subject AA also gave a far higher effort with increased HR and minute ventilation. These indicators were even more elevated at Week 14. Overall, these findings are consistent with results from studies in the general population that indicate that increases in incidental physical activity (e.g., increased tapping of foot, pacing) correlate with higher VO_2 max. For example, McGuire and Ross (10) have found that duration and intensity of incidental activities indexed by accelerometers were associated with higher VO_2 max. Other authors have reported similar results, finding "fidgeting" and incidental physical activity increasing VO_2max (11, 12).

VO_2 is an important marker of physical health, as increased VO_2 has been linked to early lower mortality (13, 14). Previous reports have documented significant lower aerobic fitness in individuals with schizophrenia (4) along with prevalence of early mortality among individuals diagnosed with schizophrenia, schizoaffective disorder, as well as bipolar disorder (15, 16). Thus, our findings of hypomanic episodes resulting in VO_2max

elevations provoke an intriguing question–does the experience of manic episodes and the resulting VO_2 increases confer potential long-term protection with regard to early mortality risk? A recent meta-analysis has found no cardiorespiratory fitness differences between diagnostic subgroups of individuals with severe mental illness (e.g., schizophrenia, bipolar disorder, and major depressive disorder) (17). Previous reports have also documented significant elevations in early mortality among individuals with severe mental illness including those diagnosed with schizophrenia, schizoaffective disorder, and bipolar disorder (15, 16). Consistent with these findings, a review of medical records of 326 patients with a psychotic disorder treated at the Mayo Clinic in Minnesota between 1950 and 1980 found no significant difference in median survival for patients with schizophrenia vs. those with schizoaffective disorder (18). However, a population cohort study in Denmark (5,558,959 persons of which 261,887 persons had been admitted to a psychiatric hospital) found both females and males admitted with a diagnosis of schizophrenia had a higher mortality rate ratio of natural causes of death, compared to persons admitted with unipolar, bipolar, and schizoaffective disorders (19). Of note, natural causes of mortality comprised of cardiovascular diseases, respiratory diseases, endocrine and metabolic conditions, as well as old age and apoplexy, and malignant neoplasms. Thus, given the complexity of the longitudinal relationship between cardiopulmonary fitness and early mortality risk, the research literature at present does not provide conclusive support for the potential of manic episodes to confer protection for early mortality risk via temporal VO_2 increases. Future studies should aim to elucidate this potential link, as it may inform the mechanisms associated with increased early mortality in individuals with severe mental illness.

The present report has a number of limitations. One limitation is the focus on a single individual. Secondly, the appraisal of (lack of) AE by Subject AA during the period prior to the follow-up assessments was based on his self-report, rather than via actigraph. Another limitation is the lack of follow-up assessments post the Week 14 assessment. Such information would have been valuable to characterize the timeline and long-term impact of hypomania on cardiopulmonary indicators. Finally, the changes in aerobic capacity and cardiopulmonary functioning may reflect, in part, Subject AA's young age, lower BMI, and relatively higher baseline aerobic capacity. Thus, the results should be interpreted with caution and future studies should aim to confirm our findings in larger and more diverse samples, including individuals who are older and have higher BMI. In contrast, the present report has a number of strengths including evaluation of naturally occurring hypomania that developed and resolved during "real world" functioning, a rigorous research assessment of clinical symptoms, as well as the use of CPET, a "gold standard" of aerobic capacity and cardiopulmonary functioning assessment.

In summary, the present report is the first characterization of changes in aerobic capacity and cardiopulmonary functioning associated with hypomanic episodes. Our results indicate that hypomanic episodes lead to substantial increases in aerobic capacity and improvements in cardiopulmonary functioning, and such increases may last for weeks and well-beyond the period of active hypomanic symptoms.

AUTHOR CONTRIBUTIONS

DK designed the study and wrote the protocol. MB and HA conducted the aerobic fitness and cardiopulmonary analyses, as well as provided the statistical data. JV conducted the diagnostic and clinical assessments. JB served as a medical director of the study and assisted with the monitoring of the participants' health. AS managed the literature searches, and along with DK, wrote the first draft of the manuscript. All authors contributed to and have approved the final version of the manuscript.

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Investigating the Agreement Between Cardiovascular Disease Risk Calculators Among People Diagnosed With Schizophrenia

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Background: People diagnosed with schizophrenia have a much reduced life expectancy compared to the general population, and a more than doubled risk of dying from cardiovascular disease (CVD). Existing CVD risk calculators can be used to detect people with an elevated predicted risk of CVD to inform interventions to reduce risk.

Aims: This study aimed to compare four different risk calculators for 10-year predicted CVD risk in a sample of people with schizophrenia.

Methods: Thirty participants with a diagnosis of schizophrenia spectrum disorders living within Greater Manchester, United Kingdom took part. Ten-year predicted cardiovascular risk scores were calculated using four different models: QRISK3, Framingham, PRIMROSE BMI, and PRIMROSE lipid. Risk estimates and classified risk categories were compared.

Results: QRISK3 identified 11 (39%) as having >10% risk of a CV event within 10 years, 4 (14%) of whom exceeded 20%. The Framingham model identified 4 (14%) as exceeding 10%, none of whom exceeded 20%. PRIMROSE risk calculators identified no participants as having >10% risk of a CV event within 10 years. Pairwise concordance correlation coefficients between types of model ranged 0.22–0.77. Mean (± SD) age was 40 (± 10) years but QRISK3's mean "Heart age" was 58 (± 14) years.

Conclusion: Risk calculators generate differing predicted CVD risk scores for patients with schizophrenia. Using one risk calculator might yield different recommended monitoring and treatment plans compared to another. Clinicians should therefore take into account other patient-related factors, such as patients' preferences and other underlying physical conditions when making treatment decisions.

Keywords: schizophrenia, cardiovascular risk, risk calculator, cardiovascular disease, risk score

INTRODUCTION

Globally, people diagnosed with schizophrenia have a mortality rate 2–3 times that of the general population (1) and their life expectancy is reduced by 10 to 30 years (1–3). As in the general population, cardiovascular disease (CVD) is the most common cause of death among these individuals (4–6). A meta-analysis of over 3 million patients with severe mental illness (SMI) and over 113 million controls from 92 studies with a cross-sectional or retrospective/prospective longitudinal design showed that people with schizophrenia are at more than double the risk of dying from CVD and are at 59% greater risk of developing coronary heart disease (CHD) compared to the remainder of the population (7).

CVD risk calculators are used to estimate an individual's absolute risk of having a heart attack or stroke within a specified amount of time, such as 5 or 10 years. These calculators have been developed in large population studies and their validity and reproducibility assessed using population-level statistics that measure calibration and discrimination (8–11). CVD risk prediction scores are used in clinical practice with the general population to guide whether early intervention could be beneficial, such as prescribing medication to lower blood pressure and cholesterol (12). Moreover, in the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE), which issues national clinical guidelines in the UK to improve health and social care (13) recommend routine monitoring of cardiovascular risk in people with schizophrenia (14).

Risk prediction scores can also be used as surrogate endpoints for intervention studies; that is, an outcome in a clinical trial would be change in CVD risk score after a certain period of time (15). In the schizophrenia population, risk prediction scores have been used as surrogate endpoints in intervention studies, for example the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial included 1,125 people with schizophrenia and compared change in predicted 10-year CHD risk using the Framingham risk score (16) during antipsychotic treatment.

There are currently more than 360 CVD risk calculators available (17). A previously published review reported that 25 different calculators allocated the same person to a different risk category 33% of the time (18). Given the differences between risk calculators when applied in the general population, it would be useful to know whether or not consistency is similarly poor when the calculators are applied specifically to people with schizophrenia. Therefore, the aim of this study was to compare the 10-year absolute CVD risk score in a sample of 30 people with schizophrenia using four different risk calculators: QRISK3 (9), Framingham (11), The PRedIction, and Management of cardiovascular Risk in peOple with SEvere mental illnesses (PRIMROSE) body mass index (BMI) and PRIMROSE lipid (10). Whilst there are a large number of calculators to select from, we decided to focus on risk calculators that include risk factors applicable to people with schizophrenia, such as an SMI diagnosis and antipsychotic use. Such risk factors may confer additional risk for CVD, independent of traditional predictors (19, 20). Furthermore, we chose to assess Framingham due to it being a calculator still commonly used worldwide, including in this patient group. **Table 1** shows a comparison of risk factors measured in each model that we have selected: QRISK3, Framingham, PRIMROSE BMI, and PRIMROSE Lipid.

TABLE 1 | Comparison of risk factors included in four cardiovascular risk calculators.

Variables	Cardiovascular risk calculators			
	Framingham	QRISK3	PRIMROSE Lipid	PRIMROSE BMI
Age	✓	✓	✓	✓
Gender	✓	✓	✓	✓
Ethnicity	✗	✓	✗	✗
HDL cholesterol	✓	✓	✓	✗
Total cholesterol	✓	✓	✓	✗
Systolic blood pressure	✓	✓	✓	✓
SD of two systolic blood pressure readings	✗	✓	✗	✗
Type 2 diabetes	✓	✓	✓	✓
Type 1 diabetes	✗	✓	✗	✗
Current smoker	✓	✓	✓	✓
Ex-smoker	✗	✓	✓	✓
Light/moderate/heavy smoker	✗	✓	✗	✗
Hypertension treatment	✓	✓	✓	✓
BMI	✗	✓	✗	✓
Townsend index of deprivation	✗	✓	✓	✓
Family history of CVD	✗	✓	✗	✗
Chronic kidney disease	✗	✓	✗	✗
Migraines	✗	✓	✗	✗
Lupus (SLE)	✗	✓	✗	✗
Rheumatoid arthritis	✗	✓	✗	✗
Erectile dysfunction	✗	✓	✗	✗
Atrial fibrillation	✗	✓	✗	✗
History of heavy drinking	✗	✗	✓	✓
SMI diagnosis	✗	✓	✓	✓
Prescription for atypical antipsychotics	✗	✓	✓	✓
Prescription for typical antipsychotics	✗	✗	✗	✓
Prescription for antidepressants	✗	✗	✓	✓
Oral steroids	✗	✓	✗	✗

METHODS

Sample

Individuals were eligible to take part if they were aged 18–65 and had a diagnosis of schizophrenia or related psychosis, according to the ICD-10 classification system (21). Individuals were excluded if they were non-English speaking, were unable to give their informed consent, or they had a history of CVD as specified by the CVD risk calculators used (9, 11), as well as NICE

guidelines (22). These individuals are already considered at high-risk of CVD events, therefore generating a risk score does not add useful additional information (22). Participants were recruited from Greater Manchester Mental Health NHS Foundation Trust services in England. All were given an information sheet to read and provided their written informed consent. The study received ethical approval from the North West Research Ethics Committee (17/NW/0368). Thirty participants were included in the study. Seventeen participants resided in the community and 13 were inpatients on mental health or rehabilitation wards. Participants' histories of diagnosed CVD were established by reviewing their medical records for related diagnoses and for any prescribed medication associated with cardiometabolic conditions.

