ASSESSING LIFESTYLE IN PSYCHIATRIC DISORDERS

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Lay Abstract

People experiencing symptoms of psychiatric disorders may also engage in more unhealthy routines and behaviours in everyday life. Lifestyle is a construct characterized by behaviours and perceptions in multiple areas of life which are fundamental for the overall well-being of a person. The aim of this thesis was to investigate the relationship between multidimensional lifestyle characteristics and symptoms of depression, anxiety, and bipolar disorder (BD). We examined the association between multidimensional lifestyle and symptoms of depression and anxiety in the general populations of Spain, Brazil, and Canada during the COVID-19 pandemic. We also assessed the relationship between unhealthy behaviours and symptomatic individuals with BD in comparison to healthy individuals, and the importance of lifestyle interventions for improvement of outcomes related to BD. The findings indicated an association between multidimensional unhealthy lifestyles and symptoms of depression and anxiety during COVID-19. Unhealthy lifestyles across all domains were also seen in people with BD currently experiencing a mood episode, while lifestyle interventions for BD have shown promising results so far. A multidimensional approach to evaluating quality of lifestyle can be beneficial for developing preventive and treatment lifestyle strategies for common psychiatric disorders.

Abstract

Introduction: Major depressive disorder (MDD), generalized anxiety disorder (GAD), and bipolar disorder (BD) are mental illnesses associated with socio-cognitive functional impairments, reduced quality of life, and increased risk of medical and psychiatric comorbidities. These disorders are also associated with unhealthy patterns in several fundamental lifestyle areas according to the current notions of lifestyle psychiatry, such as diet, physical activity, substance use, sleep, stress management, and social relationships. With the rising prevalence rates of poor mental well-being following the onset of the COVID-19 pandemic, it is essential to understand the relationship between a multifactorial lifestyle and the presence of psychiatric symptoms. Thus, the aim of this thesis was to assess the association between a multidimensional lifestyle and symptoms of MDD and GAD during the COVID-19 pandemic, and lifestyle patterns among symptomatic individuals with BD. We additionally reviewed the literature on lifestyle interventions for improvement of outcomes related to BD.

Results: Unhealthy lifestyle behaviours were associated with symptoms of MDD and GAD during the COVID-19 pandemic in Spain, Brazil, and Canada. Machine learning analyses revealed strong predictive power for detecting the presence of these symptoms through lifestyle behaviours and perceptions. Individuals with BD engage in more unhealthy lifestyles than healthy individuals across all the core areas of lifestyle psychiatry, regardless of the polarity of the mood episode. Furthermore, to date, traditional lifestyle domains such as diet, physical activity, and sleep have been the most

frequently targeted domains for interventions to improve mood symptoms and functional outcomes of BD, while domains such as substance use, stress management and social relationships have been more neglected. In addition, multidimensional lifestyle interventions have demonstrated a higher efficacy rate of improving outcomes of BD than single-domain interventions, however, there has been a lack of interventions for BD targeting majority of the core lifestyle domains.

Conclusion: The findings suggest that multidimensional unhealthy lifestyles are associated with symptoms of MDD, GAD, and BD. These results support the current notions of lifestyle psychiatry, indicating that a multidimensional assessment of lifestyle behaviours and perceptions can be a beneficial approach towards understanding the cumulative impact of various lifestyle patterns on psychiatric symptoms. This work highlights the importance of imposing a holistic approach towards studying the association between lifestyle factors and psychiatric disorders in order to implement effective, personalized preventive and treatment strategies for mental health disorders.

Keywords: depression; anxiety; bipolar disorder; lifestyle psychiatry; assessment.

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List of Abbreviations

ACLM	American College of Lifestyle Medicine
AIDS	Acquired Immunodeficiency Syndrome
AUC-ROC	Area Under the Curve – Receiver Operating Characteristic
BB	Blue-blocking
BBQ	Brief Quality of Life
BD	Bipolar Disorder
BD - D	Bipolar Disorder – Depressive episode
BDI	Beck Depression Inventory
BD – M/M	Bipolar Disorder – (hypo)manic or mixed episode
BD-NOS	Bipolar Disorder – Not Otherwise Specified
BMI	Body Mass Index
BP	Blood Pressure
BRMS	Bech-Rafaelsen Mania Scale
BRQ	Bipolar Recovery Questionnaire
CaPE	Culturally Adapted Psychoeducation
CBT	Cognitive Behavioural Therapy
CBT-BP	Cognitive Behavioural Therapy, Bipolar Disorder Specific
CBTI-BP	Cognitive Behavioural Therapy for Insomnia, Bipolar Disorder Specific
CC	Collaborative Care
CGI	Clinical Global Impressions Scale
CGI-BD	Clinical Global Impressions Scale for Persons with Bipolar Disorder
CGI-S/I	Clinical Global Impression – Improvement scale
CI	Confidence Interval
CMF	Clinical Monitoring Form
COVID-19	Coronavirus Disease – 2019
CSSRT	Clinical Status and Symptom Review Treatment
DASS-21	Depression, Anxiety and Stress Scale - 21 Items
DALY	Disability-Adjusted Life-Years
DSISD	Duke Structured Interview for Sleep Disorder
DSM-5	Diagnostic and Statistical Manual for Mental Disorders – 5
ESS	Epworth Sleepiness Scale
EuroQoL	European Quality of Life Scale
FFT	Family Focused Treatment
GAD	Generalized Anxiety Disorder
GAD-7	Generalized Anxiety Disorder – 7
GAF	Global Assessment of Functioning
GBD	Global Burden of Disease
HC	Healthy Control
HDRS	Hamilton Depression Rating Scale

HiREB	Hamilton Integrated Research Ethics Board
HIV	Human Immunodeficiency Virus
HLI	Healthy Lifestyle Intervention
HPA	Hypothalamic-Pituitary-Adrenal
HPLP	Health Promoting Lifestyle Profile
IBM SPSS	International Business Machines – Statistical Package for Social Sciences
IDS-C	Inventory of Depressive Symptomatology: Clinician
IIS	Illness Intrusiveness Scale
IPSRT	Interpersonal and Social Rhythm Therapy
IQR	Interquartile Range
IRRI	Integrated Risk Reduction Intervention
ISBD	International Society for Bipolar Disorders
ISI	Insomnia Severity Index
ISS	Internal State Scale
LGCC	Life Goals Collaborative Care
LIFE	Longitudinal Interval Follow-up Evaluation
LIFE-RIFT	Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool
LM	Lifestyle Medicine
LP	Lifestyle Psychiatry
LWB	Living with Bipolar
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MEQ	Multidimensional Emotion Questionnaire
MINI	Mini International Neuropsychiatric Interview
NEW Tx	Nutrition, Exercise, and Wellness Treatment
NPV	Negative Predictive Value
NRT	Nicotine Replacement Therapy
OR	Odds Ratio
ORBIT	Online Recovery-Focused Bipolar Individual Treatment
PA	Physical Activity
PCMM	Psychiatric Care with Medical Monitoring
PE	Psychoeducation
PHQ	Patient Health Questionnaire
PICOS	Population, Intervention, Comparison, Outcome, Study Design
PPAQ	Paffenbarger Physical Activity Questionnaire
PPV	Positive Predictive Value
PR	Prevalence Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROMIS-SD	Patient-Reported Outcomes Measurement Information System-Sleep Disturbance

PROMIS-SRI	Patient-Reported Outcomes Measurement Information System-Sleep-Related Impairment
PROSPERO	International Prospective Register of Systematic Reviews
PSQ	Personality Structure Questionnaire
PSQI	Pittsburgh Sleep Quality Index
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire
QoL	Quality of Life
QoL-BD	Quality of Life for Persons with Bipolar Disorder
QoL-BD	Quality of Life for Persons with Bipolar Disorder Program
QUID-SR	Quick Inventory of Depressive Symptomatology – Self Report
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
RF	Random Forrest
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Social Adjustment Scale
SASS	Social Adaptation Self-Evaluation Scale
SCID	Structured Clinical Interview for DSM Disorders
SD	Standard Deviation
SDS	Self-Directed Search
SF-12	12-Item Short Form Survey
SF-36	Short Form Health Survey
SIGH-ADS	Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement
SJHH	St. Joseph's Healthcare Hamilton
SM	Stress Management
SMILE	Short Multidimensional Inventory Lifestyle Evaluation
SMILE-C	Short Multidimensional Inventory Lifestyle Evaluation – Confinement
SPQ	Social Problems Questionnaire
SR	Social Relationships
SRH	Self Rated Health
SRM	Social Rhythm Metric
SSC	Specialist Supportive Care
SSS-EMA	Stanford Sleepiness Scale via Ecological Momentary Assessment
SU	Substance Use
TAU	Treatment as Usual
VAS	Visual Analogue Scales
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Scale
WHOQOL	World Health Organization Quality of Life
WSAS	Work and Social Adjustment Scale
XGBoost	Extreme Gradient Boost
YMRS	Young Mania Rating Scale

Declaration of Academic Achievement

Chapter 2

M. Simjanoski completed the statistical analysis of the data relevant to the research question, created the tables, and composed the manuscript. P. Ballester completed the machine learning analyses and created the figures. R.B. De Boni, F.I. Bastos, V. Balanzá-Martínez, and F. Kapczinski conceived the research question, designed the study, and provided critical revisions to the manuscript. B. Atienza-Carbonell helped in recruitment of the sample, while J.C. Mota helped with analysis of the sample. T. de Azevedo Cardoso provided statistical analysis guidance, and contributed to composing the manuscript. B.N. Frey and L. Minuzzi provided critical revisions to the manuscript. All authors revised and provided significant intellectual contribution to the research manuscript.

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Chapter 3

M. Simjanoski completed the data analysis, created the tables and figures, and composed the manuscript. T. de Azevedo Cardoso helped with the study design and recruitment, provided statistical analysis guidance, and provided critical revisions to the manuscript. B. Wollenhaupt-Aguiar and B. Pfaffenseller helped with the study design and recruitment, and provided critical revisions to the manuscript. B.N. Frey and L. Minuzzi provided critical revisions to the manuscript. R.B. De Boni, V. Balanzá-Martínez, and F. Kapczinski conceived the research question and study design, and provided critical revisions to the manuscript.

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Chapter 4

M. Simjanoski conceived the research question and study design, completed participant recruitment and assessment, data collection, analysis, and composed the manuscript, tables, and figures. T. de Azevedo Cardoso contributed to the study design and research question, helped with data analysis and the preparation of the manuscript. R.B. De Boni, V. Balanzá-Martínez, B.N. Frey, L. Minuzzi, and F. Kapczinski all provided critical revisions to the manuscript.

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Chapter 5

M. Simjanoski formulated the research question, performed the literature search and data extraction, performed the meta-analyses, and composed the manuscript. S. Patel assisted with the literature search and data extraction, performed the descriptive analyses, and contributed to the manuscript composition. T. de Azevedo Cardoso contributed to the study design, methodology, acted as third reviewer in article selection and provided

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Chapter 1: Introduction

1.1 Epidemiology of Mood Disorders and Anxiety

Mental disorders have become one of the leading causes of burden worldwide. According to the Global Burden of Disease Study in 2019, mental disorders remain among the top ten leading causes of burden of disease worldwide, with a notable increase of 45 million disability-adjusted life-years (DALYs) due to mental disease over the last 30 years (GBD Mental Disorders Collaborators, 2022). Mood and anxiety disorders are the most prevalent mental disorders in the world, associated with severe impairments in quality of life, cognitive and social functioning, and high rates of medical and psychiatric comorbidities (Cotrena et al., 2016; Druss and Walker, 2011; McKnight et al., 2016; Michalak et al., 2005; Plana-Ripoll et al., 2019; Rapaport et al., 2005).

Anxiety disorders are the leading cause of mental health burden in the world, affecting up to 33.7% of the global population (Bandelow and Michaelis, 2015). Generalized Anxiety Disorder (GAD) is thought to be the broadest type of all anxiety disorders, in the sense that GAD can be multifocal and related to various daily activities and events (Rowa and Antony, 2008). The lifetime prevalence of GAD is estimated to be 6.2% worldwide, although it is believed that there is a large under-recognition of clinical cases of anxiety (Bandelow and Michaelis, 2015). Symptoms of GAD are characterized by the presence of overwhelming feelings of worrying, difficulties in controlling the worry, restlessness, irritability, muscle tension, fatigue, sleep disturbance, and difficulties with concentration, which cause significant distress and impairments in socio-cognitive

functioning (American Psychiatric Association, 2013). However, many individuals may be experiencing symptoms of anxiety without a clinical diagnosis of GAD and the necessary treatments (Bandelow and Michaelis, 2015; Tylee and Walters, 2007), which may still lead to impairments in social and cognitive functioning, and reduced quality of life (Johansson et al., 2013; McKnight et al., 2016; Stillman et al., 2012). Individuals with a history of substance use, trauma, and/or family history of GAD are at an increased risk for the onset of GAD symptoms (DeMartini et al., 2019).

Major Depressive Disorder (MDD) is a mood disorder featuring episodes of persistent depressed mood and/or anhedonia that may last from at least two weeks to months, associated with several psychophysiological changes, such as disturbances in sleep, appetite, psychomotor abilities, concentration, fatigue, feelings of worthlessness, and suicidal thoughts/attempts (American Psychiatric Association, 2013). As of 2019, close to 280 million people worldwide were suffering from MDD (GBD Mental Disorders Collaborators, 2022), a number that has likely increased during the COVID-19 pandemic (Salari et al., 2020). The criteria for a clinical diagnosis of MDD requires the presence of any combination of 5 of the abovementioned symptoms, including at least one of the core symptoms, which are depressed mood and anhedonia (American Psychiatric Association, 2013). However, a large number of individuals have potentially suffered from symptoms of depression without a clinical diagnosis of MDD (Bandelow and Michaelis, 2015; Tylee and Walters, 2007). Persistent symptoms of depression among diagnosed and undiagnosed individuals can have detrimental short-term and long-term effects, such as impaired social and cognitive functioning, reduced quality of life,

and increased comorbidities with various health complications, such as diabetes, angina, arthritis, and asthma (Gutiérrez-Rojas et al., 2020; Hammar and Årdal, 2009; IsHak et al., 2011; Kupferberg et al., 2016; Williams et al., 2017). Some of the recognized risk factors for onset of MDD include history of substance use, poor social support, physical illness, and family history of the disorder (Kendler et al., 2010; Zisook et al., 2007).

Bipolar Disorder (BD) is a severe, chronic psychiatric disorder characterized by episodes of mood fluctuations, with a recent yearly prevalence estimate of 2% worldwide (Carvalho et al., 2020; Grande et al., 2016). The main features of BD are recurrent episodes of mania, hypomania, depression, and mixed episodes which comprise features of depression and (hypo)mania simultaneously (Phillips and Kupfer, 2013). Manic episodes, which last at least one week, are characterized by emotional and physical hyperactivity, irritability, distractibility, racing thoughts, and feelings of grandiosity, during which affected individuals typically need less sleep and often showcase poor decision-making (American Psychiatric Association, 2013). Up to 68% of individuals experience manic episodes that are often accompanied by psychotic symptoms such as hallucinations and delusions, which are associated with more severe outcomes of the illness (Canuso et al., 2008). Furthermore, individuals experiencing manic episodes may also be hospitalized due to the severe symptoms, requiring clinical monitoring and attentive care for adequate recovery from the mood episode (American Psychiatric Association, 2013; van Lankeren et al., 2020). In contrast, hypomanic episodes last at least four consecutive days, and are characterized by milder intensity of manic symptoms that are not accompanied by psychotic symptoms, not severe enough to cause marked

impairment in social or occupational functioning, or to require hospitalization (American Psychiatric Association, 2013). This disorder is associated with emotional dysregulation, neurocognitive deficits, decrease in overall functioning and quality of life in affected individuals, and increased rates of comorbidities with other physical and mental health conditions (Johnson et al., 2016; McIntyre et al., 2020; Sanchez-Moreno et al., 2009; Solé et al., 2017). There are many risk factors involved in the onset and clinical trajectory of BD, including genetic factors (family history of BD) and environmental risk factors, such as substance abuse and stressful life events (de Lima Bach et al., 2021; Kilbourne et al., 2007; Lalli et al., 2021; Marangoni et al., 2016; Post and Leverich, 2006).

Moreover, various stressful life events such as perceived health danger, family disagreements, financial difficulties, divorce/separation, social rhythm disruptions, and loss of a significant one, among others, are associated with the appearance of symptoms of depression, anxiety, and BD (Aldinger and Schulze, 2017; Faravelli et al., 2012; Kendler et al., 2010; McLaughlin and Hatzenbuehler, 2009). These unexpected events may cause significant changes in the everyday lifestyle routines and functioning of the person, which can further aggravate the mental health symptoms, and possibly lead to clinically significant distress. Timely prediction of risk factors associated with the appearance of symptoms is essential for devising preventive strategies as well as adaptive coping mechanism for existent symptoms. Recent developments of machine learning techniques have proven to be an extremely beneficial, promising approach for detecting risk factors predictive of the onset of mental health symptoms (Shatte et al., 2019; Walsh et al., 2017). Advancements in the use of machine learning techniques have provided an

efficient method of statistical big data analysis for early detection of mental health symptoms (Dadi et al., 2021; Rahman et al., 2020).

1.2 Mental Health Challenges during the COVID-19 Pandemic

The onset of the widespread severe acute respiratory symptom coronavirus-2 (SARS-CoV-2) in 2019 led to major changes from every aspect around the world. Due to the severe threat on people's health imposed by the exposure to the SARS-CoV-2 virus, also referred to as COVID-19, people around the world were required to make drastic changes to their everyday routines. The implementation of necessary guidelines for containing the transmission of the fatal COVID-19 virus led to extreme increases in global rates of social isolation, loneliness, psychological distress, and unhealthy lifestyle behaviours (Balanzá–Martínez et al., 2020; Hwang et al., 2020; Pfefferbaum and North, 2020). Consequently, many countries around the world reported increased prevalence rates of psychiatric symptoms, such as depression and anxiety, among the general population and healthcare workers, and increases in the severity of psychiatric symptoms among individuals with pre-existing psychiatric conditions (Vindegaard and Benros, 2020). During the early stages of the COVID-19 pandemic, the presence of symptoms of depression and anxiety among the general population around the world had risen exponentially, where a systematic review including studies conducted in various countries reported prevalence rates of up to 31.9% for anxiety and 33.7% for depression (Salari et al., 2020). In Canada, the prevalence rates of anxiety among during the early stages of the pandemic had quadrupled in comparison to before the pandemic (from 5%

to 20%), while the percentage of depressive symptoms more than doubled during this period (from 4% to 10%) (Dozois, 2020). According to the World Health Organization, the global numbers of cases had increased by 27.6% for MDD and 25.6% for anxiety during the first year of the pandemic, indicating a massive increase of affected individuals during a short period of time (World Health Organization, 2022). In addition to the fear and uncertainty among the public during these times, several psychological and lifestyle risk factors were associated with increased risk of symptoms of depression and anxiety, such as poor sleep quality, perceived stress and maladaptive coping strategies, and lack of social support (Vindegaard and Benros, 2020). Furthermore, individuals with a mental health diagnosis prior to the onset of the COVID-19 pandemic were subjects to higher levels of psychological distress and worsening of their symptoms (Alonzi et al., 2020; Vindegaard and Benros, 2020). Following the onset of the COVID-19 pandemic, individuals with a prior diagnosis of BD reported that they engaged in more negative lifestyle changes, while also experiencing higher levels of emotional distress and poor sleep quality due to the social distancing measures (Dalkner et al., 2022). Individuals with BD also reported significant increases in subjective cognitive dysfunctions that were associated with severe symptomatology, increased rates of suicidal thoughts, and reduced quality of life, further demonstrating the relationship between stressful life changes and the severe progression of clinical and functioning impairments in BD during this time (Karantonis et al., 2021). The major changes in everyday life during the COVID-19 pandemic affected every person in some way, with the stress-inducing changes potentially leading to severe mental health challenges in the

absence of healthy coping mechanisms (Balanzá–Martínez et al., 2020). The implementation of healthy coping strategies instead of maladaptive behaviours is an essential factor for strengthening psychological resilience during stressful life events, such as the COVID-19 pandemic. Positive coping strategies, such as practicing stress management techniques, having good social support, and practicing religious faith were found to be beneficial factors for improving psychological well-being and reducing symptoms of depression and anxiety, while maladaptive behaviours such as substance abuse, physical inactivity, and unhealthy dietary patterns were predictors of mental health symptoms (Ammar et al., 2021; Budimir et al., 2021). Formation of unhealthy lifestyle routines during the COVID-19 confinement periods has been associated with poor mental health (Blom et al., 2021), emphasizing the need for a timely identification of unhealthy patterns to preserve the mental well-being of individuals. Unhealthy lifestyle behaviours are major contributors to physical and mental health challenges (Farhud, 2015), and failure in preventing the rise of unhealthy behaviours during the COVID-19 pandemic may further increase the global burden of mental disease. Furthermore, different countries and populations around the world were affected by high transmission rates of COVID-19 at different stages of the pandemic. However, the psychological well-being of the general populations was influenced by the same factors across the countries, such as social isolation and loneliness due to the health guidelines in place at the time being. Hence, detection of unhealthy behaviours became highly important for predicting and preventing the development of poor mental health around the world, considering the impact of unhealthy lifestyles as risk factors for psychiatric symptoms.

1.3 Lifestyle and Mental Health

Chronic psychiatric disorders, such as anxiety, depression, and BD are associated with severe clinical outcomes, such as increased rates of comorbidity with poor physical health, suicidality, and pre-mature morbidity (GBD Mental Disorders Collaborators, 2022; Scott and Happell, 2011; Thornicroft, 2011). The high rates of physical health comorbidities, along with the poor clinical management of these problems, leads to extreme reductions in life expectancy, and increases in personal, social, and economic burdens of psychiatric disorders (Firth et al., 2019a). Unhealthy daily behaviours play a role in the onset of psychiatric symptoms and worsening of outcomes related to the symptoms, progressively impairing the quality of life of the individual (Firth et al., 2019a, 2020). In contrast, reversal of maladaptive behaviours and development of healthy routines in everyday life is a promising approach to improving psychological well-being, increasing lifespan, and reducing pre-mature mortality (Balanzá–Martínez et al., 2020; Larsson et al., 2017). Lifestyle is a complex, multifactorial concept referring to the typical way of living of an individual or a group of people, consisting of the various habits, behaviours, values, perceptions, attitudes, and routines that are characteristic of their life. People engage in various different behaviours in their day-to-day routines that have an impact on their overall well-being. The fast-growing area of Lifestyle Medicine (LM) is a branch of medicine concentrated on prevention and treatment of chronic diseases by promoting healthy behaviours in several areas of lifestyle. The ideologies of LM first appeared in the 1990's, suggesting that the integration of lifestyle practices into the modern practice of medicine can lower the risk factors for chronic disease and/or, if

disease is already present, serve as an adjunct in its typical therapy management (Yeh and Kong, 2013). According to the evidence-based guidelines suggested by experts of LM, there are six main modifiable pillars of lifestyle that are major contributors to prevention and treatment of diseases: healthy nutrition, physical activity, restorative sleep, avoiding risky substances, stress management, and positive social relationships (Katz and Karlsen, 2019; Rippe, 2019). More specifically, Lifestyle Psychiatry (LP) is the subspecialty of LM aimed at prevention of the development of psychiatric symptoms and the treatment of disorders through the application of LM guidelines (Firth et al., 2019b). Acknowledgment of the importance of lifestyle factors in psychiatry has lagged behind other medical fields, as mental health professionals have been underestimating the contribution of these factors to various psychopathologies, and it has been more difficult to recognize the exact lifestyle areas in need of interventions for mental disorders in comparison to other areas of medicine (Firth et al., 2019b; Walsh, 2011). However, recent literature has emphasized the significance of focusing on difficulties in several lifestyle factors that are prevalent across various mental disorders. Indeed, behavioural risk factors such as substance use, physical inactivity, poor diet, and poor sleep quality are highly prevalent among people with symptoms of depression, anxiety, and BD (Firth et al., 2019a). Contemporary notions of the multifactorial approach to lifestyle by experts in the field of LP have further explored the significance of other aspects of everyday life, such as exposure to nature, use of technology and social media, religious and spiritual involvement, pet ownership, and financial stability, among others (Piotrowski et al.,

2021; Walsh, 2011). As the current understandings of lifestyle progress, the importance of LP for prevention and treatment of psychiatric disorders becomes more evident.

1.3.1 Lifestyle and Anxiety

Poor lifestyle choices and perceptions related to the abovementioned areas of LP have been associated with the presence of symptoms of anxiety, the most prevalent psychiatric symptoms in the world. Correspondingly, the relationship between unhealthy lifestyles and symptoms of anxiety has been accentuated across many countries during the COVID-19 pandemic (Blom et al., 2021; Cervera-Martínez et al., 2021; De Boni et al., 2020). Evidence from a recent scoping review of the literature on the relationship between nutrition and anxiety has highlighted the association between healthy dietary patterns (including fruits, vegetables, omega-3 fatty acids, caloric restrictions, etc.) and lower levels of anxiety, while unhealthy diets (such as high-fat diet, high intake of sugar and refined carbohydrates) are associated with higher presence of anxiety symptoms (Aucoin et al., 2021). Increased physical activity has been found to positively impact a number of biological and psychological mechanisms related to symptoms of anxiety, such as lower sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis reactivity and increased self-efficacy perceptions (Anderson and Shivakumar, 2013). The relationship between sleep disturbances and anxiety disorders has also been established, with sleep disturbances becoming one of the common symptoms of consideration for diagnosis of GAD (Alvaro et al., 2013; Staner, 2022). In particular, individuals with anxiety have demonstrated poor sleep quality and sleep continuity

disturbances more often than other sleep problems (Baglioni et al., 2016). Furthermore, exposure to chronic and intense stress can induce symptoms of anxiety (Powell and Enright, 2015), and the implementation of stress management techniques, including healthy physical and cognitive relaxation, breathing exercises, and familiarization with emotional and cognitive disturbances has proven to be beneficial for reducing these symptoms (Yazdani et al., 2010). Use of risky substances is a common co-occurrence with symptoms of anxiety, where people with anxiety were up to 4.6 times more likely to have an alcohol dependence, 1.4 times more likely to be smoking cigarettes regularly, and 1.58 times more likely to have a nicotine addiction than individuals without these symptoms (Jiang et al., 2014; Smith and Randall, 2012), often leading to a worse prognosis of the disorder and poor responsivity to usual treatments of anxiety (Vorspan et al., 2015). Moreover, emotions linked to symptoms of anxiety are closely tied to the perceived quality of interpersonal relationships, with negative relations as predictors of higher levels of socially-induced anxiety (La Greca and Harrison, 2005). Evidently, the engagement in unhealthy lifestyle behaviours and perceptions can further aggravate the debilitating symptoms of anxiety and the clinical outcomes associated with them, hence, targeting improvements in these areas may be useful for the prevention and treatment of anxiety (Firth et al., 2019b).

1.3.2 Lifestyle and Depression

Unhealthy lifestyles have also been associated with symptoms of depression prior to and during the COVID-19 pandemic (De Boni et al., 2020; Scott and Happell, 2011).

As the rates of depression are trending upwards over the last few decades (GBD Mental Disorders Collaborators, 2022; Patalay and Gage, 2019), it has become extremely important to investigate the roles of unhealthy lifestyle choices and behaviours in relation to depressive symptoms. Unhealthy dietary patterns, such as poor appetite, skipping meals and increased intake of sugars often precede symptoms of depression, while malnutritional choices, such as consumption of foods high in fat and sugar, are associated with increased symptoms of depression and cognitive functioning impairment (Rao et al., 2008; Yılmaz et al., 2021). The role of physical activity has also been suggested as a preventive factor for depressive symptoms, where people with higher levels of physical activity were 17% less likely to develop depression than people with lower levels of exercise (Schuch et al., 2018). However, it appears that close to 70% of individuals with MDD do not meet the recommended daily and weekly physical activity guidelines, despite the potential of reducing the risk of cardiovascular and metabolic complications in MDD through exercise (Schuch et al., 2017). Sleep disturbances are another common feature of depression, as 75% of people with depressive symptoms experience insomnia and 40% experience hypersomnia, among other disturbances such as interrupted sleep and early morning awakenings that can severely affect the quality of life of these individuals, and increase the risk of relapse and recurrence of episodes (Nutt et al., 2022). Furthermore, nearly one third of patients with MDD are also diagnosed with substance use disorders, a comorbidity that may lead to higher risks of suicidality and greater clinical and functional impairments (Davis et al., 2008). Likewise, chronic and acute stress in daily life situations can be another significant contributor to the onset of

depressive episodes (Hammen et al., 2009), however, physical and cognitive relaxation techniques can be very beneficial for reducing the impact of these stressful events on depressive symptoms (Yazdani et al., 2010). Prevention of the onset of depressive symptoms is also reliant on healthy social relationships at different stages of the individual's life, such as parental support, spousal support, and relationships with peers (Gariépy et al., 2016). Evidently, there are strong associations between different lifestyle domains and symptoms of depression, where the absence of preventive measures can further aggravate the well-being of an individual. Indeed, people with overall unhealthy lifestyles have presented more symptoms of depression and lower quality of life, while individuals with healthier lifestyles had a decreased presence of depression (Savolainen et al., 2014).

1.3.3 Lifestyle and Bipolar Disorder

BD is another mental disorder that leads to severe functional impairment and low quality of life in affected individuals, even during their euthymic phase (McIntyre et al., 2020; Sanchez-Moreno et al., 2009). The increased rates of medical and psychiatric comorbidities with BD further highlight the relevance of maintaining a healthy lifestyle and the consequences associated with unhealthy behaviours (McIntyre et al., 2020). BD is associated with poor nutritional and exercise habits, such as high-fat/sugar/carbohydrate diets and infrequent physical activity engagements, which are correlated with worse physical and mental health outcomes and comorbidities (Beyer and Payne, 2016; Vancampfort et al., 2013). In contrast, prompting healthier behaviours in

these areas has demonstrated promising results for more favourable clinical and functional outcomes (Kilbourne et al., 2012; Sylvia et al., 2013). Sleep disturbances are a common feature of BD across all mood states, where 1) people in depressive states experience problems such as insomnia, interrupted sleep, early morning awakenings, and hypersomnia (Plante and Winkelman, 2008), 2) sleep deprivation is a recognized marker of mania and people in (hypo)manic states have a decreased need for sleep that leads to further distress (Plante and Winkelman, 2008), and 3) poor sleep quality has been reported in up to 70% of euthymic patients with BD (Harvey et al., 2005). Moreover, substance abuse is a major risk factor for the development of BD and the onset of (hypo)manic symptoms (Lalli et al., 2021), and plenty of previous studies suggested that the co-occurrence of substance use disorders and BD present a negative impact on the cognitive functioning of affected individuals (Gogia et al., 2022). In addition, the comorbidity of these disorders may have severe implications on clinical outcomes of BD, such as more frequent and prolonged affective episodes, decreased compliance with treatment, lower quality of life, and increased suicidal behaviour (Cerullo and Strakowski, 2007). Furthermore, chronic stress related to stressful life events as well as family, peer, and romantic relationships is associated with reduced improvement of mood symptoms and poor responsivity to treatments in early-onset BD (Kim et al., 2007). Consequently, individuals with BD are more likely to engage in maladaptive stress coping mechanisms, such as substance use, behavioural disengagement, and self-blame (Bridi et al., 2018), therefore, the development of healthy stress management routines and positive social interactions may prove very beneficial for improvement of mood

symptoms and overall well-being in BD. The implementation of preventive and interventive lifestyle strategies in BD could be an effective approach to improving quality of life, reducing physical and psychiatric comorbidities, and reducing the severity and frequency of mood episodes in BD (Bauer et al., 2016; Maripuu et al., 2019; Russell and Browne, 2005; Sylvia et al., 2013).

1.3.4 Clustering of health behaviours

The abovementioned lifestyle risk factors for mental disorders such as anxiety, depression and BD are not mutually exclusive. Everyday routines consist of complex combinations of patterns and behaviours characteristic of different lifestyle domains, which are intertwined and dependent on each other. The daily co-occurrence of multiple unhealthy behaviours, such as unhealthy eating, physical inactivity, and use of risky substances has been associated with high levels of psychological distress and lower quality of life, which in turn leads to engaging in maladaptive coping mechanisms (Conry et al., 2011; Deasy et al., 2015). The cumulative effect of various unhealthy behaviours could lead to more severe mental distress. Indeed, prestigious health agencies such as the WHO and the Royal College of Psychiatrists have declared that clustering of health-risk behaviours leads to greater lifetime risk of mental illnesses, as well as other social, behavioural, financial, and general health problems (Royal College of Psychiatrists, 2010). The accumulation of multiple unhealthy habits has been linked to symptoms of mood disorders, such as depression and BD, and anxiety disorders (Vermeulen-Smit et al., 2015). Considering the effects of poor behaviours on each lifestyle domain in relation

to symptoms of these disorders, it is likely that the cumulative effect of these behaviours could lead to detrimental short and long-term clinical outcomes of the affected individuals.

In contrast, the formation of healthy habits across different lifestyle domains could be very beneficial for the overall well-being of an individual. The clustering of healthy behaviours was found to be associated with lower levels of psychological distress, higher levels of vitality, and significantly lower risk of mood and anxiety symptoms than people with unhealthier lifestyle patterns (Conry et al., 2011; Vermeulen-Smit et al., 2015). Collective improvements of lifestyle areas proposed by lifestyle psychiatry may lead to better functioning, quality of life, reduced rates of comorbidities, and more favorable clinical outcomes for populations at risk and individuals diagnosed with mental disorders (Firth et al., 2019b, 2019a). Hence, it is important to study the interactions between these lifestyle factors, and the combined effects of these factors for prevention and treatment of symptoms of mental disorders.

1.3.5 Interventions for lifestyle

Considering the impact of lifestyle routines on the physical and psychological well-being of individuals with mental disorders, the implementation of effective lifestyle interventions could change the course of common mental disorders through alterations in lifestyle patterns. The main advantage of lifestyle interventions is the notion that lifestyle risk factors are modifiable, such that behaviours characteristic of the key lifestyle areas

can be adjusted towards healthier lifestyle patterns. Research on the associations between these modifiable lifestyle domains and psychiatric symptoms has led to the development of various interventions promoting healthy behaviours for affected individuals. Many interventions have proven to be effective and beneficial for improving mental health outcomes through their respective targeted domains, such as Mediterranean diet for nutrition (Ventriglio et al., 2020), aerobic and anaerobic moderate-to-vigorous exercises for physical activity (Czosnek et al., 2019), cognitive behavioural therapy (CBT) for insomnia in psychiatric disorders (Jansson-Fröjmark and Norell-Clarke, 2016), nicotine replacement therapy (NRT) for smoking cessation (Tidey and Miller, 2015), and interpersonal and social rhythm therapy (IPSRT) for management of stressful life events and social disruptions (Steardo et al., 2020), among others. However, there is still high heterogeneity in effectiveness rates of lifestyle interventions for mental disorders, possibly due to the interactions with pharmacological treatments, effectiveness of usual care, methods of intervention delivery, adherence to interventions, and heterogeneity of populations. Perhaps, differences in neglected lifestyle areas among affected individuals can also account for the heterogeneity in effectiveness of lifestyle interventions for mental health disorders, as some lifestyle domains may require more intense interventions than others. It is important to evaluate the extent to which each lifestyle area is affected, as behaviours in some domains may be unhealthier and more destructive than other behaviours, and therefore require more attentive care. Assessment of lifestyle across the key modifiable domains can reveal the areas in need of nurture and guide

towards a more personalized approach to lifestyle interventions for mental health disorders.

Furthermore, although each of the abovementioned essential areas of lifestyle are important for mental well-being and associated with severe health consequences, there may be an imbalance in the proportion and efficacy of interventions targeting each domain. A recent meta-review on digital lifestyle interventions targeting chronic diseases, including psychiatric disorders, revealed that nutrition and physical activity were the most commonly targeted domains, while sleep and social relationships were the least targeted (Castro et al., 2021). Interventions targeting nutrition and physical activity are well established due to their importance for chronic physical and mental health problems and the feasibility of measuring objective outcomes associated to these domains (e.g., BMI, weight, biochemical measures) (Castro et al., 2021). In contrast, other domains, including lifestyle areas outside of the six main areas suggested by LM, may be targeted less often by lifestyle interventions due to prioritization of other domains and the lack of objectively measured outcomes associated to them (Castro et al., 2021; Firth et al., 2019a; Piotrowski et al., 2021). Given the importance of each modifiable lifestyle factor, maintaining healthy routines in all areas is crucial for achieving the most favorable clinical outcomes associated with mental disorders.

Accordingly, given the clustering of unhealthy behaviours across different areas, and the imbalance in proportions of targeted lifestyle areas for promoting healthy behaviours, there is a need for a multidimensional approach to lifestyle evaluations and interventions. Seeing that lifestyle is a multifactorial concept, a more holistic approach to

evaluating lifestyle quality and promoting healthy behaviours in multiple areas could possibly have a greater effect on improvements in functioning, quality of life, and other meaningful outcomes of mental disorders. To date, there has been a scarcity of evidence on the multidimensional approach to lifestyle-based assessments and interventions for common mental disorders that are in line with the current notions of LP.

1.4 Aims and Objectives

Given the association between lifestyle and mental disorders such as depression, anxiety, and BD, the general aim of this thesis was to 1) identify the association between multidimensional patterns of lifestyle and symptoms of depression, anxiety, and the diagnosis of BD, and 2) investigate the availability and efficacy of lifestyle interventions for BD.

More specifically:

1. Chapter 2 is presenting a study aimed to investigate the predictive effect of different lifestyles as factors associated with the presence of symptoms of depression and anxiety during the early stages of the COVID-19 pandemic. We sought to develop machine learning models using lifestyle variables in the Spanish general population, that would be predictive of symptoms of depression and anxiety in the Brazilian general population.
2. Chapter 3 includes a study aimed to investigate the association between unhealthy lifestyle behaviours and symptoms of depression and anxiety during the COVID-

19 lockdown period in Canada, using a multidimensional lifestyle evaluation specifically adapted to lifestyle during the COVID-19 confinement period.

3. Chapter 4 is presenting a study aimed to investigate the differences between individuals with BD in a current depressive, (hypo)manic, or mixed episode, and healthy controls on combined multidimensional lifestyle patterns within 7 essential lifestyle areas.
4. Chapter 5 includes a review of the existing literature on lifestyle interventions for BD, investigating the most frequently targeted lifestyle domains, the prevalence of multidimensional lifestyle interventions, and the efficacy of the interventions for major clinical outcomes of BD.

1.5 Hypotheses

The hypotheses for each of the abovementioned objectives are as follows:

1. Given the early reports of COVID-19 pandemic impacts on common mental health symptoms, and the promising implementation of machine learning in psychiatry, we predicted that the machine learning models based on lifestyle behaviours would be able to predict symptoms of depression and anxiety in Spain and Brazil.
2. Based on findings reported from other countries during the COVID-19 pandemic, we expected to find an association between unhealthy lifestyle behaviours and

symptoms of depression and anxiety among Canadians during the pandemic-related confinement period.