CVD Risk Calculators

Framingham

The Framingham risk scores (11) apply an algorithm that calculates the predicted CVD risk from risk factors such as diabetes, dyslipidemia, hypertension (23–25), smoking, and obesity (26, 27). This risk calculator is frequently used in the general population but has also been applied to population groups with SMI (28). The prevalence of these risk factors is considerably raised in people with schizophrenia (4, 29–31) and people with schizophrenia have been shown to have higher risk scores than the general population (32–34). However, people with SMI were excluded from the Framingham cohort. As such, risk factors of particular relevance to those with an SMI diagnosis, such as antipsychotic use are not included. Yet antipsychotic use can cause significant morbidity, including weight gain (35, 36) and diabetes (37), conditions that are associated with an increased risk of CVD.

When applying the Framingham risk calculator to patients in the United Kingdom (UK), NICE recommends using the modified version (38). The modified version entails multiplying the results of the US Framingham score by 1.4 for south Asian men in the UK. Patients are considered to be at high risk of a CVD event over the next 10 years if they score 20% or greater (11). Estimates of risk include several CVD outcomes, including coronary death, myocardial infarction, coronary insufficiency, angina pectoris, ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, peripheral artery disease, and heart failure (39).

PRIMROSE

The PRIMROSE BMI and lipid models are 10-year predicted cardiovascular risk calculators specifically designed for people with SMI (10). They include risk factors relevant to people with SMI, such as prescription of antipsychotic medication, antidepressant medication, history of heavy alcohol consumption, area-level Townsend index of deprivation (in quintiles) (40) and diagnosis of an SMI. These models were validated using The Health Improvement Network (THIN) UK primary care database (10).

The PRIMROSE BMI risk calculator excludes lipid profile. Patients are considered to be at high risk of a CVD event over the next 10 years if they score 20% or greater (10). The PRIMROSE lipid model excludes BMI and, again, patients are considered to be at high risk of a CVD event over the next 10 years if they score 20% or greater (10). Outcomes for which risks are in predicted in both PRIMROSE risk calculators cover both fatal and non-fatal cardiovascular events including myocardial infarction, angina pectoris, coronary heart disease, major coronary surgery and revascularization, cerebrovascular accident, and transient ischaemic attack (10).

QRISK3

The QRISK2 risk calculator is recommended for use with the UK general population by NICE (41). NICE also recommends QRISK2 for use in those with medical conditions including SMI, whilst acknowledging it may underestimate risk in such groups (22). QRISK2 is about to be superseded by QRISK3, which includes both typical risk indicators and specific factors for SMI (i.e., an SMI diagnosis and antipsychotic use) in patients aged 25–84 years (9) and may enable more accurate assessment. The QRISK algorithms have been validated using UK primary care databases including the Clinical Practice Research Datalink (CPRD) (42) and THIN (43–45). As well as calculating the 10-year risk of CVD, QRISK3 also estimates a "heart age." This is calculated by comparing the ideal age of healthy individuals who receive the same predicted CVD risk score and have the same sex and ethnicity (46). A heart age older than the current age suggests increased risk that is modifiable (46). It is important to emphasize that this is a relative measure and heart age has been found on average to be older than chronological age in every age strata (47). It may be a useful tool to encourage lifestyle modification rather than to inform medication recommendations (48).

Using the QRISK3, patients are considered to be at high risk of a CVD event over the next 10 years if they score 10% or greater (9). This threshold was set following health economics modeling for when to offer medical intervention, such as with statins prescription (38). Risks are estimated for the following CVD outcomes: transient ischaemic attack and related syndromes, angina pectoris, myocardial infarction, subsequent myocardial infarction, complications after myocardial infarction, other acute ischaemic heart disease, chronic ischaemic heart disease, cerebral infarction, and stroke not specified as hemorrhage or infarction (9).

Anthropometric Measurements

BMI was calculated as weight/height^2 (kg/m^2). Participants were classified according to the World Health Organization (WHO) criteria as underweight (BMI $<$18.5), normal (BMI 18.5–24.99), overweight (BMI 25–29.99) obese (BMI 30–39.99), or severe obesity (BMI $\geq$40) (49). Medical records were reviewed for any diagnosed physical and mental health conditions, prescribed medication and to confirm self-reported demographic information.

Statistical Analyses

Data were analyzed using STATA (version 11; Statacorp, TX, USA). Descriptive statistics were reported as medians, means, standard deviations (SDs) and percentages. 10-year predicted cardiovascular risk scores were calculated using published algorithms (9–11). The relationship between each CVD risk

calculator model was assessed using concordance correlation coefficients (P_c). This correlation measures how far the best-fit line differs from the line y = x, by adjusting the *r*-value using a bias correction factor. P_c therefore provides a measure of correlation and agreement. Bland-Altman plots were generated to plot the difference against mean between pairs of CVD risk calculators.

RESULTS

Sociodemographic and Summary Data

The study sample included 30 participants. Their mean age was 40.4 ± 10.2 years and 83% were male. Most of the participants were overweight, with 33% being either obese (BMI ≥30 kg/m²) or severely obese (BMI ≥40 kg/m²) and the mean BMI was in the overweight range (29.9 ± 7.9; **Table 2**). Atypical antipsychotics were prescribed to 83% of participants; typical antipsychotics were prescribed to 27% of participants. Both atypical and typical antipsychotics were prescribed to 10% of these participants.

10-Year Predicted CVD Risk

Participants' absolute 10-year risk of CVD was calculated using four different risk calculators: QRISK3, Framingham, PRIMROSE BMI, and PRIMROSE lipid. Two participants were excluded from the QRISK3 analysis due to their age being below 25 years. One participant was excluded from the Framingham and PRIMROSE lipid analyses due to an inability to draw blood and obtain their lipid profile. QRISK3 identified 11 participants (39%) who were classified into the high-risk category of having a CVD event within 10 years (range 0.4–38.5%), based on a 10% threshold for high-risk. No participants were classified into the high risk category for the PRIMROSE lipid (range 0.1–8.5%), PRIMROSE BMI (range 0.2–7.4%), or Framingham (range 0.1–15.6%) risk calculators, based on a 20% threshold for high-risk. However, if a 10% threshold is imposed across all four calculators, 39% of patients are categorized as high-risk with QRISK3, 14% with Framingham and none with PRIMROSE risk calculators. If a 20% threshold is imposed across all four calculators, 14% are categorized as high risk by QRISK3 and none with other the other risk calculators (**Table 3**).

Heart Age

Frequency distributions of age and heart age calculated using QRISK3 can be seen in **Figures 1**, **2**. The mean heart age was 58.4 ± 13.5. The mean difference between age and calculated heart age was found to be over 16 years with one individual scoring a heart age 40 years above their actual age (**Figure 3**).

Agreement Between 10-Year Predicted CVD Risk Models

Pairwise concordance correlation coefficients were highest between the two PRIMROSE measures but the QRISK3 and PRIMROSE metrics had notably poor correlations, not even reaching the acceptable range at their upper CIs and close to zero at the lower CIs (**Table 4**; **Figure 4**).

TABLE 2 | Distribution of sociodemographic and clinical factors in the sample of patients diagnosed with schizophrenia.

	N	%	Mean ± SD	Median
GENDER				
Male	25	83		
Female	5	17		
Age			40.4 ± 10.2	40
18–34	9	30		
35–64	21	70		
ETHNICITY				
White British	19	63		
Black British/African	4	13		
Black British/Caribbean	2	7		
Other ethnic groups	5	17		
SMOKING				
Current smoker	22	73		
Ex-smoker	5	17		
Never smoked	3	10		
DIAGNOSIS OF TYPE 2 DIABETES				
Yes	4	13		
No	26	87		
PRESCRIBED ANTI-DEPRESSANT MEDICATION				
Yes	12	40		
No	18	60		
PRESCRIBED STATINS				
Yes	7	23		
No	23	77		
PRESCRIBED HYPERTENSIVE TREATMENT				
Yes	7	23		
No	23	77		
Systolic blood pressure			125.9 ± 16.7	125.5
<120 mmHg	11	37		
≥120–139 mmHg	12	40		
≥140 mmHg	7	23		
BMI			29.9 ± 7.9	27.5
Underweight (<18.5)	0	0		
Normal (18.5–24.99)	8	27		
Overweight (25–29.99)	12	40		
Obese (30–39.99)	7	23		
Severe obesity (≥40)	3	10		

Systolic Blood Pressure.

DISCUSSION

We applied four risk calculators to determine the predicted CVD risk for 30 patients with schizophrenia over the next 10 years. Mean QRISK3 calculated risk estimates were approximately 4 times higher than the PRIMROSE lipid calculated risk estimates, and roughly 3 times higher than PRIMROSE BMI. Moreover, agreement between calculators was poorest between QRISK3 and the PRIMROSE calculators, despite these calculators taking into account diagnosis of SMI and use of antipsychotic medication within their algorithms. These risk factors are known to have

TABLE 3 | Ten-year predicted CVD risk scores according to 4 different risk calculators.

	<10%		10–19%		20% or more		Mean* ± SD
	N	%	*N*	%	*N*	%	
QRISK3	17	61	7	25	4	14	9.3 ± 8.8
Framingham	25	86	4	14	0	0	4.1 ± 4.1
PRIMROSE Lipid	29	100	0	0	0	0	2.0 ± 2.0
PRIMROSE BMI	30	100	0	0	0	0	2.9 ± 2.1

**Mean % of 10-year predicted CVD risk.*

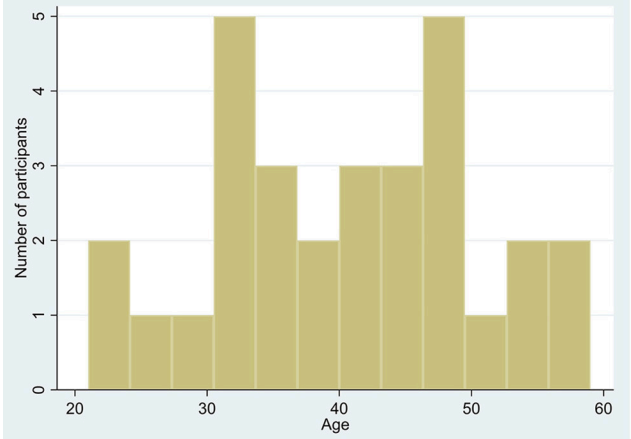

FIGURE 1 | Distribution of age.