3. Previous literature has suggested associations between independent lifestyle risk factors and symptoms of BD. In Chapter 4, we hypothesized significantly worse lifestyles among people with BD than HC on overall lifestyle quality and on lifestyle patterns within each of the 7 lifestyle areas.
4. In light of previous research focus on lifestyle areas as independent risk factors for BD, we expected to observe a higher number of interventions focusing on a single lifestyle domain for BD than multiple domains. Furthermore, we expected to observe higher rates of improvements in clinical and functional outcomes in BD following lifestyle interventions in comparison to usual treatment and other non-lifestyle interventions.

1.6 References

Aldinger, F., Schulze, T.G., 2017. Environmental factors, life events, and trauma in the course of bipolar disorder. Psychiatry and clinical neurosciences.

Alonzi, S., La Torre, A., Silverstein, M.W., 2020. The psychological impact of preexisting mental and physical health conditions during the COVID-19 pandemic. Psychological Trauma: Theory, Research, Practice, and Policy 12, S236–S238. https://doi.org/10.1037/tra0000840

Alvaro, P.K., Roberts, R.M., Harris, J.K., 2013. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep 36, 1059–1068.

Ammar, A., Trabelsi, K., Brach, M., Chtourou, H., Boukhris, O., Masmoudi, L., Bouaziz, B., Bentlage, E., How, D., Ahmed, M., 2021. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: insights from the ECLB-COVID19 multicentre study. Biology of sport 38, 9.

Anderson, E., Shivakumar, G., 2013. Effects of Exercise and Physical Activity on Anxiety. Frontiers in Psychiatry 4.

Association, A.P., 2013. DSM 5 diagnostic and statistical manual of mental disorders, in: DSM 5 Diagnostic and Statistical Manual of Mental Disorders. pp. 947-p.

Aucoin, M., LaChance, L., Naidoo, U., Remy, D., Shekdar, T., Sayar, N., Cardozo, V., Rawana, T., Chan, I., Cooley, K., 2021. Diet and Anxiety: A Scoping Review. Nutrients 13, 4418.

Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., Reynolds III, C.F., Riemann, D., 2016. Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychological bulletin 142, 969.

Balanzá–Martínez, V., Atienza–Carbonell, B., Kapczinski, F., De Boni, R.B., 2020. Lifestyle behaviours during the COVID-19–time to connect. Wiley Online Library.

Bandelow, B., Michaelis, S., 2015. Epidemiology of anxiety disorders in the 21st century. Dialogues in Clinical Neuroscience 17, 327–335. https://doi.org/10.31887/DCNS.2015.17.3/bbandelow

Bauer, I.E., Galvez, J.F., Hamilton, J.E., Balanza-Martinez, V., Zunta-Soares, G.B., Soares, J.C., Meyer, T.D., 2016. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. Journal of psychiatric research 74, 1–7.

Beyer, J.L., Payne, M.E., 2016. Nutrition and bipolar depression. Psychiatric Clinics 39, 75–86.

Blom, V., Lönn, A., Ekblom, B., Kallings, L.V., Väisänen, D., Hemmingsson, E., Andersson, G., Wallin, P., Stenling, A., Ekblom, Ö., 2021. Lifestyle habits and mental health in light of the two COVID-19 pandemic waves in Sweden, 2020. International Journal of Environmental Research and Public Health 18, 3313.

Bridi, K.P.B., Loredo-Souza, A.C.M., Fijtman, A., Moreno, M.V., Kauer-Sant'Anna, M., Ceresér, K.M.M., Kunz, M., 2018. Differences in coping strategies in adult patients with bipolar disorder and their first-degree relatives in comparison to healthy controls. Trends Psychiatry Psychother. 40, 318–325. https://doi.org/10.1590/2237-6089-2017-0140

Budimir, S., Probst, T., Pieh, C., 2021. Coping strategies and mental health during COVID-19 lockdown. Journal of Mental Health 30, 156–163. https://doi.org/10.1080/09638237.2021.1875412

Canuso, C.M., Bossie, C.A., Zhu, Y., Youssef, E., Dunner, D.L., 2008. Psychotic symptoms in patients with bipolar mania. Journal of Affective Disorders 111, 164–169. https://doi.org/10.1016/j.jad.2008.02.014

Carvalho, A.F., Firth, J., Vieta, E., 2020. Bipolar disorder. New England Journal of Medicine 383, 58–66.

Castro, R., Ribeiro-Alves, M., Oliveira, C., Romero, C.P., Perazzo, H., Simjanoski, M., Kapciznki, F., Balanzá-Martínez, V., De Boni, R.B., 2021. What are we measuring when we evaluate digital interventions for improving lifestyle? a scoping meta-review. Frontiers in public health 9.

Cerullo, M.A., Strakowski, S.M., 2007. The prevalence and significance of substance use disorders in bipolar type I and II disorder. Subst Abuse Treat Prev Policy 2, 29. https://doi.org/10.1186/1747-597X-2-29

Cervera-Martínez, J., Atienza-Carbonell, B., Mota, J.C., Bobes-Bascarán, T., Crespo-Facorro, B., Esteban, C., García-Portilla, M.P., Gomes-da-Costa, S., González-Pinto, A., Jaén-Moreno, M.J., 2021. Lifestyle changes and mental health during the COVID-19 pandemic: A repeated, cross-sectional web survey. Journal of Affective Disorders 295, 173–182.

Collaborators, G. 2019 M.D., 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry 9, 137–150.

Conry, M.C., Morgan, K., Curry, P., McGee, H., Harrington, J., Ward, M., Shelley, E., 2011. The clustering of health behaviours in Ireland and their relationship with mental health, self-rated health and quality of life. BMC public health 11, 1–10.

Cotrena, C., Branco, L.D., Shansis, F.M., Fonseca, R.P., 2016. Executive function impairments in depression and bipolar disorder: association with functional impairment and quality of life. Journal of affective disorders 190, 744–753.

Czosnek, L., Lederman, O., Cormie, P., Zopf, E., Stubbs, B., Rosenbaum, S., 2019. Health benefits, safety and cost of physical activity interventions for mental health conditions: A meta-review to inform translation efforts. Mental Health and Physical Activity 16, 140–151. https://doi.org/10.1016/j.mhpa.2018.11.001

Dadi, K., Varoquaux, G., Houenou, J., Bzdok, D., Thirion, B., Engemann, D., 2021. Population modeling with machine learning can enhance measures of mental health. GigaScience 10, giab071.

Dalkner, N., Ratzenhofer, M., Fleischmann, E., Fellendorf, F.T., Bengesser, S., Birner, A., Maget, A., Großschädl, K., Lenger, M., Platzer, M., 2022. Psychological and behavioural response on the COVID-19 pandemic in individuals with bipolar disorder: A multicenter study. Psychiatry Research 310, 114451.

Davis, L., Uezato, A., Newell, J.M., Frazier, E., 2008. Major depression and comorbid substance use disorders. Current Opinion in Psychiatry 21, 14–18. https://doi.org/10.1097/YCO.0b013e3282f32408

De Boni, R.B., Balanzá-Martínez, V., Mota, J.C., Cardoso, T.D.A., Ballester, P., Atienza-Carbonell, B., Bastos, F.I., Kapczinski, F., 2020. Depression, Anxiety, and Lifestyle Among Essential Workers: A Web Survey From Brazil and Spain During the COVID-19 Pandemic. Journal of medical Internet research 22, e22835.

de Lima Bach, S., de Azevedo Cardoso, T., Moreira, F.P., Mondin, T.C., Simjanoski, M., Kapczinski, F.P., Frey, B.N., de Mattos Souza, L.D., da Silva, R.A., Jansen, K., 2021. Risk factors for new-onset bipolar disorder in a community cohort: A five-year follow up study. Psychiatry Research 303, 114109.

Deasy, C., Coughlan, B., Pironom, J., Jourdan, D., Mcnamara, P.M., 2015. Psychological distress and lifestyle of students: implications for health promotion. Health Promotion International 30, 77–87. https://doi.org/10.1093/heapro/dau086

DeMartini, J., Patel, G., Fancher, T.L., 2019. Generalized Anxiety Disorder. Ann Intern Med 170, ITC49. https://doi.org/10.7326/AITC201904020

Dozois, D.J., 2020. Anxiety and depression in Canada during the COVID-19 pandemic: A national survey. Canadian Psychology/Psychologie canadienne.

Druss, B., Walker, E., 2011. Mental Disorders and Medical Comorbidity. The Synthesis project. Research synthesis report 1–26.

Faravelli, C., Lo Sauro, C., Lelli, L., Pietrini, F., Lazzeretti, L., Godini, L., Benni, L., Fioravanti, G., Alina Talamba, G., Castellini, G., 2012. The role of life events and HPA axis in anxiety disorders: a review. Current pharmaceutical design 18, 5663.

Farhud, D.D., 2015. Impact of lifestyle on health. Iranian journal of public health 44, 1442.

Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A.F., 2019a. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry 6, 675–712.

Firth, J., Solmi, M., Wootton, R.E., Vancampfort, D., Schuch, F.B., Hoare, E., Gilbody, S., Torous, J., Teasdale, S.B., Jackson, S.E., 2020. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry 19, 360–380.

Firth, J., Ward, P.B., Stubbs, B., 2019b. Lifestyle psychiatry. Frontiers in psychiatry 10, 597.

Gariépy, G., Honkaniemi, H., Quesnel-Vallée, A., 2016. Social support and protection from depression: systematic review of current findings in Western countries. Br J Psychiatry 209, 284–293. https://doi.org/10.1192/bjp.bp.115.169094

Gogia, M., Shah, A.Q., Kapczinski, F., de Azevedo Cardoso, T., 2022. The impact of substance use disorder comorbidity on cognition of individuals with bipolar disorder: A systematic review. Psychiatry Res 311, 114525. https://doi.org/10.1016/j.psychres.2022.114525

Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. The Lancet 387, 1561–1572.

Gutiérrez-Rojas, L., Porras-Segovia, A., Dunne, H., Andrade-González, N., Cervilla, J.A., 2020. Prevalence and correlates of major depressive disorder: a systematic review. Brazilian Journal of Psychiatry 42, 657–672.

Hammar, Å., Årdal, G., 2009. Cognitive functioning in major depression-a summary. Frontiers in human neuroscience 3, 26.

Hammen, C., Kim, E.Y., Eberhart, N.K., Brennan, P.A., 2009. Chronic and acute stress and the prediction of major depression in women. Depression and anxiety 26, 718–723.

Harvey, A.G., Schmidt, D.A., Scarnà, A., Semler, C.N., Goodwin, G.M., 2005. Sleep-Related Functioning in Euthymic Patients With Bipolar Disorder, Patients With Insomnia, and Subjects Without Sleep Problems. AJP 162, 50–57. https://doi.org/10.1176/appi.ajp.162.1.50

Hwang, T.-J., Rabheru, K., Peisah, C., Reichman, W., Ikeda, M., 2020. Loneliness and social isolation during the COVID-19 pandemic. International psychogeriatrics 32, 1217–1220.

IsHak, W.W., Greenberg, J.M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., Fakhry, H., Rapaport, M.H., 2011. Quality of life: the ultimate outcome measure of interventions in major depressive disorder. Harvard review of psychiatry 19, 229–239.

Jansson-Fröjmark, M., Norell-Clarke, A., 2016. Cognitive Behavioural Therapy for Insomnia in Psychiatric Disorders. Curr Sleep Medicine Rep 2, 233–240. https://doi.org/10.1007/s40675-016-0055-y

Jiang, F., Li, S., Pan, L., Zhang, N., Jia, C., 2014. Association of anxiety disorders with the risk of smoking behaviours: a meta-analysis of prospective observational studies. Drug Alcohol Depend 145, 69–76. https://doi.org/10.1016/j.drugalcdep.2014.10.022

Johansson, R., Carlbring, P., Heedman, Å., Paxling, B., Andersson, G., 2013. Depression, anxiety and their comorbidity in the Swedish general population: point prevalence and the effect on health-related quality of life. PeerJ 1, e98. https://doi.org/10.7717/peerj.98

Johnson, S.L., Tharp, J.A., Peckham, A.D., McMaster, K.J., 2016. Emotion in bipolar I disorder: Implications for functional and symptom outcomes. Journal of abnormal psychology 125, 40.

Karantonis, J.A., Rossell, S.L., Berk, M., Van Rheenen, T.E., 2021. The mental health and lifestyle impacts of COVID-19 on bipolar disorder. Journal of affective disorders 282, 442–447.

Katz, D.L., Karlsen, M.C., 2019. The need for a whole systems approach to evidence evaluation: an update from the American College of Lifestyle Medicine. The Journal of Alternative and Complementary Medicine 25, S19–S20.

Kendler, K.S., Kessler, R.C., Walters, E.E., MacLean, C., Neale, M.C., Heath, A.C., Eaves, L.J., 2010. Stressful life events, genetic liability, and onset of an episode of major depression in women. Focus 8, 459–470.

Kilbourne, A.M., Goodrich, D.E., Lai, Z., Clogston, J., Waxmonsky, J., Bauer, M.S., 2012. Life Goals Collaborative Care for patients with bipolar disorder and cardiovascular disease risk. Psychiatric Services 63, 1234–1238.

Kilbourne, A.M., Rofey, D.L., McCarthy, J.F., Post, E.P., Welsh, D., Blow, F.C., 2007. Nutrition and exercise behaviour among patients with bipolar disorder 1. Bipolar disorders 9, 443–452.

Kim, E.Y., Miklowitz, D.J., Biuckians, A., Mullen, K., 2007. Life stress and the course of early-onset bipolar disorder. Journal of affective disorders 99, 37–44.

Kupferberg, A., Bicks, L., Hasler, G., 2016. Social functioning in major depressive disorder. Neuroscience & Biobehavioural Reviews 69, 313–332. https://doi.org/10.1016/j.neubiorev.2016.07.002

La Greca, A., Harrison, H., 2005. Adolescent Peer Relations, Friendships, and Romantic Relationships: Do They Predict Social Anxiety and Depression? Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53 34, 49–61. https://doi.org/10.1207/s15374424jccp3401_5

Lalli, M., Brouillette, K., Kapczinski, F., de Azevedo Cardoso, T., 2021. Substance use as a risk factor for bipolar disorder: A systematic review. J Psychiatr Res 144, 285–295. https://doi.org/10.1016/j.jpsychires.2021.10.012

Larsson, S.C., Kaluza, J., Wolk, A., 2017. Combined impact of healthy lifestyle factors on lifespan: two prospective cohorts. J Intern Med 282, 209–219. https://doi.org/10.1111/joim.12637

Marangoni, C., Hernandez, M., Faedda, G.L., 2016. The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. Journal of Affective Disorders 193, 165–174. https://doi.org/10.1016/j.jad.2015.12.055

Maripuu, M., Norrback, K.-F., Adolfsson, R., 2019. Quality of life for patients diagnosed with bipolar disorder: Lifestyle and treatment. Neurology, Psychiatry and Brain Research 34, 34–40. https://doi.org/10.1016/j.npbr.2019.09.002

McIntyre, R.S., Berk, M., Brietzke, E., Goldstein, B.I., López-Jaramillo, C., Kessing, L.V., Malhi, G.S., Nierenberg, A.A., Rosenblat, J.D., Majeed, A., 2020. Bipolar disorders. The Lancet 396, 1841–1856.

McKnight, P.E., Monfort, S.S., Kashdan, T.B., Blalock, D.V., Calton, J.M., 2016. Anxiety symptoms and functional impairment: A systematic review of the correlation between the two measures. Clinical psychology review 45, 115–130.

McLaughlin, K.A., Hatzenbuehler, M.L., 2009. Stressful Life Events, Anxiety Sensitivity, and Internalizing Symptoms in Adolescents. J Abnorm Psychol 118, 659–669. https://doi.org/10.1037/a0016499

Michalak, E.E., Yatham, L.N., Lam, R.W., 2005. Quality of life in bipolar disorder: a review of the literature. Health and quality of life outcomes 3, 1–17.

Nutt, D., Wilson, S., Paterson, L., 2022. Sleep disorders as core symptoms of depression. Dialogues in clinical neuroscience.

Patalay, P., Gage, S.H., 2019. Changes in millennial adolescent mental health and health-related behaviours over 10 years: a population cohort comparison study. Int J Epidemiol 48, 1650–1664. https://doi.org/10.1093/ije/dyz006

Pfefferbaum, B., North, C.S., 2020. Mental Health and the Covid-19 Pandemic. New England Journal of Medicine 383, 510–512. https://doi.org/10.1056/NEJMp2008017

Phillips, M.L., Kupfer, D.J., 2013. Bipolar disorder diagnosis: challenges and future directions. Lancet 381, 1663–1671. https://doi.org/10.1016/S0140-6736(13)60989-7

Piotrowski, M.C., Lunsford, J., Gaynes, B.N., 2021. Lifestyle psychiatry for depression and anxiety: Beyond diet and exercise. Lifestyle Medicine 2, e21. https://doi.org/10.1002/lim2.21

Plana-Ripoll, O., Pedersen, C.B., Holtz, Y., Benros, M.E., Dalsgaard, S., De Jonge, P., Fan, C.C., Degenhardt, L., Ganna, A., Greve, A.N., 2019. Exploring comorbidity within mental disorders among a Danish national population. JAMA psychiatry 76, 259–270.

Plante, D.T., Winkelman, J.W., 2008. Sleep disturbance in bipolar disorder: therapeutic implications. American Journal of Psychiatry 165, 830–843.

Post, R.M., Leverich, G.S., 2006. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. Development and psychopathology 18, 1181–1211.

Powell, T., Enright, S., 2015. Anxiety and Stress Management. Routledge, London. https://doi.org/10.4324/9781315683867

Psychiatrists, R.C. of, 2010. No health without public mental health: The case for action.

Rahman, R.A., Omar, K., Mohd Noah, S.A., Danuri, M.S.N.M., Al-Garadi, M.A., 2020. Application of Machine Learning Methods in Mental Health Detection: A Systematic Review. IEEE Access 8, 183952–183964. https://doi.org/10.1109/ACCESS.2020.3029154

Rao, T.S.S., Asha, M.R., Ramesh, B.N., Rao, K.S.J., 2008. Understanding nutrition, depression and mental illnesses. Indian J Psychiatry 50, 77–82. https://doi.org/10.4103/0019-5545.42391

Rapaport, M.H., Clary, C., Fayyad, R., Endicott, J., 2005. Quality-of-Life Impairment in Depressive and Anxiety Disorders. AJP 162, 1171–1178. https://doi.org/10.1176/appi.ajp.162.6.1171

Rippe, J.M., 2019. Lifestyle medicine. CRC Press.

Rowa, K., Antony, M.M., 2008. Generalized anxiety disorder.

Russell, S.J., Browne, J.L., 2005. Staying Well with Bipolar Disorder. Aust N Z J Psychiatry 39, 187–193. https://doi.org/10.1080/j.1440-1614.2005.01542.x

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, Shna, Mohammadi, M., Rasoulpoor, Shabnam, Khaledi-Paveh, B., 2020. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Globalization and health 16, 1–11.

Sanchez-Moreno, J., Martinez-Aran, A., Tabarés-Seisdedos, R., Torrent, C., Vieta, E., Ayuso-Mateos, J.L., 2009. Functioning and disability in bipolar disorder: an extensive review. Psychotherapy and psychosomatics 78, 285–297.

Savolainen, J., Kautiainen, H., Miettola, J., Niskanen, L., Mäntyselkä, P., 2014. Low quality of life and depressive symptoms are connected with an unhealthy lifestyle. Scandinavian journal of public health 42, 163–170.

Schuch, F., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P., Reichert, T., Bagatini, N.C., Bgeginski, R., Stubbs, B., 2017. Physical activity and sedentary behaviour in

people with major depressive disorder: A systematic review and meta-analysis. Journal of Affective Disorders 210, 139–150. https://doi.org/10.1016/j.jad.2016.10.050

Schuch, F.B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P.B., Silva, E.S., Hallgren, M., Ponce De Leon, A., Dunn, A.L., Deslandes, A.C., 2018. Physical activity and incident depression: a meta-analysis of prospective cohort studies. American Journal of Psychiatry 175, 631–648.

Scott, D., Happell, B., 2011. The High Prevalence of Poor Physical Health and Unhealthy Lifestyle Behaviours in Individuals with Severe Mental Illness. Issues in mental health nursing 32, 589–97. https://doi.org/10.3109/01612840.2011.569846

Shatte, A.B., Hutchinson, D.M., Teague, S.J., 2019. Machine learning in mental health: a scoping review of methods and applications. Psychological medicine 49, 1426–1448.

Smith, J.P., Randall, C.L., 2012. Anxiety and Alcohol Use Disorders. Alcohol Res 34, 414–431.

Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. del M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., 2017. Cognitive impairment in bipolar disorder: treatment and prevention strategies. International Journal of Neuropsychopharmacology 20, 670–680.

Staner, L., 2022. Sleep and anxiety disorders. Dialogues in clinical neuroscience.

Steardo, L., Luciano, M., Sampogna, G., Zinno, F., Saviano, P., Staltari, F., Segura Garcia, C., De Fazio, P., Fiorillo, A., 2020. Efficacy of the interpersonal and social

rhythm therapy (IPSRT) in patients with bipolar disorder: results from a real-world, controlled trial. Ann Gen Psychiatry 19, 15. https://doi.org/10.1186/s12991-020-00266-7

Stillman, A.N., Rowe, K.C., Arndt, S., Moser, D.J., 2012. Anxious symptoms and cognitive function in non-demented elderly adults: an inverse relationship. Int J Geriatr Psychiatry 27, 792–798. https://doi.org/10.1002/gps.2785

Sylvia, L.G., Salcedo, S., Bernstein, E.E., Baek, J.H., Nierenberg, A.A., Deckersbach, T., 2013. Nutrition, Exercise, and Wellness Treatment in bipolar disorder: proof of concept for a consolidated intervention. International Journal of Bipolar Disorders 1, 24. https://doi.org/10.1186/2194-7511-1-24

Thornicroft, G., 2011. Physical health disparities and mental illness: the scandal of premature mortality. Br J Psychiatry 199, 441–442. https://doi.org/10.1192/bjp.bp.111.092718

Tidey, J.W., Miller, M.E., 2015. Smoking cessation and reduction in people with chronic mental illness. BMJ 351, h4065. https://doi.org/10.1136/bmj.h4065

Tylee, A., Walters, P., 2007. Underrecognition of anxiety and mood disorders in primary care: why does the problem exist and what can be done? Journal of Clinical Psychiatry 68, 27–30.

van Lankeren, J.E., Testerink, A.E., Daggenvoorde, T.H., Poslawsky, I.E., Goossens, P.J.J., 2020. Patient experiences with nursing care during hospitalization on a closed

ward due to a manic episode: A qualitative study. Perspect Psychiatr Care 56, 37–45. https://doi.org/10.1111/ppc.12370

Vancampfort, D., Correll, C.U., Probst, M., Sienaert, P., Wyckaert, S., De Herdt, A., Knapen, J., De Wachter, D., De Hert, M., 2013. A review of physical activity correlates in patients with bipolar disorder. Journal of Affective Disorders 145, 285–291. https://doi.org/10.1016/j.jad.2012.07.020

Ventriglio, A., Sancassiani, F., Contu, M.P., Latorre, M., Di Slavatore, M., Fornaro, M., Bhugra, D., 2020. Mediterranean diet and its benefits on health and mental health: a literature review. Clinical practice and epidemiology in mental health: CP & EMH 16, 156.

Vermeulen-Smit, E., Ten Have, M., Van Laar, M., De Graaf, R., 2015. Clustering of health risk behaviours and the relationship with mental disorders. Journal of affective disorders 171, 111–119.

Vindegaard, N., Benros, M.E., 2020. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain, behaviour, and immunity 89, 531–542.

Vorspan, F., Mehtelli, W., Dupuy, G., Bloch, V., Lépine, J.-P., 2015. Anxiety and Substance Use Disorders: Co-occurrence and Clinical Issues. Curr Psychiatry Rep 17, 4. https://doi.org/10.1007/s11920-014-0544-y

Walsh, C.G., Ribeiro, J.D., Franklin, J.C., 2017. Predicting risk of suicide attempts over time through machine learning. Clinical Psychological Science 5, 457–469.

Walsh, R., 2011. Lifestyle and mental health. American Psychologist 66, 579.

Williams, S.Z., Chung, G.S., Muennig, P.A., 2017. Undiagnosed depression: A community diagnosis. SSM Popul Health 3, 633–638. https://doi.org/10.1016/j.ssmph.2017.07.012

World Health Organization, 2022. Mental Health and COVID-19: Early evidence of the pandemic's impact (Scientific Brief).

Yazdani, M., Rezaei, S., Pahlavanzadeh, S., 2010. The effectiveness of stress management training program on depression, anxiety and stress of the nursing students. Iran J Nurs Midwifery Res 15, 208–215.

Yeh, B.-I., Kong, I.D., 2013. The Advent of Lifestyle Medicine. J Lifestyle Med 3, 1–8.

Yılmaz, N., Özyürek, H., Çetin, N., Gunes, B., Erbas, O., 2021. Nutrition and Depression 2, 147–157. https://doi.org/10.5606/jebms.2021.75651

Zisook, S., Lesser, I., Stewart, J.W., Wisniewski, S.R., Balasubramani, G.K., Fava, M., Gilmer, W.S., Dresselhaus, T.R., Thase, M.E., Nierenberg, A.A., 2007. Effect of age at onset on the course of major depressive disorder. American Journal of Psychiatry 164, 1539–1546.

Chapter 2: Lifestyle Predictors of Depression and Anxiety during COVID-19: a machine learning approach

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Abstract

Introduction: Recent research has suggested an increase in the global prevalence of psychiatric symptoms during the COVID-19 pandemic. This study aimed to assess whether lifestyle behaviours can predict the presence of depression and anxiety in the Brazilian general population, using a model developed in Spain.

Methods: A web survey was conducted during April-May 2020, which included the Short Multidimensional Inventory Lifestyle Evaluation (SMILE) scale, assessing lifestyle behaviours during the COVID-19 pandemic. Depression and anxiety were examined using the PHQ-2 and the GAD-7, respectively. Elastic net, random forest, and gradient tree boosting were used to develop predictive models. Each technique used a subset of the Spanish sample to train the models, which were then tested internally (vs. the remainder of the Spanish sample) and externally (vs. the full Brazilian sample), evaluating their effectiveness.

Results: The study sample included 22,562 individuals (19,069 from Brazil, and 3,493 from Spain). The models developed performed similarly and were equally effective in predicting depression and anxiety in both tests, with internal test AUC-ROC values of 0.85 (depression) and 0.86 (anxiety), and external test AUC-ROC values of 0.85 (depression) and 0.84 (anxiety). Meaning of life was the strongest predictor of depression, while sleep quality was the strongest predictor of anxiety during the COVID-19 epidemic.

Conclusions: Specific lifestyle behaviours during the early COVID-19 epidemic successfully predicted the presence of depression and anxiety in a large Brazilian sample

using machine learning models developed on a Spanish sample. Targeted interventions focused on promoting healthier lifestyles are encouraged.

Keywords: Mental health, SARS-CoV-2, lifestyle, machine learning, pandemic.

2.1 Introduction

The widespread global COVID-19 crisis continues to affect people in different ways, with many people becoming vulnerable to mental health challenges during the pandemic.[1] Since the onset of this pandemic, fears arising from uncertainties about their well-being have led to major changes in people's lifestyles around the world.[2] The sudden deviation from daily routines has resulted in increased prevalence of psychiatric symptoms relative to before the COVID-19 pandemic.[1] In particular, online web-surveys have been used to assess symptoms of mental disorders and have found an increase of the prevalence of symptoms of common mental disorders such as depression and anxiety in the general population in many countries, such as China, Italy, and Denmark, among others.[3-5]

Two of the most severely affected countries in the world were Spain and Brazil, where citizens experienced high levels of psychological distress in the early stages of the COVID-19 epidemic.[6,7] Using online assessment tools, research studies conducted during the initial stages of the pandemic in Spain indicated a high prevalence of depressive symptoms, ranging between 18.7%[8] and 41%[9], as well as of anxiety symptoms, ranging between 21.6%[8] and 25%[9] among the general population. Similarly, a study in Brazil conducted during the COVID-19 epidemic found anxiety and depression to be the most commonly prevalent psychiatric symptoms in the general population, with a staggering 81.9% of participants indicating symptoms of anxiety, and 68% presenting symptoms of depression.[10] Furthermore, another Brazilian study found a positive association between psychological symptoms (i.e. depression and anxiety) and social isolation variables (i.e.

loneliness, days in isolation, level of concern about the COVID-19 situation in Brazil), suggesting the impact that these challenging routine changes may have had on the mental well-being of people.[11]

The major lifestyle adjustments people have had to make during this pandemic might be considered as risk factors for the appearance of unstable psychological symptoms during the quarantine period.[2] Unhealthy behaviours, such as poor dietary habits, poor sleep quality, and lack of exercise, to name a few, have been found to contribute to the burden of mental health around the globe.[12,13] Given the unusual circumstances people across the world have been affected by, it is not uncommon for people to have developed unhealthy behaviours during the quarantine period that may trigger stress-related symptoms of depression and anxiety.[2]

A recent systematic review including studies from various countries suggests a global increase in prevalence of psychiatric symptoms during the COVID-19 pandemic,[1] with changes in everyday routines potentially playing a major role in this regard. However, it is not clear which specific changes to lifestyle behaviours and daily routines have had the greatest impact in triggering symptoms of depression and anxiety in people in highly affected countries. Further examination of this question is important in order to plan effective strategies to target prevention of mental health issues. A significant component of the present study relies on using machine learning techniques to analyze the importance of different lifestyle variables for predicting depressive and anxiety symptoms. Machine learning has become an efficient and accurate instrumental technique for analyzing big data.[14] Thus, the aim of the present study was to analyze the

predictive effect of different lifestyle behaviours as risk factors for depression and anxiety in the general Spanish and Brazilian populations during the COVID-19 pandemic.

2.2 Methods

Data were used from web surveys conducted from April 15 to May 15, 2020 (Spain) and from April 20 to May 20, 2020 (Brazil), as detailed elsewhere.[15,16] Briefly, individuals aged 18 years or older, living in Brazil or Spain, and having access to the Internet were recruited via social networks (Facebook, WhatsApp, and Twitter) using a snowball technique and sponsored social network advertisements. Individuals who agreed to participate after reading the information and terms of the study provided electronic informed consent. Subsequently, they answered a 101-question questionnaire covering demographics, COVID-19 experience, lifestyle, self-rated health, and previously diagnosed medical and psychiatric conditions, and including brief screenings for depression, anxiety, and risky drinking.

The study was approved by the Ethics Committee at the Hospital Universitari i Politècnic La Fe in Valencia, Spain, and by the Comissão Nacional de Ética em Pesquisa (CONEP, Brazil –3.968.686).

2.2.1 Predictors assessed

Sociodemographic predictors included age, sex, employment status, educational level, number of people living in the household, and country of residence (Brazil or Spain). Information related to COVID-19 included questions such as, “Did a health

professional formally diagnose you with COVID-19?" and "Have you lost a loved one during the pandemic?"

The main predictors of interest were lifestyle behaviours during the COVID-19 quarantine period. These were assessed using the Short Multidimensional Inventory Lifestyle Evaluation (SMILE) scale, a 43-item, self-rated questionnaire comprising 7 lifestyle domains (Diet and Nutrition, Substance abuse, Physical activity, Stress management, Restorative sleep, Social support, and Environmental exposures) developed for multidimensional 30-day lifestyle assessment.[15] On the SMILE scale, response options are measured with a 4-point Likert scale (Always, Often, Seldom, Never) and the final score is obtained by summing the scores for all questions (noting that some questions are reverse-scored). The higher the score, the better (healthier) the lifestyle. In addition, self-rated health (SRH) was measured using the question "How would you rate your health in general?", with response options of "Very good", "Good", "Regular", "Bad", and "Very bad", scored from 1 to 5, respectively. For the purpose of the present study, all the items were independently included in the model.

2.2.2 Outcome

Our main outcome was presence of a positive screening result for depression or anxiety. Current depression and anxiety were assessed using Patient Health Questionnaire-2 (PHQ-2)[17] for depression, with a cut-off of ≥ 3, and the Generalized Anxiety Disorder 7-item (GAD-7)[18] scale for anxiety, with a cut-off of ≥ 10. Two dichotomous variables were created, where scores on the two scales that were equal to or above the cut-offs were defined as "Positive Depression" and "Positive Anxiety".

2.2.3 Dealing with non-responses

First, all participants that had missing variables, which would prevent us from building the final model, were excluded from the analysis. Secondly, columns containing more than 5% of missing data were removed. Finally, the remaining variables were imputed as follows: (1) for every variable, the mode, in case of categorical, or the mean, in case of continuous data, was computed from the training set; (2) the internal test set was imputed with the previously computed modes and means; (3) the same was done for the external test set (Brazil).

2.2.4 Statistical analysis

The statistical analyses performed to compare groups in terms of sociodemographic and clinical characteristics were conducted using SPSS 21. Independent variables were described by outcome and compared using chi-square tests and Student's *t* test for independent samples. All variables, with the exception of SMILE scores, were categorized and analyzed using chi-square tests between the respective outcome groups. For SMILE scores, the samples were compared using Student's *t* test. All machine learning experiments were conducted using R software (version 4.04), and the *caret* library (version 6.0-86).[19] The data were analyzed using 3 different machine learning algorithms: elastic net, random forest, and gradient tree boosting (extreme gradient boosting [XGBoost] library). Elastic net is a regularized linear model that penalizes high weights, and thus is focused on generalization of the model for unseen samples.[20] Random forest is a machine learning algorithm that combines and averages the predictions of multiple decision trees with random subsets of features and instances,

resulting in a single predictive model.[21] XGBoost is a scalable technique that creates a predictive model by efficiently adding new models to correct the errors of existing models (also known as 'gradient boosting'), until the best possible model is reached.[22] The dataset was trained and tested with each of the three models separately to examine their performance in comparison to each other. For each model, the data from Brazil were separated from the dataset and were not used until testing time; referred to as the *external test*. Then, the Spain dataset was split into two (75% for a training sample and 25% for an internal test) using class-stratified sampling. The training sample was then used to train the model, according to the training procedures for each machine learning technique. For each model, a grid search with the *caret* default hyperparameters was used to identify the best model in a 10-fold cross-validation procedure. Downsampling of the majority class was used to fix class imbalance. Variables with more than 5% missing data were removed and the remaining variables were imputed by either the mode (for categorical variables) or the mean (for numeric variables). Generalization of the model was then assessed in the internal test sample, and used to generate all performance metrics (e.g., accuracy, sensitivity, and others) for the Spanish sample. Finally, the model was evaluated on every individual from the Brazilian sample without any retraining or fine tuning. Model predictions were also used to create risk quintiles. Participants were sorted by their corresponding predicted probabilities and separated into five groups (20% highest predictions allocated to group 1, 20-40% allocated to group 2, and so on), then, the percentage of participants with presence of the outcome was calculated. This

approach provides a broad idea of how predicted probabilities translate into actual probabilities of the outcome in test data (i.e. model calibration).

2.2.5 Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.3 Results

2.3.1 Sample size and sociodemographic characteristics

The final sample for this study comprised 22,562 individuals, with 19,069 subjects from Brazil and 3,493 subjects from Spain. The sociodemographic characteristics were analyzed separately for each country (Brazil or Spain) and further differentiated based on the current clinical symptoms of the individuals, as evaluated by the PHQ-2 and GAD-7 for depression and anxiety symptoms, respectively. The comparisons were performed within the specific subsets of the sample, leading to 4 main comparisons: depression vs. no depression in Brazil, depression vs. no depression in Spain, anxiety vs. no anxiety in Brazil, and anxiety vs. no anxiety in Spain. The sociodemographic differences are described in Table 1 (depression screening) and Table 2 (anxiety screening).

2.3.2 Model performance

Model performance was assessed using several metrics. Table 3 presents all the metrics for the elastic net, random forest, and XGBoost models, comparing the results when the Brazilian sample is used for testing and when the Spanish sample is used for

testing. The 3 models performed very similarly for the internal and external tests. Differences can be perceived between the performance with the internal test set (Spain) and external test set (Brazil), although, overall, the results are reliable in both scenarios. For instance, the main differences between the two tests were in the positive and negative predictive values (PPV and NPV), where the external tests had higher PPV, but lower NPV than the internal tests for depression and anxiety. Despite these differences, the balanced accuracy, sensitivity, and specificity values were consistent for all models across the internal and external tests for depression and anxiety.

The elastic net model was used for subsequent analyses because of its effectiveness, interpretability, and simplicity. The elastic net AUC-ROC for depression was 0.85 for both the internal and external test (Figure 1A). Its AUC-ROC values for the anxiety model were 0.86 and 0.84 for the internal and external test, respectively (Figure 1B). In both cases, the curves for the internal and external sets are very similar, with performance for the Spain data being slightly better overall.

The calibration of the model was also analyzed, by evaluating the concentration of the outcome within the percentiles of predictions. In Figures 1C and 1D, significant differences were identified between the countries. In order to generate the image, participants were sorted by their predicted value into 5 defined quintiles of predictions. For each of these groups, the percentage of participants that had the outcome with respect to the total number of individuals with the outcome were assessed. More specifically, almost 60% of the participants with depression (first red bar) are within the 20% highest predictions (Figure 1C). In other words, a high prediction from the model is highly

predictive of the outcome. However, a reduction was observed in the Brazilian sample. Notably, around 35% of the participants within the 20% highest predictions have depression. This may indicate signs of prediction bias coming from the Spanish sample. Almost the exact same pattern is observed for anxiety (Figure 1D).

In addition, the importance of each question on the SMILE scale was examined as an independent lifestyle variable for predicting the presence of depression and anxiety symptoms. Each question was separately evaluated for its projective capacity to suggest presence of depression and presence of anxiety symptoms in the Spanish sample. All questions considered were based on respondents' daily routines and feelings within the last month. Analysis of the predictors of depression identified the question, "Do you feel that your life has a meaning?" as the most important predictor of the disorder, followed by the question, "How would you rate your health in general?" (from the SRH) and "Do you use sleeping pills?" (Figure 2A). With regards to the predictors of anxiety, the most important SMILE question to predict the presence of the disorder was, "Do you feel rested with the number of hours you sleep?", followed by "Do you use sleeping pills?" and "Do you feel that you have a good work-life balance?" (Figure 2B).

2.4 Discussion

Findings from this study indicate that variables related to lifestyle, as assessed by the SMILE scale, successfully predicted common mental disorders such as depression and anxiety in a Brazilian sample using a machine learning model developed on a Spanish sample during the early stages of the COVID-19 epidemic. Additionally, the results highlight the importance of different lifestyle factors and general self-concerns as

predictors of these disorders, with perception about meaning of life, self-rated health, and use of sleeping pills being the most important predictors of depression, and restful sleep, use of sleeping pills, and perception about work-life balance being the most important predictors of anxiety.

The COVID-19 epidemic started at different times in Spain and Brazil, where the population of Spain was affected by the first wave of the contagious virus prior to escalation of the outbreak in the Brazilian population. By assessing lifestyle behaviours in the early stages of the epidemic in Spain using a multidimensional lifestyle questionnaire (SMILE), we developed predictive models with three different machine learning methods using a subset of the Spanish sample. The models were then tested internally (with the remaining subset of the Spanish sample) and later tested externally with the full Brazilian sample. The consistency in performance metrics between the different methods, as well as the similarities between the internal and external tests suggest that the internally developed models were able to predict the presence of depression and anxiety during the COVID-19 pandemic in the external set, which is the main, novel finding from this research study.

To our knowledge, this is the first study to develop machine learning models in one country that are equally effective in predicting the presence of common mental health disorders in a different country. Implications from this study indicate that elastic net, random forest, and XGBoost are reliable techniques for transnational prediction of common mental disorders such as depression and anxiety. The cross-fertilization of independent analyses carried out in different contexts is a much-desired goal of

contemporary epistemology, decision science, and computer science, among other fields of knowledge. Prior literature has found many similarities in lifestyle factors that correlate to presence of mental disorders such as depression and anxiety in underdeveloped, developing, and developed countries.[23,24] Recent studies conducted during the COVID-19 outbreak have also indicated higher prevalence of depression and anxiety symptoms in the general population during this period.[25,26] Considering the severe consequences of the pandemic in highly affected countries such as Brazil and Spain, a recent study conducted in these regions found an association between unhealthy lifestyle changes and presence of depression and anxiety among essential workers during the COVID-19 pandemic.[16] With this in mind, taking into consideration the similarities across different countries in lifestyle adversities due to the COVID-19 crisis, it is possible that the models developed and used in this study may be able to reliably capture predictive factors of the presence of common mental disorders in different regions of the world.

We also assessed the importance of each lifestyle variable on the SMILE scale as independent factors associated with presence of depression and anxiety using machine learning methods. We used the Spain training sample to evaluate the importance of each independent question in predicting presence of the mental disorders of interest. Intriguingly, we found the answers to the question, “Do you feel that your life has a meaning?” to be the predictor most associated with presence of depression. Prior studies have reported an inverse relationship between self-perceived meaning of life and symptoms of depression, concurring with the current findings of our study.[27,28] However,

we believe this to be the first study indicating that perception of meaning of life carries greater significance in predicting symptoms of depression than other lifestyle factors. The high importance factor seen in this variable could be due to the cumulative contribution of many different aspects of lifestyle towards a sense that life is meaningless during the COVID-19 pandemic. Self-rated health was the second most important predictor of presence of depression in this sample during the pandemic, with prior literature also suggesting a strong association between subjective well-being and symptoms of depression.[29,30] Among the rest of the factors, sleep medications and sleep quality were found to be among the strongest predictors of depression, which has also been suggested in previous findings.[31,32]

Furthermore, we assessed the importance of each lifestyle variable on the SMILE scale as independent predictors of anxiety in the Spanish training sample. The leading, most significant predictor of presence of anxiety was the answer to the question, “In the last month, how often do you feel rested with the number of hours you sleep?”. Similarly, the second most important predictor was related to daily use of sleeping medications during the COVID-19 pandemic. It is known that sleep disturbances and anxiety are bidirectionally associated,[33] and this association was expectedly evident during the early stages of the pandemic.[34] Stressful life events, such as the COVID-19 pandemic, which threaten one’s psychological and physical well-being are likely to cause increased sleep disturbances in the population.[35] Indeed, sleep problems have been highly prevalent during COVID-19, with approximately 40% of the general population reporting poor sleep quality in the early stages of the pandemic.[36] The confinement period during the

pandemic has led to changes in social and environmental cues important for circadian rhythms and the sleep-wake cycle, including the lack of fixed schedules for working, eating, exercising, socializing, and similar daily routines.[35] Changes in the sleep-wake cycle can result in desynchronization between the circadian rhythm and important immune functions, which can affect a person's physical and mental well-being.[35,37] In particular, reduced sleep quality was associated with higher levels of depression and anxiety symptoms early on during the COVID-19 lockdown in Italy.[38] Similarly, our findings indicate that sleep disturbances may be the most important factor in predicting presence of anxiety in the general population in different countries during the COVID-19 pandemic. Additionally, perception of work-life balance, meaning of life, and consumption of fast food were other variables from the SMILE scale related to the presence of anxiety, corresponding with previous studies indicating associations between these variables and anxiety.[39-41]

Findings from our study could have essential clinical implications for clinical professionals and researchers around the world. Considering the effectiveness of our models across different countries, the method developed could be adapted and used across a vast number of countries, especially when countries are in similar situations such as during the global COVID-19 pandemic. In addition, to our knowledge, this is the first study using machine learning methods to predict which lifestyle behaviours are able to accurately indicate positive screening for depression and anxiety, two of the most common mental disorders globally. Observing the most prevalent lifestyle behaviours among people with depression and anxiety using this model could be the first step

towards creating a protocol of targeted interventions addressing unhealthy lifestyle behaviours that increase the likelihood of presence of these symptoms, such as sleep hygiene.

The main limitation of our study is the cross-sectional design. Considering that the lifestyle behaviours (predictors) and the presence of depression/anxiety symptoms (outcomes) were assessed at the same point in time, inference of a causal relationship between the variables is limited. Instead, it depicts a snapshot of a very dynamic process (comprising both the dynamics of the epidemic itself and how people cope with the challenges it poses over time). Furthermore, it is important to highlight that presence of anxiety and depression was assessed using a screening test, and replication of this data assessing them using a structured, albeit much more labor-intensive, clinical interview is encouraged. There are also limitations regarding the lack of fine-tuning of the model for the Brazilian sample; although we showed that the model performs similarly in both countries, the model was not further trained on a subset of Brazilian data, which could potentially improve the model for that sample. In contrast, a major advantage of this study is the consistency in performance metrics across three highly reliable machine learning methods for development of predictive models, which also achieved high AUC-ROC values for the internal and external tests. In addition, another major advantage is that the trained sample of the model was from Spain, one of the first countries affected by the pandemic, which was then tested in Brazil, where the epidemic started at a later period. This is an encouraging sign for development of prevention guides using this model. Lastly, the findings from this paper are in accordance with previous research

indicating important mental health burdens related to lifestyle behaviours, especially during the COVID-19 pandemic.

Implications from this study could be highly significant in the approach towards developing targeted approaches to promote healthy lifestyles that might help reducing the burden of common mental disorders.

2.5 Acknowledgments

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2.6 Declaration of conflicting interests

MS, PLB, JCM, RBDB, BAC, FIB, TAC, BNF, LM: None.

VBM has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini; Ferrer; Lundbeck; Nutrición Médica; and Otsuka.

FK has been a consultant for Janssen - Johnson & Johnson, and reports grants from INCT-CNPq/ Brazil and Canada Foundation for Innovation.

2.7 References

1. Xiong J, Lipsitz O, Nasri F, Lui LM, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. J Affect Disord. 2020;

2. Balanzá–Martínez V, Atienza–Carbonell B, Kapczinski F, De Boni RB. Lifestyle behaviours during the COVID-19–time to connect. Wiley Online Library; 2020.

3. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020;288:112954.

4. Mazza C, Ricci E, Biondi S, Colasanti M, Ferracuti S, Napoli C, et al. A nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: immediate psychological responses and associated factors. Int J Environ Res Public Health. 2020;17(9):3165.

5. Sønderskov KM, Dinesen PT, Santini ZI, Østergaard SD. The depressive state of Denmark during the COVID-19 pandemic. Acta Neuropsychiatr. 2020;32(4):226–8.

6. Ozamiz-Etxebarria N, Dosil-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. Cad Saude Publica. 2020;36:e00054020.

7. Serafim A de P, Goncalves PD, Rocca CC, Lotufo Neto F. The impact of COVID-19 on Brazilian mental health through vicarious traumatization. Braz J Psychiatry. 2020;(AHEAD).

8. González-Sanguino C, Ausín B, Castellanos MÁ, Saiz J, López-Gómez A, Ugidos C, et al. Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain. Brain Behav Immun. 2020;87:172–6.

9. Rodríguez-Rey R, Garrido-Hernansaiz H, Collado S. Psychological impact and associated factors during the initial stage of the coronavirus (COVID-19) pandemic among the general population in Spain. Front Psychol. 2020;11:1540.

10. Goularte JF, Serafim SD, Colombo R, Hogg B, Caldieraro MA, Rosa AR. COVID-19 and mental health in Brazil: psychiatric symptoms in the general population. J Psychiatr Res. 2021;132:32–7.

11. Gonçalves AP, Zuanazzi AC, Salvador AP, Jaloto A, Pianowski G, Carvalho L de F. Preliminary findings on the associations between mental health indicators and social isolation during the COVID-19 pandemic. Arch Psychiatry Psychother. 2020;22(2):10–9.

12. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry. 2019;6(8):675–712.

13. Jacka FN, Berk M. Depression, diet and exercise. Med J Aust. 2013;199(6):S21–3.

14. Alpaydin E. Introduction to machine learning. MIT press; 2020.

15. Balanzá-Martínez V, Kapczinski F, de Azevedo Cardoso T, Atienza-Carbonell B, Rosa AR, Mota JC, et al. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. Rev Psiquiatr Salud Ment. 2021;14(1):16–26.

16. De Boni RB, Balanzá-Martínez V, Mota JC, Cardoso TDA, Ballester P, Atienza-Carbonell B, et al. Depression, Anxiety, and Lifestyle Among Essential Workers: A Web Survey From Brazil and Spain During the COVID-19 Pandemic. J Med Internet Res. 2020;22(10):e22835.

17. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care. 2003;1284–92.

18. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7.

19. Kuhn M. Building predictive models in R using the caret package. J Stat Softw. 2008;28(5):1–26.

20. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Stat Soc Ser B Stat Methodol. 2005;67(2):301–20.

21. Biau G, Scornet E. A random forest guided tour. Test. 2016;25(2):197–227.

22. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. In: Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining. 2016. p. 785–94.

23. Cabello M, Miret M, Caballero FF, Chatterji S, Naidoo N, Kowal P, et al. The role of unhealthy lifestyles in the incidence and persistence of depression: a longitudinal general population study in four emerging countries. Glob Health. 2017;13(1):1–8.

24. Lotfaliany M, Hoare E, Jacka FN, Kowal P, Berk M, Mohebbi M. Variation in the prevalence of depression and patterns of association, sociodemographic and lifestyle factors in community-dwelling older adults in six low-and middle-income countries. J Affect Disord. 2019;251:218–26.

25. Barzilay R, Moore TM, Greenberg DM, DiDomenico GE, Brown LA, White LK, et al. Resilience, COVID-19-related stress, anxiety and depression during the pandemic in a large population enriched for healthcare providers. Transl Psychiatry. 2020;10(1):1–8.

26. Salari N, Hosseinian-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Glob Health. 2020;16(1):1–11.

27. Hedayati MM, Khazaei MM. An investigation of the relationship between depression, meaning in life and adult hope. Procedia-Soc Behav Sci. 2014;114:598–601.

28. Steger MF, Mann JR, Michels P, Cooper TC. Meaning in life, anxiety, depression, and general health among smoking cessation patients. J Psychosom Res. 2009;67(4):353–8.

29. Derdikman-Eiron R, Indredavik MS, Bratberg GH, Taraldsen G, Bakken IJ, Colton M. Gender differences in subjective well-being, self-esteem and psychosocial functioning in adolescents with symptoms of anxiety and depression: Findings from the Nord-Trøndelag health study. Scand J Psychol. 2011;52(3):261–7.

30. Perna L, Zhang Y, Matias-Garcia PR, Ladwig K-H, Wiechmann T, Wild B, et al. Subjective mental health, incidence of depressive symptoms in later life, and the role of epigenetics: results from two longitudinal cohort studies. Transl Psychiatry. 2020;10(1):1–8.

31. Augner C. Associations of subjective sleep quality with depression score, anxiety, physical symptoms and sleep onset latency in young students. Cent Eur J Public Health. 2011;19(2):115–7.

32. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 2008;10(3):329.

33. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep. 2013;36(7):1059–68.

34. Sher L. COVID-19, anxiety, sleep disturbances and suicide. Sleep Med. 2020;

35. Morin CM, Carrier J, Bastien C, Godbout R. Sleep and circadian rhythm in response to the COVID-19 pandemic. Can J Public Health. 2020;111(5):654–7.

36. Jahrami H, BaHammam AS, Bragazzi NL, Saif Z, Faris M, Vitiello MV. Sleep problems during the COVID-19 pandemic by population: a systematic review and meta-analysis. J Clin Sleep Med. 2021;17(2):299–313.

37. Bryson WJ. Circadian rhythm sleep-wake disorders and the COVID-19 pandemic. J Clin Sleep Med. 2020;16(8):1423–1423.

38. Cellini N, Canale N, Mioni G, Costa S. Changes in sleep pattern, sense of time and digital media use during COVID-19 lockdown in Italy. J Sleep Res. 2020;29(4):e13074.

39. Bakhtiyari M, Ehrampoush E, Enayati N, Joodi G, Sadr S, Delpisheh A, et al. Anxiety as a consequence of modern dietary pattern in adults in Tehran—Iran. Eat Behav. 2013;14(2):107–12.

40. Sprung JM, Rogers A. Work-life balance as a predictor of college student anxiety and depression. J Am Coll Health. 2020;1–8.

41. Yek MH, Olendzki N, Kekecs Z, Patterson V, Elkins G. Presence of meaning in life and search for meaning in life and relationship to health anxiety. Psychol Rep. 2017;120(3):383–90.

2.8 Figures and Tables

Figure 1. Results for depression and anxiety by training with the Spain sample and testing it in the Spain internal set and the Brazil external set:

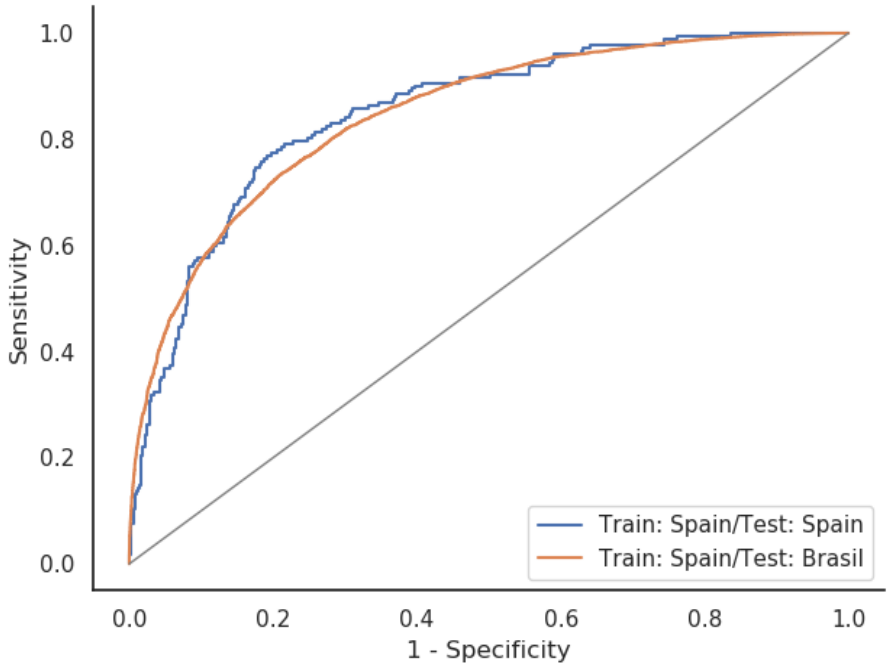


Figure 1A: ROC curves of the internal (AUC-ROC = 0.85) and external (AUC-ROC = 0.85) tests for presence of depression.

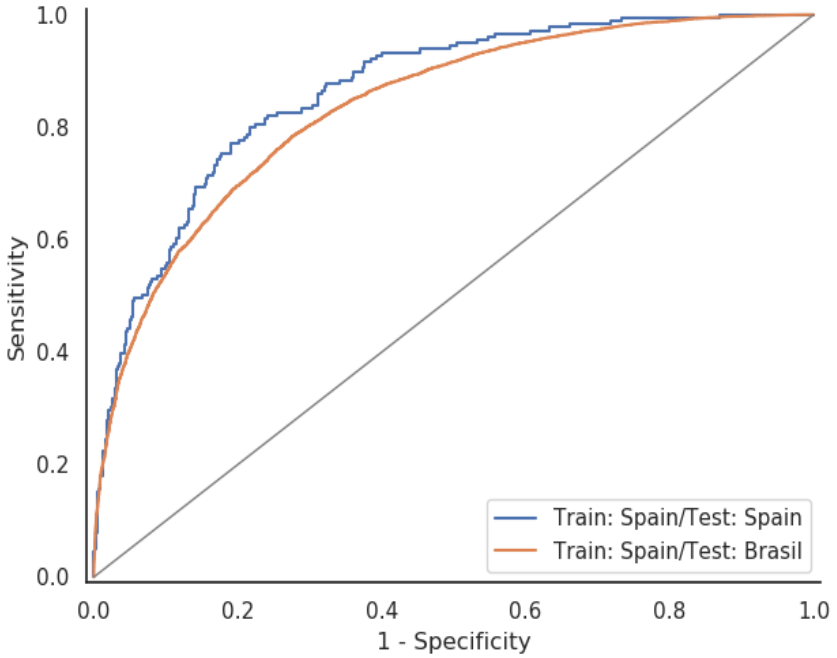


Figure 1B: ROC curves of internal (AUC-ROC = 0.86) and external (AUC-ROC = 0.84) tests for presence of anxiety.

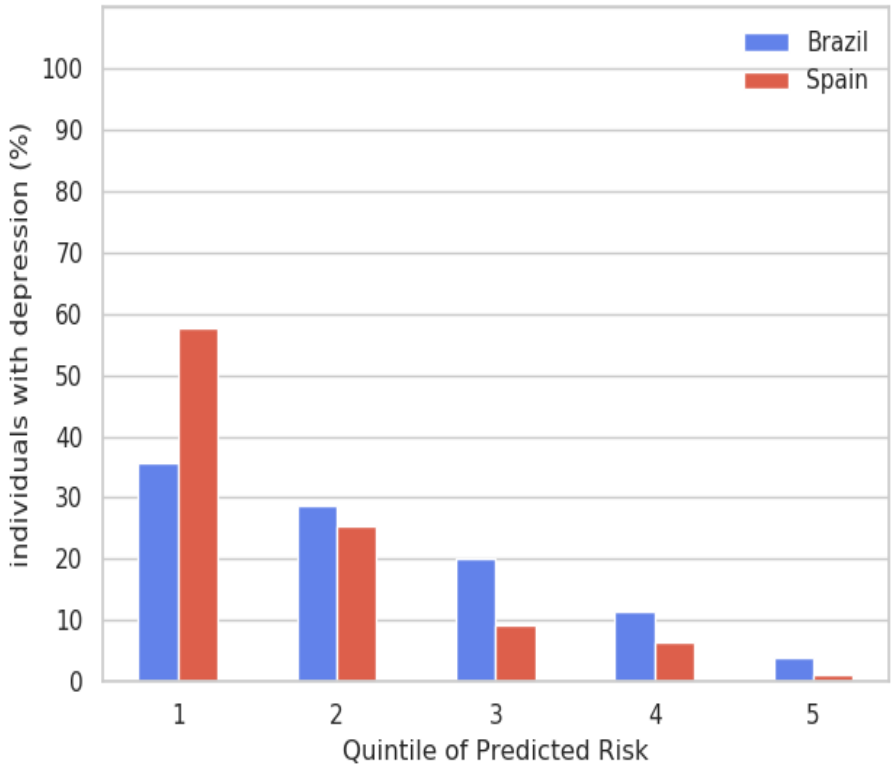


Figure 1C: Percentage of individuals with symptoms of depression by defined quintiles of predicted risk;

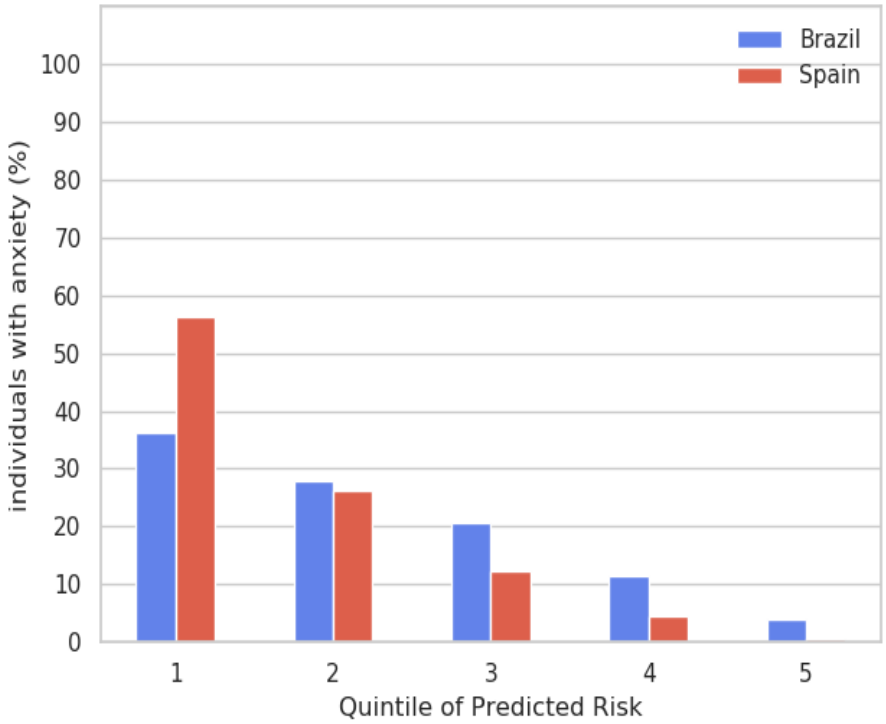
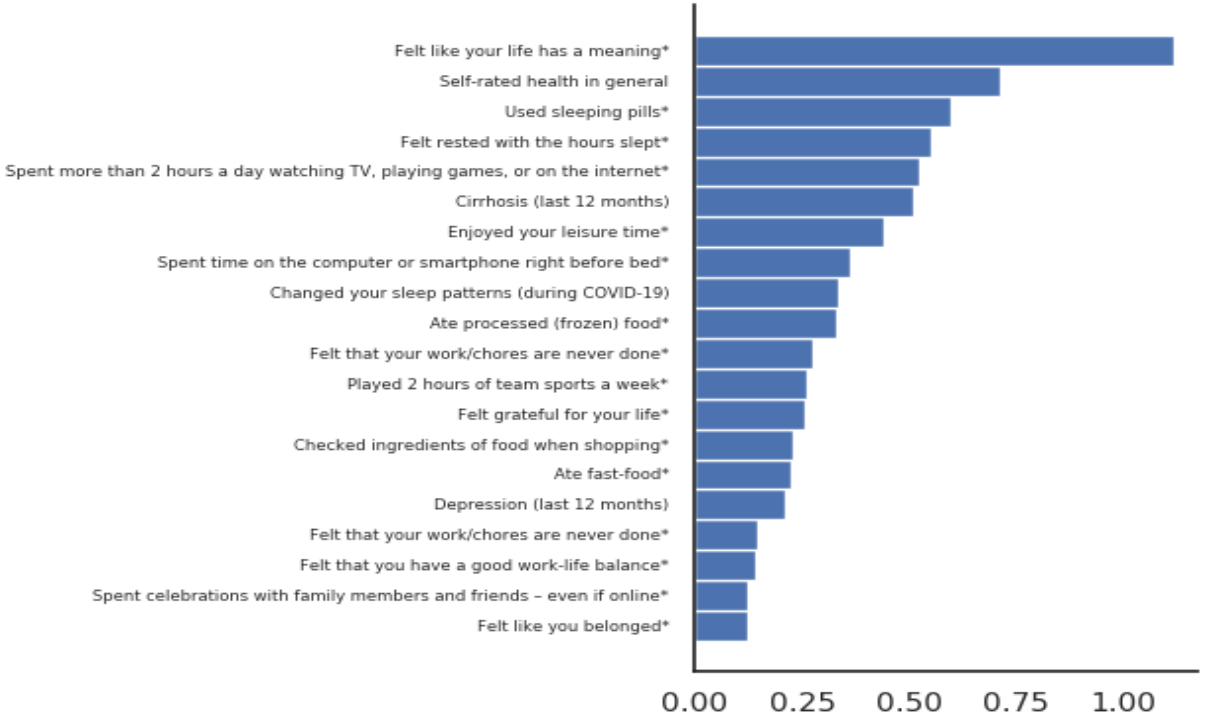


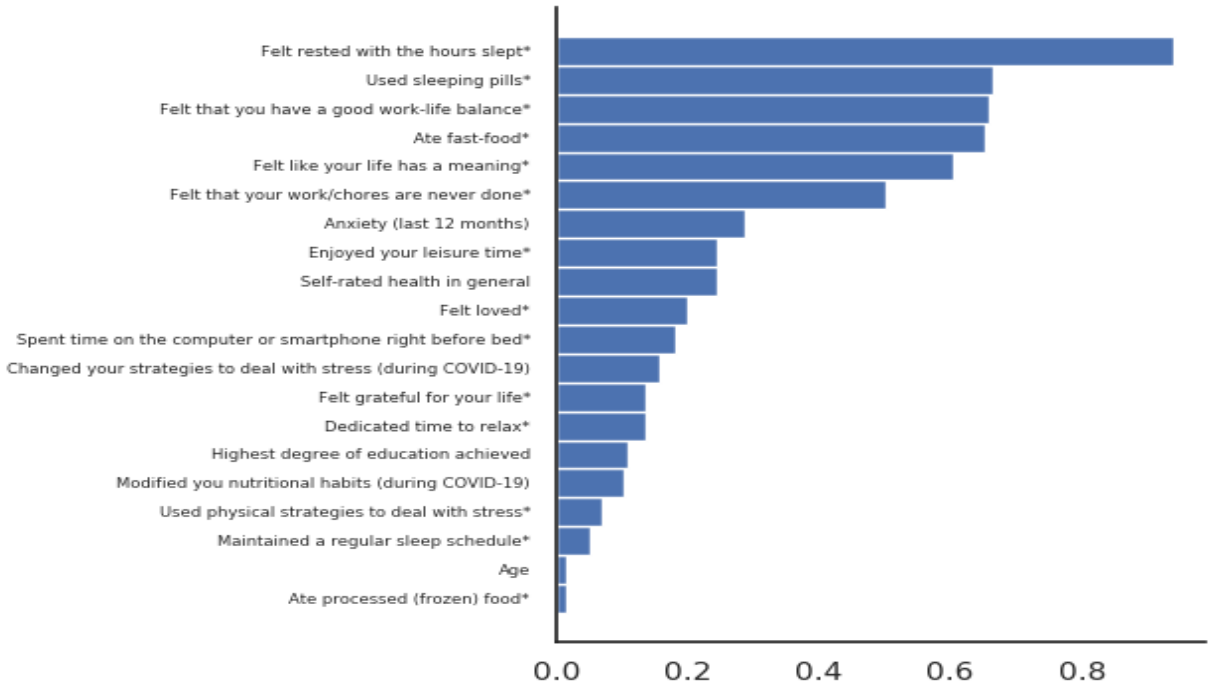
Figure 1D: Percentage of individuals with symptoms of anxiety by defined quintiles of predicted risk.

Figure 2. Importance of different variables as predictors of depression and anxiety according to the Spain sample.



* Indicates in the last 30 days.

Figure 2A: Predictors of depression.



* Indicates in the last 30 days.

Figure 2B: Predictors of anxiety.

Table 1: Sociodemographic and clinical variables in the Brazilian and Spanish samples based on presence of depression.

		Brazil			Spain		
		Depression			Depression		
	N=22562	Yes (9816)	No (9253)	p-value	Yes (728)	No (2765)	p-value
Sex				<0.001			<0.001
Female	15379	6930 (70.6%)	6064 (65.5%)		537 (73.8%)	1848 (66.8%)	
Male	7183	2886 (29.4%)	3189 (34.5%)		191 (26.2%)	917 (33.2%)	
Age				<0.001			<0.001
18-41	13687	7466 (76.1%)	4337 (46.9%)		514 (70.6%)	1370 (49.5%)	
42 or more	8875	2350 (23.9%)	4916 (53.1%)		214 (29.4%)	1395 (50.5%)	
Educational Attainment				<0.001			<0.001
Fundamental/High School	5749	2945 (30.0%)	1601 (17.3%)		328 (45.1%)	875 (31.6%)	
University	11463	4988 (50.8%)	5073 (54.8%)		258 (35.4%)	1144 (41.4%)	
Graduate School	5349	1883 (19.2%)	2578 (27.9%)		142 (19.5%)	746 (27.0%)	
People in the household				<0.001			0.151
1	2856	1169 (11.9%)	1335 (14.4%)		71 (9.8%)	281 (10.2%)	
2 or 3	12976	5641 (57.6%)	5408 (58.5%)		382 (52.5%)	1545 (56.0%)	
4 to 9	6695	2988 (30.5%)	2499 (27.0%)		274 (37.7%)	934 (33.8%)	
Working				<0.001			<0.001
No	8653	4043 (41.2%)	3201 (34.6%)		389 (53.4%)	1020 (36.9%)	
Yes	13135	5336 (54.4%)	5900 (63.8%)		286 (39.3%)	1613 (58.3%)	
Lost job during the pandemic	774	437 (4.5%)	152 (1.6%)		53 (7.3%)	132 (4.8%)	
Essential worker (Yes)	3717	1193 (22.4%)	1626(27.6%)	<0.001	135 (47.2%)	763 (47.3%)	0.975
Frontline worker (Yes)	1266	369 (30.9%)	443 (27.2%)	0.033	73 (54.1%)	381 (49.9%)	0.375
Studying (Yes)	3508	1930(47.6%)	888 (27.7%)	<0.001	250 (64.1%)	440 (42.8%)	<0.001

Self-isolated (Yes)	17388	8260 (84.8%)	7459 (81.1%)	<0.001	408 (56.7%)	1261 (45.9%)	<0.001
Diagnosed with COVID-19	215	80 (0.8%)	69 (0.7%)	0.587	18 (2.5%)	48 (1.7%)	0.196
Lost someone in the pandemic (Yes)	1724	771 (7.9%)	617 (6.7%)	0.002	60 (8.3%)	276 (10.0%)	0.161
Chronic disease*	6958	3009 (30.9%)	3002 (32.6%)	0.009	220 (30.5%)	727 (26.5%)	0.032
Mental Health Disorder*	7070	4386 (46.3%)	2126 (23.2%)	<0.001	224 (32.0%)	334 (12.2%)	<0.001
Infectious Disease*	762	439 (4.5%)	310 (3.4%)	<0.001	4 (0.6%)	9 (0.3%)	0.373
Depression Diagnosis*	3884	2672 (28.0%)	944 (10.3%)	<0.001	135 (19.1%)	133 (4.8%)	<0.001
Anxiety Diagnosis*	6451	4059 (42.7%)	1885 (20.6%)	<0.001	205 (29.0%)	302 (11.0%)	<0.001
Alcohol Abuse	19257	4811 (48.7%)	3976 (42.4%)	<0.001	234 (32.0%)	855 (30.6%)	0.469
Self-rated health (Good/Very good)	16323	5953 (60.7%)	7863 (85.0%)	<0.001	363 (50.1%)	2144 (77.4%)	<0.001
SMILE (Mean, standard deviation)	15822	115.6 (12.3)	105.4 (11.6)	<0.001	114.5 (11.1)	106.2 (10.3)	<0.001

* = Yes, diagnosed within the last 12 months

Table 2: Sociodemographic and clinical variables in the Brazilian and Spanish samples based on presence of anxiety.

		Brazil			Spain		
		Anxiety			Anxiety		
	N=22355	Yes (9400)	No (9492)	p-value	Yes (716)	No (2747)	p-value
Sex				<0.001			<0.001
Female	15192	6789 (72.2%)	6045 (63.7%)		537 (75.0%)	1821 (66.3%)	
Male	7163	2611 (27.8%)	3447 (36.3%)		179 (25.0%)	926 (33.7%)	
Age				<0.001			<0.001
18-41	13592	6970 (74.1%)	4750 (50.0%)		502 (70.1%)	1370 (49.9%)	
42 or more	8763	2430 (25.9%)	4742 (50.0%)		214 (29.9%)	1377 (50.1%)	
Educational Attainment				<0.001			<0.001
Fundamental/High School	5667	2674 (28.4%)	1804 (19.0%)		295 (41.2%)	894 (32.5%)	
University	11365	4796 (51.0%)	5178 (54.6%)		275 (38.4%)	1116 (40.6%)	
Graduate School	5322	1930 (20.5%)	2509 (26.4%)		146 (20.4%)	737 (26.8%)	
People in the household				<0.001			<0.001
1	2804	992 (10.6%)	1466 (15.6%)		50 (7.0%)	296 (10.8%)	
2 or 3	12889	5448 (58.1%)	5528 (58.3%)		372 (52.0%)	1541 (56.2%)	
4 to 9	6626	2945 (31.4%)	2483 (26.2%)		294 (41.0%)	904 (33.0%)	
Working				<0.001			<0.001
No	8520	3645 (38.8%)	3485 (36.7%)		352 (49.2%)	1038 (37.8%)	
Yes	13066	5355 (57.0%)	5822 (61.3%)		313 (43.7%)	1576 (57.4%)	
Lost job during the pandemic	769	400 (4.3%)	185 (1.9%)		51 (7.1%)	133 (4.8%)	
Essential worker (Yes)	3692	1281 (23.9%)	1518 (26.1%)	0.009	160 (51.1%)	733 (46.5%)	0.136
Frontline worker (Yes)	1257	441 (34.4%)	365 (24.0%)	<0.001	88 (55.0%)	363 (49.5%)	0.209
Studying (Yes)	3459	1688 (46.2%)	1087 (31.2%)	<0.001	235 (66.4%)	449 (42.9%)	<0.001
Self-isolated (Yes)	17220	7810 (83.7%)	7759 (82.2%)	0.007	365 (51.6%)	1286 (47.1%)	0.033

Diagnosed with COVID-19	212	83 (0.9%)	65 (0.7%)	0.122	23 (3.2%)	41 (1.5%)	0.002
Lost someone in the pandemic (Yes)	1712	782 (8.3%)	596 (6.3%)	<0.001	65 (9.2%)	269 (9.8%)	0.593
Chronic disease*	6886	2991 (32.1%)	2956 (31.3%)	0.254	225 (31.8%)	714 (26.2%)	0.003
Mental Health Disorder*	6987	4433 (48.8%)	2005 (21.4%)	<0.001	247 (36.0%)	302 (11.1%)	<0.001
Infectious disease*	751	420 (4.5%)	319 (3.4%)	<0.001	5 (0.7%)	7 (0.3%)	0.071
Depression Diagnosis*	3836	2564 (28.0%)	1006 (10.7%)	<0.001	133 (19.3%)	133 (4.9%)	<0.001
Anxiety Diagnosis*	6379	4176 (45.9%)	1702 (18.1%)	<0.001	233 (33.7%)	268 (9.8%)	<0.001
Alcohol Abuse	19257	4670 (48.7%)	4117 (42.6%)	<0.001	218 (30.1%)	871 (31.1%)	0.602
Self-rated health (Good/Very good)	16203	5710 (60.8%)	8000 (84.3%)	<0.001	376 (52.7%)	2117 (77.2%)	<0.001
SMILE (Mean, standard deviation)	15822	115.0 (12.6)	106.3 (11.9)	<0.001	114.0 (11.2)	106.4 (10.4)	<0.001

* = Yes, diagnosed within the last 12 months

Table 3. Performance metrics presented based on the results of 3 different models. Results for Spain represent the internal test set results, while those for Brazil are the external set results.

	Test Spain			***Test Brazil***		
Metric	**Elastic net**	**RF**	**XGB**	**Elastic net**	**RF**	**XGB**
Depression						
Balanced accuracy	0.79	0.78	0.77	0.76	0.76	0.76
Sensitivity	0.78	0.74	0.74	0.74	0.74	0.75
Specificity	0.79	0.81	0.80	0.78	0.79	0.77
PPV	0.49	0.51	0.49	0.78	0.79	0.77
NPV	0.93	0.92	0.92	0.74	0.74	0.74
Anxiety						
Balanced accuracy	0.78	0.78	0.77	0.75	0.74	0.75
Sensitivity	0.78	0.78	0.77	0.73	0.78	0.74
Specificity	0.79	0.78	0.78	0.77	0.71	0.77
PPV	0.49	0.48	0.48	0.76	0.73	0.76
NPV	0.93	0.93	0.93	0.74	0.76	0.75

Legend: RF: Random Forest; XGB: XGBoost; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

Chapter 3: Lifestyle behaviours, depression, and anxiety among individuals living in Canada during the COVID-19 pandemic

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Abstract

Objective: The aim of our study was to investigate the association between lifestyle behaviours and symptoms of depression and anxiety during the COVID-19 pandemic in Canada.

Methods: A web survey was conducted between July 3-August 3, 2020, across Canada. The main outcomes considered were a positive screening for depression, as evaluated by the PHQ-2 and positive screening for anxiety, as evaluated by the GAD-7. Lifestyle behaviours were assessed using the Short Multidimensional Lifestyle Inventory Evaluation – Confinement (SMILE-C), an instrument adapted for lifestyle behaviours during the COVID-19 pandemic.

Results: The total sample size included 404 participants, of which 24.3% had a positive screen for depression, 20.5% for anxiety, and 15.5% for both. We found significant differences in SMILE-C scores between individuals with a positive and individuals with a negative screen for depression ($p<0.001$). Likewise, there were significant differences in SMILE-C scores between individuals with a positive and individuals with a negative screen for anxiety ($p<0.001$).

Discussion: We found an association between unhealthy lifestyle behaviours and symptoms of depression and anxiety during the COVID-19 lockdown in Canada. The findings highlight the importance of lifestyle medicine education and targeted lifestyle interventions to promote healthy behaviours and help reduce the burden of mental disorders.