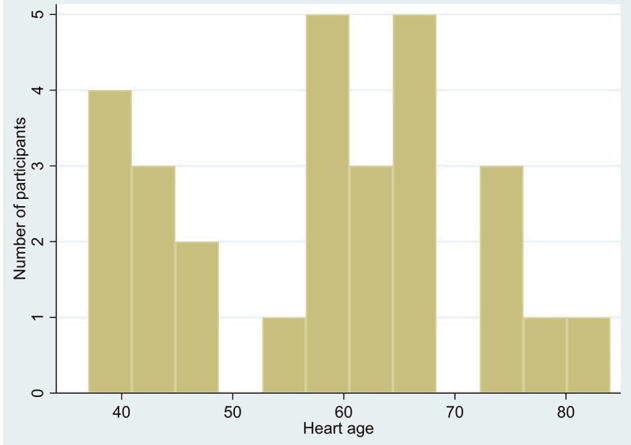

FIGURE 2 | Distribution of heart age.

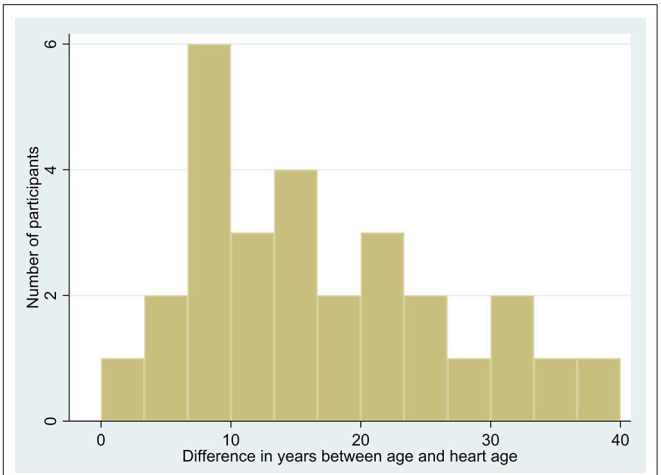

FIGURE 3 | Difference between age and heart age.

a complex effect on cardiovascular risk (9) and the lack of agreement highlights the variability in the weighting of risk factors between these models, which impacts the relative risk. Agreement between Framingham and the three other risk calculators was more acceptable but not high. People with SMI were excluded from the Framingham heart study cohort and previous research comparing cardiovascular risk calculators in the general population has recommended selecting calculators that have been developed from a population similar to the patient (50).

People with schizophrenia and related conditions are recommended to attend for regular physical health assessments, including checking for cardiometabolic indicators specifically so that clinicians may offer any required interventions (51). For the purposes of CVD prevention, it is therefore important for clinicians to be able to identify individuals at highest risk of developing CVD. There is currently a lack of reliable evidence indicating the superiority of one CVD risk calculator over another, particularly in relation to persons with SMI. Our data suggest that there are important differences between calculators.

The threshold for classifying a patient as high-risk of having a CVD event over the next 10 years differed between the models. Thirty nine percent of participants were classified as high-risk using QRISK3, but all were classified as low-risk using the other calculators. Framingham and the PRIMROSE risk calculators both set the threshold as 20% or greater, while QRISK3 sets the threshold as 10% or greater. NICE guidelines recommend using a 10% threshold for initiating preventative therapy with statins (52). It is however not clear whether this is the optimal threshold for modifying risk in people with schizophrenia. For clinicians it is therefore not clear when to initiate preventative therapy or which risk calculator to use with patients with SMI. NICE emphasizes that faced with the challenge of applying population-based measures to individuals, clinicians should exercise their judgement and include patients' preferences when making clinical decisions in relation to CVD risk scores (53). There may also be other patient-related factors that should be considered, such as socioeconomic status or other underlying medical conditions (53).

The risk factors included in the algorithms for CVD risk calculators typically include age, gender, medical diagnoses, prescription to medications, BMI, blood pressure, and lipid profile. With the exception of smoking in all risk calculators,

TABLE 4 | Agreement among 10-year predicted CVD risk models (%).

	Difference		95% Limits of agreement	P_C (95% CI)
	Mean	SD		
QRISK3 vs. Framingham	5.0	5.4	−5.7 to 15.7	0.549 (0.41 to 0.69)
QRISK3 vs. PRIMROSE Lipid	7.2	7.3	−7.1 to 21.6	0.224 (0.12 to 0.32)
QRISK3 vs. PRIMROSE BMI	6.2	7.4	−8.2 to 20.6	0.226 (0.12 to 0.33)
Framingham vs. PRIMROSE Lipid	2.1	2.6	−3.0 to 7.3	0.543 (0.38 to 0.70)
Framingham vs. PRIMROSE BMI	1.2	2.8	−4.3 to 6.7	0.581 (0.41 to 0.75)
PRIMROSE Lipid vs. PRIMROSE BMI	−0.9	1.2	−3.2 to 1.4	0.767 (0.63 to 0.91)

P_c, Concordance correlation coefficient; CI, confidence intervals.

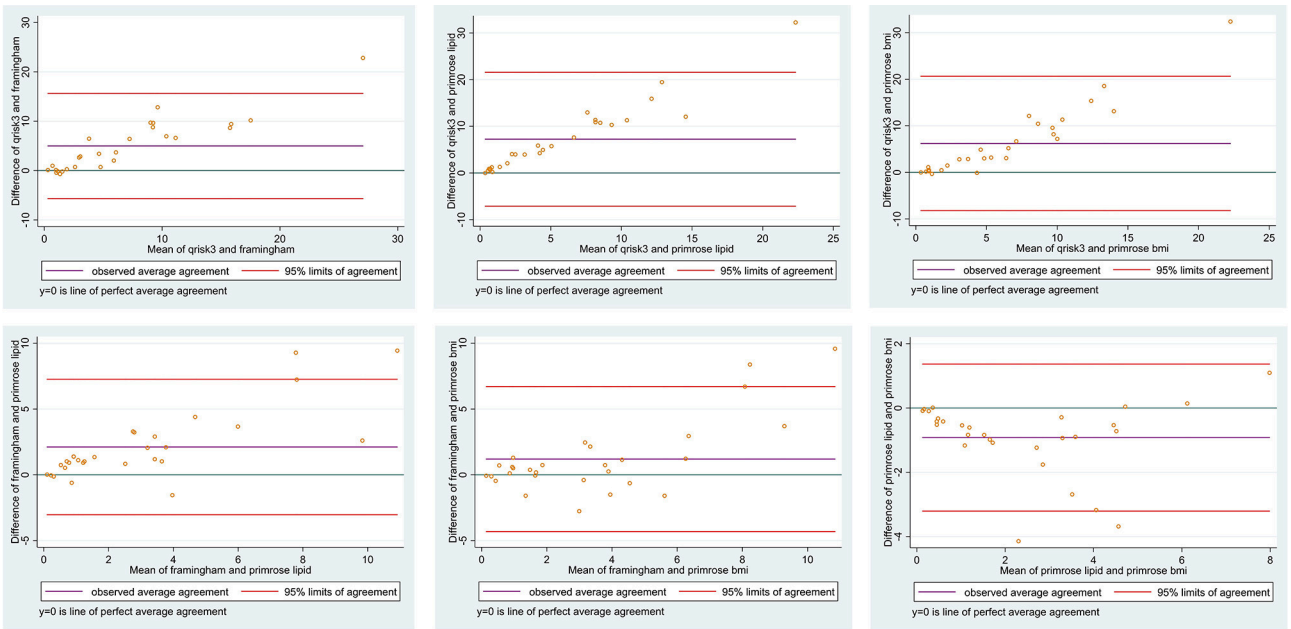

FIGURE 4 | Difference against mean between 10-year predicted CVD risk calculators.

and history of heavy drinking within PRIMROSE risk calculators (10), lifestyle screening is not included. Lifestyle screening contributes little to CVD risk calculator algorithms, partly because resource limitations mean lifestyle factors are not routinely recorded within primary care databases from which risk models derive. However, many lifestyle factors have been found to increase the risk of CVD both in the general population and SMI groups. Meta-analyses show that sedentary behavior in the general population is associated with increased risks of diabetes, CVD and cardiovascular and all-cause mortality (54); and that those with schizophrenia group engage in high levels of sedentary behavior (55). Furthermore, sleep disorders are reported in 30–80% of people with schizophrenia (56, 57). They take longer to fall asleep, sleep longer, take daytime naps and have severely fragmented sleep compared to healthy controls (58). There is emerging evidence that disrupting sleep can cause health problems, such as CVD (59). It may be that sleep quality needs to be routinely enquired about and its role in CVD risk calculators investigated

Comparing models, it is notable that the low PRIMROSE and Framingham risk scores seem at odds with clinical impressions of participants and with studies of life expectancy, CVD and CVD risk factor prevalence in people with schizophrenia. People with schizophrenia have 2.5 times the risk of dying compared to the general population (1), and a mean age of death from CVD in schizophrenia patients was found to be 51 years (60). Moreover, general population life expectancy in the UK is lowest in northern urban England, including Manchester (61), with healthy male life expectancy at birth in Greater Manchester in the 50s (54). This implies that a substantial proportion of this sample should be in a high-risk category. QRISK3 estimated our participant heart ages to be a mean of 16 years older than chronological age. Whilst "heart age" may not be an accurate enough tool to inform medical decision-making (48), an age adjustment of this size may be similar to the substantial reduction in life expectancy in this group.

Our study was limited by its small sample size, which makes it difficult to draw generalisable conclusions and we

therefore recommend repeating this study on a considerably large scale. The sample was recruited from Greater Manchester in England by volunteers. This is an area where health and life expectancy is unusually poor in the general population (54), so this sample may well not be representative. However, this may have enabled us to detect higher rates of predicted CVD risk in this group. A longitudinal study of a representative cohort of sufficient size to accurately estimate agreement among CVD risk calculators is indicated. This study underlines the importance of such work in that, even in a small study, differences were observed between algorithms in their risk predictions.