Keywords: Mental Health; SMILE-C; Lockdown; Pandemic; North America; Lifestyle Medicine;

3.1 Introduction

The global coronavirus disease 2019 (COVID-19) pandemic has taken a toll on the mental well-being of individuals from various regions in the world. The unpredictable longevity of the pandemic has forced many countries to apply various restrictions on everyday activities for their citizens, including Canada.[1] Since the onset of the COVID-19 pandemic, people have been advised to limit in-person social interactions and adjust their day-to-day routines in order to contain the spread of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. In addition to the documented physical health consequences of the virus, the sudden lifestyle changes have resulted in rising uncertainty, fear, stress, and higher levels of mental health challenges among the general population.[2] During this time, online tools and web surveys have been widely used to collect data and investigate the psychological well-being of the general population.[3,4] Among the most pronounced mental health challenges are the increased prevalence of depression and anxiety, with recent reports combining data from multiple countries indicating symptoms of anxiety in 31.9% and symptoms of depression in 33.7% of the general population.[5,6]

As in other countries, people in Canada have also been affected by the COVID-19 pandemic in this sense; the percentage of high anxiety among Canadians has quadrupled (5% to 20%), while the percentage of severe symptoms of depression has more than doubled during this period (4% to 10%).[7] Another study in Canada reported very high prevalence of symptoms of anxiety (47.2%) and depression (44.1%),[8] demonstrating the serious level of concern in Canada and beyond. In addition, the high mental health burden

is significantly present among some of the most overwhelmed essential workers in Canada, critical care nurses, with 57% of them reporting mild to severe symptoms of depression, and 67% reporting mild to severe symptoms of anxiety.[9]

Seeking to contain the transmission of the SARS-CoV-2 virus, many people had to change their everyday routines and lifestyles relative to before the onset of the pandemic. Diet, physical activity, sleep, substance use, and many other essential lifestyle behaviours are strongly linked to symptoms of common mental disorders, such as depression and anxiety.[10–12] In accordance with surges of COVID-19, the provincial governments of Canada have continuously adjusted the lockdown measures required to contain the spread of the virus since March of 2020. The restrictive measures put in place have led to Canadians becoming less physically active, having more sleep difficulties, fewer social interactions, and other negative lifestyle changes detrimental to physical and psychological well-being.[7,13,14] The relationship between these factors with mental health symptoms and disorders has been further emphasized during the COVID-19 pandemic, with the home-confinement measures introduced around the world leading to lifestyle changes in North Africa, Western Asia, and Europe.[15,16] The urgency to suddenly change many aspects of these lifestyle behaviours has led to serious negative impacts on people's overall mental well-being. In Brazil, a study found a positive association between the presence of psychological symptoms (e.g., depression, anxiety, stress) and social isolation variables (e.g., days of isolation, loneliness, social distancing) adopted for containment of the wide-spreading virus.[17] Furthermore, unhealthy lifestyle patterns

during COVID-19 were found to increase the likelihood of depression and anxiety among essential workers in Brazil and Spain.[18]

The significant focus on different lifestyle behaviours during this period stems from the scope of Lifestyle Medicine (LM), an area of medicine that studies how daily habits and behaviours impact short and long-term health and quality of life, and uses evidence-based approaches to prevent and treat the progression of chronic diseases.[19,20] According to the American College of Lifestyle Medicine, LM is particularly focused on six lifestyle domains: diet, physical activity, avoiding substance use, sleep, social relationships, and stress management.[21] These domains are deemed to be 'modifiable factors', meaning, targeting prevention or improvement of unhealthy daily lifestyle behaviours could help in reducing the risk for development of poor mental health and other chronic diseases.[19,22] Maintaining a healthy lifestyle can be a protective factor for many physical and mental health challenges, especially during times of adversity, such as the COVID-19 pandemic.

Although recent studies have reported increased prevalence of depression and anxiety in Canada during the pandemic, the role of unhealthy lifestyle habits on people's mental well-being, associated with the changes in daily routines during this period, has not been investigated. In this sense, the aim of this study was to examine the association between several lifestyle behaviours and the presence of symptoms of depression and anxiety during the COVID-19 pandemic in a Canadian sample.

3.2 Methods

3.2.1 Study Design:

A cross-sectional web survey was conducted from July 3 to August 3, 2020, across all regions in Canada. The web survey was created using SurveyGizmo®,[23] and included questions regarding demographics, COVID-19 experience, lifestyle behaviours, substance use, self-rated health status and previously diagnosed conditions, as well as current symptoms of depression and anxiety. The usability and technical functionality of the survey were tested prior to the start of recruitment.

3.2.2 Ethical Aspects:

The study was approved by the Hamilton Integrated Research Ethics Board (HiREB) under protocol #10870.

3.2.3 Study Population and Recruitment:

A convenience sample of individuals living in Canada that were 18 and older, had access to the internet, and agreed to participate in the study after reviewing the informed consent form, was recruited to complete the web survey. The weblink to the online survey was available on a Facebook page (fb.me/lifestyleandcovid19) created for this project. Advertising boost to promote the questionnaire was prepared using multiple key words (i.e., healthy lifestyles, sad, happiness, fear, physical exercise, stress, well-being etc.). In addition, the study was shared through other social media outlets, such as Instagram (instagram.com/lifestyleandcovid19), Twitter (twitter.com/LifestyleCovid), WhatsApp, and email. Individuals who reported they had already previously completed the online questionnaire were excluded.

3.2.4 Independent Variables:

Demographic information included questions regarding sex, age, educational level, number of people living in the household, current studying and current working status (essential/frontline worker). Age groups were dichotomized according to the median age of the sample (62) into age groups 18-61 and 62 and over.

Questions related to COVID-19 experience included 'Have you been under quarantine (self-isolation) due to the COVID-19 outbreak?', 'Did a health professional formally diagnose you with COVID-19?' and 'Have you lost a significant one during the COVID-19 pandemic?' Possible answers were yes/no.

Lifestyle behaviours were assessed using the Short Multidimensional Inventory Lifestyle Evaluation – Confinement (SMILE-C), which assesses the extent of one's healthy lifestyle behaviours during the previous 30 days.[24] The SMILE-C scale is comprised of 27 items evaluating 7 different lifestyle domains: Diet and Nutrition, Substance abuse, Physical activity, Stress management, Restorative sleep, Social support, and Environmental exposures. Response options are measured on a 4-point Likert scale (always, often, seldom, never), resulting in a maximum possible score of 108. Higher scores indicated healthier lifestyle patterns. After the questions of each domain, an additional question exploring the perceived change in lifestyle patterns during the pandemic as compared to previous, regular behaviours of participants, was added, with possible answer choices of 'Completely', 'Moderately', 'Slightly', and 'Not at all'. For the purposes of statistical analysis, the responses 'Completely' and 'Moderately' were combined as a 'Yes' answer, and the responses 'Slightly' and 'Not at all' were combined

as a ‘No’ answer. The additional questions regarding change in lifestyle patterns during the pandemic were not included as part of the SMILE-C assessment or the SMILE-C scoring; they were considered as individual and independent questions in addition to the assessment. Self-rated health (SRH) was evaluated using the question `How would you rate your health in general?’, with possible answer choices of ‘Very bad`, ‘Bad’, ‘Regular’, ‘Good’ and ‘Very good'. The responses ‘Good’ and ‘Very Good’ were combined for the analysis.

Previously diagnosed conditions were assessed using the question ‘In the last 12 months, have you been diagnosed by a medical doctor or health professional, or received treatment for any of the following conditions?’ The investigated health problems were combined into chronic diseases, mental health disorders, and infectious diseases. History of chronic diseases included a diagnosis or treatment in the past 12 months of any one or more of the following: diabetes, heart disease, hypertension, asthma, anemia, bronchitis, cancer, cirrhosis, and renal disease. Positive mental health disorders screening included a diagnosis or treatment of depression, anxiety, schizophrenia, bipolar disorder, and/or anorexia/bulimia nervosa. For infectious diseases, we combined cases of participants diagnosed or treated for HIV/AIDS and/or tuberculosis in the past 12 months.

3.2.5 Outcomes:

Two outcomes were considered: positive screening for depression and positive screening for anxiety. Depression was screened using the Patient Health Questionnaire-2 (PHQ-2; cut-off ≥ 3), and anxiety was screened using the Generalized Anxiety Disorder 7-item (GAD-7; cut-off≥10).

3.2.6 Statistical Analysis:

The statistical analysis was conducted using the IBM® SPSS® 27.[25] All variables, with the exception of SMILE-C scores, were categorized and analyzed using chi-square tests between the respective outcome groups. In addition, we calculated the prevalence ratio (PR) for the significant associations between independent factors and symptoms of depression and anxiety using Epi Info™. Due to the normal distribution of SMILE-C scores, the groups were compared using a student t-test for independent samples. Box plot graphs of the analyses were created using Prisma GraphPad 6.0. Then, multivariate logistic regression analyses were performed to reach the final models for depression and anxiety screening as the two outcomes of interest. The analyses included as independent factors those variables that presented an association of $p<0.20$ in the bivariate analysis. The final models were reached using a manual stepwise removal of each non-statistically significant variable. Statistical significance was set at $p<0.05$.

3.3 Results

A total of 471 participants completed the online web survey. Of those, 62 participants were excluded because they had already completed the survey previously, 3 participants were excluded because they lived outside of Canada, and 2 participants were excluded for being under the age of 18. The final sample size included 404 participants, of which most were female (83.9%), with median age of 62 (IQR: 50 – 69), had a college/university diploma (76.8%), and were currently unemployed (63.9%). The sample characteristics are described in Table 1.

The prevalence of positive screenings among the total sample was 24.3% for depression and 20.5% for anxiety, while 15.5% of the sample had positive screenings for both depression and anxiety. Table 2 describes the sociodemographic and clinical characteristics of the sample across the groups of screening for depression. There was an association between age and symptoms of depression in our sample ($p<0.001$), where individuals aged 18-61 years old were 2.21 times (PR: 2.21 [95% CI: 1.51 - 3.22]) more likely to present symptoms of depression than older individuals (62 years old or older). There was also a statistically significant association between employment status and screening for depression in our sample ($p=0.006$). We conducted an additional analysis comparing individuals who were currently working and those not working, and found that people currently working were 1.63 times (PR: 1.63 [95% CI: 1.14 - 2.33]) more likely to present symptoms of depression than people that were not working ($p=0.008$). Moreover, when comparing individuals who had lost their job during the pandemic with people currently not working, we found that people who had lost their job during the pandemic were 2.17 times (PR: 2.17 [95%CI: 1.21 - 3.90]) more likely to have symptoms of depression than people that were not working ($p=0.019$). There was no difference between groups (positive/negative screening for depression) when comparing people who had lost their job during the pandemic and people that were currently working. There was an association between a previous mental health diagnosis/treatment within the past 12 months and symptoms of depression in our sample ($p<0.001$), where people with a previous diagnosis were 2.15 times (PR: 2.15 [95% CI: 1.53 - 3.03]) more likely to present symptoms of depression than people without a previous mental health diagnosis.

We also found an association between SRH and symptoms of depression (p=0.001), where people that rated their health as bad/very bad were 1.83 times (PR: 1.83 [95% CI: 1.30 - 2.58]) more likely to present symptoms of depression than those who rated it as 'very good/good'. Furthermore, individuals who presented complete or moderate changes in their lifestyle patterns were more likely to present symptoms of depression in comparison to people with slight changes or no changes are all in their patterns. This included changes in dietary patterns (PR: 1.60 [95% CI: 1.13 – 2.25], p=0.008), substance use (PR: 1.97 [95% CI: 1.24 – 3.13], p=0.011), restorative sleep (PR: 1.89 [95% CI: 1.35 – 2.65], p<0.001), and social support (PR: 2.13 [95% CI: 1.47 – 3.09], p<0.001).

Table 3 describes the sociodemographic and clinical characteristics of the sample across the groups of screening for anxiety. Similarly, there was an association between age and symptoms of anxiety in our sample (p<0.001), where individuals aged 18-61 years old were 2.56 times (PR: 2.56 [95% CI: 1.64 - 3.97]) more likely to present symptoms of anxiety than older individuals (62 and over). There was also a statistically significant association between employment status and screening for anxiety in our sample (p=0.022). Additional analyses revealed that when comparing individuals who had lost their job during the pandemic with people currently not working, people who had lost their job during the pandemic were 2.42 times (PR: 2.42 [95% CI: 1.29 - 4.55]) more likely to present symptoms of anxiety than people who were not working (p=0.019). There were no differences between groups (negative/positive screening for anxiety) when comparing people who were currently working and those not working, as well as the

comparison between people who had lost their job during the pandemic and people currently working. There was an association between a previous mental health diagnosis/treatment within the past 12 months and symptoms of anxiety in our sample ($p<0.001$), where people with a previous diagnosis were 3.21 times (PR: 3.21 [95% CI: 2.17 - 4.74]) more likely to present symptoms of anxiety than people without a previous mental health diagnosis. We also found an association between SRH and symptoms of anxiety ($p=0.002$), where people that rated their health as bad/very bad were 1.85 times (PR: 1.85 [95% CI: 1.25 - 2.73]) more likely to present symptoms of anxiety than those who rated it as 'very good/good'. Furthermore, individuals who presented complete or moderate changes in their lifestyle patterns were more likely to present symptoms of anxiety in comparison to people with slight changes or no changes are all in their patterns. This included changes in dietary patterns (PR: 1.55 [95% CI: 1.05 – 2.29], $p=0.029$), restorative sleep (PR: 2.42 [95% CI: 1.66 – 3.54], $p<0.001$), and social support (PR: 1.96 [95% CI: 1.30 – 2.96], $p<0.001$).

Individuals with symptoms of depression showed significantly lower SMILE-C scores (mean: 73.65; S.D. 8.12) as compared to individuals without symptoms of depression (mean: 82.85; S.D. 7.28, $p<0.001$) (Figure 1A). The difference in scores between the groups indicates significantly unhealthier lifestyle behaviours in people with symptoms of depression during the COVID-19 pandemic.

Similarly, participants with symptoms of anxiety also had lower scores in the SMILE-C (mean: 73.63; S.D. 8.25) as compared to participants without symptoms of anxiety (mean: 82.46; S.D. 7.63, $p<0.001$) (Figure 1B). This difference suggests

significantly unhealthier lifestyle behaviours in people with symptoms of anxiety during the COVID-19 confinement period.

Table 4 presents the final multivariate model for depression, while table 5 presents the final multivariate model for anxiety. In the final multivariate models for depression and anxiety, being between the ages of 18-61 was associated with an increased prevalence of depression (adjusted odds ratio (OR): 2.64; 95% CI: 1.46 to 4.76) as well as anxiety (OR: 2.57; 95% CI: 1.34 - 4.94), as compared to individuals aged 62 or older. Furthermore, complete or moderate changes in social support during the pandemic were associated with increased likelihood for both depression (OR: 2.91; 95% CI: 1.61 - 5.24), and anxiety (OR: 2.11; 95% CI: 1.11 - 4.01), as compared to mild or no changes in social support during the pandemic. A mental health diagnosis within the past 12 months increased the likelihood for anxiety (OR: 2.71; 95% CI: 1.45 - 5.05), as did complete or moderate changes in sleep patterns (OR: 2.31; 95% CI: 1.22 to 4.38). Lower SMILE-C scores remained associated with symptoms of depression (OR: 0.86; CI: 0.82 to 0.89) and anxiety (OR: 0.89; CI: 0.85 to 0.92) in the final multivariate models.

3.4 Discussion

To the best of our knowledge, this is the first study indicating an association between lifestyle behaviours and mental health symptoms during the COVID-19 confinement period in Canada, where people with symptoms of depression or anxiety engaged in more unhealthy lifestyle patterns than individuals with a negative screen for these symptoms. Findings from our study are in line with reports previously discussed, highlighting the relationship between different lifestyle domains, such as diet, physical

activity, social relationships, and sleep quality, and symptoms of common mental health problems,[11,26–28] which have been further emphasized during the COVID-19 pandemic around the world.[15,16]

In correspondence to our findings, unhealthy lifestyle changes measured using the SMILE-C scale were also associated with depression and anxiety among essential workers in Brazil and Spain at the early stages of the pandemic.[18] Recent evidence suggests that the bidirectional relationship between lifestyle behaviours and mental health that has emerged during the pandemic will persist over a long period, as overall lifestyle quality worsened among Spanish citizens as the confinement period continued.[29] Findings from our study are in line with these reports, highlighting the association between unhealthy lifestyle behaviours and mental health symptoms during the COVID-19 lockdown in Canada. Generally, adults that had experienced complete or moderate changes in their sleep and social support pattens, and reported overall unhealthier lifestyle behaviours during the confinement period were more likely to present symptoms of depression and anxiety during the COVID-19 pandemic.

Furthermore, our findings suggest an association between some sociodemographic factors and symptoms of depression and anxiety. In our sample, we found that older individuals were less likely to report symptoms of depression and anxiety than younger adults, a trend which has been suggested by reports from other countries during the pandemic.[30,31] It is possible that younger adults have experienced greater changes in their everyday life during the COVID-19 pandemic, leading to psychological distress and feelings of loneliness, while older adults may have had fewer

pandemic-based life disruptions and may be more psychologically resilient in the face of stressful events.[32,33] In addition, we found that individuals who reported changes in their social support during the pandemic were more likely to present with symptoms of depression and anxiety. With the social isolation measures that have been put in place since the onset of the COVID-19 pandemic, many people have experienced loneliness and have had to adjust their social communication methods, leading to elevated levels of mental health symptoms.[33] Indeed, reports from the early stages of the pandemic found an inverse relationship between social support and symptoms of depression and anxiety,[34] highlighting the impact of the isolation measures on the global mental health burden. We also found that individuals who reported changes in their sleep patterns were more likely to present with symptoms of anxiety during the pandemic in Canada. The association between poor sleep quality and anxiety is well-established,[35] and has been documented during the COVID-19 pandemic in Canada and worldwide.[36,37] As the pandemic progresses and affects people around the globe, more resources will be needed to help people with sleep disturbances. Furthermore, individuals with a previous mental health diagnosis or treatment within the past 12 months were more likely to have a positive screen for anxiety at the time of the survey. The ongoing concerns and challenges related to the pandemic, as well as the decline in access to care at the beginning of the pandemic, may have led to more severe psychological impacts in people with pre-existing psychiatric conditions than those without a pre-existing condition.[38] Just as we have seen a rise in the incidence rates of anxiety during the pandemic, individuals with pre-existing

anxiety in Canada have experienced clinically significant worsening of these symptoms, suggesting the need for urgent interventions in this population.[38]

The frequency of unhealthy lifestyle behaviours in this study was detected using the SMILE-C scale, which is an instrument specifically designed to identify unhealthy patterns during the COVID-19 pandemic using a multidimensional approach.[24] The importance of lifestyle domains in relation to mental health has traditionally been evaluated through separate assessments for each individual domain, such as the Food Frequency Questionnaire,[39] International Physical Activity Questionnaire,[40] and the Pittsburgh Sleep Quality Index,[41] to name a few. However, the fast-growing perspective of lifestyle medicine implies that the combined focus on different lifestyle behaviours could have a greater effect on prevention and treatment of psychiatric symptoms and disorders.[42,43] Domains included in the SMILE-C scale are considered to be modifiable factors that have the potential to improve both physical and mental well-being, as well as possibly prevent the onset of common mental health disorders.[44] Considering the sudden, distressing changes of various lifestyle areas during the COVID-19 confinement period, a multidimensional approach to lifestyle assessment could help us better understand the combined effect of various unhealthy behaviours on the appearance of psychological symptoms in the general population.

Findings from this study should be interpreted considering some limitations. The cross-sectional design of the study limits our ability to attribute the symptoms of depression and anxiety to the unhealthy lifestyle behaviours indicated by the SMILE-C. However, an association between these variables is suggested. Also, considering that the

collection of data was completed using a web-survey, and the sample was not probabilistic, any generalization of the results must be made with caution. For instance, our sample consisted predominantly of older adults (median age 62), unemployed individuals, and females, which is not representative of the general population of Canada and could potentially impact the interpretation of the findings. Lastly, the assessment of psychological symptoms was completed using self-report screening tests such as the PHQ-2 and GAD-7; the replication of this data using a structured clinical interview is encouraged.

3.4.1 Conclusion

This is the first study to examine the association between lifestyle behaviours and symptoms of common mental disorders during the COVID-19 pandemic in Canada. Our findings revealed an association between self-reported unhealthy lifestyle behaviours and positive screenings for symptoms of depression and anxiety during the COVID-19 lockdown period in Canada. These findings are concurrent with reports from various parts of the world, further demonstrating the global importance of the relationship between lifestyle and mental health challenges during the COVID-19 pandemic. In addition, the multidimensional approach to lifestyle assessments and treatments is gaining attraction and becoming more frequent along with the field of lifestyle medicine. Unhealthy behaviours in different lifestyle domains tend to cluster and have a cumulative effect on the mental well-being of a person,[45] however, most epidemiological studies to date have considered unhealthy behaviours as independent risk factors of mental health disorders. Therefore, it is important to raise awareness and educate the public, as well as

healthcare providers, on the significance of cumulative, modifiable, lifestyle factors for population mental health, especially during the ongoing pandemic.[46–48] Findings from this study highlight the need for developing targeted approaches to promote healthy lifestyles, which could help in reducing the burden of common mental disorders in Canada and worldwide.

3.5 Declaration of Competing Interest

MS, TAC, BWA, BP, RDB, BF, LM, FK declare no competing interests.

Vicent Balanzá-Martínez has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini, Lundbeck, Nutrición Médica, and Otsuka.

3.6 References

1. Detsky AS, Bogoch II. COVID-19 in Canada: experience and response. *Jama*. Published online 2020.

2. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. *Brain Behav Immun*. 2020;89:531-542.

3. De Boni RB. Web surveys in the time of COVID-19. Published online 2020.

4. Pierce M, Hope H, Ford T, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry*. 2020;7(10):883-892.

5. Salari N, Hosseinian-Far A, Jalali R, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Glob Health*. 2020;16(1):1-11.

6. Liu X, Zhu M, Zhang R, et al. Public mental health problems during COVID-19 pandemic: a large-scale meta-analysis of the evidence. *Transl Psychiatry*. 2021;11(1):1-10.

7. Dozois DJ. Anxiety and depression in Canada during the COVID-19 pandemic: A national survey. *Can Psychol Can*. Published online 2020.

8. Nwachukwu I, Nkire N, Shalaby R, et al. COVID-19 Pandemic: Age-Related Differences in Measures of Stress, Anxiety and Depression in Canada. *Int J Environ Res Public Health*. 2020;17(17):6366.

9. Crowe S, Howard AF, Vanderspank-Wright B, et al. The effect of COVID-19 pandemic on the mental health of Canadian critical care nurses providing patient care during the early phase pandemic: A mixed method study. *Intensive Crit Care Nurs*. 2021;63:102999.

10. Jacka FN, Berk M. Depression, diet and exercise. *Med J Aust*. 2013;199(6):S21-S23.

11. Deslandes A, Moraes H, Ferreira C, et al. Exercise and mental health: many reasons to move. *Neuropsychobiology*. 2009;59(4):191-198.

12. Spoormaker VI, van den Bout J. Depression and anxiety complaints; relations with sleep disturbances. *Eur Psychiatry*. 2005;20(3):243-245.

13. Lesser IA, Nienhuis CP. The impact of COVID-19 on physical activity behaviour and well-being of Canadians. *Int J Environ Res Public Health*. 2020;17(11):3899.

14. Robillard R, Dion K, Pennestri MH, et al. Profiles of sleep changes during the COVID-19 pandemic: Demographic, behavioural and psychological factors. *J Sleep Res*. 2021;30(1):e13231.

15. Ammar A, Trabelsi K, Brach M, et al. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: insights from the ECLB-COVID19 multicentre study. *Biol Sport*. 2021;38(1):9.

16. Giner-Murillo M, Atienza-Carbonell B, Cervera-Martínez J, et al. Lifestyle in undergraduate students and demographically matched controls during the COVID-19 pandemic in Spain. *Int J Environ Res Public Health*. 2021;18(15):8133.

17. Gonçalves AP, Zuanazzi AC, Salvador AP, Jaloto A, Pianowski G, Carvalho L de F. Preliminary findings on the associations between mental health indicators and social isolation during the COVID-19 pandemic. *Arch Psychiatry Psychother*. 2020;22(2):10-19.

18. De Boni RB, Balanzá-Martínez V, Mota JC, et al. Depression, Anxiety, and Lifestyle Among Essential Workers: A Web Survey From Brazil and Spain During the COVID-19 Pandemic. *J Med Internet Res*. 2020;22(10):e22835.

19. Hyman MA, Ornish D, Roizen M. Lifestyle medicine: treating the causes of disease. *Altern Ther Health Med*. 2009;15(6):12.

20. Rippe JM. *Lifestyle Medicine*. CRC Press; 2019.

21. Katz DL, Karlsen MC. The need for a whole systems approach to evidence evaluation: an update from the American College of Lifestyle Medicine. *J Altern Complement Med*. 2019;25(S1):S19-S20.

22. Velten J, Lavallee KL, Scholten S, et al. Lifestyle choices and mental health: a representative population survey. *BMC Psychol*. 2014;2(1):1-11.

23. SurveyGizmo. SurveyGizmo Survey Software. Published online 2005.

24. Balanzá-Martínez V, Kapczinski F, de Azevedo Cardoso T, et al. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. *Rev Psiquiatr Salud Ment*. 2021;14(1):16-26.

25. Levesque R. SPSS programming and data management. *Guide SPSS SAS Users*. Published online 2007.

26. Owen L, Corfe B. The role of diet and nutrition on mental health and wellbeing. *Proc Nutr Soc*. 2017;76(4):425-426.

27. Riemann D. Sleep hygiene, insomnia and mental health. *J Sleep Res*. 2018;27(1):3. doi:10.1111/jsr.12661

28. Schön UK, Denhov A, Topor A. Social relationships as a decisive factor in recovering from severe mental illness. *Int J Soc Psychiatry*. 2009;55(4):336-347.

29. Cervera-Martínez J, Atienza-Carbonell B, Mota JC, et al. Lifestyle changes and mental health during the COVID-19 pandemic: A repeated, cross-sectional web survey. *J Affect Disord*. 2021;295:173-182.

30. Wilson JM, Lee J, Shook NJ. COVID-19 worries and mental health: the moderating effect of age. *Aging Ment Health*. 2021;25(7):1289-1296.

31. Levy I, Cohen-Louck K. Predicting individual function during COVID-19 lockdown: depression, fear of COVID-19, age, and employment. *Front Psychol*. 2021;12.

32. Carstensen LL, Shavit YZ, Barnes JT. Age advantages in emotional experience persist even under threat from the COVID-19 pandemic. *Psychol Sci*. 2020;31(11):1374-1385.

33. Palgi Y, Shrira A, Ring L, et al. The loneliness pandemic: Loneliness and other concomitants of depression, anxiety and their comorbidity during the COVID-19 outbreak. *J Affect Disord*. 2020;275:109.

34. Grey I, Arora T, Thomas J, Saneh A, Tohme P, Abi-Habib R. The role of perceived social support on depression and sleep during the COVID-19 pandemic. *Psychiatry Res*. 2020;293:113452.

35. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep*. 2013;36(7):1059-1068.

36. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. *Psychiatry Res*. 2020;288:112954.

37. Osiogo F, Shalaby R, Adegboyega S, et al. COVID-19 pandemic: demographic and clinical correlates of disturbed sleep among 6,041 Canadians. *Int J Psychiatry Clin Pract*. Published online 2021:1-8.

38. Robillard R, Daros AR, Phillips JL, et al. Emerging New Psychiatric Symptoms and the Worsening of Pre-existing Mental Disorders during the COVID-19 Pandemic: A Canadian Multisite Study: Nouveaux symptômes psychiatriques émergents et détérioration des troubles mentaux préexistants durant la pandémie de la COVID-19: une étude canadienne multisite. *Can J Psychiatry*. Published online 2021:0706743720986786.

39. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51-65.

40. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395.

41. Smyth C. The Pittsburgh sleep quality index (PSQI). Published online 1999.

42. Firth J, Ward PB, Stubbs B. Lifestyle psychiatry. *Front Psychiatry*. 2019;10:597.

43. De Boni RB, Ribeiro-Alves M, Mota JC, et al. The cumulative effect of multiple dimensions of lifestyle on risky drinking during the Covid-19 pandemic. *Prev Med*. 2021;150:106718.

44. Firth J, Solmi M, Wootton RE, et al. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. *World Psychiatry*. 2020;19(3):360-380.

45. Conry MC, Morgan K, Curry P, et al. The clustering of health behaviours in Ireland and their relationship with mental health, self-rated health and quality of life. *BMC Public Health*. 2011;11(1):1-10.

46. Polak R, Pojednic RM, Phillips EM. Lifestyle medicine education. *Am J Lifestyle Med*. 2015;9(5):361-367.

47. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. *BMC Psychiatry*. 2014;14(1):1-13.

48. Egger GJ, Binns AF, Rossner SR. The emergence of "lifestyle medicine" as a structured approach for management of chronic disease. *Med J Aust*. 2009;190(3):143-145.

3.7 Figures and Tables

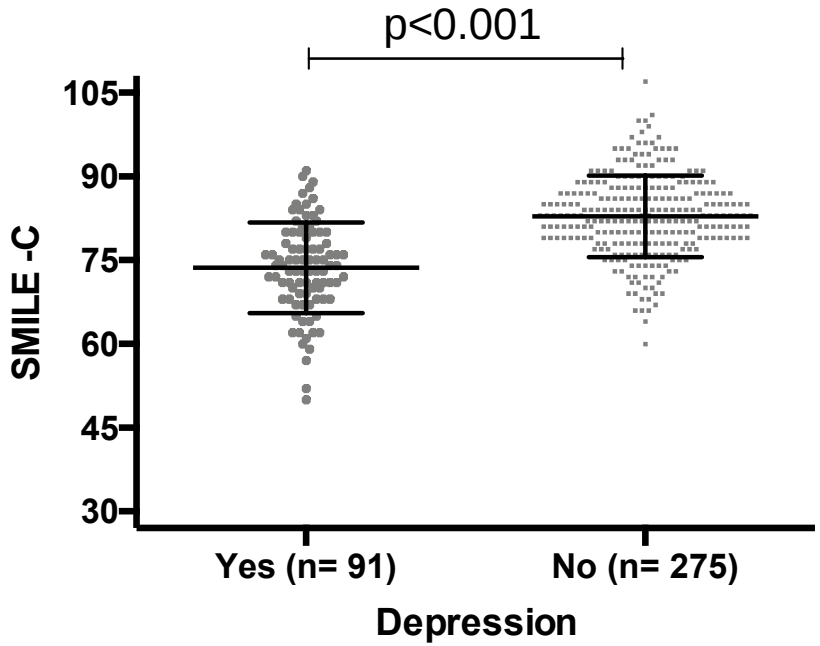

Figure 1A: Mean SMILE-C scores categorized based on screening for depression.

Legend: SMILE-C: Short Multidimensional Inventory Lifestyle Evaluation - Confinement

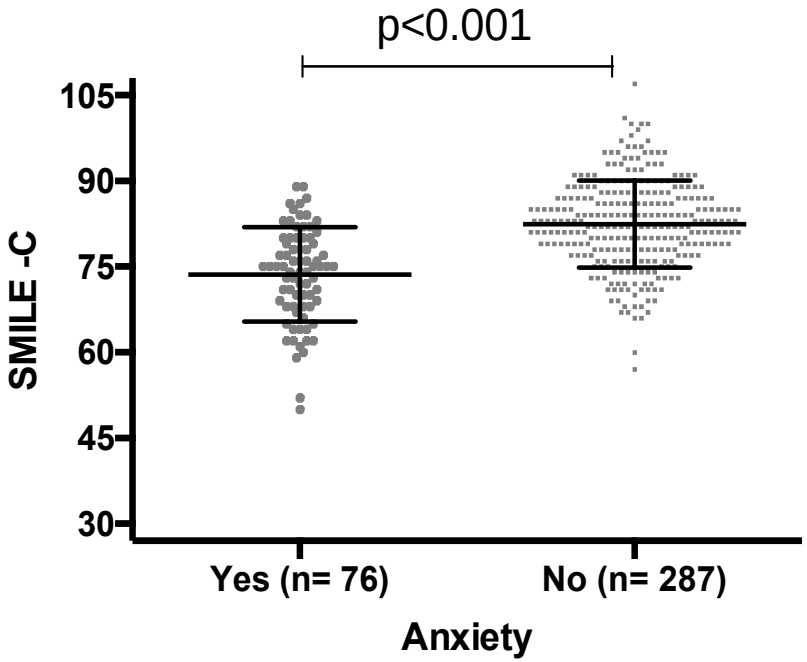

Figure 1B: Mean SMILE-C scores categorized based on screening for anxiety.

Legend: SMILE-C: Short Multidimensional Inventory Lifestyle Evaluation - Confinement

Table 1: Sociodemographic and clinical characteristics of the total sample.

	Total (n=404)
Sex	
Female	339 (83.9%)
Male	65 (16.1%)
Age	
18-61	196 (48.5%)
62 or more	208 (51.5%)
Educational Attainment	
Elementary/High School	94 (23.3%)
College/University	258 (63.9%)
Graduate School	52 (12.9%)
People in the household	
1	106 (26.2%)
2 or 3	236 (58.4%)
4 to 9	61 (15.1%)
Working	
No	258 (63.9%)
Yes	127 (31.4%)
Lost job during the pandemic	19 (4.7%)
Essential worker (Yes)	33 (8.2%)
Frontline worker (Yes)	15 (3.7%)
Studying (Yes)	42 (10.4%)
Self-isolated (Yes)	60 (14.9%)
Lost someone in the pandemic (Yes)	22 (5.4%)

Chronic disease*	173 (42.8%)
Mental Health Disorder*	111 (27.4%)
Infectious Disease*	2 (0.5%)
Self-rated health (Good/Very good)	248 (61.4%)
Changed dietary habits during the pandemic (Yes)	129 (31.9%)
Changed substance use habits during the pandemic (Yes)	27 (6.7%)
Changed physical activity routine during the pandemic (Yes)	202 (50.0%)
Changed stress management strategies during the pandemic (Yes)	142 (35.1%)
Changed sleep pattern during the pandemic (Yes)	111 (27.5%)
Changes in social support during the pandemic (Yes)	191 (47.3%)
Changed indoor/outdoor time pattern during the pandemic (Yes)	233 (57.7%)
SMILE-C (Mean, S.D.)	80.65 (S.D. 8.53)

* = Yes, diagnosed/treated within the last 12 months

Table 2: Sociodemographic and clinical variables based on presence of depression.

	Depression Screen		
	Yes (n= 97)	**No (n= 302)**	**p-value**
Sex			0.134
Female	77 (79.4%)	259 (85.8%)	
Male	20 (20.6%)	43 (14.2%)	
Age			<0.001
18-61	66 (68.0%)	130 (43.0%)	
62 or more	31 (32.0%)	172 (57.0%)	
Educational Attainment			0.817
Elementary/High School	23 (23.7%)	69 (22.8%)	
College/University	60 (61.9%)	196 (64.9%)	
Graduate School	14 (14.4%)	37 (12.3%)	
People in the household			0.370
1	29 (29.9%)	74 (24.6%)	
2 or 3	57 (58.8%)	178 (59.1%)	
4 to 9	11 (11.3%)	49 (16.3%)	
Working			0.006
No	49 (50.5%)	204 (67.5%)	
Yes	40 (41.2%)	87 (28.8%)	
Lost job during the pandemic	8 (8.2%)	11 (3.6%)	
Studying (Yes)	11 (11.3%)	31 (10.3%)	0.764
Self-isolated (Yes)	16 (16.7%)	43 (14.2%)	0.560
Lost someone in the pandemic (Yes)	7 (7.2%)	13 (4.3%)	0.253
Chronic disease*	43 (44.3%)	129 (42.7%)	0.780

Mental Health Disorder*	43 (44.3%)	67 (22.2%)	<0.001
Infectious Disease*	0	2 (0.7%)	1.000
Self-rated health (Good/Very good)	45 (46.4%)	199 (65.9%)	0.001
Changed dietary habits during the pandemic (Yes)	42 (43.3%)	87 (28.8%)	0.008
Changed substance use habits during the pandemic (Yes)	12 (12.4%)	15 (5.0%)	0.011
Changed physical activity routine during the pandemic (Yes)	56 (57.7%)	142 (47.0%)	0.061
Changed stress management strategies during the pandemic (Yes)	35 (36.1%)	105 (34.8%)	0.795
Changed sleep pattern during the pandemic (Yes)	40 (41.2%)	68 (22.5%)	<0.001
Changes in social support during the pandemic (Yes)	63 (64.9%)	125 (41.4%)	<0.001
Changed indoor/outdoor time pattern during the pandemic (Yes)	64 (66.0%)	167 (55.3%)	0.064
SMILE-C (Mean, S.D.)	73.65 (S.D. 8.12)	82.85 (S.D. 7.28)	<0.001

* = Yes, diagnosed/treated within the last 12 months

Table 3: Sociodemographic and clinical variables based on presence of anxiety.

	Anxiety Screen		
	Yes (n= 80)	**No (n= 310)**	**p-value**
Sex			0.260
Female	64 (80.0%)	264 (85.2%)	
Male	16 (20.0%)	46 (14.8%)	
Age			<0.001
18-61	57 (71.3%)	135 (43.5%)	
62 or more	23 (28.8%)	175 (56.5%)	
Educational Attainment			0.136
Elementary/High School	25 (31.3%)	65 (21.0%)	
College/University	47 (58.8%)	203 (65.5%)	
Graduate School	8 (10.0%)	42 (13.5%)	
People in the household			0.231
1	16 (20.0%)	83 (26.9%)	
2 or 3	54 (67.5%)	176 (57.0%)	
4 to 9	10 (12.5%)	50 (16.2%)	
Working			0.022
No	42 (52.5%)	205 (66.1%)	
Yes	31 (38.8%)	95 (30.6%)	
Lost job during the pandemic	7 (8.8%)	10 (3.2%)	
Studying (Yes)	9 (11.3%)	32 (10.3%)	0.809
Self-isolated (Yes)	13 (16.5%)	46 (14.8%)	0.721
Lost someone in the pandemic (Yes)	3 (3.8%)	18 (5.8%)	0.654
Chronic disease*	36 (45.0%)	130 (41.9%)	0.621
Mental Health Disorder*	43 (53.8%)	65 (21.0%)	<0.001

Infectious Disease*	1 (1.3%)	1 (0.3%)	0.875
Self-rated health (Good/Very good)	37 (46.3%)	202 (65.2%)	0.002
Changed dietary habits during the pandemic (Yes)	34 (42.5%)	92 (29.7%)	0.029
Changed substance use habits during the pandemic (Yes)	9 (11.3%)	17 (5.5%)	0.063
Changed physical activity routine during the pandemic (Yes)	40 (50.0%)	154 (49.7%)	0.920
Changed stress management strategies during the pandemic (Yes)	25 (31.3%)	113 (36.5%)	0.425
Changed sleep pattern during the pandemic (Yes)	38 (47.5%)	68 (21.9%)	<0.001
Changes in social support during the pandemic (Yes)	50 (62.5%)	132 (42.6%)	0.001
Changed indoor/outdoor time pattern during the pandemic (Yes)	48 (60.0%)	175 (56.5%)	0.567
SMILE-C (Mean, S.D.)	73.63 (S.D. 8.25)	82.46 (S.D. 7.63)	<0.001

* = Yes, diagnosed/treated within the last 12 months

Table 4: Multivariable logistic regression examining the associations between depression and sociodemographic variables (n = 365).

		Depression Multivariable Adjusted		
Variable		**OR**	**95% CI**	**p-value**
Age				
	62 or more	1		
	18 to 61	2.64	1.464 to 4.762	0.001
Changes in social support during the pandemic				
	No	1		
	Yes	2.909	1.613 to 5.245	<0.001
SMILE-C		0.859	0.824 to 0.896	<0.001

Legend: OR: Odds Ratio; CI: Confidence Interval.

Table 5: Multivariable logistic regression examining the associations between anxiety and sociodemographic variables (n = 355).

Variable		Anxiety Multivariable Adjusted OR	95% CI	p-value
Age				
	62 or more	1		
	18 to 61	2.575	1.342 to 4.940	0.004
Mental Health Disorder*				
	No	1		
	Yes	2.707	1.453 to 5.046	0.002
Changed sleep pattern during the pandemic				
	No	1		
	Yes	2.311	1.219 to 4.382	0.010
Changes in social support during the pandemic (Yes)				
	No	1		
	Yes	2.112	1.113 to 4.007	0.022
SMILE-C		0.887	0.851 to 0.925	<0.001

Legend: OR: Odds Ratio; CI: Confidence Interval. * = Yes, diagnosed/treated within the last 12 months

Chapter 4: Lifestyle in bipolar disorder: a cross-sectional study

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Abstract

Background: Modifiable lifestyle behaviours are important factors for improving mental health, yet there has been a lack of research studying lifestyle as a multidimensional construct in bipolar disorder (BD). The aim of this cross-sectional study was to compare the lifestyle patterns of individuals with BD in a current mood episode with healthy controls (HC) using the Short Multidimensional Inventory Lifestyle Evaluation (SMILE).

Materials and Methods: The sample consisted of 46 individuals with BD currently experiencing a depressive, manic, or mixed episode and 50 HC, assessed using the MINI International Neuropsychiatric Interview, Montgomery-Asberg Depression Rating Scale (MADRS), and the Young Mania Rating Scale (YMRS). The SMILE scale assesses lifestyle across seven domains: diet and nutrition, substance abuse, physical activity, stress management, restorative sleep, social support, and environmental exposures. Between-groups comparisons were performed based on the presence of a psychiatric diagnosis and the type of BD episode.

Results: We found significant differences in the total SMILE score ($r=0.75$, $p<0.001$) and in scores from each domain of the scale between BD and HC ($p<0.05$), where individuals with BD in a depressive or manic/mixed episodes reported worse lifestyle across all domains. Differences between individuals with BD in different mood episodes across domains on the SMILE scale were non-significant.

Conclusion: Findings from this study highlight the presence of unhealthy lifestyle patterns in people with BD regardless of the polarity of their mood episode.

Implementation of multidimensional lifestyle assessments is an essential step towards detecting the clustering of unhealthy lifestyle patterns in BD.

Keywords: lifestyle, bipolar disorder, depressive, manic, mixed, mood episode.

4.1 Introduction

Bipolar disorder (BD) is a severe psychiatric disorder, with an estimated annual prevalence rate of 2% worldwide.[1] BD is associated with severe functional impairments in work, family and social settings, as well as with a lower quality of life across all mood states.[2,3] The accumulating evidence on challenges in everyday functioning of people with BD,[4] along with the high comorbidity rates with other physical and mental health disorders,[5] has raised awareness to the burden of BD and the immediate need for effective strategies to reduce it.[6]

There is growing interest in the field of Lifestyle Medicine (LM), an area of medicine that focuses on improving everyday lifestyle behaviours using evidence-based strategies in order to prevent and intervene on the progression of chronic physical and mental health challenges.[7] Unhealthy behaviours in different areas of everyday life can aggregate and have a detrimental cumulative effect on short and long-term health outcomes, such as cardiovascular complications, respiratory diseases, and the risk of mortality.[8–10] Lifestyle Psychiatry (LP) is a subspecialty of LM focused on the application of preventive and treatment strategies for mental illnesses following the LM guidelines.[11] Recognizing the importance of lifestyle factors for mental health has lagged behind other subspecialties of medicine, although recent reports have shed light on the significance of these factors for reducing the burden of mental disease.[12] For many years, different lifestyle areas have been regarded as independent risk factors for mental disorders. However, the fast-growing area of LP suggests a multidimensional focus on lifestyle behaviours for achieving a significant improvement of mental health outcomes.[11]

According to the American College of Lifestyle Medicine (ACLM), there are six main areas to be targeted: diet, physical activity, avoiding substance use, restorative sleep, stress management, and social support.[13]

There is evidence showing the close association of symptoms and clinical outcomes of BD with unhealthy behaviours.[12] Unhealthy behaviours related to dietary patterns,[14] physical activity levels,[15] substance abuse,[16] sleep quality,[17] chronic stress management,[18] and social support[19] are each linked to poorer clinical outcomes in BD, such as metabolic and cardiovascular diseases, and increased risk of mortality. To date, majority of lifestyle assessments and interventions for BD have been directed to a single lifestyle domain at a time. However, following recent suggestions from the ACLM and findings related to lifestyle and mental health,[20,21] supported by evidence from the field of LP, a multidimensional approach can help better understand the various lifestyle areas affected in people with BD, and the clustering of unhealthy behaviours. Moreover, people suffering from BD may need help in different lifestyle areas depending on the current mood state they are experiencing. Hence, an approach that takes into account the multidimensional nature of lifestyle and its likely changes across clinical mood states can pave the way for more personalized, tailored lifestyle interventions to improve the clinical and functional outcomes of individuals suffering from severe mental health conditions, such as BD.

Therefore, the aim of this study was to compare the lifestyle patterns between people with BD in a current mood episode and healthy controls using a multidimensional lifestyle assessment. We also aim to compare the seven lifestyle domains (diet and

nutrition, substance abuse, physical activity, stress management, restorative sleep, social support, and environmental exposures) across people with BD in different mood states.

4.2 Methods

4.2.1 Study Design and setting

This is a cross-sectional study conducted between October 2021 and July 2022 as part of a larger, cross-sectional study validating a new questionnaire evaluating emotional states in people with BD in a current mood episode. Study interviews were administered at the Mood Disorders Clinic in St. Joseph's Healthcare Hamilton (SJHH) in Hamilton, Canada, or using online video platforms, such as Zoom. Depending on the current COVID-19 restrictions at SJHH and the preference of interested participants, the screening process and data collection were conducted either in-person or remotely. The study was approved by the Hamilton Integrated Research Ethics Board (HiREB) under protocol #8193.

4.2.2 Participants

Potential participants that were 18 and older were invited for an interview to determine their eligibility for the study according to the inclusion and exclusion criteria, which differed for the BD and HC groups. Participants from the BD and HC groups were matched by age and sex at the time of recruitment. For the current study, the inclusion criteria for BD were 1) a diagnosis of BD according to DSM-5 criteria using the Mini International Neuropsychiatric Interview (MINI),[22] and 2) currently experiencing a depressive, (hypo)manic, or mixed episode according to the MINI. Exclusion criteria for

the BD group were 1) severe psychotic symptoms, determined according to the presence of current psychotic symptoms on the MINI and the severity of these symptoms based on clinical judgment, (2) severe suicide risk, indicated by a score of ≥ 17 on the suicidality module of the MINI, and (3) severe cognitive disability that could impact on their understanding of the assessments based on clinical judgment. In contrast, inclusion criteria for healthy controls were 1) absence of any psychiatric diagnosis according to the MINI for DSM-5, and 2) did not demonstrate any severe cognitive disability that could impact their understanding of the assessments based on clinical judgment. The study was advertised using paper flyers in the community, as well as online advertisements posted on advertising websites and social media outlets (Facebook, Instagram, Reddit, and Kijiji). After receiving verbal and written information about the study, all participants provided informed consent prior to the screening interview. Assessments consisted of a diagnostic interview, clinical assessments of current mood state, and lifestyle assessments.

4.2.3 Measurements

Demographic information was collected for all participants, which included questions regarding the individual's age, sex, years of education, highest educational degree attained, and current occupational status (working/studying). In this study, we only included sociodemographic variables that were assessed in the larger study based on previous validation studies.

4.2.3.1 Clinical Assessments

All clinical assessments were conducted by a trained PhD candidate with extensive data collection experience using these instruments.

The MINI was used to evaluate for the presence of psychiatric diagnosis according to the DSM-5.[22] For the purpose of the current study, participants in the BD group had to satisfy the criteria for BD, as well as the criteria for a current depressive and/or (hypo)manic episode according to the MINI. In contrast, participants in the HC group were eligible if they did not have a positive screening on any module on the MINI. Presence of psychotic symptoms and suicide risk was also assessed using the MINI.

The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to evaluate the severity of current depressive symptoms.[23] The MADRS consists of 10 items that are rated from 0 to 6, evaluating features related to a depressive state within the past week (e.g., sadness, lassitude, pessimism, etc.). The 10 items combine for a total score between 0 and 60. The cut-off score of ≥ 7 for a current depressive episode was an inclusion criterion in the larger study.[24]

The Young Mania Rating Scale (YMRS) was used to evaluate the severity of current (hypo)manic symptoms.[25] The YMRS is an 11-item scale used to assess the severity of (hypo)manic symptoms within the past week. There are 4 items graded on a 0 to 8 scale, and 7 items graded on a 0 to 4 scale, each one assessing a different feature associated with a manic mood state (e.g. irritability, motor activity, decreased need for regular sleep, etc.). The 11 items combine for a total score between 0 and 60. The cut-off

score of ≥ 7 for a current (hypo)manic episode was an inclusion criterion in the larger study.[26,27]

Participants were considered to be in a current depressive episode if they satisfied the current depressive episode, but not the current (hypo)manic episode criteria on the MINI. Likewise, participants were regarded as currently experiencing a (hypo)manic episode if they satisfied those criteria, but not the criteria for a depressive episode on the MINI. Participants that satisfied the criteria for both depressive and (hypo)manic episode were considered to be experiencing a mixed episode. We grouped manic and mixed states together as there were only 9 participants exclusively in a manic state.

4.2.3.2 Lifestyle Assessments

Lifestyle in the previous 30-days was assessed using the Short Multidimensional Inventory Lifestyle Evaluation (SMILE).[20] The SMILE is comprised of 43 items evaluating 7 different lifestyle domains: diet and nutrition, substance abuse, physical activity, stress management, restorative sleep, social support, and environmental exposures. Response options are measured on a 4-point Likert scale (always, often, seldom, never), resulting in a maximum possible score of 172 (noting that some questions are reverse-scored). In addition, we considered scores on each domain individually for subanalysis of differences between the groups. Higher scores on the total SMILE scores, as well as on the diet and nutrition (7-28), substance abuse (4-16), physical activity (4-16), stress management (9-36), restorative sleep (5-20), social support (10-40), and environmental exposures (4-16) domains indicated healthier lifestyle.

4.2.4 Statistical Analysis

The data were collected directly on REDCap, a secure web platform for collection and storage of data.[28] After, the data were transferred to SPSS v.28.0 where the statistical analyses were performed.[29] We tested the normality of continuous variables using the Shapiro-Wilk test for normality.[30] To describe the sample characteristics between the two groups, HC vs BD, we performed chi-square and Mann-Whitney U tests, for categorical variables and nonparametric continuous data, respectively. We also performed a Mann-Whitney U test to analyze these two groups on the total SMILE scores. We used a non-parametric test for the bivariate analysis because the distribution of the outcome (SMILE scores) was asymmetric. We used Student's t-test for the comparisons of the domains with normal distributions of the scores, and Mann-Whitney U test for the comparisons with asymmetric distribution of the scores. We created two box plot graphs using the Prism GraphPad v.9 to demonstrate the findings of the comparison between HC and BD, and the comparison between HC, BD in a depressive episode, and BD in a manic/mixed episode across the different SMILE domains (Figures 1 and 2). We also calculated effect size of the differences between the groups using r values for nonparametric comparisons and Cohen's *d* for parametric comparisons. We calculated the post hoc statistical power of the main comparison using Epi Info™. Multivariate linear regression was performed to evaluate the effect of independent factors (predictors) on the SMILE score. The analyses included variables that presented an association of $p<0.20$ with the outcome (SMILE scores). We did not include the 'highest degree of education' variable in this analysis, as it measures the same construct as the years of education variable. The final

model was reached using a manual stepwise removal of each non-statistically significant variable. Furthermore, we compared total scores on the SMILE scale, as well as scores for each domain of the SMILE across HCs, BD in a current depressive episode, and BD in a current manic/mixed episode. Significance for all comparisons was set at $p<0.05$.

4.3 Results

4.3.1 Sample Characteristics and group differences

The total sample of this study consisted of 96 participants (46 BD and 50 HC). The sociodemographic characteristics of the sample are described in Table 1. There were no significant differences between groups regarding sex (p=0.957) or age (p=0.445). Consistent with the well-known educational and occupational burden of BD, the HC group had completed significantly more years of education (p<0.001), attained a higher educational degree (p < 0.001), and were more likely to be working/studying (88.0%) at the time of assessment than the BD group (60.9%, p = 0.002). The groups also differed in scores on the clinical assessments, as expected. The HC group had significantly lower median scores on the MADRS (2.0, IQR: 0 – 3.0) and on the YMRS (1.0, IQR: 0 – 2.0) than the BD group (MADRS: 24.0, IQR: 20.0 – 30.5, p < 0.001; YMRS: 8.5, IQR: 2.75 – 17.5, p < 0.001).

4.3.2 Lifestyle across diagnostic groups

Our analysis revealed significant differences with a large effect size on the total SMILE score between the HC (median: 133.5 [IQR: 125.75 – 141.25]) and BD (median: 103.5 [IQR: 95.0 - 114.25], r = 0.75, p<0.001) groups (Figure 1). The post hoc statistical power for the comparison between BD and HC was 100%. These differences indicate a

significantly worse lifestyle among individuals with BD than healthy controls. Furthermore, our analysis revealed significantly lower scores in BD in comparison to HC with a large effect size across all domains on the SMILE scale:

- Diet and nutrition (BD: median: 17.5 [IQR: 14.75 – 20.0], HC: median: 22.0 [IQR: 19.0 – 23.0], r = 0.53, p<0.001)
- Substance use (BD: median: 13.0 [IQR: 12.0 – 16.0], HC: median: 16.0 [IQR: 15.0 – 16.0], r = 0.45, p<0.001)
- Physical activity (BD: median: 8.0 [IQR: 7.0 – 9.0], HC: median: 11.0 [IQR: 9.0 – 12.0], r = 0.53, p<0.001)
- Stress management (BD: mean: 19.3 (+/- 4.07), HC: mean: 26.58 (+/- 4.01), Cohen's *d* = 1.87, p<0.001)
- Sleep (BD: median: 12.0 [IQR: 10.0 – 13.0], HC: median: 15.0 [IQR: 14.0 – 17.0], r = 0.63, p<0.001)
- Social support (BD: median: 26.5 [IQR: 22.0 – 29.0], HC: median: 34.0 [IQR: 30.0 – 37.0], r = 0.66, p<0.001)
- Environmental exposures (BD: mean: 8.48 (+/- 2.04), HC: mean: 10.28 (+/- 2.23), Cohen's *d* = 0.85, p<0.001).

In the final adjusted linear regression model, we included years of education, current working/studying status, and diagnosis (HC or BD) as predictors of SMILE scores. After the removal of the least significant factor in the model (currently working/studying), we performed another linear regression with years of education and SMILE scores. Years of

education was also non-significant in the model, and after the removal of this factor, diagnosis (HC/BD) remained as the only significant predictor of total SMILE scores, where a diagnosis of BD was predictive of worse scores on the SMILE. The multivariate linear regression models are presented in Supplementary Material 1.

4.3.3 Lifestyle across mood states

For the analysis of scores on the SMILE scale across different mood states, we included 26 participants in a depressive state, 20 participants in a manic/mixed state (manic = 9, mixed = 11), and 50 healthy controls. In addition to the total SMILE scores, we analyzed the scores of the 7 subdomains of the SMILE scale across the 3 groups (Table 2, Figure 2). Once again, participants in both BD groups had significantly lower median scores on the total SMILE scale, as well as all 7 subdomains of the scale than HC ($p < 0.05$). In contrast, BD in a depressive episode and BD in a manic/mixed episode did not show any differences in total SMILE scores or in any of the subdomains of the scale.

4.4 Discussion

To our knowledge, this is the first cross-sectional study evaluating differences in lifestyle between healthy individuals and people with BD in a current mood episode, using a multidimensional lifestyle approach based on contemporary notions of lifestyle. Our findings revealed significantly healthier lifestyle across all domains in healthy controls in comparison to BD in a current depressive, manic, or mixed state. Regardless of the type of mood episode they were experiencing, people with BD reported unhealthier lifestyle than age and sex-matched healthy individuals. Intriguingly, individuals with BD

reported worse lifestyle across all domains on the scale, suggesting that all areas of their everyday life are affected during mood episodes.

Our findings are in line with previous reports suggesting differences between BD and healthy individuals on these lifestyle domains. In comparison to healthy controls, individuals with BD have showed unhealthier dietary patterns and increased intake of obesogenic nutrients,[31–33] significantly lower physical activity and higher rates of sedentary behaviour,[34] and higher rates of sleep-wake and circadian rhythm disruptions.[35,36] Moreover, previous findings have also suggested the reduced use of adaptive coping strategies (such as stress management techniques and social relationships) and increased use of maladaptive coping strategies (such as substance abuse) in individuals with BD in comparison to healthy controls.[37] There is evidence that unhealthy lifestyles such as low physical activity and poor sleep quality may further compound the neurocognitive dysfunction associated with BD and may cumulatively aggravate the social and occupational disability of these patients.[38]

Furthermore, the clustering of unhealthy lifestyle behaviours across different areas, such as unhealthy eating, physical activity, and substance use patterns, has been associated with an increased risk of depressive symptoms, higher levels of psychological distress, lower vitality, and lower quality of life.[39–43] The patterns in different areas of everyday life are intertwined and dependent on each other, and the formation of unhealthy habits can lead to detrimental effects on the individual's physical and mental well-being. Importantly, our analysis highlights the clustering of unhealthy lifestyle domains across individuals with BD in depressive, manic, and mixed episodes.

Importantly, previous findings have also suggested the presence of unhealthy behaviours in euthymic individuals with BD, such as unhealthy dietary patterns, physical inactivity, hindered personal relationships, and sleep disturbances.[44–47]

The implementation of a multidimensional lifestyle assessment is very important for both detecting the clustering of unhealthy behaviours in everyday life routines of individuals with BD in any mood state and developing more informed and personalized lifestyle-based interventions. Of note, all lifestyle behaviours are modifiable, and growing evidence supports that multimodal strategies targeting exercise, nutrition and wellness are feasible and effective to improve mental and somatic health in individuals with BD.[48,49] The clustering of unhealthy behaviours from different domains may lead to more severe clinical trajectories and increase the rates of physical and mental health comorbidities with BD. The main lifestyle areas, as recognized by LP, are deemed to be "modifiable" domains, with assessments and subsequent interventions in these domains showing promising results for improving mental health outcomes and reducing the burden of these disorders.[11] A multidimensional approach to evaluating lifestyle behaviours in BD should be implemented in the clinical setting, as it allows for a more detailed assessment of the person's everyday behaviours and the complex interactions between these behaviours and symptoms of BD, which would be an essential step towards developing more personalized, tailored interventions for improving clinical outcomes and quality of life in individuals with BD.

4.4.1 Limitations

Findings from our study should be interpreted considering some limitations. Considering that this cross-sectional study was part of a larger study designed to validate an emotional reactivity scale in people with BD in a current mood episode, we did not include any data of euthymic individuals with BD, which would be helpful for understanding whether unhealthy lifestyles are associated to the disorder even when individuals are asymptomatic. Furthermore, 37 out of the 46 individuals in the BD group had a positive screening for a depressive episode, which prevented us from including a manic only group in our analysis and led to the grouping of individuals in a manic and mixed state. Also, our sample predominantly consisted of females, although this could be explained by the higher prevalence of females than males with BD.[6] Lastly, we did not collect information regarding the socio-economic status, current medications use of participants, comorbid medical conditions and other psychiatric disorders which may be related to the observed behaviours on some of the SMILE domains. Despite these limitations, this is the first cross-sectional study to compare lifestyle across healthy individuals and people with BD in different mood episodes using a multidimensional approach based on contemporary notions of lifestyle.

4.4.2 Conclusion

Findings from this study confirm the association between multidimensional unhealthy lifestyle behaviours and symptomatic people with BD. Furthermore, this association is present across multiple areas of lifestyle, an important consideration for the onset and progression of physical and psychiatric comorbidities in BD. There is a strong

need for future research on implementing a multidimensional approach to lifestyle assessments in BD across all mood states of the disorder, including euthymia, and evaluating the clustering of unhealthy lifestyle behaviours across different areas of everyday life that could potentially lead to worse clinical and functional outcomes for the affected individuals.

4.5 Conflict of interest:

MS, TAC, BNF, LM, RDB, and FK have nothing to disclose.

VB-M has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini, Lundbeck, and Nutrición Médica, all of them unrelated to the present work. FK has been a consultant for Janssen - Johnson & Johnson, unrelated to the present work.

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4.8 References

1. Carvalho AF, Firth J, Vieta E. Bipolar disorder. New England Journal of Medicine. 2020;383:58-66.

2. Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. Health and quality of life outcomes. 2005;3:1-17.

3. Sanchez-Moreno J, Martinez-Aran A, Tabarés-Seisdedos R, Torrent C, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorder: an extensive review. Psychotherapy and psychosomatics. 2009;78:285-97.

4. Henry BL, Minassian A, Perry W. Everyday functional ability across different phases of bipolar disorder. Psychiatry research. 2013;210:850-6.

5. Krishnan KRR. Psychiatric and medical comorbidities of bipolar disorder. Psychosomatic medicine. 2005;67:1-8.

6. Ferrari AJ, Stockings E, Khoo J-P, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar disorders. 2016;18:440-50.

7. Rippe JM. Lifestyle medicine. CRC Press; 2019.

8. Loef M, Walach H. The combined effects of healthy lifestyle behaviours on all cause mortality: a systematic review and meta-analysis. Preventive medicine. 2012;55:163-70.

9. Nyberg ST, Singh-Manoux A, Pentti J, Madsen IE, Sabia S, Alfredsson L, et al. Association of healthy lifestyle with years lived without major chronic diseases. JAMA internal medicine. 2020;180:760-8.

10. Wu M, Wang J, Zhu Y, Lu J, Li D, Yu Z, et al. Impact of individual and combined lifestyle factors on mortality in china: a cohort study. American Journal of Preventive Medicine. 2020;59:461-8.

11. Firth J, Ward PB, Stubbs B. Lifestyle psychiatry. Frontiers in psychiatry. 2019;10:597.

12. Firth J, Solmi M, Wootton RE, Vancampfort D, Schuch FB, Hoare E, et al. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry. 2020;19:360-80.

13. Katz DL, Karlsen MC. The need for a whole systems approach to evidence evaluation: an update from the American College of Lifestyle Medicine. The Journal of Alternative and Complementary Medicine. 2019;25:S19-20.

14. Gabriel FC, Oliveira M, Martella BDM, Berk M, Brietzke E, Jacka FN, et al. Nutrition and bipolar disorder: a systematic review. Nutritional Neuroscience. 2022:1-15.

15. Vancampfort D, Firth J, Schuch F, Rosenbaum S, De Hert M, Mugisha J, et al. Physical activity and sedentary behaviour in people with bipolar disorder: a systematic review and meta-analysis. Journal of affective disorders. 2016;201:145-52.

16. Messer T, Lammers G, Müller-Siecheneder F, Schmidt R-F, Latifi S. Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry research. 2017;253:338-50.

17. Gruber J, Miklowitz DJ, Harvey AG, Frank E, Kupfer D, Thase ME, et al. Sleep matters: sleep functioning and course of illness in bipolar disorder. Journal of affective disorders. 2011;134:416-20.

18. Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. Journal of affective disorders. 2007;99:37-44.

19. Johnson L, Lundström O, Åberg-Wistedt A, Mathé AA. Social support in bipolar disorder: its relevance to remission and relapse. Bipolar Disorders. 2003;5:129-37.

20. Balanzá-Martínez V, Kapczinski F, de Azevedo Cardoso T, Atienza-Carbonell B, Rosa AR, Mota JC, et al. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. Revista de psiquiatria y salud mental. 2021;14:16-26.

21. De Boni RB, Balanzá-Martínez V, Mota JC, Cardoso TDA, Ballester P, Atienza-Carbonell B, et al. Depression, Anxiety, and Lifestyle Among Essential Workers: A Web Survey From Brazil and Spain During the COVID-19 Pandemic. Journal of medical Internet research. 2020;22:e22835.

22. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and

validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of clinical psychiatry. 1998;59:22-33.

23. Davidson J, Turnbull CD, Strickland R, Miller R, Graves K. The Montgomery-Åsberg Depression Scale: reliability and validity. Acta psychiatrica scandinavica. 1986;73:544-8.

24. Müller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery–Åsberg depression rating scale (MADRS). Journal of affective disorders. 2003;77:255-60.

25. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry. 1978;133:429-35.

26. Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Gonçalves CA, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neuroscience letters. 2006;398:215-9.

27. del Mar Bonnin C, Valls E, Rosa AR, Reinares M, Jimenez E, Solé B, et al. Functional remediation improves bipolar disorder functioning with no effects on brain-derived neurotrophic factor levels. European Neuropsychopharmacology. 2019;29:701-10.

28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow

process for providing translational research informatics support. Journal of biomedical informatics. 2009;42:377-81.

29. Levesque R. SPSS programming and data management. A guide for SPSS and SAS Users. 2007.

30. Razali NM, Wah YB. Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. Journal of statistical modeling and analytics. 2011;2:21-33.

31. Firth J, Stubbs B, Teasdale SB, Ward PB, Veronese N, Shivappa N, et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. World Psychiatry. 2018;17:365.

32. Lopresti AL, Jacka FN. Diet and bipolar disorder: a review of its relationship and potential therapeutic mechanisms of action. The Journal of Alternative and Complementary Medicine. 2015;21:733-9.

33. Teasdale SB, Ward PB, Samaras K, Firth J, Stubbs B, Tripodi E, et al. Dietary intake of people with severe mental illness: systematic review and meta-analysis. The British Journal of Psychiatry. 2019;214:251-9.

34. Vancampfort D, Stubbs B, Sienaert P, Wyckaert S, De Hert M, Soundy A, et al. A comparison of physical fitness in patients with bipolar disorder, schizophrenia and healthy controls. Disability and Rehabilitation. 2016;38:2047-51.

35. Mondin TC, Cardoso T de A, Souza LD de M, Jansen K, da Silva Magalhães PV, Kapczinski F, et al. Mood disorders and biological rhythms in young adults: A large population-based study. J Psychiatr Res. 2017;84:98-104.

36. Scott J, Etain B, Miklowitz D, Crouse JJ, Carpenter J, Marwaha S, et al. A systematic review and meta-analysis of sleep and circadian rhythms disturbances in individuals at high-risk of developing or with early onset of bipolar disorders. Neuroscience & Biobehavioural Reviews. 2022:104585.

37. Bridi KPB, Loredo-Souza ACM, Fijtman A, Moreno MV, Kauer-Sant'Anna M, Ceresér KMM, et al. Differences in coping strategies in adult patients with bipolar disorder and their first-degree relatives in comparison to healthy controls. Trends Psychiatry Psychother. 2018;40:318-25.

38. Van Rheenen TE, Lewandowski KE, Bauer IE, Kapczinski F, Miskowiak K, Burdick KE, et al. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. Bipolar disorders. 2020;22:13-27.

39. Conry MC, Morgan K, Curry P, McGee H, Harrington J, Ward M, et al. The clustering of health behaviours in Ireland and their relationship with mental health, self-rated health and quality of life. BMC public health. 2011;11:1-10.

40. Griffin B, Sherman KA, Jones M, Bayl-Smith P. The clustering of health behaviours in older Australians and its association with physical and psychological status, and sociodemographic indicators. Annals of Behavioural Medicine. 2014;48:205-14.

41. Cervera-Martínez J, Atienza-Carbonell B, Mota JC, Bobes-Bascarán T, Crespo-Facorro B, Esteban C, et al. Lifestyle changes and mental health during the COVID-19 pandemic: A repeated, cross-sectional web survey. Journal of Affective Disorders. 2021;295:173-82.

42. Vermeulen-Smit E, Ten Have M, Van Laar M, De Graaf R. Clustering of health risk behaviours and the relationship with mental disorders. Journal of affective disorders. 2015;171:111-9.

43. Ye Y, Wang P, Qu G, Yuan S, Phongsavan P, He Q. Associations between multiple health risk behaviours and mental health among Chinese college students. Psychology, health & medicine. 2016;21:377-85.

44. \Lojko D, Stelmach-Mardas M, Suwalska A. Diet quality and eating patterns in euthymic bipolar patients. Eur Rev Med Pharmacol Sci. 2019;23:1221-38.

45. Miranda-Pettersen K, Bezerra-Filho S, Pinheiro TB, Oliva-Costa SF, Miranda-Scippa Â. Is there a relationship between physical activity and residual mood symptoms in patients with bipolar I disorder? Mental Health and Physical Activity. 2020;19:100352.

46. Steinan MK, Krane-Gartiser K, Morken G, Scott J. Sleep problems in euthymic bipolar disorders: a review of clinical studies. Current Psychiatry Reviews. 2015;11:235-43.

47. Bo Q, Tian L, Li F, Mao Z, Wang Z, Ma X, et al. Quality of life in euthymic patients with unipolar major depressive disorder and bipolar disorder. Neuropsychiatr Dis Treat. 2019;15:1649-57.

48. Bauer IE, Galvez JF, Hamilton JE, Balanza-Martinez V, Zunta-Soares GB, Soares JC, et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. Journal of psychiatric research. 2016;74:1-7.

49. Sylvia LG, Pegg SL, Dufour SC, Janos JA, Bernstein EE, Chang WC, et al. Pilot study of a lifestyle intervention for bipolar disorder: nutrition exercise wellness treatment (NEW Tx). Journal of affective disorders. 2019;250:278-83.

4.9 Figures and Tables

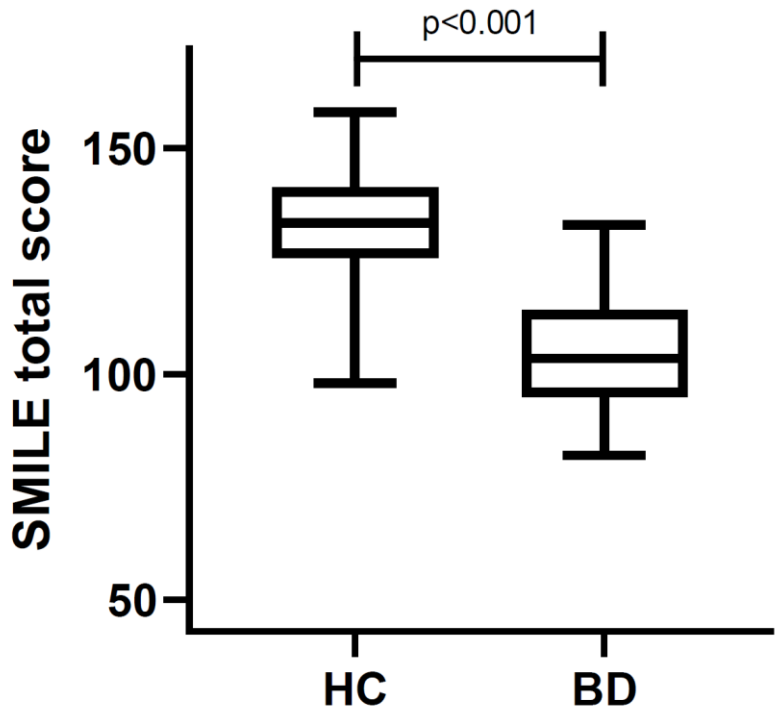

Figure 1: Comparison of total SMILE scores between healthy controls (HC) and individuals with bipolar disorder (BD) in a current mood episode. Healthy individuals reported significantly higher median scores on the SMILE scale (median: 133.5 [IQR: 125.75 – 141.25]) than individuals with BD in a current mood episode (median: 104.0 [IQR: 95.0 - 115.0], p<0.001), suggesting unhealthier behaviours in individuals with BD.

Legend: BD = Bipolar Disorder; HC = Healthy Controls; SMILE = Short Multidimensional Inventory Lifestyle Evaluation

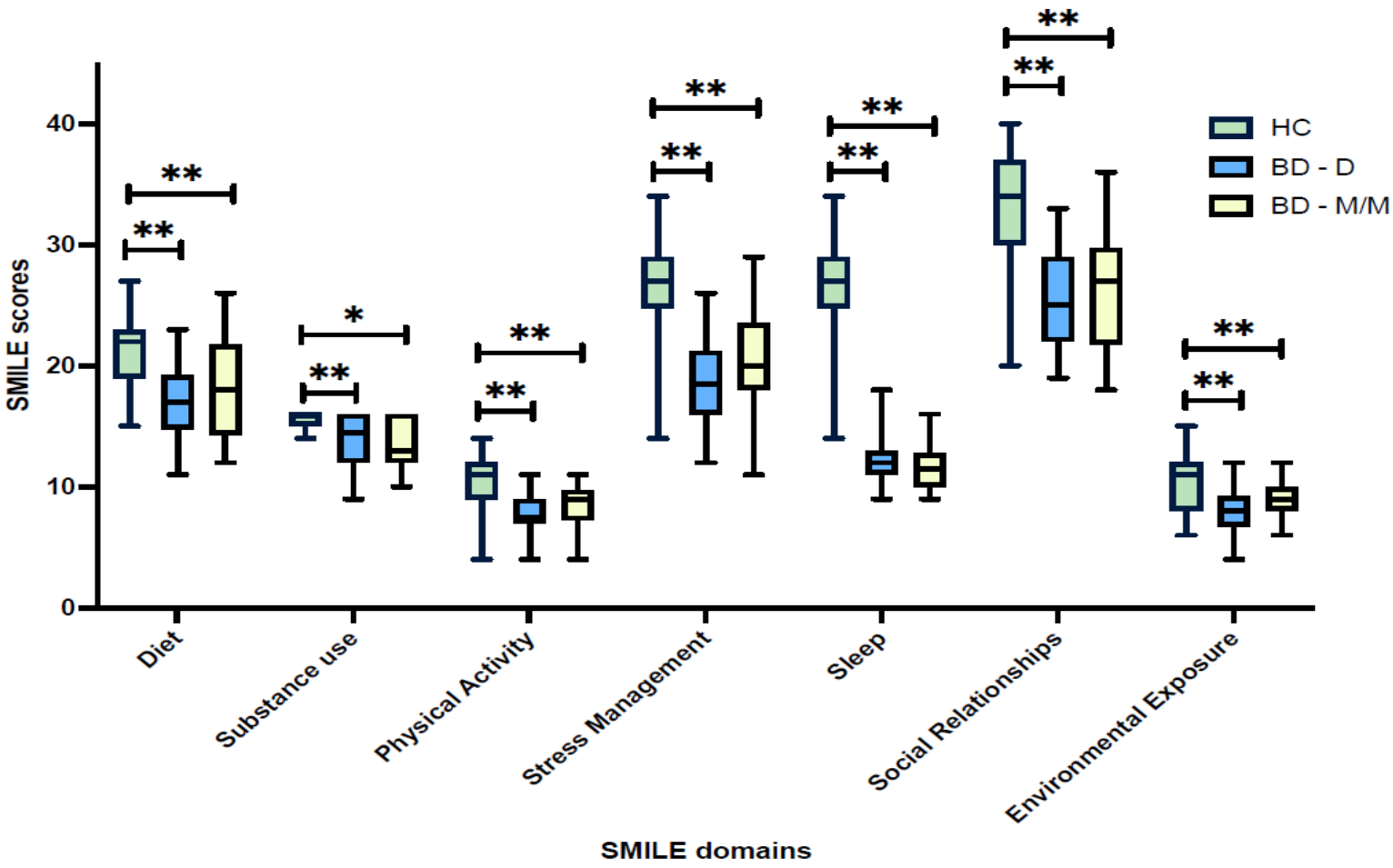

Figure 2: Comparison of SMILE scores across different lifestyle domains between healthy individuals, individuals with bipolar disorder in a depressive episode, and individuals with bipolar disorder in a manic or mixed episode.

Legend: BD - D = Bipolar Disorder in a depressive episode; BD – M/M = Bipolar Disorder in a manic or mixed episode; HC = Healthy Controls; SMILE = Short Multidimensional Inventory Lifestyle Evaluation; * = $p<0.05$; ** = $p<0.001$.

Table 1: Characteristics of the sample according to the diagnostic groups.

	BD (n=46)	**HC (n=50)**	**p-value**
Sex			0.957
Female	37 (80.4%)	40 (80.0%)	
Male	9 (19.6%)	10 (20.0%)	
Age (MD, IQR)	35.5 (24.75 – 45.0)	29.5 (25.0 – 40.25)	0.445
Years of Education (MD, IQR)	15.0 (13.75 – 16.0)	16.5 (16.0 – 18.0)	<0.001
Educational Attainment			<0.001
Elementary/High School	16 (34.8%)	3 (6.0%)	
College/University	26 (56.5%)	31 (62.0%)	
Graduate School	4 (8.7%)	16 (32.0%)	
Working/Studying			0.002
No	18 (39.1%)	6 (12.0%)	
Yes	28 (60.9%)	44 (88.0%)	
MADRS (MD, IQR)	24.0 (20.0 – 30.25)	2.0 (0 – 3.0)	<0.001
YMRS (MD, IQR)	8.5 (2.75 – 17.5)	1.0 (0 – 2.0)	<0.001
SMILE (MD, IQR)	103.5 (95.0 – 114.25)	133.5 (125.75 – 141.25)	<0.001

Legend: IQR = Interquartile Range; MADRS = Montgomery- Åsberg Depression Rating Scale; MD = Median; SMILE = Short Multidimensional Inventory Lifestyle Evaluation; YMRS = Young Mania Rating Scale

Table 2: Comparison of SMILE scores across healthy controls and individuals with BD in different mood states.