CONCLUSIONS

Existing CVD risk calculators have low agreement with each other in our sample of people diagnosed with schizophrenia. This makes it challenging to draw conclusions about which tool is most suitable for clinicians to use with this population group, and how to treat patients who fall in different categories when using one calculator rather than another. It is recommended that clinicians consider multiple patient-related factors in addition to predicted CVD risk score when recommending treatment. Furthermore, participants in our study had a calculated heart age that was much older than their actual ages. Of interest would be whether adjusting the age of patients with schizophrenia more accurately predicts CVD events. Further research is needed with larger numbers and with longitudinal follow-up to assess actual CVD events to understand this further. Also of interest would be the use of large datasets to examine the question of CVD risk in schizophrenia. Such studies should also investigate if any of the factors known to increase risk of CVD in the general population that are also common in schizophrenia, such as physical inactivity (55–57), high rates of sedentary behavior (58), and sleep disturbance (59, 62) impact on CVD risk, independent of the risk factors already included in existing CVD risk calculators.

AUTHOR CONTRIBUTIONS

AB, AY, and RD contributed conception and design of the study. AB collected the data. AB and RD performed the statistical analysis. AB and AY wrote the first draft of the manuscript. AB, AY, and RD wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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BRIEF RESEARCH REPORT
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Objectively Assessed Daily Steps—Not Light Intensity Physical Activity, Moderate-to-Vigorous Physical Activity and Sedentary Time—Is Associated With Cardiorespiratory Fitness in Patients With Schizophrenia

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People with schizophrenia often have an unhealthy sedentary lifestyle with low level of physical activity and poor cardiorespiratory fitness—an important predictor of cardiovascular disease. We investigated the relations between cardiorespiratory fitness and both sedentary time and different aspects of physical activity, such as daily steps, light intensity physical activity, and moderate-to-vigorous physical activity. Using accelerometer as an objective measure of sedentary time and physical activity we estimated their relations to cardiorespiratory fitness in 62 patients with schizophrenia with roughly equal gender distribution, mean age of 36 and 15 years illness duration. We found a significant association between daily steps and cardiorespiratory fitness when accounting for gender, age, sedentary time, light intensity physical activity, and respiratory exchange ratio (maximal effort). Moderate-to-vigorous physical activity was not significantly associated with cardiorespiratory fitness. In conclusion, the amount of steps throughout the day contributes to cardiorespiratory fitness in people with schizophrenia, independently of light intensity physical activity and sedentary time. We did not find a significant relationship between moderate-to-vigorous physical activity and cardiorespiratory fitness. This may have implications for the choice of strategies when helping patients with schizophrenia improve their cardiorespiratory fitness.

Keywords: schizophrenia, lifestyle, cardiovascular disease, daily steps, physical activity, cardiorespiratory fitness, accelerometer, sedentary time

INTRODUCTION

People with schizophrenia are prone to overweight, diabetes and chronic metabolic disease (1) and often have a deleterious lifestyle, including low levels of moderate-to-vigorous physical activity (MVPA) and high levels of sedentary time (2). The average life expectancy is 15–20 years shorter than the general population, and cardiovascular disease (CVD) is the largest contributing factor to the increase in mortality (3). Low cardiorespiratory fitness (CRF) is a strong independent risk factor for all-cause mortality (4, 5) associated with low life expectancy and increased risk for CVD in the general population (4–6) and in schizophrenia (7, 8). Thus, knowledge on how to effectively improve CRF in schizophrenia is urgently needed. The beneficial effects of MVPA and the smaller effects of light intensity physical activity (PA) on CRF in the general population are well documented (9, 10). Less is known about the relations in people with schizophrenia. Another aspect of interest is the extent sedentary time influences CRF in the patient group. Sedentary time refers to the time spent for any duration or in any context in sedentary behaviors, defined as any waking behavior characterized by an energy expenditure equal to or less than 1.5 the resting metabolic rate while in a sitting, reclining or lying posture (11–13). Recent studies suggest that sedentary time is an important determinant of CRF levels, which is independent of physical activity (14, 15) A third aspect of interest is the total PA level. The number of daily steps have been associated with positive health effects in the general population (16) and in individuals with high cardiovascular risk (17). Studies on healthy overweight persons have indicated that reduced total daily PA causes reduction in CRF as well as worsening of other cardiometabolic health outcomes (18, 19). Increasing the total PA by walking (i.e., daily steps), as well as breaking the sedentary habit could be a path to improved CRF distinct from light intensity PA and MVPA (20, 21). It is not known whether the potential health effects facilitated by daily steps in people with schizophrenia are cumulative, increasing with the amount of total PA. The aim of the current study was to examine whether objectively assessed light intensity PA, MVPA, total daily steps, and sedentary time, exert *independent* influences on CRF in people with schizophrenia.

MATERIALS AND METHODS

Participants

Sixty-two patients were recruited from the main study Effects of physical activity in psychosis (EPHAPS) from August 2014 through September 2016 in catchment area-based and publicly funded outpatient psychiatric clinics in Vestfold County, Norway. A subgroup of the patients was referred from primary health care to the outpatient clinics for specific participation in the project. Patients diagnosed with schizophrenia spectrum disorder established using SCID I (22) who were aged 18–67 and understood and spoke a Scandinavian language were eligible for the study. Interviews were conducted by a clinical psychologist or a specialist in psychiatry. For further details on study design see Engh et al. (23) and on patient recruitment, study eligibility and data collection see Engh et al. (23) and Andersen et al. (24). All except one patient received antipsychotic treatment. Demographic and clinical characteristics are presented in **Table 1**.

TABLE 1 | Demographic and clinical characteristics, physical activity and sedentary time of the participants.

	N	Value	*SD*
Age (years), mean	62	36.3	13.7
Gender (women, %)	62	27 (43.5)	–
Duration illness (years)	61	14.9	12.2
Smokers (%)	62	40 (64.5)	–
Body mass index ($kg*m^{-2}$)	62	29.2	5.7
PANSS positive subscale* (score range 7–42)	62	15.2	5.1
PANSS negative subscale* (score range 7–42)	61	17.9	7.0
PANSS total score* (score range 30–210)	61	65.3	17.5
Antipsychotic medication DDD**	62	1.7	0.9
Light intensity Physical activity (min/day^{-1})	62	216	92.4
Moderate/vigorous physical activity (min/day^{-1})	62	28.7	31.0
Steps/day ($steps*day^{-1}$)	62	5685.0	3641.0
Sedentary time ($h*day^{-1}$)	62	8.6	1.6
VO_{2peak} ($mL*kg^{-1*}min^{-1}$), all participants	62	30.2	11.6
VO_{2peak} ($mL*kg^{-1*}min^{-1}$), participants fulfilling maximal effort criteria***	52	31.5	11.8
VO_{2peak} ($mL*kg^{-1*}min^{-1}$), participants not fulfilling maximal effort criteria****	10	33.9	7.7

*Data presented in % or mean. *PANSS, Positive and Negative Syndrome Scale; **DDD, defined daily dose, dose equivalence estimate based on total intake of antipsychotics per day; ***Respiratory exchange ratio≥ 1.00. ****Respiratory exchange ratio < 1.00.*

Assessments

For further details on measurement of physical activity, sedentary time, and oxygen uptake see (24). PA and sedentary time was assessed using the ActiGraph GT3X+ (ActiGraph, LLC, Pensacola, FL, USA) worn over the left hip while awake for four consecutive days. Analyses were restricted to participants who wore the accelerometer for a minimum of 10 h per day for 2 days or more. To identify different intensities of PA, count thresholds corresponding to the energy cost of the given intensity were applied to the data set. Sedentary time was defined as all activity <100 counts per minute (CPM), a threshold that corresponds with sitting, reclining, or lying down (25). Light intensity PA was defined as 100–2019 CPM, moderate as 2020–5998 CPM, and vigorous as CPM ≥ 5999 (26). The amount of minutes per day at different intensities was based on summing the time where the activity count met the criteria for the specific intensity. Cardiorespiratory fitness (CRF) was operationalized as VO_{2peak} measuring the highest oxygen uptake in a maximum exercise test on a treadmill (Woodway, Würzburg, Germany). Some individuals may fail to reach true VO_{2max}, and for the sake of conservative reporting, we therefore use the term VO_{2peak} ($mL*kg^{-1}*min^{-1}$). We used a modified Balke protocol (27), where speed was held constant at 5 $km{\cdot}h^{-1}$ and the inclination angle was increased by one degree every minute until exhaustion within 6–12 min. Gas exchange was continuously sampled in a

TABLE 2 | Correlation coefficients between physical activity measures, sedentary time, and VO_{2peak}.

	Gender	Age	Light intensity physical activity	Moderate/vigorous physical activity	Steps/day	Sedentary time
Light intensity physical activity	0.11	0.18	–	–	–	–
Moderate/vigorous physical activity	−0.11	−0.35**	0.09	–	–	–
Steps/day	0.16	−0.25	0.45**	0.73**	–	–
Sedentary time	−0.09	0.01	−0.44**	−0.31*	0.42**	–
VO_{2peak}	−0.22	−0.64**	−0.002	0.28*	0.34**	0.02

*$p < 0.05$; **$p < 0.001$.

TABLE 3 | Regression analysis presenting explained variance in VO_{2peak}.

	R	R^2	Unstand-ardized coefficie-nt (B)	Standard error	Standar-dized coefficient (Beta)	*t*-value	Variance inflation factor (VIF)	*P*- value
Gender	−0.164	0.027	−3.914	2.270	−0.169	−1.724	1.068	0.090
Age	−0.510	0.260	−0.481	0.090	−0.568	−5.368	1.243	<0.001**
Light intensity physical activity	0.054	0.0008	0.008	0.015	0.067	0.569	1.535	0.572
Steps/day	0.206	0.042	11.747	5.404	0.262	2.174	1.615	0.034*
Sedentary time	0.134	0.018	0.018	0.013	0.156	1.412	1.346	0.163

N = 62 for all variables. All physical activity variables and sedentary time were assessed by accelerometer.
*Partial correlation to VO_{2peak} (R), uniquely explained variance (R^2) by each of the predictors, unstandardized coefficients (B), standard error of the coefficients, standardized coefficients (Beta), t-values, variance inflation factors (VIF), and p-values are presented in the standard regression model. *$p < 0.05$; **$p < 0.001$.*

mixing chamber every 30 s by breathing into a two-way breathing valve (2700 series, Hans Rudolph Inc., Kansas City, USA). The breathing valve was connected to a Jaeger Oxycon Pro used to analyze the oxygen and carbon content. Maximal effort was assessed by the respiratory exchange ratio (RER). Participants reached the criteria when RER $\geq$ 1.00. Participants' psychotropic drugs prescription was presented as defined daily dose (DDD) based on approved dose recommendations. DDD provides a rough estimate of participants' drugs consumption utilizing the assumed average maintenance dose per day for each specific drug used independent of dosage form for its main indication on adults (i.e., schizophrenia for antipsychotics). For example, the DDDs for chlorpromazine and risperidone are 300 mg and 5 mg respectively. DDD were calculated in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd). Information on smoking, illness duration and medication was obtained through interview and the use of hospital records. Weight was measured without shoes in light clothing by a SECA electronic scale to the nearest 0.5 kg. Height was measured without shoes with a transportable stadiometer and set to the nearest 0.5 cm.

Statistics

Variables that were not normally distributed (*steps/day*; *MVPA*) were log-transformed in the statistical analyses. Multiple regression analyses (all covariates entered concomitantly in the model) were employed to examine the relationships between independent variables and VO_{2peak}. VO_{2peak} was used to represent the outcome, cardiorespiratory fitness. Selection of variables in the regression model was based on Pearson correlation tests between VO_{2peak}, measures of physical activity and sedentary time and other variables with assumed clinical importance. Correlation coefficients are shown in **Table 2**. Due to high correlation between the independent variables MVPA and steps/day ($r = 0.73$) two separate regression analyses were employed using each of these two independent variables and all other selected variables. The independent variable steps/day, and not MVPA, was included in the final regression model. When testing for multicollinearity correlations between independent variables were sufficiently low ($r < 0.70$) and the variation inflation factor fell within the criteria (VIF < 10). All statistical analyses were performed using IBM SPSS (Statistical Pack- age for the Social Sciences for Windows, version 24, IBM, Inc., Chicago, IL, USA).

RESULTS

As shown in **Table 3**, VO_{2peak} was significantly associated with gender, age and steps/day when all other covariates were controlled. Regression coefficients and standard errors can be found in the table. In a separate regression analysis encompassing MVPA in addition to the independent variables gender, age, light intensity PA and sedentary time, MVPA did not contribute to VO_{2peak}. Eighty-four percent of the participants obtained the criteria for RER. The main results were unaltered in a multiple regression analysis with participants attaining RER $\geq$ 1.00.

DISCUSSION

The main finding in the current study was that total daily steps was significantly associated with VO_{2peak}, independently of light

intensity physical activity, the amount of time spent sedentary and maximal effort during testing of oxygen consumption. Moderate-to-vigorous physical activity was not significantly associated with VO_{2peak}. Our findings suggest that the amount of daily walking activity is of importance for patients with schizophrenia by contributing to the established health indicator VO_{2peak}. As a measure of the total physical activity daily steps differs from the measures of physical activity at defined levels of activity. VO_{2peak} may reflect the individual's participation in physical activity of different intensity. The influence of physical activity at specific intensity levels on VO_{2peak} has been focus of previous research. A meta-regression of moderators of physical activity showed that low VO_{2peak} was associated with low levels of moderate-to-vigorous physical activity (2). In a recent study of patients with psychosis using a 6 min-walking test as a proxy for CRF, both MVPA and total PA showed significant moderate positive correlations with CRF (28). The findings in the current study indicate that repeated or prolonged sequences of walking could have favorable health effects in schizophrenia. However, the current study investigating the relations between VO_{2peak} and physical activity at different intensity levels, sedentary behavior and daily steps in patients with schizophrenia needs to be replicated.

A comparison of studies using objective assessments of PA and sedentary behavior with studies based on self-reports suggests that people with schizophrenia underestimate the amount of sedentary time and overestimate the duration of their PA (2). The objective assessment of PA is a strength of the current study. A limitation is the cross sectional design without the opportunity to draw inferences concerning causal effects. The encouragement of repeated indoor, as well as outdoor physical activity, could be organized according to personal preference and implemented as part of treatment in community-based mental health care. In conclusion, the amount of steps throughout the day contributes to VO_{2peak} in people with schizophrenia, independently of light intensity physical activity and sedentary time. Moderate-to-vigorous physical activity was not significantly associated with VO_{2peak}. This may have implications for the choice of strategies when helping patients with schizophrenia improve their cardiorespiratory fitness.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Regional Ethics Committee of Southern and Eastern Norway (REK Sør-Øst) under file number 2014/372/REK Sør-Øst C 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 Regional Ethics Committee of Southern and Eastern Norway (REK Sør-Øst).

AUTHOR CONTRIBUTIONS

JAE and EA conceived the study. JAE, JE, EA, and JM acquired funding and approval of the ethics committee. These four researchers, in addition to EWM and OAA, contributed to study design. TLH, TTB, GB-K and JM carried out parts of the clinical testing. The manuscript has been drafted by JAE, EA, JE, OAA, GB-K, TTB, TLH, EWM, and JM. All authors read, worked on and approved the final manuscript.

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Augmenting Mental Health in Primary Care: A 1-Year Study of Deploying Smartphone Apps in a Multi-site Primary Care/Behavioral Health Integration Program

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Background: Integrating behavioral health (BH) services into primary care is an evidence-based intervention that can increase access to care, improve patient outcomes, and decrease costs. Digital technology, including smartphone apps, has the potential to augment and extend the reach of these integrated behavioral health services through self-management support impacting lifestyle behaviors. To date, the feasibility and acceptability of using mental health mobile apps within an integrated primary care setting has not yet been explored as part of routine clinical care.

Objectives: The objectives of this study were to (a) test the feasibility of using mental health applications to augment integrated primary care services; (b) solicit feedback from patients and providers to guide implementation, and (c) develop a mental health apps toolkit for system-wide dissemination.

Methods: Cambridge Health Alliance (CHA) is a safety-net healthcare system that includes three community hospitals and 12 Primary Care (PC) clinics serving nearly 150,000 ethnically and socioeconomically diverse patients around Boston. To select and disseminate mental health apps, a four-phase implementation was undertaken: (1) Evaluation of mental health mobile applications (2) Development of an apps toolkit with stakeholder input, (3) Conducting initial pilot at six primary care locations, and (4) Rolling out the app toolkit across 12 primary care sites and conducting 1-year follow-up survey.

Results: Among BH providers, 24 (75%) responded to the follow-up survey and 19 (83%) indicated they use apps as part of their clinical care. Anxiety was the most common condition for which app use was recommended by providers, and 10 (42%) expressed interest in further developing their knowledge of mental health apps. Among patients, 35 (65%) of participants provided feedback; 23 (66%) reported the tools to be helpful, especially for managing stress and anxiety.

Conclusions: Our findings indicate mental health apps are applicable and relevant to patients within integrated primary care settings in safety-net health systems. Behavioral health providers perceive the clinical value of using these tools as part of patient care, but require training to increase their comfort-level and confidence applying these tools with patients. To increase provider and patient engagement, mobile apps must be accessible, simple, intuitive and directly relevant to patients' treatment needs.

Keywords: mental health, mobile apps, smartphone apps, integrated primary care, behavioral health integration, mental health integration

INTRODUCTION

Integrating behavioral health care services into primary care is an evidence-based intervention that can increase access to care, improve patient outcomes, and decrease costs (1). The need for integrated behavioral health (BH) is driven by the heavy burden of mental health conditions, including depression, which is now recognized by the World Health Organization as the leading global cause of disability (2), as well as insufficient numbers of specialized behavioral health clinicians like social workers, psychiatrists, psychologists, and case managers. Key elements of integrated care models include screening for high prevalence mental health conditions, integration of behavioral health clinicians into primary care settings, collaborative team building, and care management for patients (3). With ∼40% of mental health care in the United States delivered in the primary care setting, the demand for integrated BH services has outpaced availability (4).

Like other areas of healthcare, digital technology has been proposed as a means to augment and extend the reach of BH integrated care services. These technologies can be classified into three categories: (1) patient facing, (2) primary care facing, and (3) virtual visits (5). Patient facing technologies to extend integrated care may include smartphone apps that offer self-management or guided interventions like Cognitive Behavioral Therapy. Primary care facing technologies include tools to support increased capacity and confidence to offer mental health treatment such as consultation platforms, tele-mentoring, and clinical decision support for integrated care teams. Virtual visits reflect the ability to offer telemedicine services to support integrated care. While there is a growing evidence base and clinical experience with using both virtual visits and primary care facing technologies (5) there is limited to no research or clinical evidence for using smartphone apps to support integrated care.

The lack of knowledge on incorporating mental health-related smartphone apps into integrated care systems is especially surprising considering the potential of mobile technology in mental health. Numerous survey studies have demonstrated those with mental health conditions own smartphones and are interested in using apps for their care (6–8). Meta-analysis of randomized clinical studies of smartphone apps for depressive symptoms (9) and anxiety disorders (10) have demonstrated early efficacy data. In many cases, consumers with mental health conditions are not waiting for the evidence to catch up; today over 10,000 mental health related apps are available from the iTunes and Android app stores (11). Case reports and clinical experience support that people are using these apps to learn about their mental health, track symptoms, and self-manage their condition (12, 13). However, exploring the utility of these apps outside of research studies remains largely uncharted.

Prior efforts transitioning promising mental health research apps into actual clinical care settings underscores the need for careful assessment. One substance use disorder app that showed promising evidence to reduce frequency of alcohol consumption (14) was later found to be difficult to support and maintain in actual clinical settings without the additional support and structure offered in the research setting (15). Reviews of smartphone app adoption by healthcare professionals, beyond mental health and integrated care settings, suggest that perceived barriers can include concerns about privacy, legal ramifications, cost, workload, and need for increased information technology (IT) support (16). Despite barriers, there is evidence that apps are being introduced to care. For instance, research from the United Kingdom suggests that already 30% of mental health providers recommend apps to patients (17). On the patient side, there is also concern that many commercially available mental health apps may not be designed for those with more severe symptoms (18).