	HC (n=50)	BD - Depressive (n=26)	BD - Manic/Mixed (n=20)	Between groups comparisons	Effect size
SMILE Total[a]	133.5 (125.75 – 141.25)	100.5 (94.75 – 111.5)	106.0 (97.25 – 118.0)	HC > D**	0.75
				HC > M/M **	0.64
				D = M/M	0.18
SMILE – Diet[a]	22.0 (19.0 – 23.0)	17.0 (14.75 – 19.25)	18.0 (14.25 – 21.75)	HC > D**	0.59
				HC > M/M *	0.37
				D = M/M	0.12
SMILE – Physical Activity[a]	11.0 (9.0 – 12.0)	7.5 (7.0 – 9.0)	9.0 (7.25 – 9.75)	HC > D**	0.55
				HC > M/M **	0.43
				D = M/M	0.2
SMILE – Substance Use[a]	16.0 (15.0 – 16.0)	14.5 (12.0 – 16.0)	13.0 (12.0 – 16.0)	HC > D**	0.38
				HC > M/M **	0.49
				D = M/M	0.09
SMILE – Restorative Sleep[a]	15.0 (14.0 – 17.0)	12.0 (11.0 – 13.0)	11.5 (10.0 – 12.75)	HC > D**	0.57
				HC > M/M **	0.59

				D = M/M	0.13
SMILE – Stress Management[b]	26.58 (+/- 4.01)	18.54 (+/- 3.82)	20.3 (+/- 4.27)	HC > D**	2.05
				HC > M/M **	1.52
				D = M/M	0.43
SMILE – Social Support[a]	34.0 (30.0 – 37.0)	25.0 (22.0 – 29.0)	27.0 (21.75 – 29.75)	HC > D**	0.67
				HC > M/M **	0.53
				D = M/M	0.11
SMILE – Environment Exposure[b]	10.28 (+/- 2.23)	8.08 (+/- 2.28)	9.0 (+/- 1.59)	HC > D**	0.92
				HC > M/M**	0.66
				D = M/M	0.47

Legend: [a] **=** Data shown as median and interquartile range, between groups comparisons analyzed with Mann-Whitney U Test, effect size as r values; [b] = Data shown as mean and standard deviation, between groups comparisons analyzed with Student's t-test, effect size as Cohen's *d* values; * = $p < 0.05$; ** = $p < 0.01$; D = Depressive; HC = Healthy Controls; M/M = Manic/Mixed; SMILE = Short Multidimensional Inventory Lifestyle Evaluation

4.10 Supplementary Material

Table 1: Multivariable linear regression evaluating variables associated with higher SMILE scores (n = 96).

		SMILE score Multivariable Adjusted		
Variable		***B***	**95% CI**	**p-value**
Years of Education		0.598	-0.634 to 1.830	0.338
Currently working/studying				
	No	1		
	Yes	2.926	-3.221 to 9.072	0.347
Diagnosis (HC/BD)	HC	1		
	BD	-25.981	-31.711 to -20.252	<0.001

Legend: BD = Bipolar Disorder CI = Confidence Interval; SMILE: Short Multidimensional Inventory Lifestyle Evaluation; Positive B indicates increase in the SMILE score (better lifestyle), while negative B indicates decrease in the SMILE score (worse lifestyle).

Table 2: Multivariable linear regression evaluating variables associated with higher SMILE scores after removal of the variable 'currently working/studying' (n = 96).

		SMILE score Multivariable Adjusted		
Variable		***B***	**95% CI**	**p-value**
Years of Education		0.646	-0.581 to 1.873	0.298
Diagnosis (HC/BD)	HC	1		
	BD	-26.685	-32.216 to -21.155	<0.001

Legend: BD = Bipolar Disorder CI = Confidence Interval; SMILE: Short Multidimensional Inventory Lifestyle Evaluation; Positive B indicates increase in the SMILE score (better lifestyle), while negative B indicates decrease in the SMILE score (worse lifestyle).

Table 3: Multivariable linear regression evaluating variables associated with higher SMILE scores after removal of non-significant predictors (n = 96).

		SMILE score Multivariable Adjusted		
Variable		***B***	**95% CI**	**p-value**
Diagnosis (HC/BD)	HC	1		
	BD	-27.886	-32.927 to -22.845	<0.001

Legend: BD = Bipolar Disorder CI = Confidence Interval; SMILE: Short Multidimensional Inventory Lifestyle Evaluation; Positive B indicates increase in the SMILE score (better lifestyle), while negative B indicates decrease in the SMILE score (worse lifestyle).

Chapter 5: Lifestyle interventions for bipolar disorders: A Systematic Review and Meta-Analysis

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Abstract

This review and meta-analysis aimed to describe the existing literature on interventions for bipolar disorder (BD) targeting the 6 pillars of Lifestyle Psychiatry: diet, physical activity (PA), substance use (SU), sleep, stress management, and social relationships (SR). Randomized Controlled Trials that examined the efficacy of lifestyle interventions targeting improvement in depressive/(hypo)manic symptom severity, lifestyle patterns, functioning, quality of life, and/or circadian rhythms were included. The systematic review included 18 studies, where the meta-analysis included studies targeting the same lifestyle domains and outcomes. Sleep (n=10), PA (n=9), and diet (n=8) were the most targeted domains, while SU, SM and SR were least targeted (n=4 each). Combined diet and PA interventions led to significant improvements in depressive symptoms (SMD: -0.46; 95%CI: -0.88, -0.04; p=0.03), and functioning (SMD: -0.47; 95%CI: -0.89, -0.05; p=0.03). Sleep interventions also led to significant improvements in depressive symptoms (SMD: -0.80; 95%CI: -1.21, -0.39; p<0.01). Future research should focus on developing more multidimensional lifestyle interventions for a potentially greater impact on clinical and functional outcomes of BD.

Keywords: Bipolar disorder; lifestyle interventions; systematic review; meta-analysis; RCT; lifestyle psychiatry; lifestyle medicine; diet; exercise; substance use; stress; sleep; social relationships;

5.1 Introduction

Bipolar Disorder (BD) is a severe mental health disorder associated with poor quality of life (Pascual-Sanchez et al., 2019), functional and cognitive impairment (Rosa et al., 2014; Van Rheenen et al., 2020), and increased suicide risk (Sverdlichenko et al., 2020). Individuals with BD are also at an increased risk for physical health problems, obesity, cardiovascular problems, and early mortality (Fiedorowicz et al., 2008), often driven by the daily lifestyle habits of the individual (Kapczinski et al., 2017; Malhotra et al., 2016). Importantly, a recent large cohort study found that BD was associated with elevated risk of receiving disability services, emphasizing that effective early intervention strategies targeting the improvement of the clinical trajectory of this disorder are necessary (Frey et al., 2020).

Lifestyle Medicine (LM) is an area of medicine which focuses on the prevention, treatment and management of chronic, non-communicable diseases using evidence-based behavioural interventions (Rippe, 2019). According to the American College of Lifestyle Medicine (ACLM), there are six essential pillars of LM: diet, physical activity, avoiding substance use, stress management, restorative sleep, and social relationships (Katz and Karlsen, 2019). The predominant focus of LM on these six domains stems from the perception of them as “modifiable factors”, given that daily patterns can be altered and promoting healthier behaviours in these areas could reduce the risk of aggregating mental and physical health problems (Hyman et al., 2009; Velten et al., 2014). Recent literature has showed that unhealthy lifestyle behaviours tend to cluster, but most interventions thus far have only targeted one or two lifestyle domains (mostly diet and physical activity).

Evidence on the effectiveness of multidimensional interventions is scarce (Castro et al., 2021; De Boni et al., 2021; Firth et al., 2019).

The growing field of Lifestyle Psychiatry (LP) is aimed at the treatment and even prevention of severe and common mental disorders (Firth et al., 2020). The benefits of implementing LP interventions to improve mental health and wellbeing have been widely investigated. Previous literature has established the close relationships between BD and dietary/nutritional, physical activity, sleep, and substance abuse patterns, advising for the implementation of interventive strategies to improve the severity of mood symptoms, social functioning, and overall quality of life, among other key outcomes (Harvey et al., 2015a; Lopresti and Jacka, 2015; Melo et al., 2016; Quello et al., 2005). Moreover, chronic stress management and healthy social support play a key role in maintaining mood stability in people with BD (Kim et al., 2007; Owen et al., 2017). Indeed, growing evidence has highlighted the importance of lifestyle management in patients with BD for improving rates of recovery (Frank et al., 1997), reducing clinical symptoms (Huang et al., 2018), and improving quality of life (Malhotra et al., 2016). However, most interventions in BD to date have approached these domains as independent risk factors for the onset and progression of the disorder. The multidimensional evaluation of lifestyle behaviours has been suggested as a possible way forward to improve health outcomes (Balanzá-Martínez et al., 2021; Castro et al., 2021). In this regard, the development of multidimensional intervention strategies, including digital interventions, holds promise to benefit people with BD (Firth et al., 2020).

To date, a systematic review by Bauer et al. (2016) found that lifestyle interventions targeting nutrition, exercise, and wellbeing are feasible and show promise for developing multi-modal interventions for patients with BD (Bauer et al., 2016). However, this previous review only focused on two of the six lifestyle domains, namely diet/nutrition and physical activity. A more recent meta-review of meta-analyses investigating effective lifestyle interventions for mental disorders, including BD, focused on meta-analyses of diet, physical activity, smoking cessation, and sleep interventions for mental disorders (Firth et al., 2020). However, there were no reports of any meta-analyses on interventions for BD across any of the four domains included in this meta-review. While there is clinical evidence showing the association between worse lifestyle patterns and BD (Beyer and Payne, 2016; Bridi et al., 2018; Vancampfort et al., 2013), to the best of our knowledge, there are no systematic reviews investigating the availability of interventions in all six domains, and the effects of multidimensional interventions for improvement of meaningful/relevant outcomes in BD.

Thus, the current systematic review has four primary aims: (1) to describe which lifestyle domains are most frequently targeted for interventions in BD, (2) to describe the proportion of interventions that are targeting single versus multiple domains, (3) to compare the effectiveness of single vs multidimensional interventions, and (4) to describe the effectiveness of interventions on each domain in terms of symptom improvement, change in lifestyle behaviours, improvement in functioning, quality of life, and circadian rhythms regulation. As secondary aims, we also explored which lifestyle domains are most

frequently targeted together for BD, as well as the prevalence of digital lifestyle interventions in comparison to more traditional/conventional interventions.

5.2 Methods

5.2.1 Search Strategy and Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for the present review (Arya et al., 2021). The systematic review has been registered by the International Prospective Register of Systematic Reviews (PROSPERO) under registration ID: CRD42022346102.

A literature search without language or year restriction was conducted on January 6th, 2022 using the following databases: PubMed, Embase, and Cochrane Library. We searched for a combination of the following search terms: (‘Bipolar Disorder’ OR ‘Bipolar Disorders’ OR ‘Mania’ OR ‘Bipolar Affective Disorders’ OR ‘Manic-Depressive Psychosis’) AND (‘Lifestyle’ OR ‘Life Style’ OR ‘Lifestyles’ OR ‘Life Styles’) AND (‘Intervention’ OR ‘RCT’ OR ‘Randomized Controlled Trial’). After removal of duplicated references, the articles were assessed for eligibility independently by two blind reviewers (MS and SP) who determined if studies met the inclusion criteria. Any disagreements between the two raters were resolved by consensus in a meeting with a third researcher (TAC). Firstly, the raters screened articles based on the title and abstract. Then, the researchers screened the selected relevant articles by full text. Finally, the reference lists of the selected articles after the full text screening were manually searched for any other studies that meet the inclusion criteria but did not appear in the electronic search.

5.2.2 Inclusion and Exclusion Criteria

To determine whether an article was relevant to our study, we used the following PICOS inclusion criteria:

1) **P**opulation: Adults (18+) with a clinical diagnosis of bipolar disorder;
2) **I**ntervention: In-person and/or digital interventions on any of the following lifestyle domains: diet, physical activity, substance abuse, sleep, social relationships, and stress management. Studies were eligible if the interventions were promoting healthy behaviours on one or more of the lifestyle domains by suggesting specific actions/goals;
3) **C**omparison: No intervention or any other intervention that is not an active lifestyle intervention or novel medication treatments;
4) **O**utcomes: Efficacy of intervention on (1) BD mood symptoms improvement, (2) lifestyle domain changes, (3) functioning, (4) quality of life, and/or (5) circadian rhythms regulation;
5) **S**tudy Design: Randomized controlled trials.

The exclusion criteria were any reviews, meta-analyses, case reports, observational studies, study protocols, articles unavailable in English language, and any other types of publications different from full articles, such as conference abstracts, letters, or comments to the editor.

5.2.3 Data Extraction

Two researchers (MS and SP) completed the data extraction process using Excel spreadsheet (Microsoft 365). The developed spreadsheet was created by the researchers and calibrated before starting the data extraction. The following information was extracted from each included study: publication description (author(s), journal, year, country), diagnostic criteria and method of diagnosis of BD, types of BD included, current mood state of included participants, targeted lifestyle domains for the intervention, sample description of the intervention and control groups (sample size, mean age), classification of intervention as traditional or digital, number of intervention sessions, time points assessed, types of outcomes assessed and the method of assessment, and effectiveness of the intervention on the outcomes. Descriptions of extracted data variables are presented in Table 1.

5.2.4 Quality Assessment

Each manuscript included in the review was independently assessed by two blinded researchers (MS and SP) using the Cochrane Risk of Bias Tool for randomized controlled trials (Higgins et al., 2011). This tool assesses for selection bias (random sequence generation and allocation concealment), reporting bias (selective reporting), performance bias (blinding participants and personnel), detection bias (blinding outcome assessments), attrition bias (incomplete outcome data), and other bias (other sources of bias). Disagreements were resolved by consensus in a meeting with a third researcher (TAC).

5.2.5 Meta-Analyses

Random effects meta-analyses were performed using the Review Manager software (version 5.4, Cochrane Training). We conducted a meta-analysis to assess the efficacy of interventions targeting the same domains across different RCT studies. For this purpose, we performed multiple meta-analyses by grouping data from studies that 1) included the same number of lifestyle domains in their interventions, 2) targeted the same lifestyle domains and, 3) same outcomes of interest. Studies were eligible for inclusion in the meta-analysis if 1) raw values of outcome assessments were available in the published article for baseline and endpoint measurements for each group, and 2) there were no significant differences ($p>0.05$) between the intervention and control groups on the outcome assessments at baseline. The values included in the meta-analysis were from the last timepoint of measurement for each study, as the intervention and measurement durations varied between the studies. We performed meta-analysis only if the studies fit these criteria, and if there were at least two different studies targeting the same lifestyle domain and the same outcome. We analyzed the reported sample sizes, means, and standard deviations for each outcome assessment, and used this data to compute the mean difference (if the same tool was used to assess the outcome across different studies) or the standardized mean difference (if different tools were used to assess the outcome across the studies) on the tests between the intervention and the control groups. Significance was set as $p<0.05$. Cochrane's Q test was performed to assess for statistical heterogeneity and the Higgins I2 statistic was used to determine the extent of variation between sample estimates with values ranging from 0-100%.

5.3 Results

The search strategy yielded 706 articles (PubMed= 460, Embase= 149, and Cochrane Library= 97), with 650 remaining after duplicate removal. Of these, 594 studies were excluded as their titles and abstracts were not relevant to the research topic, leaving 56 potentially eligible studies for which the full text was reviewed. After this stage, 42 studies did not meet the inclusion criteria as 15 were registration trials only, 11 studies did not have results specifically for BD as the sample was not entirely of individuals with BD, 6 did not include a lifestyle intervention defined by the ACLM, 4 were published as a conference abstract or poster only, 2 were not RCTs, 2 did not include participants with BD, 1 was published as a protocol only, and 1 had an overlapping sample with another included study. Following the full-text screening, 4 additional studies that met the inclusion criteria were found during the hand-searching process, resulting in a total of 18 studies to be included in the systematic review (Figure 1).

5.3.1 Characteristics of Included Studies

Table 2 provides a summary of all included studies. All RCTs were published between 1997 (Frank et al., 1997) and 2021 (Murray et al., 2021) with total sample sizes ranging from 23 (Henriksen et al., 2016) to 302 (Murray et al., 2021) participants. Among all included studies, 9 were conducted in the United States of America (Depp et al., 2015; Frank et al., 2015, 1997; Harvey et al., 2015b; Kaplan et al., 2018; Kilbourne et al., 2012; Miklowitz et al., 2007; Sit et al., 2018; Sylvia et al., 2019), and the rest were single studies conducted in Spain (Colom et al., 2003), Japan (Esaki et al., 2020), Switzerland (Gillhoff et al., 2010), Italy (Goracci et al., 2016), Norway (Henriksen et al., 2016), Pakistan (Husain

et al., 2017), New Zealand (Inder et al., 2015), Australia (Murray et al., 2021), and the United Kingdom (Todd et al., 2014). Although all studies aimed to investigate the effects of a lifestyle intervention in patients with BD, the type of intervention they employed or the number of domains that each intervention targeted differed between each study.

5.3.2 Risk of Bias assessment

The Cochrane Risk of Bias Tool for randomized controlled trials was utilized to assess the included studies (Table 3). We identified a high risk of performance bias in 8 out of the 18 included RCT studies (Colom et al., 2003; Depp et al., 2015; Gillhoff et al., 2010; Goracci et al., 2016; Harvey et al., 2015b; Husain et al., 2017; Sylvia et al., 2019; Todd et al., 2014). We found that performance bias may have been present in these studies due to improper blinding of the participants and study personnel from knowing the participants allocation in the intervention or control condition. In addition, we found one study to be at a high risk of detection bias, where the outcome assessors were not blind to whether the participants were part of the intervention or the control condition at the time of assessment (Henriksen et al., 2016). All other measures in the Cochrane Risk of Bias Tool showed low or unclear risk of bias for the rest of the studies.

5.3.3 Descriptive Results of Lifestyle Interventions on individuals with BD

Two studies seemed to target multiple lifestyle domains, but failed to indicate the specific lifestyle domains their respective interventions were targeting, and therefore were not included in any of the analysis (Depp et al., 2015; Todd et al., 2014). Both of these studies used digital interventions, named ‘Living with Bipolar’ (Todd et al., 2014) and Personalized Real-Time Intervention for Stabilizing Mood (PRISM) (Depp et al., 2015) in

which participants had access to digital interactive self-monitoring strategies for symptom management. The 'Living with Bipolar' intervention was more effective than treatment as usual for improving psychological and physical quality of life, overall wellbeing, and clinical recovery (Todd et al., 2014), while the PRISM condition was more effective than paper-and-pencil condition for improving depressive symptoms, but not manic symptoms or overall functioning (Depp et al., 2015).

We found that of the 16 studies included in the descriptive analysis, 5 (31.3%) targeted a single domain in their interventions and 11 (68.7%) targeted multiple lifestyle domains in their intervention, indicating that majority of active lifestyle interventions so far have included at least 2 different domains (Figure 2A). Among the most targeted domains for lifestyle interventions were the more 'traditional' areas of lifestyle, such as sleep (n = 10), physical activity (n = 9), and diet (n = 8), while other areas such as substance use, social relationships, and stress management (n = 4 each) have been less included (Figure 2B).

Up to January of 2022, there were 11 published RCT studies with multidimensional lifestyle interventions of BD, of which 4 studies targeted 2 domains (Colom et al., 2003; Husain et al., 2017; Kilbourne et al., 2012; Sylvia et al., 2019), 2 targeted 3 domains (Gillhoff et al., 2010; Kaplan et al., 2018), and 5 targeted 4 domains (Frank et al., 2015, 1997; Goracci et al., 2016; Inder et al., 2015; Miklowitz et al., 2007). Intriguingly, there were no multidimensional interventions that targeted all 6 core areas of lifestyle.

Among the multidimensional interventions, we found that diet and physical activity were most commonly targeted together (8/11 studies) (Figure 2C). There was a large heterogeneity among the types, methods, and duration of interventions across the studies. The Interpersonal and Social Rhythm Therapy (IPSRT) was the most commonly implemented multidimensional intervention, with 3 studies including this therapy that promotes healthy behaviours in diet, physical activity, sleep, and social relationships (Frank et al., 1997; Inder et al., 2015; Miklowitz et al., 2007).

Looking at the types of interventions used, out of the 18 studies included in this review only 3 (16.7%) studies used digital interventions (smartphone apps, online platforms) (Depp et al., 2015; Murray et al., 2021; Todd et al., 2014), while the other 15 (83.3%) studies used a traditional/conventional intervention (in-person sessions, pen/paper method, phone calls, etc.) (Figure 2D).

5.3.4 Effectiveness of Lifestyle Interventions for BD

The efficacy of interventions targeting different numbers of domains was analyzed based on improvements in any of the 5 outcomes of interest in comparison to the control conditions. In Table 4, we described the proportion of effective interventions out of the total number of studies with the same number of domains in the intervention and targeting the same outcomes. Majority of the interventions that were considered ‘not effective’ still led to significant improvements within the intervention group, but there were non-significant differences in comparison to improvements in the control conditions. Although there was a small number of studies within each group, there was a trend of higher efficacy rates among interventions targeting 3 or 4 domains in comparison to interventions aimed

at 1 or 2 domains. In particular, improvements in severity of depressive or manic symptoms, overall functioning, and circadian rhythm appear to be more likely when the lifestyle interventions include 3 or 4 domains relative to interventions on 1 or 2 domains. Furthermore, our analysis also revealed a lack of studies targeting some of the outcomes which are very important and greatly affected in BD, such as overall functioning, quality of life, and circadian rhythm regulation.

5.3.5 Meta-analysis – Diet/Nutrition and Physical Activity

The 2 studies including multidimensional interventions targeting at diet and physical activity both included severity of BD symptoms and overall functioning as outcomes. For depressive symptoms, 1 study evaluated severity according to Montgomery–Åsberg Depression Rating Scale (MADRS), and the other study used the Internal State Scale (ISS) (Kilbourne et al., 2012; Sylvia et al., 2019). The 2 studies made up for a total of 45 patients in the intervention group, and 45 patients in the control group. The meta-analysis showed significant differences between scores in the intervention and control groups, with a standardized mean difference of -0.46 (95% CI: -0.88, -0.04, p=0.03), suggesting a greater improvement of depressive symptoms in the intervention group in comparison to the control group (Figure 3A). Improvement of manic symptoms was evaluated according to the Young Mania Rating Scale (YMRS) and ISS (Kilbourne et al., 2012; Sylvia et al., 2019). There were no significant differences in improvement of manic symptoms between the 2 groups, with a standardized mean difference of -0.46 (95% CI: -1.18, 0.25, p=0.20) (Figure 3B). Improvement in overall functioning was assessed using the World Health Organization Disability Assessment Scale (WHODAS) and the

Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE RIFT). There were significant differences between the groups in overall functioning at the last assessment point, with a standardized mean difference of -0.47 (95% CI: -0.89, -0.05, p=0.03) (Figure 3C), suggesting a reduction in functional impairment among the intervention group.

5.3.6 Meta-analysis – Sleep

Among the single-domain interventions, 2 focused solely on the sleep domain aiming to improve severity of depressive symptoms and change in sleep patterns. To evaluate improvement in depressive symptoms, 1 study used the MADRS scale, and the other study the Inventory of Depressive Symptomatology: Clinician (IDS-C) assessment (Esaki et al., 2020; Harvey et al., 2015b). The studies combined for a total of 51 patients in the intervention group, and 50 in the control group. We found a significant difference between the groups in scores on the abovementioned assessments, with a standardized mean difference of -0.80 (95% CI: -1.21, -0.39, $p<0.01$), suggesting greater reduction in severity of depressive symptoms in the intervention group in comparison to the control group (Figure 3D).

The 2 studies also aimed to improve sleep disturbances in this sample, both of which used the Insomnia Severity Index (ISI) to assess the efficacy of their interventions (Esaki et al., 2020; Harvey et al., 2015b). However, we did not find any differences between the intervention and the control group in the scores on this scale, with a mean difference of -3.43 (95% CI: -8.04, 1.19, p=0.15) (Figure 3E).

5.4 Discussion

To our knowledge, this is the first systematic review and meta-analysis investigating the availability and efficacy of lifestyle interventions for BD, focusing on the six essential domains of lifestyle psychiatry. In this systematic review, we found that majority of the RCT studies on lifestyle interventions for BD have targeted more than one lifestyle domain, however, none of them have included an intervention on all six core areas of lifestyle. According to the current guidelines of LP, a multidimensional approach to interventions focused on various lifestyle behaviours can be more beneficial for psychiatric symptoms and the overall clinical trajectory of the disorder (Firth et al., 2019). Based on the analysis of the current review, multidimensional interventions including a higher number of domains appear to have a higher probability of being effective in improving the outcomes of interest relative to interventions focused on one or two domains.

Our descriptive analyses revealed that sleep, diet, and physical activity were the most frequently targeted lifestyle domains. These findings are in line with previous literature, considering the significance of sleep disturbances in BD, and the focus on diet and physical activity as fundamental factors for promoting a healthy lifestyle. Sleep disturbance is indeed a common symptom of BD which appears frequently across any mood state of the disorder (Harvey et al., 2009; Plante and Winkelman, 2008), hence a lot of attention has been aimed at developing effective sleep management strategies for affected individuals. Moreover, in addition to diet and physical activity being the key areas for a healthy lifestyle (Castro et al., 2021; Koehler and Drenowatz, 2019), extensive literature has suggested the combined efforts for improving physical activity and nutrition

may have a greater effect on the clinical trajectory of BD, such as decreased severity of mood episodes, improved overall functioning and cognitive functioning, and reduced risk of cardiovascular comorbidities (Balanzá-Martínez et al., 2020; Bauer et al., 2016; Kilbourne et al., 2007; Miskowiak et al., 2022). These results are in line with our findings, considering that 8 studies in our review had included an intervention targeting both diet and physical activity (Frank et al., 2015, 1997; Gillhoff et al., 2010; Goracci et al., 2016; Kilbourne et al., 2007; Miklowitz et al., 2007; Sylvia et al., 2019). In contrast, we found that substance use, stress management, and social relationships were less targeted, with only 4 interventions aimed at each one of these domains separately, an unexpected finding considering the close association between these domains and BD. Given that substance abuse is a known risk factor for the development of BD and triggering the onset of (hypo)manic symptoms (Lalli et al., 2021), more focus is needed on preventing and improving this domain. Likewise, chronic stress in everyday life is associated with reduced improvement of mood symptoms in BD (Kim et al., 2007), and people with BD are more likely to engage in maladaptive coping mechanisms during stressful periods (Bridi et al., 2018). Promoting healthy stress management techniques should be considered as an essential part of lifestyle treatment strategies. Furthermore, social support is another extremely important area for improvement of the clinical trajectory of BD, since lack of quality social support may increase the risk of relapse in BD (Cohen et al., 2004; Johnson et al., 2003). The development and inclusion of more interventions targeting these domains is essential for improving symptom reoccurrence, functioning, and quality of life of individuals with BD.

Another interesting finding was the relatively small number of RCT studies with digital lifestyle interventions for BD, with only 3 studies looking at the efficacy of digital interventions (Depp et al., 2015; Murray et al., 2021; Todd et al., 2014). With the recent rise of digital health, it is important to develop standardized, effective lifestyle interventions that are easily accessible to individuals in need. This approach is particularly significant following the COVID-19 pandemic, which demonstrated the importance of instant access to helpful, cost-effective interventions and the increased use of technology for those needs (Castro et al., 2021). Although promising, further work is required to refine the existing digital techniques for improving the essential lifestyle behaviours that are necessary for long-term mental health outcomes. In line with this idea, findings from a recent meta-analysis on smartphone-based interventions for BD conducted by the International Society for Bipolar Disorders (ISBD) Big Data task force did not find any evidence supporting the idea that smartphone interventions may reduce the severity of mood symptoms in BD, reporting high heterogeneity among existing studies and interventions, and suggesting the need for a more standardized approach of studies before making conclusive statements on their effectiveness (Anmella et al., 2022).

Despite the small number of studies included in our meta-analyses, we found promising results for the efficacy of diet, physical activity, and sleep interventions on reducing depressive symptoms and improving overall functioning in BD. These findings further support the existing evidence of the relationships between healthy dietary, physical activity, and sleep behaviours with improvement in severity of depressive symptoms (Archer et al., 2014; Cervera-Martínez et al., 2021; Gee et al., 2019; Ljungberg et al., 2020).

Moreover, it appears that engaging in healthier dietary and exercising patterns also improves overall functioning across different areas of everyday life for individuals with BD. However, more RCT studies involving all six lifestyle domains are needed to evaluate the effectiveness of lifestyle interventions on a larger scale, and the potential for long-term positive impacts in these clinical and functional outcomes.

Given the lack of consensus of the concept of lifestyle, in addition to the complex nature of symptoms in BD, further work is required for the development of effective lifestyle interventions for BD. Perhaps a more personalized approach to assessment, treatment, and prevention of unhealthy lifestyle behaviours may be more efficient when addressing symptoms of BD. The need for a personalized assessment of behaviours across different lifestyle areas has progressed with the development of comprehensive assessments such as the Short Multidimensional Inventory Lifestyle Evaluation (SMILE), which evaluates behaviours across all six domains as recommended by the ACLM (Balanzá-Martínez et al., 2021). An assessment such as the SMILE scale has the ability to simultaneously evaluate multiple lifestyle domains and indicate the primary focus for improvement. Close monitoring different lifestyle domains would allow for finding the most effective intervention strategies for each affected individual (Castro et al., 2021).

Our findings should be interpreted considering some limitations. First, we detected a high risk of performance bias in 8 of the 18 studies included, although this type of bias is expected in RCT studies assessing psychological interventions, considering that it is difficult to blind who is delivering and who is receiving the intervention. Another limitation is the small number of studies included in the meta-analysis, having included 2 studies for

each analysis. However, despite of these limitations, this is the first systematic review and meta-analysis describing the efficacy of interventions for BD targeting the six fundamental lifestyle domains according to contemporary views and showing the differences in efficacy of the interventions across different domains and outcomes. Moreover, our systematic review emphasizes the importance of promoting healthy behaviours across multiple domains of lifestyle using multidimensional interventions and highlights the need for more interventions targeting important areas for BD, such as substance use, stress management, and social support.

Considering the complexity of symptoms associated with BD, along with the complex interactions of different areas of everyday life, it is important to develop assessments and interventions for BD with a more holistic approach to lifestyle factors. The implementation of multi-modal lifestyle assessments could be beneficial for investigating the relationship between multiple lifestyle factors to clinical symptoms of BD, which would open the opportunity for more personalized interventions attending to each individual's specific needs.

5.5 Conflict of Interest

MS, SP, TAC, BNF, RDB, and LM have nothing to disclose.

VB-M has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini, Lundbeck, and Nutrición Médica, all of them unrelated to the present work. FK has been a consultant for Janssen - Johnson & Johnson, unrelated to the present work.

5.6 References

Anmella, G., Faurholt-Jepsen, M., Hidalgo-Mazzei, D., Radua, J., Passos, I.C., Kapczinski, F., Minuzzi, L., Alda, M., Meier, S., Hajek, T., 2022. Smartphone-based interventions in bipolar disorder: systematic review and meta-analyses of efficacy. A position paper from the International Society for Bipolar Disorders (ISBD) Big Data Task Force. Bipolar Disorders.

Archer, T., Josefsson, T., Lindwall, M., 2014. Effects of physical exercise on depressive symptoms and biomarkers in depression. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 13, 1640–1653.

Arya, S., Kaji, A.H., Boermeester, M.A., 2021. PRISMA reporting guidelines for meta-analyses and systematic reviews. JAMA surgery 156, 789–790.

Balanzá-Martínez, V., Kapczinski, F., de Azevedo Cardoso, T., Atienza-Carbonell, B., Rosa, A.R., Mota, J.C., De Boni, R.B., 2021. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. Revista de psiquiatria y salud mental 14, 16–26.

Balanzá-Martínez, V., Shansis, F.M., Tatay-Manteiga, A., López-García, P., 2020. Diet and Neurocognition in Mood Disorders - An Overview of the Overlooked. Curr Pharm Des 26, 2353–2362. https://doi.org/10.2174/1381612826666200318152530

Bauer, I.E., Galvez, J.F., Hamilton, J.E., Balanza-Martinez, V., Zunta-Soares, G.B., Soares, J.C., Meyer, T.D., 2016. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. Journal of psychiatric research 74, 1–7.

Beyer, J.L., Payne, M.E., 2016. Nutrition and bipolar depression. Psychiatric Clinics 39, 75–86.

Bridi, K.P.B., Loredo-Souza, A.C.M., Fijtman, A., Moreno, M.V., Kauer-Sant'Anna, M., Ceresér, K.M.M., Kunz, M., 2018. Differences in coping strategies in adult patients with bipolar disorder and their first-degree relatives in comparison to healthy controls. Trends Psychiatry Psychother. 40, 318–325. https://doi.org/10.1590/2237-6089-2017-0140

Castro, R., Ribeiro-Alves, M., Oliveira, C., Romero, C.P., Perazzo, H., Simjanoski, M., Kapciznki, F., Balanzá-Martínez, V., De Boni, R.B., 2021. What are we measuring when we evaluate digital interventions for improving lifestyle? a scoping meta-review. Frontiers in public health 9.

Cervera-Martínez, J., Atienza-Carbonell, B., Mota, J.C., Bobes-Bascarán, T., Crespo-Facorro, B., Esteban, C., García-Portilla, M.P., Gomes-da-Costa, S., González-Pinto, A., Jaén-Moreno, M.J., 2021. Lifestyle changes and mental health during the COVID-19 pandemic: A repeated, cross-sectional web survey. Journal of Affective Disorders 295, 173–182.

Cohen, A.N., Hammen, C., Henry, R.M., Daley, S.E., 2004. Effects of stress and social support on recurrence in bipolar disorder. Journal of affective disorders 82, 143–147.

Colom, F., Vieta, E., Reinares, M., Martínez-Arán, A., Torrent, C., Goikolea, J.M., Gastó, C., 2003. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. J Clin Psychiatry 64, 1101–1105. https://doi.org/10.4088/jcp.v64n0917

De Boni, R.B., Ribeiro-Alves, M., Mota, J.C., Gomes, M., Balanzá-Martínez, V., Kapczinski, F., Bastos, F.I., 2021. The cumulative effect of multiple dimensions of lifestyle on risky drinking during the Covid-19 pandemic. Preventive medicine 150, 106718.

Depp, C.A., Ceglowski, J., Wang, V.C., Yaghouti, F., Mausbach, B.T., Thompson, W.K., Granholm, E.L., 2015. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. Journal of affective disorders 174, 23–30.

Esaki, Y., Takeuchi, I., Tsuboi, S., Fujita, K., Iwata, N., Kitajima, T., 2020. A double-blind, randomized, placebo-controlled trial of adjunctive blue-blocking glasses for the treatment of sleep and circadian rhythm in patients with bipolar disorder. Bipolar Disorders 22, 739–748.

Fiedorowicz, J.G., Palagummi, N.M., Forman-Hoffman, V.L., Miller, D.D., Haynes, W.G., 2008. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Annals of Clinical Psychiatry 20, 131–137.

Firth, J., Solmi, M., Wootton, R.E., Vancampfort, D., Schuch, F.B., Hoare, E., Gilbody, S., Torous, J., Teasdale, S.B., Jackson, S.E., 2020. A meta-review of “lifestyle psychiatry”: the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry 19, 360–380.

Firth, J., Ward, P.B., Stubbs, B., 2019. Lifestyle psychiatry. Frontiers in psychiatry 10, 597.

Frank, E., Hlastala, S., Ritenour, A., Houck, P., Tu, X.M., Monk, T.H., Mallinger, A.G., Kupfer, D.J., 1997. Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. Biological Psychiatry 41, 1165–1173.

Frank, E., Wallace, M.L., Hall, M., Hasler, B., Levenson, J.C., Janney, C.A., Soreca, I., Fleming, M.C., Buttenfield, J., Ritchey, F.C., 2015. An Integrated Risk Reduction Intervention can reduce body mass index in individuals being treated for bipolar I disorder: results from a randomized trial. Bipolar disorders 17, 424–437.

Frey, B.N., Vigod, S., de Azevedo Cardoso, T., Librenza-Garcia, D., Favotto, L., Perez, R., Kapczinski, F., 2020. The Early Burden of Disability in Individuals With Mood and Other Common Mental Disorders in Ontario, Canada. JAMA network open 3, e2020213–e2020213.

Gee, B., Orchard, F., Clarke, E., Joy, A., Clarke, T., Reynolds, S., 2019. The effect of non-pharmacological sleep interventions on depression symptoms: a meta-analysis of randomised controlled trials. Sleep Medicine Reviews 43, 118–128.

Gillhoff, K., Gaab, J., Emini, L., Maroni, C., Tholuck, J., Greil, W., 2010. Effects of a multimodal lifestyle intervention on body mass index in patients with bipolar disorder: a randomized controlled trial. The Primary Care Companion for CNS Disorders 12, 26299.

Goracci, A., Rucci, P., Forgione, R.N., Campinoti, G., Valdagno, M., Casolaro, I., Carretta, E., Bolognesi, S., Fagiolini, A., 2016. Development, acceptability and efficacy

of a standardized healthy lifestyle intervention in recurrent depression. Journal of Affective Disorders 196, 20–31.

Harvey, A.G., Kaplan, K.A., Soehner, A.M., 2015a. Interventions for sleep disturbance in bipolar disorder. Sleep medicine clinics 10, 101–105.

Harvey, A.G., Soehner, A.M., Kaplan, K.A., Hein, K., Lee, J., Kanady, J., Li, D., Rabe-Hesketh, S., Ketter, T.A., Neylan, T.C., 2015b. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. Journal of consulting and clinical psychology 83, 564.

Harvey, A.G., Talbot, L.S., Gershon, A., 2009. Sleep disturbance in bipolar disorder across the lifespan. Clinical Psychology: Science and Practice 16, 256.

Henriksen, T.E., Skrede, S., Fasmer, O.B., Schoeyen, H., Leskauskaite, I., Bjørke-Bertheussen, J., Assmus, J., Hamre, B., Grønli, J., Lund, A., 2016. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar disorders 18, 221–232.

Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 343.

Huang, J., Yuan, C.M., Xu, X.R., Wang, Yong, Hong, W., Wang, Z.W., song Su, Y., Hu, Y.Y., Cao, L., Wang, Yu, 2018. The relationship between lifestyle factors and clinical

symptoms of bipolar disorder patients in a Chinese population. Psychiatry Research 266, 97–102.

Husain, M.I., Chaudhry, I.B., Rahman, R.R., Hamirani, M.M., Mehmood, N., Haddad, P.M., Hodsoll, J., Young, A.H., Naeem, F., Husain, N., 2017. Pilot study of a culturally adapted psychoeducation (CaPE) intervention for bipolar disorder in Pakistan. International journal of bipolar disorders 5, 1–9.

Hyman, M.A., Ornish, D., Roizen, M., 2009. Lifestyle medicine: treating the causes of disease. Alternative Therapies in Health & Medicine 15, 12.

Inder, M.L., Crowe, M.T., Luty, S.E., Carter, J.D., Moor, S., Frampton, C.M., Joyce, P.R., 2015. Randomized, controlled trial of Interpersonal and Social Rhythm Therapy for young people with bipolar disorder. Bipolar disorders 17, 128–138.

Johnson, L., Lundström, O., Åberg-Wistedt, A., Mathé, A.A., 2003. Social support in bipolar disorder: its relevance to remission and relapse. Bipolar Disorders 5, 129–137.