In this study, we sought to provide early clinical data from both the patient and clinician perspective on the usage and integration of mental health apps in a busy integrated BH care service at Cambridge Health Alliance (CHA), a safety net healthcare system that includes three community hospitals and 12 Primary Care (PC) clinics which serve nearly 150,000 ethnically and socioeconomically diverse patients in the greater Boston area (19). The healthcare system had implemented an integrated model of care, based on the collaborative care model (20) and Screening, Brief Intervention and Referral to Treatment (SBIRT) (21), to support screening, assessment, and treatment of behavioral health conditions in primary care clinics. The integrated BH staff provide evidence-based brief clinical interventions focusing on patients primarily experiencing low to moderate anxiety, depression, and substance use disorders. Consult psychiatrists provide diagnostic clarification and management strategies for the primary care team. Integrated psychotherapists provide brief treatment (6–8 sessions) grounded in evidence-based treatment modalities including Cognitive Behavioral Therapy (CBT), Problem-Solving Therapy (PST), Behavioral Activation (BA), and Mindfulness Based Stress Reduction (MBSR). Care managers work primarily

with patients experiencing low to moderate anxiety and depression; they use interventions including Motivational Interviewing (MI) and BA to support patients in reaching health and lifestyle-related goals and to bridge patients to BH providers. To answer the question of whether mental health apps can be adopted within routine BH care and serve as a helpful tool for patients, we present the results of one institution's experience evaluating, piloting, and disseminating mental health apps across an integrated primary care system.

METHODS

Step 1: Selecting Apps

The first step in introducing apps into care was to identify a series of existing apps that could be recommended to patients receiving integrated care services. Given that the vast majority of these apps fall outside of the Food and Drug Administration (FDA) regulation and there is no formal evaluation or gold standard for judging these apps, we assembled a seven-person multi-disciplinary team of integrated therapists, care managers, administrative and Informational Technology (IT) leadership, and patients to identify and evaluate mental health self-management apps over the course of 10 months. We sought apps that offered patient facing interventions, avoided direct use with a clinician, were free, and claimed to provide privacy protections for patient generated data—understanding there is no set of gold standard apps or criteria to pick apps. Thus, we focused on apps that were: (1) aligned with clinical interventions utilized in our program; (2) developed by a "trusted" source such as medical, academic, and/or research institutions, and/or companies with clinical consultants; (3) free to download, and (4) contained privacy statements at the time of our evaluation. Drawing from our workgroup's clinical knowledge and experience caring for CHA's safety-net patient population, we also considered apps' accessibility in terms of our patients' language needs, literacy levels, and alignment with treatment goals (22). In seeking such apps, we read select literature to help orient us to broader findings and challenges in the mHealth space (23), consulted with app researchers and designers, and sought feedback from our clinical teams and the patients they serve. Without validated app evaluation tools to guide our selection process, we relied on expert consensus throughout the four-stage study process to select a set of apps that best supported our clinical interventions and the needs of our patient population.

Step 2: Creating a Toolkit Around Apps

We identified an initial list of 13 applications and sought guidance from our institution's Patient Partner Lead who represents CHA's patient partners, a group of patient volunteers who serve on quality improvement teams to advise on key projects. Drawing on feedback from our Patient Partner Lead, staff member expertise, papers on app evaluation (24), and elements of the user version of the Mobile Apps Rating System (U-MARS) (25), the workgroup next narrowed the list to nine apps and drafted a process for introducing the apps through the Primary Care Behavioral Health Integration program (PCBHI) in Primary Care. In drafting the process for introducing these apps to patients, we aimed to incorporate several elements: (a) suggestions to staff as to when to introduce the apps; (b) appropriate language for staff to use in discussing the apps with patients, and (c) brief descriptions of the apps in patient-facing materials. The evaluation team and Patient Partner Lead co-designed a set of tools for introducing the BH apps, including a patient-facing summary sheet describing the risks/benefits of using smartphone applications and a mobile apps "toolkit" that contained descriptions of the purpose and main features of the nine selected apps. We then trained six care managers to identify patients who might benefit from using mobile apps and introduce the tools to patients (including clinical rationale, product demonstration, goal setting, and plan for follow-up). Care managers were given additional training around discussing app privacy/security with patients and reviewed all points detailed within the patient-facing summary sheet. As a quality improvement project to improve access to high quality self-management tools within primary care, this implementation study was not subject to formal approval by our Institutional Review Board as per Cambridge Health Alliance's ethics guidelines and national regulations. Before introducing the selected mobile apps to patients, care managers obtained informed verbal and written consent from all pilot participants and no personally identifiable information was collected during the course of the pilot.

Step 3: Initial Pilot Testing

Before disseminating the apps toolkit across our integrated care system, the team conducted pilot-testing over 2 months at the six primary care clinics where the trained care managers were located. During the pilot, patients were referred to care managers by consult psychiatrists, integrated therapists, and primary care providers through "warm handoffs" or the real-time transfer of patients from one provider to another. When demonstrating mobile applications, care managers used iPads available in the clinic or their own smartphones (with appropriate security measures in place). After ∼2–4 weeks, care managers followed up with patients either in person or by phone to conduct structured interviews in which patients were asked the following questions: Did you use the app? Did you find it to be helpful? Do you have any additional comments?

Following the formal conclusion of the pilot, care managers continued to gather feedback related to patients' experience over the course of 1 year. Preliminary themes were identified through review of all available data, several group discussions leading to consensus in our multidisciplinary team, and updated with data gathered in the larger roll out as described below.

Following the pilot test, we evaluated patient and care manager feedback and adapted procedures to roll out the program to all 12 of our primary-care practices. Our final toolkit contained seven apps as we removed two apps from the list of nine used during the pilot. As smartphone apps are dynamic and always changing, during this phase of the study new information about a smoking app became available that led our team to substitute for one from the pilot—reflecting the real-world challenge of using apps in health care (see **Figure 1**).

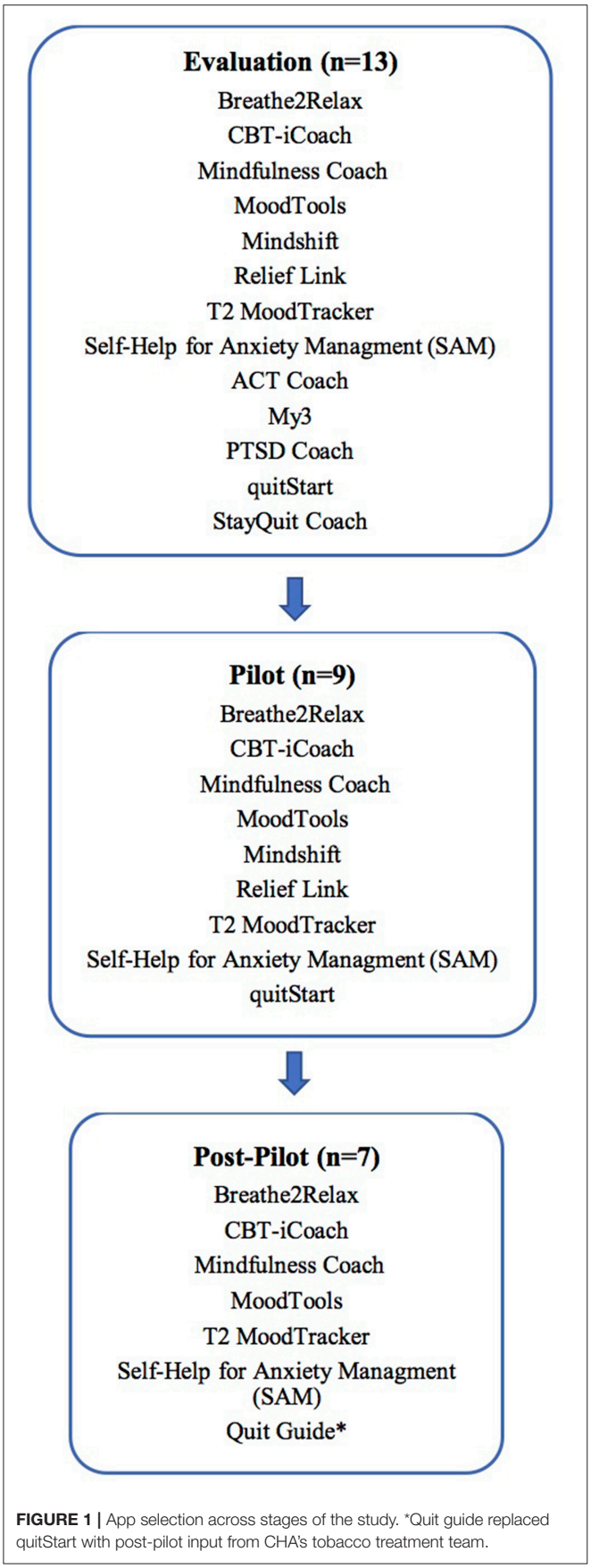

FIGURE 1 | App selection across stages of the study. *Quit guide replaced quitStart with post-pilot input from CHA's tobacco treatment team.

Step 4: Staff Training and App Dissemination

To facilitate use of apps by staff, we wrote two electronic medical record (EMR) standardized "smart phrases" which could be incorporated into patient-facing after-visit summary documents. These "smart phrases" contained the list of recommended self-management apps and the patient-facing summary sheet explaining risks/benefits of using mobile apps. Through a series of staff meetings, we trained all integrated BH staff (therapists, consult psychiatrists, care managers) on best practices for utilizing mental health apps within clinical care. Because of the pilot testing and early staff engagement in the project, many were already familiar with the basic premise of the project and supportive of its goals.

One year after staff training and dissemination of CHA's mobile apps toolkit across all 12 primary care clinics, we followed up by sending a survey to integrated BH staff. In this survey, we asked questions exploring (a) staff utilization of apps; (b) perceived clinical impact, and (c) experience introducing apps to patients.

RESULTS

Quantitative Patient Experience

Over the 2-month duration of the pilot intervention, care managers introduced mental health apps to 56 adult patients. Fifty-four (96.4%) patients agreed to use the tools while 2 (3.5%) patients declined (1 due to security concerns and 1 due to time constraints). Patients in the pilot were 18–70 years old with a mean age of 36.5 years, and 37 (66.1%) were female. English was not the language of medical care for 6 (10.7%) patients; 4 (7.1%) primarily spoke Portuguese and 2 (3.5%) primarily spoke Spanish. The tools were introduced to 35 (62.5%) patients for anxiety and stress-related issues and to 20 (35.7%) patients for depression. Eight (14.2%) patients received apps to target sleep issues and 3 (5.3%) patients were introduced to apps for other issues. Thirteen (23.2%) of the 56 patients were introduced to the tools for multiple conditions/issues.