Kapczinski, N.S., Mwangi, B., Cassidy, R.M., Librenza-Garcia, D., Bermudez, M.B., Kauer-Sant'anna, M., Kapczinski, F., Passos, I.C., 2017. Neuroprogression and illness trajectories in bipolar disorder. Expert review of neurotherapeutics 17, 277–285.

Kaplan, K.A., Talavera, D.C., Harvey, A.G., 2018. Rise and shine: A treatment experiment testing a morning routine to decrease subjective sleep inertia in insomnia and bipolar disorder. Behaviour research and therapy 111, 106–112.

Katz, D.L., Karlsen, M.C., 2019. The need for a whole systems approach to evidence evaluation: an update from the American College of Lifestyle Medicine. The Journal of Alternative and Complementary Medicine 25, S19–S20.

Kilbourne, A.M., Goodrich, D.E., Lai, Z., Clogston, J., Waxmonsky, J., Bauer, M.S., 2012. Life Goals Collaborative Care for patients with bipolar disorder and cardiovascular disease risk. Psychiatric Services 63, 1234–1238.

Kilbourne, A.M., Rofey, D.L., McCarthy, J.F., Post, E.P., Welsh, D., Blow, F.C., 2007. Nutrition and exercise behaviour among patients with bipolar disorder 1. Bipolar disorders 9, 443–452.

Kim, E.Y., Miklowitz, D.J., Biuckians, A., Mullen, K., 2007. Life stress and the course of early-onset bipolar disorder. Journal of affective disorders 99, 37–44.

Koehler, K., Drenowatz, C., 2019. Integrated role of nutrition and physical activity for lifelong health. Nutrients.

Lalli, M., Brouillette, K., Kapczinski, F., de Azevedo Cardoso, T., 2021. Substance use as a risk factor for bipolar disorder: A systematic review. J Psychiatr Res 144, 285–295. https://doi.org/10.1016/j.jpsychires.2021.10.012

Ljungberg, T., Bondza, E., Lethin, C., 2020. Evidence of the importance of dietary habits regarding depressive symptoms and depression. International journal of environmental research and public health 17, 1616.

Lopresti, A.L., Jacka, F.N., 2015. Diet and bipolar disorder: a review of its relationship and potential therapeutic mechanisms of action. The Journal of Alternative and Complementary Medicine 21, 733–739.

Malhotra, N., Kulhara, P., Chakrabarti, S., Grover, S., 2016. Lifestyle related factors & impact of metabolic syndrome on quality of life, level of functioning & self-esteem in patients with bipolar disorder & schizophrenia. The Indian journal of medical research 143, 434.

Melo, M.C.A., Daher, E.D.F., Albuquerque, S.G.C., de Bruin, V.M.S., 2016. Exercise in bipolar patients: a systematic review. Journal of affective disorders 198, 32–38.

Miklowitz, D.J., Otto, M.W., Frank, E., Reilly-Harrington, N.A., Wisniewski, S.R., Kogan, J.N., Nierenberg, A.A., Calabrese, J.R., Marangell, L.B., Gyulai, L., 2007. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Archives of general psychiatry 64, 419–426.

Miskowiak, K.W., Seeberg, I., Jensen, M.B., Balanzá-Martínez, V., Del Mar Bonnin, C., Bowie, C.R., Carvalho, A.F., Dols, A., Douglas, K., Gallagher, P., Hasler, G., Lafer, B., Lewandowski, K.E., López-Jaramillo, C., Martinez-Aran, A., McIntyre, R.S., Porter, R.J., Purdon, S.E., Schaffer, A., Stokes, P., Sumiyoshi, T., Torres, I.J., Van Rheenen, T.E., Yatham, L.N., Young, A.H., Kessing, L.V., Burdick, K.E., Vieta, E., 2022. Randomised controlled cognition trials in remitted patients with mood disorders published between 2015 and 2021: A systematic review by the International Society for

Bipolar Disorders Targeting Cognition Task Force. Bipolar Disord 24, 354–374. https://doi.org/10.1111/bdi.13193

Murray, G., Thomas, N., Michalak, E.E., Jones, S.H., Lapsley, S., Bowe, S.J., Foley, F., Fletcher, K., Perich, T., Johnson, S.L., 2021. Mindfulness-based online intervention to improve quality of life in late-stage bipolar disorder: A randomized clinical trial. Journal of Consulting and Clinical Psychology 89, 830.

Owen, R., Gooding, P., Dempsey, R., Jones, S., 2017. The reciprocal relationship between bipolar disorder and social interaction: A qualitative investigation. Clinical psychology & psychotherapy 24, 911–918.

Pascual-Sanchez, A., Jenaro, C., Montes-Rodríguez, J.M., 2019. Quality of life in euthymic bipolar patients: a systematic review and meta-analysis. Journal of affective disorders 255, 105–115.

Plante, D.T., Winkelman, J.W., 2008. Sleep disturbance in bipolar disorder: therapeutic implications. American Journal of Psychiatry 165, 830–843.

Quello, S.B., Brady, K.T., Sonne, S.C., 2005. Mood disorders and substance use disorder: a complex comorbidity. Science & practice perspectives 3, 13.

Rippe, J.M., 2019. Lifestyle medicine. CRC Press.

Rosa, A.R., Magalhães, P.V., Czepielewski, L., Sulzbach, M.V., Goi, P.D., Vieta, E., Gama, C.S., Kapczinski, F., 2014. Clinical staging in bipolar disorder: focus on cognition and functioning. The Journal of clinical psychiatry 75, 2951.

Sit, D.K., McGowan, J., Wiltrout, C., Diler, R.S., Dills, J., Luther, J., Yang, A., Ciolino, J.D., Seltman, H., Wisniewski, S.R., 2018. Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial. American Journal of Psychiatry 175, 131–139.

Sverdlichenko, I., Jansen, K., de Mattos Souza, L.D., da Silva, R.A., Kapczinski, F., de Azevedo Cardoso, T., 2020. Mixed episodes and suicide risk: A community sample of young adults. Journal of affective disorders 266, 252–257.

Sylvia, L.G., Pegg, S.L., Dufour, S.C., Janos, J.A., Bernstein, E.E., Chang, W.C., Hall, N.E., Ellard, K.K., Nierenberg, A.A., Deckersbach, T., 2019. Pilot study of a lifestyle intervention for bipolar disorder: nutrition exercise wellness treatment (NEW Tx). Journal of affective disorders 250, 278–283.

Todd, N.J., Jones, S.H., Hart, A., Lobban, F.A., 2014. A web-based self-management intervention for bipolar disorder 'living with bipolar': a feasibility randomised controlled trial. Journal of affective disorders 169, 21–29.

Van Rheenen, T.E., Lewandowski, K.E., Bauer, I.E., Kapczinski, F., Miskowiak, K., Burdick, K.E., Balanzá-Martínez, V., 2020. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. Bipolar disorders 22, 13–27.

Vancampfort, D., Correll, C.U., Probst, M., Sienaert, P., Wyckaert, S., De Herdt, A., Knapen, J., De Wachter, D., De Hert, M., 2013. A review of physical activity correlates

in patients with bipolar disorder. Journal of Affective Disorders 145, 285–291. https://doi.org/10.1016/j.jad.2012.07.020

Velten, J., Lavallee, K.L., Scholten, S., Meyer, A.H., Zhang, X.-C., Schneider, S., Margraf, J., 2014. Lifestyle choices and mental health: a representative population survey. BMC psychology 2, 1–11.

5.7 Figures and Tables

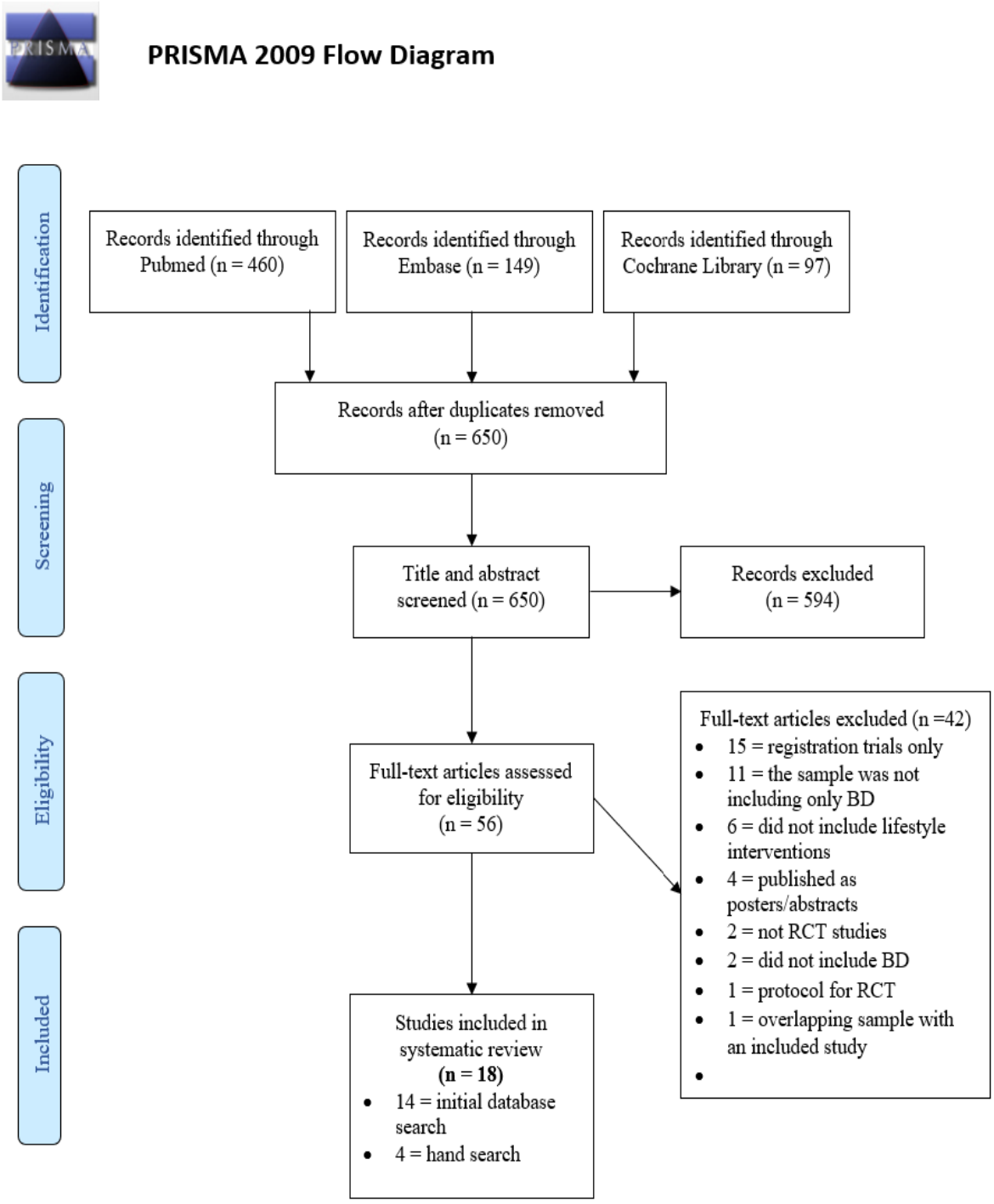


Figure 1: PRISMA flow chart.

Figure 2: Descriptive analysis of Randomized Controlled Trial studies on lifestyle interventions for bipolar disorders.

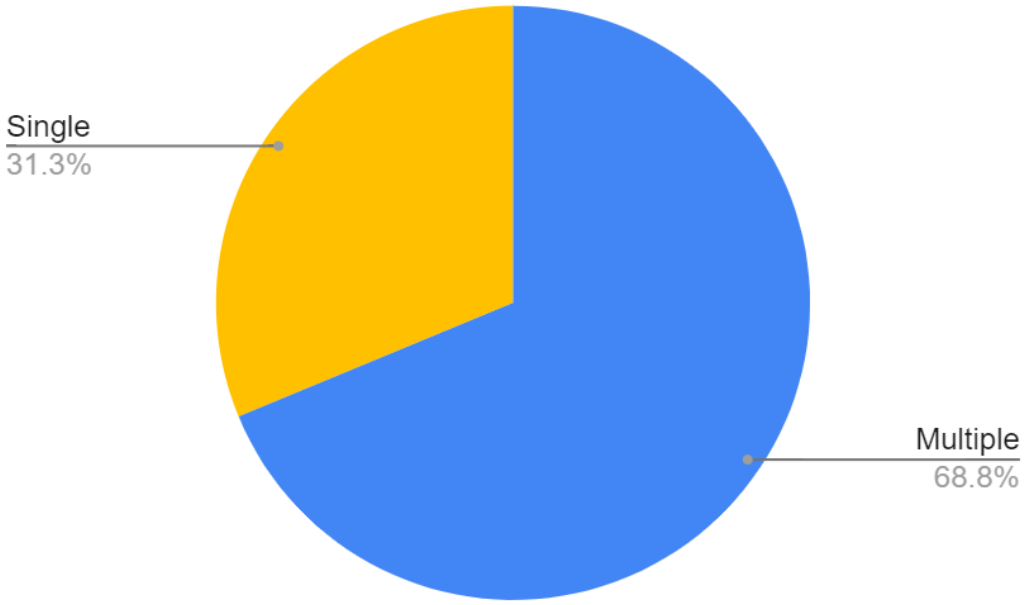
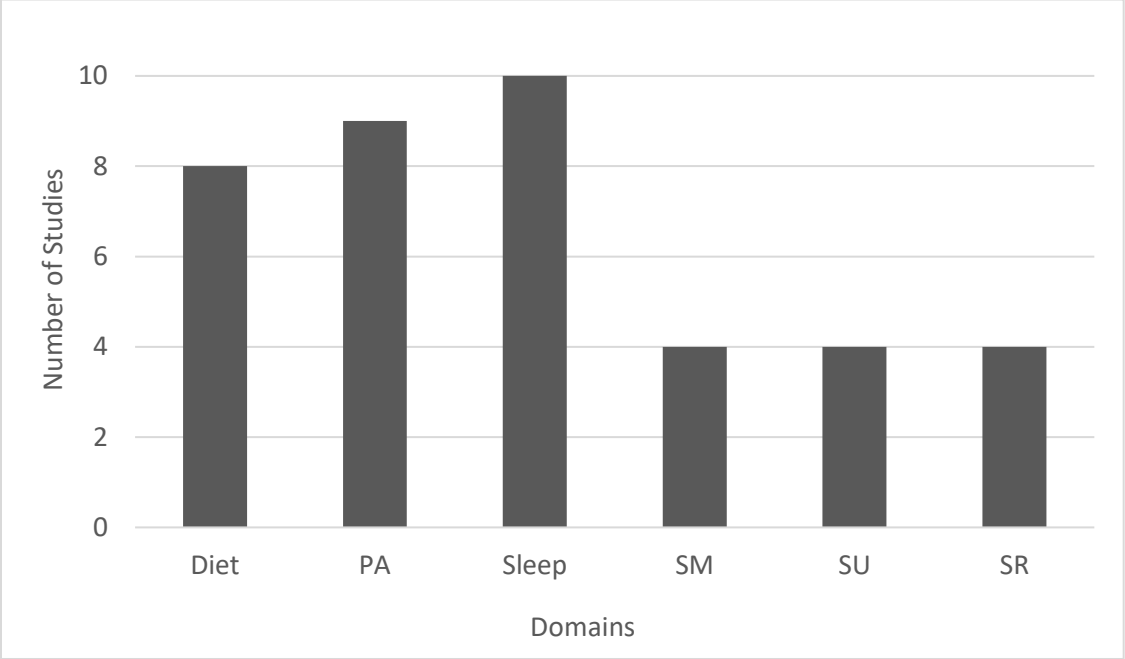
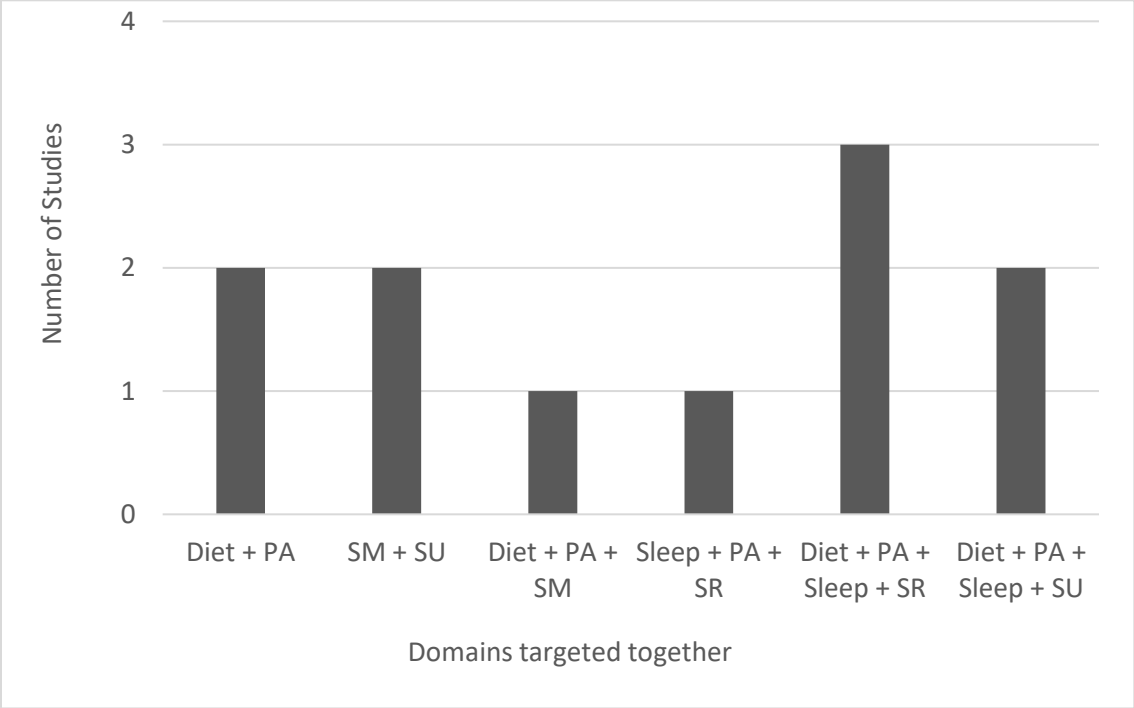


Figure 2A is showing the proportion of single-domain (5/16, 31.3%) and multidimensional (11/16, 68.7%) lifestyle interventions.



PA = Physical Activity; S = Sleep; SM = Stress Management; SR = Social Relationships; SU = Substance Use

Figure 2B is number of studies targeting each domain. Sleep was the most targeted domain (n = 10), followed by PA (n = 9) and diet (n = 8). SM, SU, and SR were all targeted equally (n = 4).



PA = Physical Activity; S = Sleep; SM = Stress Management; SR = Social Relationships; SU = Substance Use

Figure 2C is showing the domains targeted together in multidimensional interventions: 2 studies targeted diet and PA, 2 studies targeted SU and SM, 1 study targeted diet, PA, and SM, 1 study targeted sleep, PA, and SR, 3 studies targeted diet, PA, sleep, and SR, and 3 studies targeted diet, PA, sleep, and SU.

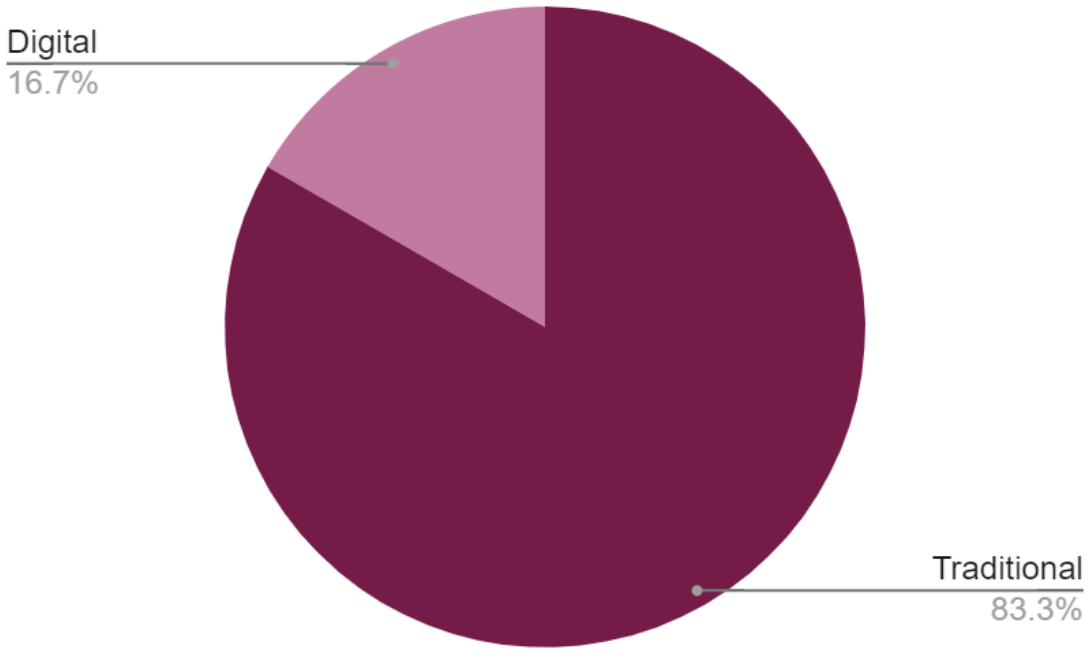
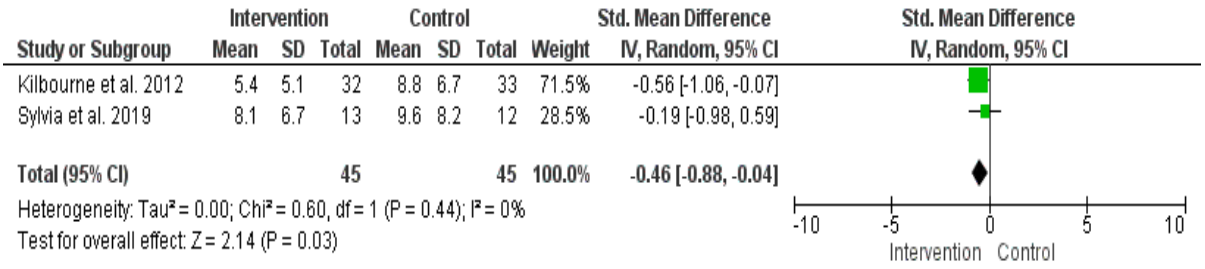
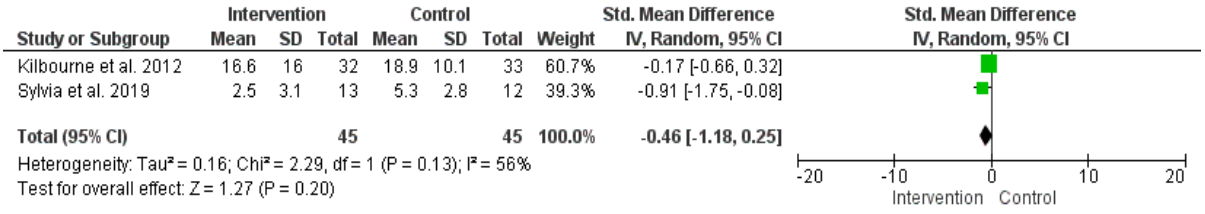


Figure 2D is showing the proportion of interventions using digital (16.7%) vs traditional techniques (83.3%).

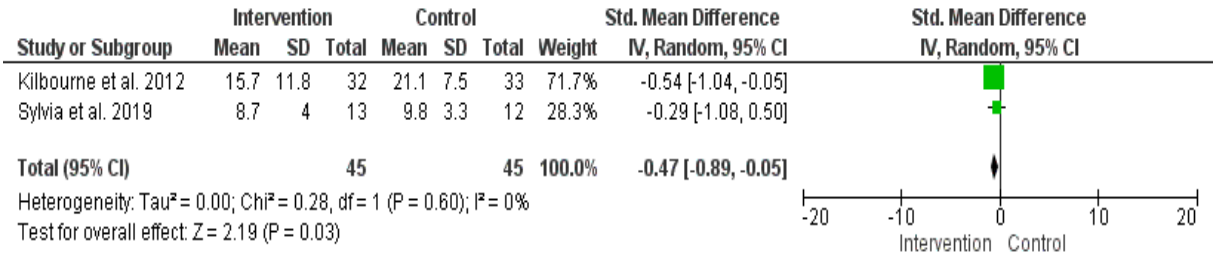
Figure 3: Meta-analysis results per lifestyle domain and outcome.



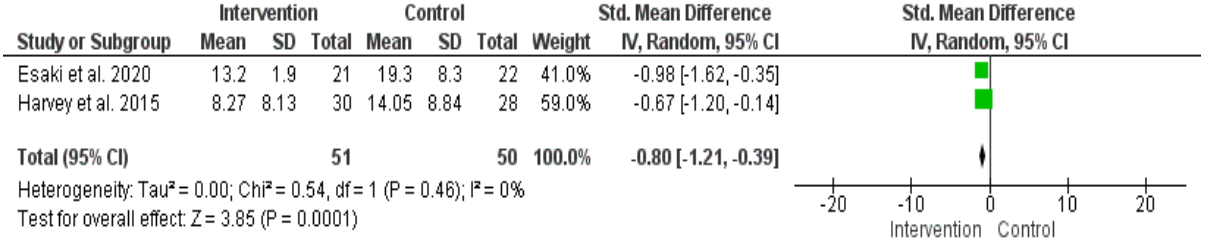
A) Diet & Physical Activity – Depressive symptoms



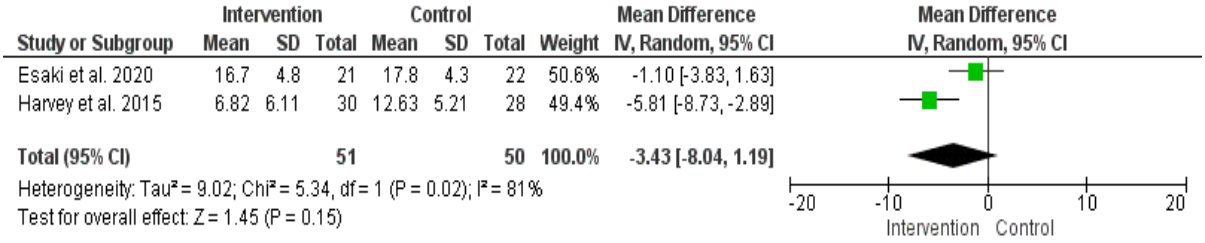
B) Diet & Physical Activity – Manic symptoms



C) Diet & Physical Activity – Functioning



D) Sleep – Depressive Symptoms



E) Sleep – Change in Sleep patterns

Table 1: Description of extracted variables.

Item	Description/classification
Publication Description	• Author(s) • Year of Publication • Journal • Country

Diagnosis of BD	• How was BD diagnosed?
	• BD type(s)
	  ○ BD-I
	  ○ BD-II
	  ○ BD-NOS
	  ○ Any
	• Mood state(s) included
	  ○ Euthymic
	  ○ Depressive
	  ○ (Hypo)manic
	  ○ Mixed

Lifestyle Domain	• Nutrition/diet • Physical activity • Substance use • Stress management • Sleep • Social relationships
Intervention Group Sample and Description	• Sample size of intervention group • Mean and standard deviation of age • Traditional/digital • Number of sessions and duration • Time points
Comparison Group Sample and Description	• Sample size of intervention group • Mean and standard deviation of age • Usual care/other intervention for BD • Traditional/digital (if applicable) • Number of sessions and duration (if applicable)

Outcome	• Symptoms improvement • Change in lifestyle domains • Functioning • Quality of life • Circadian rhythm regulation
Outcome Description	• Assessments used (e.g., scales, objective measurements, actigraphy, anthropometry) • Clinical measurements
Effectiveness	• Yes/No • Describe effectiveness results

Legend: BD: Bipolar Disorder; BD-NOS: BD-not otherwise specified.

Table 2: Characteristics of the included studies.

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
Colom et al., 2003; Spain	Psychiatrist (DSM-IV); BD-I; Euthymic	SM, SU	25 (35.36 ± 10.87)	PE; 90-minute session/week for 20 weeks; traditional	25 (34.48 ± 7.8)	TAU	BD Symptoms	SCID I/II, YMRS, HDRS	- Less recurrence of depressive/total episodes* - Higher time-to-relapse* - Less hospitalizations*
Depp et al., 2015; USA	Psychiatrist; BD-I and BD-II; Any	Not specified	41 (46.9 ± 11.8)	PRISM Interactive web-based system; 2 surveys/day; 4 sessions for 10 weeks; digital	41 (48.1 ± 12.9)	Mood charts; 1/day for 10 weeks; traditional	BD Symptoms; Functioning	MADRS, YMRS; IIS	- Greater decline in depressive symptoms during treatment* - No differences in manic symptoms or functioning
Esaki et al., 2020; Japan	Psychiatrist (DSM-V); BD-I and BD-II; Euthymic	Sleep	21 (44.1 ± 11.8)	BB glasses; 8:00 pm to bedtime for 2 weeks; traditional	22 (41.1 ± 10.4)	TAU	BD Symptoms; Change in sleep; Circadian rhythms regulation	CGI, MADRS, YMRS; VAS, ISI, actigraphy, sleep diary;	- No differences in BD symptoms or sleep quality

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
								MEQ	- Improvements in circadian rhythms regulation*
Frank et al., 1997; USA	Psychiatrist; BD-I; (hypo)manic or depressive	Diet, PA, Sleep, SR	18 (38.3 ± 8.5)	IPSRT; 1 log/week log for 1 year; traditional	20 (38.1 ± 10.2)	CSSRT; traditional	BD Symptoms; Change in lifestyle behaviours; Circadian Rhythms Regulation	HDRS, BRMS; SRM	- Greater stability of daily routines/social rhythms* - No difference in BD symptoms
Frank et al., 2015; USA	Psychiatrist; BD-I; Euthymic	Diet, PA, SU, Sleep	58 (41.8 ± 9.5)	IRRI; 1 hour session/week for the first 5-6 months followed by weekly and additional monthly sessions for 18 months; traditional	56 (41.4 ± 9.7)	PCMM; traditional	Change in lifestyle behaviours	BMI	- Greater rate of decrease in BMI over time*
Gillhoff et al., 2010;	MINI (DSM-IV); BD-I and	Diet, PA, Stress	26 (48.1 ± 11.5)	QoL-BD; sessions = 7 (lifestyle), 4	24 (48.9 ± 12.0)	TAU	Change in lifestyle behaviours	BMI	- Lower BMI*

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
Switzerland	BD-II; Euthymic			(nutrition), weekly (physical activity) for 5 months; traditional					
Gorraci et al., 2016; Italy	SCID; BD-I and BD-II; Euthymic	Diet, PA, SU, Sleep	105 across intervention and control (N/A)	HLI; 12 45- to 60-minute, sessions; traditional	105 across intervention and control (N/A)	TAU	BD Symptoms;	CGI-S/I, PHQ-9, YMRS	- Lower percentage of relapses* - Lower risk of relapse*
Harvey et al., 2015; USA	DSM-IV-TV, SCID; BD-I; Euthymic	Sleep	30 (37.7 ± 12.4)	CBTI-BP; 8 50- to 60-minute sessions for 6 months; traditional	28 (35.5 ± 9.3)	PE; traditional	BD Symptoms; Change in lifestyle behaviours; Functioning; QoL	SCID, YMRS, IDS-C; DSISD, ISI, PSQI, PROMIS-SD, PROMIS-SRI, sleep journal, pharmaco-therapy tracking log; SDS; Q-LES-Q-SF	- Lower mania/hypomania relapse rates* - Less time spend BD episodes* - Reduced insomnia severity* - No differences in functioning or QoL

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
Henricksen et al., 2016; Norway	MINI (DSM-IV); any BD type; (Hypo)manic	Sleep	12 (43.0 ± 11.0)	BB glasses; 6:00 pm - 8:00 am for 7 consecutive days; traditional	11 (49.8 ± 13.8)	Clear-lensed glasses; traditional	BD Symptoms; Circadian Rhythms regulation	YMRS, actigraph	- Lower scores on YMRS* - No differences in actigraphy scores
Husain et al., 2017; Pakistan	Psychiatrist (DSM-IV); any BD type; Euthymic	SM, SU	18 (34.5)	CaPE; 1-hour session/week for 12 weeks; traditional	16 (34.5)	TAU	BD symptoms; QoL	YMRS, BDI; EuroQoL	- Lower scores on YMRS and BDI* - Better scores on EuroQoL*
Inder et al., 2015; New Zealand	SCID I and SCID II; any BD type; any mood state	Diet, PA, Sleep, SR	49 (26.6 ± 5.9)	IPSRT; weekly (0-3 months), biweekly (3-6 months), bi-weekly or monthly (6-18 months) sessions; traditional	51 (26.5 ± 6.0)	SSC; traditional	BD Symptoms; Change in lifestyle behaviours; Functioning	LIFE; SAS	- No differences between groups
Kaplan et al., 2018; USA	SCID (DSM-IV) ; BD-I; Euthymic	PA, Sleep, SR	20 (39.3 ± 14.2)	CBT-BP with RISE-UP sleep inertia routine; traditional	20 (35.4 ± 8.9)	PE; traditional	Change in lifestyle behaviours; Circadian rhythms regulation	Sleep diary, SSS-EMA; actigraph	- Decreased sleep inertia duration*

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
									- Improved sleep inertia severity* - Greater activity during 1st hour post waking up*
Kilbourne et al., 2012; USA	Psychiatrist; Any BD type ; Any mood state	Diet; PA	32 (47.2 ± 11.8)	LGCC; 4 2-hour session/week for 6 months; traditional	33 (43.4 ± 13.6)	enhanced TAU	BD symptoms; Functioning; QoL	BMI, systolic BP, diastolic BP; ISS; WHODAS; SF-36	- No differences between groups
Miklowitz et al., 2007; USA	SCID, MINI (DSM-IV) ; BD-I and BD-II; Depressive	Diet, PA, Sleep, SR	62 (N/A)	IPSRT: 30 sessions over 9 months; traditional	130 (N/A)	CC; 3 50-minute sessions over 6 weeks; traditional	BD Symptoms	CMF, MADRS, YMRS	- Greater recovery rate* - Less time to recovery* - More likely to be clinically well*
Murray et al., 2021; Australia	MINI (DSM-IV) ; Any BD type; Euthymic	SM	152 (44.5 ± 10.9)	Orbit 2.0; 1 module/week for 4 weeks + 1 extra week; digital	150 (44.6 ± 12.4)	PE; digital	BD Symptoms; Quality of Life	MADRS, QIDS-SR, DASS-21; QoL-BD	- No differences between groups

Author(s), Year; Country	BD eligibility (Method of diagnosis); BD type; Mood state	Targeted Lifestyle Domain (s)	Intervention sample size (age +/- std)	Description of intervention (Method; Assessment period; Traditional or digital)	Comparison sample size (age +/- std)	Description of comparison (Method; assessment period; Traditional or digital)	Outcomes	Outcome measurements (Assessments, clinical measurements)	Effectiveness of intervention
Sit et al., 2018; USA	SCID ; BD-I and BD-II; Depressive	Sleep	23 (45.7 ± 14.3)	Active bright white light therapy; 15-minute session/day (increased by 15 minutes each week) for 4-6 weeks; traditional	23 (43.7 ± 15.0)	Inactive red dim light therapy	BD Symptoms; Change in lifestyle behaviours; Functioning	SIGH-ADS; CGI-BD; HDRS; PSQ; GAF, SPQ	- Higher remission rates at weeks 4-6* - Lower depression scores* - Improved global functioning*
Sylvia et al., 2019; USA	MINI ; BD-I and BD-II; (Hypo)manic and Depressive	Diet; PA	19 (39.7 ± 12.5)	NEW Tx; 18 sessions over 20 weeks; traditional	19 (44.3 ± 11.9)	TAU	BD Symptoms; Change in lifestyle behaviours; Functioning	MADRS, CGI-BD, YMRS; weight, BMI, exercise duration; LIFE-RIFT	- Improvements in overall functioning* - No differences in weight loss or mood symptoms between the groups
Todd et al., 2014; UK	Self reported clinical diagnosis; BD-I and BD-II; any mood state	Not specified	61 (42 ± 10.3)	LWB; 10 modules over 6 months; digital	61 (45 ± 11.9)	TAU	BD Symptoms; Functioning; QoL	BRQ; ISS; SASS; QoL-BD; WHOQOL	- Improvements in all outcomes*

Legend: * = $p \leq 0.05$;

BB = Blue-blocking; BDI = Beck Depression Inventory; BMI = Body Mass Index; BP = Blood Pressure; BRMS = Bech-Rafaelsen Mania Scale; BRQ = Bipolar Recovery Questionnaire; CaPE = Culturally Adapted Psychoeducation; CBT = Cognitive Behavioural Therapy; CBT-BP = Cognitive Behavioural Therapy, Bipolar Disorder Specific; CBTI-BP = Cognitive Behavioural Therapy for Insomnia, Bipolar Disorder Specific; CC = Collaborative Care; CGI = Clinical Global Impressions Scale; CGI-BD = Clinical Global Impressions Scale for Persons with Bipolar Disorder; CGI-S/I = Clinical Global Impression – Improvement scale; CMF = Clinical Monitoring Form; CSSRT = Clinical Status and Symptom Review Treatment; DASS-21 = Depression, Anxiety and Stress Scale - 21 Items; DSISD = Duke Structured Interview for Sleep Disorder; ESS = Epworth Sleepiness Scale; EuroQoL = European Quality of Life Scale; FFT = Family Focused Treatment; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; HLI = Healthy Lifestyle Intervention; IDS-C = Inventory of Depressive Symptomatology: Clinician; IIS = Illness Intrusiveness Scale; IPSRT = Interpersonal and Social Rhythm Therapy; IRRI = Integrated Risk Reduction Intervention; ISI = Insomnia Severity Index; ISS = Internal State Scale; LGCC = Life Goals Collaborative Care; LIFE = Longitudinal Interval Follow-up Evaluation; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; LWB = Living with Bipolar; MADRS = Montgomery–Åsberg Depression Rating Scale; MEQ = Multidimensional Emotion Questionnaire; NEW Tx = Nutrition, Exercise, and Wellness Treatment; ORBIT = Online Recovery-Focused Bipolar Individual Treatment; PA = Physical Activity; PCMM = Psychiatric Care with Medical Monitoring; PE = Psychoeducation; PHQ-9 = Patient Health Questionnaire; PPAQ = Paffenbarger Physical Activity Questionnaire; PROMIS-SD = Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; PROMIS-SRI = Patient-Reported Outcomes Measurement Information System-Sleep-Related Impairment; PSQ = Personality Structure Questionnaire; PSQI = Pittsburgh Sleep Quality Index; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire; QoL-BD = Quality of Life for Persons with Bipolar Disorder; QUID-SR = Quick Inventory of Depressive Symptomatology – Self Report; SAS = Social Adjustment Scale; SASS = Social Adaptation Self-Evaluation Scale; SCID = Structured Clinical Interview for DSM Disorders; SDS = Self-Directed Search; SF-12 = 12-Item Short Form Survey; SF-36 = Short Form Health Survey; SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; SM = Stress Management; SPQ = Social Problems Questionnaire; SR = Social Relationships; SRM = Social Rhythm Metric; SSC = Specialist Supportive Care; SSS-EMA = Stanford Sleepiness Scale via Ecological Momentary Assessment; SU = Substance Use; TAU = Treatment as Usual; VAS = Visual analogue scales; WHODAS = World Health Organization Disability Assessment Scale; WHOQOL = World Health Organisation Quality of Life; WSAS = Work and Social Adjustment Scale; YMRS = Young Mania Rating Scale

Table 3: Risk of Bias according to Cochrane Risk of Bias Tool for RCTs.