The care managers were unable to follow-up with 19 patients during the 2-month pilot period. Of the 35 (64.8%) patients who provided feedback on usage of the tools, 7 (20%) patients were unable to use the tools (3 due to equipment limitations, 4 for other reasons). Twenty-three (65.7%) of patients who provided feedback found the apps to be helpful. Twenty-four (68.5%) of patients reported using Breathe2Relax and 24 (68.5%) reported using Self-Help for Anxiety Management (SAM). Patients used Breathe2Relax to help them sleep, to manage anxiety, and to prepare for stressful or mentally taxing situations. When using SAM, patients tended to access just a few of the features that focused on symptom relief, education about anxiety, strategies for managing strong emotions, and mood tracking. (**Figure 2**)

Qualitative Patient Experience

After the 2-month pilot and over the course of the following year, care managers collected general feedback from patients that is presented in **Table 1** as a combination of paraphrasing and direct quotes. Review of this feedback by our multidisciplinary team

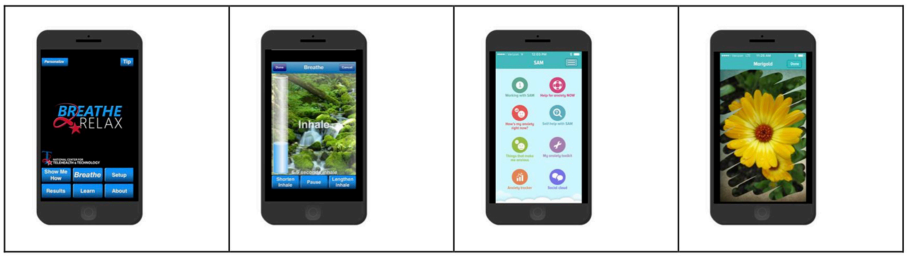

FIGURE 2 | Screenshots of Breathe2Relax (Left two) and Self-Help for Anxiety Management (Right two).

and discussion yielded consensus around 7 broad themes: ease of use, educational value, role in self-monitoring and enhancing self-awareness, relaxation/mindfulness, ability to incorporate into daily life, data and security concerns, and value of staff role in encouraging engagement with mental health apps.

Quantitative Staff Experience

After 1 year of the intervention (which involved 32 integrated BH staff), 24 (75%) completed the follow-up survey. Within the integrated BH team roles, nine (100%) care managers, 12 (75%) psychotherapists, and 3 (43%) consult psychiatrists responded. The number of responses to each survey item varied.

Twenty-three (95.8%) BH staff members answered the survey question regarding their utilization of mobile tools with patients; nineteen people (82.6%) indicated that they incorporate BH apps into their clinical work. Five (25%) BH staff members out of 20 indicated that they introduce apps to patients 25–50% of the time, and 9 (45%) introduce mobile tools <25% of the time. When using apps with patients, the condition addressed most often by BH staff was anxiety 20 (83.3%), followed by stress 18 (75%), depression 14 (58.3%), alcohol use 6 (25%), and tobacco use 6 (25%). Of the 23 (95.8%) staff members who reported on their experience using the CHA's mobile app toolkit, the apps most commonly used were Breathe2Relax, Mindfulness Coach, and Self-Help for Anxiety Management (see **Table 2** below). The survey also assessed techniques and strategies staff employed in introducing apps to patients: 19 (79.1%) reported discussing access/interest/ability, 14 (58.3%) discussed clinical basis for recommending that app and how it connects with the patient's goals, 14 (58.3%) demonstrated how to use the app, 13 (54.1%) helped the patient download the app, 13 (54.1%) followed up and discussed app use with patients at later visits, 12 (50%) set a follow up plan for app use, 9 (37.5%) discussed security and privacy risk associated with app use, and 7 (29.1%) created an action plan around app use.

BH staff found a variety of benefits and challenges to incorporating apps into clinical care (see **Table 3**) and 10 out of 24 BH staff (42%) expressed a need for more practice and training on using each tool within the CHA's mobile app toolkit.

Qualitative Staff Experience

Consult psychiatrists, therapists, and care managers were also asked to provide qualitative/free-text feedback on apps in the 1 year follow-up survey. Representative responses for the three most utilized apps are presented below in **Table 4** alongside patient feedback. Feedback concerning clinical use, accessibility, patient engagement/motivation, and other areas is presented below in **Table 5**.

DISCUSSION

Our results of piloting the use of smartphone apps in a primary care setting with integrated BH staff demonstrate the feasibility, opportunity, and challenges of introducing mobile technologies into formal care settings. Through our program of mobile app evaluation, pilot-testing, and 1 year long local dissemination into routine practice we demonstrated that mental health apps can be introduced to patients of varying ages, literacy levels, and English-language proficiency. On the patient side, our results suggest that patients found the mobile tools helpful in learning about their mental health conditions, practicing relaxation skills, and monitoring mood symptoms. Barriers to use included technical limitations (e.g., lack of smartphone, limited data), difficulty incorporating into daily life, low motivation, and limited mental health app options for non-English speaking patients. On the clinical side, members of the integrated care teams were receptive to apps but used them with patients <50% of the time—with chief barriers including lack of time to discuss apps and being unfamiliar or uncomfortable with apps.

While our study results reflect the experience at a single healthcare system in an urban environment, several lessons learned in our experience are generalizable. Reflecting on both the successes as well as areas for further improvement in our development and rollout of apps for integrated care teams offers insights for others seeking to build their own app libraries, develop app toolkits, onboard staff, and engage patients.

Selecting Apps and the Need to Update

Selecting appropriate apps to recommend for use in integrated care is a core element in a successful rollout, but also a moving target as these apps are constantly updating and evolving. Relying on websites or services that claim to curate apps and score them based on certain metrics is not helpful, as such scores do not take into account the unique needs of intended users (e.g., lower literacy levels), and do not reflect the simple reality that apps frequently update and change. We found that gathering a multidisciplinary panel to search, evaluate, and test apps was

TABLE 1 | Key themes and illustrative quotes from the 1 year study.

Theme	Illustrative quote
Ease of use	"I like that this app is simple and easy to navigate"
	"I do the breathing exercise every time I get into the car. I also shared it with my boyfriend who speaks Portuguese. We do the exercise together."
	"I use this app when I'm waiting in the car at my daughter's school"
	"I like short exercises. I can use them in different places"
	"I can do a walking meditation during my lunch break"
Education	"The TED talks were helpful"
	"I re-read the education sections as a reminder"
	"I like being told I'm not crazy"
	"It was helpful learning more about anxiety and coping thoughts"
Self-monitoring and Self-awareness	"I want to track my mood so I can show the data to my therapist. I can't always remember how I felt during the week"
	"I like data. Recording my mood every day helps me to know I'm doing ok"
	"I track my mood before and after I do an activity. The next time I think about exercising, I can look back to see how I felt afterwards"
	"The sleep diary helps me to keep track of my sleep patterns. It's easier than trying to remember later on"
	"I record how I'm feeling and also what's making me anxious"
	"I had a hard time identifying my thoughts. Maybe I could focus on this in therapy?"
	"Doing the exercise helped me to recognize how tense and anxious I can be"
	"When I use the app, it's easier for me to size up my thoughts. I can then figure out whether they're trivial or beyond my control"
Relaxation/ Mindfulness	"The progressive muscle relaxation exercise helps me to fall asleep"
	"I enjoyed the exercise focusing on one sensation. I think this app could be helpful to many patients"
	"The app was calming and relaxing"
	"I love the app and guided relaxation for mindfulness"
	"I use the guided imagery exercise with a student at my school. We do it every day during nap time. It helps him and it helps me too!"
	"It used to take me hours to fall asleep. Now it takes me 7 min"
Difficulty incorporating into daily life	"I don't always remember to use the app when I'm stressed"
	"Sometimes I forget to use it. I tell myself I'm going to do it later and then I forget"
	"I looked at the app, but I didn't use it on a regular basis"
	"Apps are overwhelming when I'm stressed. I need to get away from technology"
Data and security concerns	"I worry about my virtual image. I'd feel more comfortable using an app from CHA that is protected in the same way my EMR is protected"
	"I don't have space on my phone"
	"I'm worried about my data"
Staff support	"It was helpful learning about the different parts of the app. I downloaded it in the past, but I didn't understand the point of the exercises"
	"Having you check in with me helped to keep me on track"

TABLE 2 | Apps most frequently recommended by BH staff.

Survey Item: Which apps from CHA's mobile app toolkit do you introduce to patients?	Reponses (*N* = 23) *n* (%)
Breathe2Relax	14 (61)
Mindfulness coach	12 (52)
SAM	10 (43)
CBT-iCoach	9 (39)
Moodtools	5 (22)
T2Moodtracker	3 (13)
QuitforLife	3 (13)

TABLE 3 | Staff views on the benefits and challenges of utilizing BH apps.

Survey Item	Response (*N* = 23) *n* (%)
IN GENERAL, WHAT DO YOU THINK ARE THE BENEFITS OF INCORPORATING APPS INTO CLINICAL CARE? (SELECT ALL THAT APPLY)	
Patients have the opportunity to practice self-management skills between meetings	15 (65)
Using apps enhances care provided by therapist and primary care provider	13 (57)
Patients' ability to manage mood/anxiety/substance use improves when using apps	13 (57)
Patients are excited to try self-management tools	11 (48)
Patients feel more confident in managing their BH conditions independently	9 (38)
IN GENERAL, WHAT DO YOU THINK ARE SOME CHALLENGES TO INCORPORATING APPS INTO CLINICAL CARE? (SELECT ALL THAT APPLY)	
My patients do not have enough data on phones to use apps	6 (26)
I do not have enough time during my sessions to introduce self-help tools	5 (22)
I am unfamiliar with apps' content and functionality	5 (22)
I do not feel comfortable navigating apps and demonstrating use to patient	5 (22)
My patients are not interested in using apps	2 (8)
I do not believe they would be helpful for my patients	0 (0)
My patients are concerned about data security	0 (0)
I am unsure how to assess whether a patient could benefit from using an app	0 (0)

useful and practical. Such a panel should remain an ongoing and integral part of any app rollout and ideally meet at least quarterly to continue to update and evaluate new apps and new evidence. In terms of searching for new apps to support integrated care, we noted that apps selected in our search focused on helping patients learn more about their mental health conditions, enhance self-awareness, develop skills related to distress tolerance, and improve anxiety management. While we realize that today's mental health apps offer functionalities that can allow for real time monitoring and facilitate communication with the treatment team, such functionalities raise a number of complex questions related to risk/privacy/liability that

TABLE 4 | Top three apps utilized by staff during the 1 year study (as reported through the staff survey).

App	Developer	Description	Popular features	Patient feedback	Staff feedback
Breathe2Relax	Defense health agency connected health (formerly the National Center for Telehealth and Technology)	Developed for military personnel. Contains step-by-step instructions for diaphragmatic breathing, provides a visually engaging audio guided breathing exercise, and enables users to record their stress levels using a tracking function. http://t2health.dcoe.mil/apps/breathe2relax	Guided diaphragmatic breathing exercise	"I have been doing it every day. I feel like it is cleaning my brain. I have been suggesting it to my friends. I learned that problems we will always have, but I feel more patient now. I noticed some changes on my self-esteem I am becoming more optimistic. I used to have mind racing and not anymore"	"I like Breathe2Relax's visuals" "Breathe2Relax is more popular because it is easier - no language barrier" "Breathe2Relax is very useful as it contains education about deep breathing, a basic exercise and the option to personalize settings"
Self-Help for Anxiety Management (SAM)	The University of the West of England	Developed for college students with low to moderate anxiety. SAM is a "platform of interactive, therapeutic, and well-being exercises" meant to assist users with learning about anxiety, cognitive reframing, relaxation, distress tolerance, lifestyle change and self-monitoring of physical and emotional states related to anxiety. http://sam-app.org.uk	"Picture Peace" "Stop That Thought" "It's Only a Thought" Anxiety Tracker Anxiety Education	Picture Peace: "I slow down and think about what's bothering me" Stop That Thought: "I noticed my thoughts going from "this is annoying" to "I've made a horrible mistake taking this job". Writing my thoughts down makes me realize how absurd they are and banishing them in the app helps me to better reframe the situation and get more perspective"	"For SAM, I use the picture peace, stop that thought, and it's only a thought features most often" "Patients really like the picture peace feature; I use it too!"
Mindfulness coach	VA's National Center for PTSD and DoD's National Center for Telehealth & Technology	This app was developed to help Veterans, Service members, and others learn how to practice mindfulness. It offers exercises, information, and a tracking log so that you can optimize your practice. https://mobile.va.gov/app/mindfulness-coach	Guided mindfulness exercises	"I used to get jammed up about small things. Doing these exercises helped me to realize that burnt pizza isn't the end of the world"	"Mindfulness coach is great, but I wish it were also available for android. I like the guided mindfulness better than on moodtools especially if it is for a patient not with depression"

could not be addressed within the scope of this quality improvement project.

Building a Toolkit and the Need for More Hands-On Training or a New Digital Navigator

Although the app toolkit that we developed to help the clinical teams introduce, integrate, and support app use was critical to success, it was not sufficient in and of itself. Offering the clinical team a list of apps, core information and talking points on each app, and electronic medical record smart phrases to document app usage was key to the feasibility of the intervention. Clinical staff recommended apps that had a clear purpose, simple user-interface, and were easy to navigate and demonstrate within a brief period of time. When introducing Breathe2Relax, for example, staff were often able to review the technique of diaphragmatic breathing, help patients to personalize settings, and practice the app's guided breathing exercise in under 10 min. Mental health apps that have a clear purpose and that are easy to review during staff trainings may enhance BH staff confidence and efficiency in introducing these tools to patients and facilitate higher adoption across the primary care system.

However, we found that the clinical teams sought additional support in understanding how each app worked, in demonstrating apps to patients, and having enough time in clinical visits to discuss an app. This suggests two possible responses: either (a) further hands-on training for clinical staff or (b) the introduction of a new member of the care team in the form of a digital navigator. While there is little evidence to support optimal teaching strategies for app use, we propose that hands on training involving role playing introducing and using apps with patients may offer an effective means to help the clinical team feel more confident in using apps in care settings. Another option would be to refer patients to a new member of the care team called a digital navigator—much as we did in the initial pilot study with the care manager—who is an expert at setting up, teaching, and supporting use of apps. This is akin to

TABLE 5 | Organizing themes and illustrative quotes from staff survey.

Theme	Illustrative quote
Clinical use	"For CBT-iCoach, I use the "quiet your mind" tools that contains progressive muscle relaxation exercises and guided imagery"
	"Before the app, I tried to do sleep diaries with patients on paper. They were mostly unsuccessful since the patient would lose the paper or forget to complete it. With the app, patients have access to their phones all the time and can send reminders to themselves"
	"Great way to have patients practice exercises between sessions; both provider and patient happy to have concrete tool"
	"Apps are containing when patients feeling stressed; some are fun to use"
	"The positive is that the app is free and easy to utilize, the downside is that a patient may spend too much time engaging on their phone and not building relationships with others/community. The young adult patients enjoy the apps, while the older patients want to belong to a community, i.e., yoga, tai chi, or meditation class"
	"I don't use them very often because I do a lot of guided relaxation in session and have my patients record them on their phone. Usually I think this kind of approach is best because it allows me to make the exercise specific to their needs. That some of the apps are helpful for specific skills like breathing with the metronome (if that is what it is called I am not sure)"
	"Sometimes I think my training in behavioral medicine allows me to create a different tool with the patient that is more specific to them"
	"I like PTSD Coach and Insight Timer as well"
	"The simple practice of using the app(phone) as a way to relax and take a mindful minute"
	"I use them very often. Mostly Breathe2Relax and SAM"
Accessibility	"To me, it is very difficult to incorporate the apps because they are only in English"
	"Some apps too complicated to explain quickly; patient seems overwhelmed"
	"Sometimes it takes too long to download an app with the patient, sometimes they need to come and see me for a second time to practice together"
	"Definitely language is a barrier for some of them"
Patient engagement & motivation	"Patients are generally receptive to the idea. Most that have put it into practice have been practicing mindful breathing, some are still having trouble maintaining ongoing use in order to derive any benefit"
	"Most of them don't end up downloading it/using it"
	"Patient only used app one time to learn deep breathing exercise, but continued practicing deep breathing before bed without assistance of app"
	"Usually I do not have negative feedback but I notice a good number of patients mentions they did not continue using in home. Sometimes they say: "I forgot to use it." Maybe because this area is still new for patients? I am not sure"
	"Patients like it- they like that they have an option to do something on their own to look at after the visit"
	"Recently I had a good feedback from a patient (serious case of DV) that the breathing exercises was helping her a lot and she was even teaching her friends. I was impressed how excited she was about the exercises. Patient states feeling more calm, has been sleeping much better. She is still not completely free of nightmares but improved a lot. She used to have nightmares every day but this week had two times a week"
	"Usually I get good feedback from patients. I call them about 2 weeks after my visit and check with them but I do not have the info if they continue using for a long time"
Additional feedback	"Technology is in"
	"Re: question 7: training the PCPs about the tools; a lot of them don't know about it. They could introduce patients to tools then do a warm handoff to the care partner"
	"Instead of formal training, I think more case examples of how the apps were incorporated can be a helpful reminder about using the apps. I admit that since I see both kids and young adults, I sometimes forget about the many options available to someone 18+"

referring a patient to a pharmacist on the team to learn more about medication or dietician to craft a customized healthy eating plan.

Supporting Patients With Apps and Ensuring Apps Are Accessible

Patients in our study found apps useful and preferred those with clear purpose that had an engaging interface, were intuitive to use, and easy to navigate. The preference for simplicity aligns with findings within the field of user experience and design (26) as well as emerging research (27, 28) suggesting that apps containing a limited number of concepts and activities may be more appealing than those with a number of features. Apps containing limited text and simple/concrete language demand less from a cognitive standpoint (29) and may prove most accessible if patients are turning to apps during times of emotional distress when their cognitive abilities are compromised. Of note, the most popular feature within our mobile apps "toolkit" was "Picture Peace" a grounding exercise within Self-Help for Anxiety Management (SAM) that involves swiping across a blank screen to reveal a nature photo beneath. Patients described this feature as being "fun" and chose to use it over other exercises that were less visually pleasing and that demanded more from a cognitive standpoint.

However, the lack of apps available in multiple languages was also a limiting factor that made it impossible to use apps with

some patients who may have benefited from this intervention. Several patients were also unable to run apps on their phone because of issues installing the apps or lacking sufficient memory on their smartphone to run the apps.

Connecting to Care Through Apps

Our results also suggest new clinical applications for mental health apps beyond those studied and implemented in our study. Within our integrated primary care model, care managers often serve as a "bridge" to longer-term BH care, providing education about BH conditions, teaching basic distress-tolerance skills, and focusing on brief interventions related to lifestyle behavior change. In using mental health apps, patients can begin to develop greater insight into their thoughts, feelings, and behaviors, an essential component of any therapeutic treatment intervention. Providing patients with self-management apps while they are waiting for in-person BH services may also help patients to stay connected to their care team and cultivate a sense of "emotional holding" during this bridging period (29). These apps may also spread awareness and interest in BH services, as evidenced by multiple patients who shared a recommended app with friends and family because they thought it may be useful to them as well.

These same apps may help introduce patients to BH treatment who would have otherwise not been interested or declined to engage because of stigma, discomfort or misunderstanding about the field and treatments offered. Thus, the potential of population health enabled through apps and digital technology will remain a focus of our continued research. While our study did not explore potential cost-savings associated with our intervention, we plan to investigate the financial implications of digitally augmented integrated BH care in future studies.

Limitations

Like all studies, ours has several limitations. As a real-world implementation study that sought to understand feasibility of app selection, uptake, and introduction into integrated care clinics—we were unable to control for many variables including patient severity, disease state, and clinician participation among others. In considering our patients' feedback that was not incorporated into a formal qualitative framework, we recognize that having care managers solicit feedback directly from patients may have influenced patient self-report and the subsequent interpretation of this data. Also given how often apps update and change—we realize that our results are difficult for others to replicate especially as we tailored our research to the local needs of the patients we serve. While we believe our study included a representative sample, it is difficult to quantify the number of types of patients, or clinicians, who are willing to engage and use apps as part of care. Further, we realize there are currently no gold standard apps, gold standard methods to select apps, or gold standard tools to quantify the impact of apps on care. Thus, we hope that the process and results of this present research can help guide others in taking the first steps to study the best ways to introduce digital technologies like apps into their clinical settings.

CONCLUSIONS

Although there are barriers to implementing digital technologies like smartphone apps into integrated BH settings, with careful planning and stakeholder engagement they can be useful tools in real-world clinical settings. While apps alone are not a panacea to addressing limited access to mental health care and lifestyle interventions, when deployed thoughtfully, they can help extend care to support patients with mild and moderate behavioral health conditions on a personal level and communities on a population level.

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

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