Author(s), Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Selective Reporting (Reporting Bias)	Blinding Participants and Personnel (Performance Bias)	Blinding outcome assessment (Detection Bias)	Incomplete Outcome Bias (Attrition Bias)	Other Sources of Bias (Other bias)
Colom et al., 2003;	Low	Low	Low	High	Low	Unclear	Low
Depp et al., 2015;	Low	Low	Low	High	Low	Low	Low
Esaki et al., 2020;	Low	Low	Low	Low	Low	Low	Low
Frank et al., 1997;	Unclear	Unclear	Low	Low	Unclear	Low	Low
Frank et al., 2015;	Low	Low	Low	Low	Low	Low	Low
Gillhoff et al., 2010;	Unclear	Unclear	Low	High	Low	Low	Low
Gorraci et al., 2016;	Unclear	Unclear	Low	High	Unclear	Low	Low
Harvey et al., 2015;	Low	Low	Low	High	Low	Low	Low
Henricksen et al., 2016;	Low	Low	Low	Low	High	Low	Low
Husain et al., 2017;	Low	Low	Low	High	Low	Low	Low
Inder et al., 2015;	Low	Low	Low	Low	Low	Low	Low
Kaplan et al., 2018;	Low	Low	Low	Low	Low	Low	Low
Kilbourne et al., 2012;	Low	Low	Low	Unclear	Unclear	Low	Low
Miklowitz et al., 2007;	Low	Low	Low	Low	Low	Low	Low
Murray et al., 2021;	Low	Low	Low	Low	Low	Low	Low
Sit et al., 2018;	Low	Low	Low	Low	Low	Low	Low
Sylvia et al., 2019;	Unclear	Unclear	Low	High	Low	Low	Low
Todd et al., 2014;	Low	Low	Low	High	Low	Low	Low

Table 4: Proportion of effective interventions for improving outcomes of interest in comparison to control conditions based on number of domains targeted. Values indicate the number of effective interventions out of the total number of interventions targeting that outcome within each column;

	Domains Targeted			
	1 Domain (n = 5)	**2 Domains (n = 4)**	**3 Domains (n = 2)**	**4 Domains (n = 5)**
BD Symptom Improvement	3/5 (60%)	3/4 (75%)	1/1 (100%)	3/4 (75%)
Change in Lifestyle	3/3 (100%)	1/1 (100%)	1/1 (100%)	3/4 (75%)
Functioning	1/2 (50%)	1/2 (50%)	-	1/1 (100%)
Quality of Life	0/2 (0%)	1/2 (50%)	-	-
Circadian Rhythm	1/2 (50%)	-	1/1 (100%)	-

Legend: BD = bipolar disorder.

Appendix

Description of Interventions

Intervention	Description
Psychoeducation (PE)	Program that focuses on symptom monitoring, treatment adherence, and illness management skills.
PRISM Interactive Web-based System	Personalized questionnaires capable of delivering pre-programmed interactive algorithm-based responses based on reported symptoms or early warning signs.
Blue-blocking (BB) Glasses	Glasses that virtually eliminate blue wavelengths.
CSSRT – Clinical Status and Symptom Review Treatment	Program that focuses on provision of support and education while assessing the presence of depressive or manic symptoms and medication side effects.
PCMM – Psychiatric Care with Medical Monitoring	Consists of two components: (i) psychiatric treatment by a study psychiatrist; and (ii) assessment and referral by a psychiatric research nurse for medical treatment provided by the patient's own primary care physician.
Interpersonal and Social Rhythm Therapy (IPSRT)	Disorder-specific psychotherapy based on the instability model of BD and addresses three mechanisms of relapse: medication non-adherence, disrupted social rhythms, and interpersonal-related life events.
Integrated Risk Reduction Intervention (IRRI)	Program that focuses on enhancing regularity of sleep/wake cycles, increasing regularity of

	social rhythms, activities and meals, increasing physical activity, improving eating habits, and improving management of cardiometabolic risk factors and/or disease.
Quality of Life for Persons with Bipolar Disorder Program (QoL-BD)	Program that focuses on controlling weight and relapse prevention, balancing nutrition, and engaging in regular physical activity.
Healthy Lifestyle Intervention (HLI)	Comprehensive, standardized, and integrated manualized program that helps patients to develop and maintain a healthy and active lifestyle.
Cognitive Behavioural Therapy for Insomnia, Bipolar Disorder Specific (CBTI-BP)	Modification of CBT for insomnia, focused on improving safety and targeting the unique features of sleep in bipolar disorder by integrating elements from IPSRT, chronotherapy, and motivational interviewing.
Culturally Adapted Psychoeducation (CaPE)	Psychoeducation program that is culturally adapted to the Pakistani community.
Specialist Supportive Care (SSC)	Combination of supportive psychotherapy and PE, with the focus of each session initiated by the patient.
Cognitive Behavioural Therapy, Bipolar Disorder Specific (CBT-BP)	Cognitive Behavioural Therapy for individuals with bipolar disorder. This type of psychotherapy in which negative patterns of thought about the self and the world are challenged.
Life Goals Collaborative Care (LGCC)	Program that consists of sessions that have guided discussions and exercises designed to help patients set personal self-management goals.

Enhanced TAU	Monthly mailings on wellness topics, available mental health care, and referral to off-site primary care services.
Family Focused Treatment (FFT)	Psychoeducational treatment for patients with BD and their families, focused on alleviation of mood symptoms, relapse prevention and enhanced psychosocial functioning
Collaborative Care (CC)	PE material to develop a treatment contract.
Online Recovery-Focused Bipolar Individual Treatment (ORBIT)	Online intervention addressing five overlapping skills: mindfulness, values and committed action, acceptance, self-compassion, and defusion.
Nutrition, Exercise, and Wellness Treatment (NEW Tx)	CBT-based intervention with three main modules: Nutrition, Exercise, and Wellness.
Living with Bipolar (LWB)	Online interactive recovery informed self-management intervention, broadly based on the principles of CBT and PE.

Chapter 6: General Discussion

6.1 Summary of Findings

This thesis examined the importance of lifestyle in association to symptoms of common mental disorders such as anxiety, depression, and BD. Unhealthy behaviours in fundamental lifestyle domains, such as diet/nutrition, physical activity, restorative sleep, substance use, stress management, social relationships, and environmental exposures have been linked with more severe symptoms, socio-cognitive functional deficits, and higher prevalence of comorbidities in mental disorders (Fagiolini et al., 2015; Noordsy, 2019; Scott and Happell, 2011). Prior reports have studied the relationships between each lifestyle risk factor and these disorders, however, the literature on multidimensional assessments of healthy and unhealthy lifestyle patterns in core domains of lifestyle psychiatry has been scarce. Moreover, there has been very limited research on the impact of accumulating unhealthy lifestyle behaviours during the COVID-19 pandemic for symptoms of common mental disorders, a crucial risk factor for the global burden of mental disease during and post-pandemic.

In the first study, described in Chapter 2, we used data from lifestyle variables associated with symptoms of depression and anxiety in Spain to develop three different machine learning models that accurately predicted the presence of symptoms of depression and anxiety in a Brazilian sample during the early stages of the COVID-19 pandemic. Implementation of the SMILE scale for evaluating lifestyle behaviours and perceptions showed strong predictive power of lifestyle as a multidimensional construct

for detecting symptoms of common mental disorders (anxiety and depression). In addition to the high accuracy of the machine learning models to predict the presence of mental health symptoms in both Spain and Brazil, a novel finding of this study was that the models using lifestyle variables were developed in a Spain, a country where people were severely impacted by the pandemic already, which were able to predict the presence of these symptoms in Brazil, a country severely affected by the pandemic at a later time. Findings from this study suggest that unhealthy lifestyle behaviours and perceptions can be used as risk factors for transnational prediction of symptoms of common mental disorders such as depression and anxiety.

Moreover, in the aforementioned study, we analyzed the importance of specific lifestyle behaviours and perceptions associated with symptoms of depression and anxiety. The analysis suggested that the question on the SMILE scale regarding the meaningfulness of their life was the most significant predictor of symptoms of depression, while factors related to the sleep domain, such as restfulness after sleep and use of sleeping pills, were the most significant predictors of symptoms of anxiety. Findings from the secondary analysis of this study further contribute to the literature on specific lifestyle factors important for predicting and preventing, as well as for the treatment of common mental health symptoms during the COVID-19 pandemic.

Subsequent to the findings of the study presented in Chapter 2, the aim of our study in Chapter 3 was to investigate the relationship between lifestyle and symptoms of depression and anxiety during the COVID-19 lockdown period in July and August of 2020 in Canada. For this study, we used the SMILE-C scale, which only included

questions within the 7 lifestyle domains that were relevant to behaviours and perceptions during the confinement period in Canada. We found significant inverse relationships between lifestyle quality and symptoms of depression and anxiety, where individuals indicating symptoms of anxiety or depression were more likely to be engaged in unhealthy lifestyle behaviours and perceptions according to the SMILE-C scale than individuals without reports of symptoms of anxiety or depression. Furthermore, in this study we presented some novel sociodemographic trends related to symptoms of depression and anxiety in Canada during this period. For instance, we found that older adults were less likely to report symptoms of depression and anxiety, while people who had lost their job during the pandemic were more likely to present symptoms of depression and anxiety. Changes from typical patterns prior to the pandemic in lifestyle domains, such as diet, sleep, and social support, were associated with common mental health symptoms in our sample. Findings from this study once again emphasize the importance of detecting unhealthy lifestyles for prevention and treatment of symptoms and outcomes associated with depression and anxiety.

Chapter 4 presents a cross-sectional study comparing the overall lifestyle as well as lifestyle patterns across each of the 7 domains of the SMILE scale among individuals with BD in a depressive, (hypo)manic, or mixed episode, and healthy controls. Regardless of the current mood episode they were experiencing, individuals with BD reported worse overall lifestyle and worse lifestyle patterns across each domain of the scale than healthy individuals. Further comparisons among individuals with BD suggested equal levels of unhealthy lifestyles in people in depressive states, and people in

(hypo)manic or mixed states. Implications from this study support the idea for evaluating lifestyle across multiple modalities in individuals with BD, advocating for close monitoring of lifestyle patterns across the different mood states for more effective treatment strategies.

In Chapter 5, we reviewed the literature of RCTs evaluating the efficacy of lifestyle interventions for individuals with BD in comparison to usual treatments or non-lifestyle interventions. The focus on lifestyle interventions in this review was directed towards interventions targeting the six core domains of lifestyle psychiatry. Up to January 6, 2022, sleep, diet, and physical activity were the most targeted domains for interventions, while substance use, stress management, and social relationships were less targeted.

A major focus of the study presented in Chapter 5 was the proportion and efficacy of multidimensional interventions in comparison to single-domain interventions. We found that majority of the included RCTs had a multidimensional approach to their respective interventions, which also indicated higher efficacy rates for improving clinical and functional outcomes in comparison to single-domain interventions. However, none of the RCTs included a multidimensional intervention that comprised of active suggestions to promote healthy behaviours on all six core domains of lifestyle. Furthermore, findings from our meta-analyses revealed that interventions on sleep, diet and physical activity are effective for reducing the severity of depressive symptoms in BD and improvement in overall functioning, although in a relatively small sample size of studies. Overall, implications from this study point to the promising efficacy of lifestyle interventions for

BD, however, further research on more multidimensional interventions is needed for assessing the possibility of greater improvements in symptoms and outcomes of BD.

6.2 Significance and General Discussion

Overall, the work presented in this thesis emphasizes the importance of multimodal lifestyle assessments for common mental disorders such as depression, anxiety, and BD. The positive and negative contributions of various lifestyle behaviours have been well-established over the years, however, recent progressions in the field of lifestyle psychiatry have raised attention towards the impact of lifestyle as a multifactorial construct for prevention, and even treatment of psychiatric disorders (Firth et al., 2019b). The four studies comprising this thesis further illustrate the cumulative significance of multiple lifestyle areas for psychiatric symptoms.

Throughout the COVID-19 pandemic, various countries around the world reported increased prevalence rates of depression and anxiety in their general population following the sudden life-changing pandemic-related events (Salari et al., 2020; Xiong et al., 2020). While adding to this body of literature, demonstrating the rise of these symptoms in Spain, Brazil, and Canada during COVID-19, the studies in Chapters 2 and 3 also indicate an association between unhealthy lifestyles and these symptoms. These findings are concurrent with similar reports from China, Sweden, and Spain reporting the presence of unhealthy lifestyle behaviours and negative lifestyle changes in association to poor subjective mental well-being and psychiatric symptoms in the general population

(Blom et al., 2021; Cervera-Martínez et al., 2021; Hu et al., 2020). A major, novel contribution from the study in Chapter 2 towards the relationship between lifestyle and mental health symptoms is the implementation of machine learning analysis. Prior studies have explored the effectiveness of machine learning for diagnosis, prognosis, and treatment of mental health (Shatte et al., 2019), however, this was the first study to use machine learning algorithms for transnational prediction of common mental health symptoms using lifestyle variables. In addition to affirming the importance of lifestyle behaviours for mental health, this study suggests the possibility of using big data analysis for large-scale investigations of lifestyle risk factors as predictors of psychiatric symptoms. Furthermore, reports from Chapters 2 and 3 also shed light on the significance of evaluating pandemic-related changes in lifestyle which could lead to harmful effects on the person's well-being. Considering the possibility of long-lasting consequences on psychological distress following the pandemic, it is important to recognize the lifestyle factors impacting the individual's well-being (Veldhuis et al., 2021). Timely recognition and intervention on these risk factors could help reduce the rise of the global mental health burden during and after the COVID-19 pandemic.

Chapters 4 and 5 direct the attention to the importance of lifestyle for BD, a complex mood disorder with a detrimental clinical trajectory for a subset of affected individuals (Kapczinski et al., 2017). Similar to previous reports (Firth et al., 2019a; Huang et al., 2018; Karantonis et al., 2021; Kasper, 2004; Zhang et al., 2006), the study in Chapter 4 also found unhealthy lifestyle behaviours among individuals with BD in a depressive, (hypo)manic, and mixed state. While prior literature has indicated the

presence of unhealthy behaviours during these episodes, Chapter 4 presents a novel approach to evaluating lifestyle behaviours in BD using a multidimensional scale. Given the vast differences in emotions and behaviours characteristic of each mood episode in BD, a multifactorial assessment of the fundamental areas of lifestyle psychiatry provides the opportunity to monitor different lifestyle domains simultaneously and the co-occurrence of unhealthy behaviours across these domains in each mood episode. We found similar levels of unhealthy lifestyle behaviours and perceptions across individuals in a depressive episode and those in a (hypo)manic or mixed episode, in line with previous reports of unhealthy lifestyles across both depressive and (hypo)manic states (Firth et al., 2019a; Lopresti et al., 2013). Although the prevalence of behavioural risk factors in BD has been established (Firth et al., 2019a), a closer look into specific areas and behaviours can be very beneficial for prognosis and treatment of the disorder. Lifestyle behaviours may be affected differently based on the severity of the mood episode and the presence of overlapping features of depressive and (hypo)manic episodes, further emphasizing the importance of detailed monitoring of the extent to which multiple areas of everyday life are affected.

Following the findings of the study in Chapter 4, we explored the existing literature on lifestyle-based interventions for improvement of mood symptoms, quality of life, and functional outcomes of BD. To date, the most impactful review of this area has been a meta-review of meta-analyses on diet, physical activity, sleep, and substance use interventions for mental disorders, including BD (Firth et al., 2020). However, there were no reports of meta-analyses on interventions for BD across any of the four domains

included in this meta-review. Moreover, a systematic review by Bauer et al. (2016) examined the therapeutic effectiveness of interventions focused on nutrition and physical activity for improvement of symptoms and outcomes in BD (Bauer et al., 2016). This review consisted of 6 studies, 3 of which were recognized as RCT studies. The overall findings from this systematic review suggest a beneficial effect of interventions on diet, physical activity, self-motivation, and beliefs surrounding wellbeing for outcomes such as mood improvement, weight, blood pressure, metabolic lipid profile, physical activity and overall wellbeing. The main implications from this review were that diet and physical activity interventions are feasible and efficacious in individuals with BD, and could potentially lead to improvements in long-term management of BD, keeping in mind these implications were based on a small number of RCTs (Bauer et al., 2016). However, to date, there has been a lack of systematic reviews and meta-analyses exploring the efficacy of interventions for BD across all the core domains of lifestyle psychiatry, and the efficacy of multimodal interventions for improvements in major clinical and functional outcomes associated to BD. Our review and meta-analysis presented in Chapter 5 found promising rates of efficacy of lifestyle interventions, and emphasizes the focus on diet, physical activity, sleep, and the types of multidimensional interventions implemented so far. Moreover, in Chapter 5 we highlight fundamental missing aspects for the progression in our understanding of lifestyle psychiatry contributions, such as the lack of focus on substance use, stress management, and social relationships interventions, and the lack of interventions targeting majority of the core lifestyle domains simultaneously. Research on multidimensional lifestyle interventions for BD is still in the

early stages, although these findings have demonstrated promising signs for implementing lifestyle strategies in the long-term management of the disorder.

A significant step forward for the field of lifestyle psychiatry is the application of multimodal lifestyle evaluations for clinical and at-risk populations. The wide-spread acceptance of lifestyle as a multifactorial construct beyond the traditional areas of diet, physical activity and sleep has raised the need for a rapid evaluation of recent lifestyle-related behaviours and perceptions (Balanzá-Martínez et al., 2021). Studying the extent to which an individual's habits and routines are characteristic of a healthy lifestyle has been a topic of interest for decades. However, majority of the focus on lifestyle assessments has been directed towards creating and implementing assessments specific to a single lifestyle area. Although the importance of each lifestyle area has been evident for many years, there has been a lack of widely implemented instruments assessing all the domains simultaneously for psychiatric disorders. The early stages of interest in multimodal lifestyle lead to the development of the Health Promoting Lifestyle Profile (HPLP), one of the first renowned assessments to cover multiple factors of modern notions of lifestyle (Walker et al., 1987). The original version of this instrument consisted of questions rated on a 4-point Likert scale (never, sometimes, often, routinely) regarding self-actualization, health responsibility, exercise, nutrition, interpersonal support, and stress management. Over the next several years, new research findings and feedback on the original scale led to refinements of the questions and development of a newer version, HPLP-II, comprising of newly adapted domains such as nutrition, physical activity, stress management, interpersonal relations, spiritual growth, and health responsibility (Walker

et al., 1995). This version of the scale was subsequently validated in various countries around the world and served as the basis of other lifestyle questionnaires (Gillis, 1997; Kuan et al., 2019; Pinar et al., 2009; Tanjani et al., 2016). The ability to detect unhealthy lifestyle behaviours in association to mental health symptoms using the HPLP-II has been demonstrated across several studies, reporting inverse relationships between scores on the HPLP II and symptoms of depression, supporting the idea of assessing lifestyle comprehensively in individuals with mental illnesses (Jensen et al., 2006; Safaie et al., 2020). With the progression of research findings over the years, our understanding of modifiable factors of lifestyle has deepened and led to the exploration of more specific lifestyle behaviours, identifying core lifestyle domains, and further evaluating their association to psychiatric symptoms. While many instruments have been created and widely used for evaluating quality of behaviours specific to one lifestyle domain, there are no known widely validated and implemented questionnaires for a comprehensive, multidimensional evaluation of all lifestyle areas recognized by present day ideologies of lifestyle psychiatry. The SMILE and SMILE-C scales, used in Chapters 2, 3 and 4, provide a holistic overview of lifestyle as well as a closer look at behaviours in specific domains associated to psychiatric symptoms. In comparison to the HPLP-II, the SMILE scales have incorporated seven domains, replacing spiritual growth and health responsibility with sleep, substance use, and environmental exposures, which are more in line with contemporary evidence-based strategies of lifestyle psychiatry. Answers on the HPLP-II scale are based on the individual's 'present way of living', susceptible to a subjective interpretation of the time frame for each question, while the SMILE scale is

focused on lifestyle behaviours within the past 30 days. Items on the SMILE scale are also more specific to behaviours and perceptions in mental disorders, as they have been designed and approved by clinicians and researchers practicing lifestyle psychiatry. Furthermore, with the lifestyle adversities following the onset of the COVID-19 pandemic, it is important to consider lifestyle behaviours adapted to routines during and post-pandemic, which is made possible through the SMILE-C scale (Balanzá-Martínez et al., 2021). The quantification of unhealthy lifestyle behaviours also enables assessors to analyze the correlation between these behaviours and severity of psychiatric symptoms on widely validated psychiatric instruments, such as the PHQ-9, MADRS, YMRS, and GAD-7 (Davidson et al., 1986; Kroenke et al., 2003; Spitzer et al., 2006; Young et al., 1978). Detection of unhealthy behaviours using the SMILE scales was an instrumental element of this thesis, particularly in Chapters 2-4, making it possible to study patterns across multiple distinguished areas of lifestyle psychiatry through a holistic, yet detailed assessment tool.

One of the major advantages of the SMILE scale is the ability to detect the clustering of unhealthy behaviours across different domains using a single instrument. This scale has proven to be a rapid, feasible method of detecting unhealthy lifestyles in the general and clinical populations. Considering the severe implications associated to clustering of unhealthy behaviours, the rapid multidimensional detection of unhealthy lifestyles provides an opportunity for early recognition of lifestyle areas in need of improvement. In particular, the clustering of unhealthy behaviours in the general population during the COVID-19 pandemic could lead to an increased prevalence of

depression and anxiety symptoms, as demonstrated in Chapters 2 and 3, potentially increasing the already large global burden of these disorders (Campion et al., 2020). The clustering of unhealthy behaviours among people with BD, reported in Chapter 4, could further aggravate the severity of symptoms and outcomes associated with the mood episodes, lead to shorter relapse of episodes, and increase the risk of comorbidities for these individuals. Furthermore, the lifestyle behaviours assessed by the SMILE scales are also established risk factors for the onset of psychiatric symptoms (Firth et al., 2020), which may be especially important with the accumulation of unhealthy behaviours in these areas during and post-COVID-19 pandemic. People may also be engaging in some unhealthy lifestyle patterns subconsciously, where increased mindfulness to the differences between healthy and unhealthy lifestyles and the effects of unhealthy behaviours could incite better decision-making among the general population and potentially decrease the rates of psychiatric symptoms. Therefore, the implementation of a practicable multidimensional lifestyle assessment is highly valuable for timely prevention and treatment of psychiatric symptoms.

The findings from Chapters 2-5 all highlight the importance of developing multimodal lifestyle-based interventions for a combined effect of improvements in multiple lifestyle areas. In Chapters 2 and 3, we emphasize the need for focusing on preventive and treatment strategies for the cumulative effects of multiple unhealthy lifestyle factors associated with symptoms of depression and anxiety during the COVID-19 pandemic. Chapters 4 and 5 highlight the importance of focusing on multiple lifestyle areas for improvement of symptoms in BD, where findings from Chapter 5 suggest

promising rates of efficacy of multidimensional interventions so far. These findings and suggestions are in agreement with major principles of lifestyle psychiatry, advocating for more attention to combined lifestyle interventions to further understand their prospective impact on long-term psychiatric outcomes (Firth et al., 2019b; Walsh, 2011). Combined interventions could have a greater cumulative effect on the well-being of the individual, with promising signs that maintaining healthy behaviours can result in increased mood stability and long-term improvements in psychological and cognitive well-being (Conry et al., 2011; Merrill and Small, 2011; Vermeulen-Smit et al., 2015). Given the complex symptomatology of psychiatric disorders, and the heterogeneity in treatment responses of usual therapeutic strategies, lifestyle interventions can be implemented complementary to usual care for a greater effect on outcomes, or even as alternatives to pharmacotherapy for depressive and anxiety disorders (Manger, 2019; Noordsy, 2019). In contrast to usual pharmacotherapies for mental disorders, lifestyle-based interventions are associated with fewer side effects and can also serve as neuroprotective factors and reduce the risk of subsequent age-related cognitive deficits (Manger, 2019; Walsh, 2011). Moreover, lifestyle interventions can be cost-effective alternatives to pharmacotherapies, especially in low- and middle-income countries where there is a scarcity of easily-attainable, conventional psychiatric services (Firth et al., 2020; Manger, 2019; Walsh, 2011).

However, the implementation of lifestyle interventions is not simple. Unhealthy lifestyle behaviours may stem from various social risk factors, such as social isolation, unemployment and financial distress, lower levels of education, and living arrangements (World Health Organization and Calouste Gulbenkian Foundation, 2014). A notable

drawback to the idea of lifestyle interventions are the challenges in implementation of these evidence-based interventions in a clinical setting. The translation from research findings to clinical practice has not been straight-forward, as it depends on many factors, such as the delivery, availability and openness to these therapeutic strategies in mental disorders (Deenik et al., 2020). One of the reasons for the under-exploitation of lifestyle interventions is that it can be a challenging process for the patients, the clinicians, and even society as it is (Walsh, 2011). Changes in lifestyle may seem like a process requiring a lot of effort, motivation, and discipline, which could be challenging for the patient. The implementation of lifestyle treatment strategies can be a challenging process for the therapist as well, as it may be more time intensive and require significant knowledge in each lifestyle domain. Moreover, many industries in society are prone to promoting unhealthy behaviours, such as the fast food industry and the easy accessibility to harmful substances (Walsh, 2011). One of the major proposals of this thesis is the move towards more personalized lifestyle interventive strategies, designed based on the presence and extent of unhealthy behaviours across the proposed areas of lifestyle psychiatry for each individual. Perhaps, a multidisciplinary team comprised of various professionals such as a psychiatrist, social worker, dietitian, exercise physiologist, psychologist, nurse, and other trained lifestyle experts could be very beneficial for improving long-term outcomes in individuals suffering from mental illness (Manger, 2019). Alternatively, the recent rise in digital health makes it possible to monitor and obtain data on lifestyle behaviours of the general and clinical populations and provide instant access to personalized suggestions for lifestyle improvements, as suggested in

Chapter 5. Digital lifestyle interventions could prove to be a cost-effective method of providing multidimensional lifestyle care, however, there is currently a lack of strong evidence on the efficacy of digital delivery methods for depression, anxiety, and BD (Anmella et al., 2022; Castro et al., 2021).

6.3 Strengths

The specific strengths of each study presented in this thesis are described in detail within each chapter. Overall, the findings from each study contribute towards the current understandings of lifestyle psychiatry, and the combined importance of multiple lifestyle areas in association to psychiatric disorders. Collectively, these novel findings corroborate previous reports on the significance of perceiving lifestyle as a multifactorial concept for the prevention and treatment of depression, anxiety, and BD, and provide new considerations for future research and clinical directions. In addition, the studies presented in Chapters 2-4 used the SMILE scale, the only quantifiable multidimensional lifestyle assessment examining domains following contemporary notions of lifestyle psychiatry.

The machine learning models developed and utilized in Chapter 2 provide a novel approach to predicting symptoms of depression and anxiety using multidimensional lifestyle behaviours as predictors. In this innovative study, we showed the performance of elastic net, random forest, and XGBoost, three of the most frequently used machine learning techniques, for training a model in different ways to predict symptoms of the

most globally prevalent psychiatric disorders with high accuracy. The significant findings of this study promote the opportunity of using these machine learning models for predicting psychiatric symptoms using lifestyle behaviours and perceptions on a larger scale and progressing our understanding for necessary globally preventive strategies.

The study presented in Chapter 3 was the first study to investigate the associations between multifactorial unhealthy lifestyles and symptoms of depression and anxiety in Canada. In fact, this was not the case only during the COVID-19 pandemic; this was the first ever study to apply a multidimensional lifestyle evaluation following the current notions of lifestyle psychiatry in association to symptoms of depression and anxiety in a Canadian population. This is a significant step forward for tackling the burden of mental disorders in Canada, especially considering the increased prevalence rates of depression and anxiety associated to lifestyle changes following the onset of the pandemic.

Another essential part of this thesis is the analysis of lifestyle behaviours per mood episode in BD, described in Chapter 4. For many years, it has been known that lifestyle factors are associated with symptoms of BD, however, this is the first study to provide a closer comparison between overall lifestyle behaviours and perceptions during depressive and (hypo)manic or mixed states, as well as the core domains of lifestyle psychiatry individually. While the results did not indicate any differences in lifestyle quality between the groups, this approach to evaluating multiple lifestyle areas in BD opens the door for future investigations of changes in lifestyle across different mood states. The ability to closely identify changes in specific behaviours could potentially

predict the onset of symptoms in the future and lead to more effective preventive and treatment strategies.

The systematic review and meta-analysis presented in Chapter 5 emphasize the current gaps in RCT studies of lifestyle interventions for BD. Similar to the abovementioned chapters, this is the first study to investigate the availability and efficacy of interventions for BD in all of the core domains of lifestyle psychiatry. This detailed overview on the frequency of interventions in each domain, multidimensional interventions, and the efficacy of these interventions provides the necessary information for detecting the missing steps in research for the progression towards more comprehensive intervention strategies for BD.

6.4 Limitations

The limitations of each individual study are elaborated within each chapter of this thesis. The overall limitations of this thesis are highlighted below.

The SMILE scale is a self-report assessment of lifestyle within the past 30 days, meaning, it is possible that participants did not report their behaviours with maximum accuracy. Perhaps, memory bias and social desirability may have contributed to their perceived behaviours during this period. However, it is important to note that the SMILE scales were used in the studies presented in Chapters 2-4, which were conducted during the COVID-19 confinement periods at a time where web surveys were the main method of data collection. Although objective lifestyle measurements could minimize inaccuracy

in lifestyle data, the SMILE scale has still proven to be a strong, rapid multidimensional assessment tool. In addition, the screenings for depression and anxiety in the studies presented in Chapters 2 and 3 were conducted using self-report measures, the PHQ-2 and GAD-7. These widely validated questionnaires are often used in research studies for detecting symptoms of depression and anxiety, however, assessment of symptoms using a structured clinical interview is needed in future studies for more detailed and accurate evaluation of current symptomatology. The cross-sectional design of the studies in Chapters 2-4 has also limited the interpretations of any causal relationships attributing unhealthy lifestyles to psychiatric symptoms, but the current findings still shed light to the important associations between the variables. Moreover, the samples included in the studies in Chapters 2 and 3 preclude the generalization of these results to the total Brazilian, Spanish, and Canadian populations, which was a predicted challenge of studies using web-surveys for data collection during the pandemic (De Boni, 2020). The sample in the study in Chapter 4 was also selected by convenience, and further generalization of these findings should be carefully examined.

An important limitation to the studies presented in this thesis was the lack of information obtained on the current use of medications of the participants. It is possible that participants diagnosed with depression, anxiety, or BD were receiving pharmacological therapies at the time of participation. Certain prescribed medications for these disorders could interfere with patterns and behaviours on some of the SMILE domains, such as diet, physical activity, and sleep. Furthermore, we did not account for the presence of any medical or psychiatric comorbidities in participants with BD included

in the study from Chapter 4. Given the presence of high rates of comorbidities in BD, it is important to consider the effects of potential co-occurring physical and psychiatric symptoms during lifestyle evaluations. Also, the non-inclusion of euthymic individuals with BD was a limitation in Chapter 4, which prevented the complete analysis of lifestyle behaviours across all mood states of BD.

In Chapter 5, it is possible that some RCTs eligible for inclusion according to the criteria were not captured during the literature search and the subsequent hand search of references, which could be the case due to the differences in conceptualization of 'lifestyle' and the domains that fall under the umbrella of lifestyle.

6.5 Future Directions

The research presented in this thesis contributes to the basis of future research and clinical implementations of lifestyle psychiatry. Considering the relative novelty of the multidimensional lifestyle approach to preventive and treatment strategies for psychiatric disorders, there are still several major concerns to address in this field in future investigations. The primary proposition of the studies in this thesis for future research is the adaptivity of a multifactorial lifestyle approach to assessments and interventions for improving our understanding of lifestyle as a multimodal construct, and investigating the potentially greater effect of multidimensional interventions for individuals with mental health challenges. Lifestyle changes can be very complex and temporary, so there is a need for more longitudinal studies monitoring lifestyle behaviours, short-term impact of

interventions, adherence to treatment guidelines, and long-term assessments of clinical and functional outcomes following the interventions. Namely, there has been a high heterogeneity of types of interventions, outcomes assessed, duration, populations included, and the improvement of outcomes following the interventions, which makes it difficult to draw certain conclusions about the effectiveness of this approach (Firth et al., 2020). Future work is needed on a more detailed, standardized approach to evaluating lifestyle interventions and preventive strategies for depression, anxiety, and BD.

Furthermore, in complex psychiatric disorders such as BD, it is important to monitor lifestyle behaviours across all mood states, including euthymia, to understand the changes in behaviours, perceptions, and routines across the mood states, as suggested in Chapter 4. Further longitudinal research of multidimensional assessments can be very beneficial for the development of preventive and treatment strategies for BD. However, another major consideration for future research is the interactions between medications and lifestyle behaviours during lifestyle assessments and interventions. Perhaps, the current pharmacological therapies could be a factor contributing towards unhealthier lifestyle behaviours and interfering with the effectiveness of non-pharmacological therapies. Future studies should investigate this relationship in order to establish the effectiveness of lifestyle interventions as complementary treatment strategies to usual pharmacological care.

However, as mentioned above, the translation from research findings to clinical implementations is not straight-forward, and there are several obstacles to overcome. The dissemination and implementation stages of interventions can be impeded by many

factors, such as the motivation and willingness of the patient to adopt the suggested strategies, adequate knowledge on necessary interventions, and environmental and organizational factors (Deenik et al., 2020; Firth et al., 2019b). Implementation studies are needed for investigating the acceptability, adoption, fidelity, implementation costs, and sustainability of lifestyle interventions in clinical practice (Deenik et al., 2020). Furthermore, future studies should also investigate the burden of implementing these strategies on clinicians, such as time required for attending to the needs of each individual to ensure the effectiveness of the treatments (Walsh, 2011). Wide-scale adoption of lifestyle interventions may also rely on public health systems, educational and marketing campaigns to raise awareness of unhealthy lifestyle choices to reduce the burden of mental disorders (Walsh, 2011).

The widespread use of digital technologies has become an alternative for easier monitoring of lifestyle behaviours, gathering data from participants, and providing preventive and treatment interventions for mental disorders (Firth et al., 2020, 2019b). While this appears like a possibility for a large-scale, cost-effective delivery of lifestyle interventions, there is still a need for further research the standardization, operationalization, and effectiveness of digitally delivered lifestyle interventions for psychiatric disorders (Castro et al., 2021; Firth et al., 2020, 2019b).

The relatively novel field of lifestyle psychiatry holds great promise for reducing the rates of mental health symptoms, however, future work is needed across many levels to reach the desired effects of lifestyle interventions.

6.6 Conclusion

The work in this thesis highlights the association between multidimensional lifestyle behaviours and perceptions and common psychiatric disorders, such as anxiety, depression, and BD. We found that the presence of symptoms related to anxiety, depression, and/or (hypo)mania is associated with detrimental clustering of unhealthy lifestyle patterns across areas such as diet, physical activity, substance use, sleep, stress management, social relationships, and environmental exposures. Additionally, we found promising results for multidimensional lifestyle interventions for improvement of clinical and functional outcomes in BD. Overall, this thesis suggests that a multidimensional lifestyle approach can be very beneficial for the development of preventive and treatment strategies for anxiety, depression, and BD.

6.7 References

Anmella, G., Faurholt-Jepsen, M., Hidalgo-Mazzei, D., Radua, J., Passos, I.C., Kapczinski, F., Minuzzi, L., Alda, M., Meier, S., Hajek, T., 2022. Smartphone-based interventions in bipolar disorder: systematic review and meta-analyses of efficacy. A position paper from the International Society for Bipolar Disorders (ISBD) Big Data Task Force. Bipolar Disorders.

Balanzá-Martínez, V., Kapczinski, F., de Azevedo Cardoso, T., Atienza-Carbonell, B., Rosa, A.R., Mota, J.C., De Boni, R.B., 2021. The assessment of lifestyle changes during the COVID-19 pandemic using a multidimensional scale. Revista de psiquiatria y salud mental 14, 16–26.

Bauer, I.E., Galvez, J.F., Hamilton, J.E., Balanza-Martinez, V., Zunta-Soares, G.B., Soares, J.C., Meyer, T.D., 2016. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. Journal of psychiatric research 74, 1–7.

Blom, V., Lönn, A., Ekblom, B., Kallings, L.V., Väisänen, D., Hemmingsson, E., Andersson, G., Wallin, P., Stenling, A., Ekblom, Ö., 2021. Lifestyle habits and mental health in light of the two COVID-19 pandemic waves in Sweden, 2020. International Journal of Environmental Research and Public Health 18, 3313.

Campion, J., Javed, A., Sartorius, N., Marmot, M., 2020. Addressing the public mental health challenge of COVID-19. The Lancet Psychiatry 7, 657–659.

Castro, R., Ribeiro-Alves, M., Oliveira, C., Romero, C.P., Perazzo, H., Simjanoski, M., Kapciznki, F., Balanzá-Martínez, V., De Boni, R.B., 2021. What are we measuring when we evaluate digital interventions for improving lifestyle? a scoping meta-review. Frontiers in public health 9.

Cervera-Martínez, J., Atienza-Carbonell, B., Mota, J.C., Bobes-Bascarán, T., Crespo-Facorro, B., Esteban, C., García-Portilla, M.P., Gomes-da-Costa, S., González-Pinto, A., Jaén-Moreno, M.J., 2021. Lifestyle changes and mental health during the COVID-19 pandemic: A repeated, cross-sectional web survey. Journal of Affective Disorders 295, 173–182.

Conry, M.C., Morgan, K., Curry, P., McGee, H., Harrington, J., Ward, M., Shelley, E., 2011. The clustering of health behaviours in Ireland and their relationship with mental health, self-rated health and quality of life. BMC public health 11, 1–10.

Davidson, J., Turnbull, C.D., Strickland, R., Miller, R., Graves, K., 1986. The Montgomery-Åsberg Depression Scale: reliability and validity. Acta psychiatrica scandinavica 73, 544–548.

De Boni, R.B., 2020. Web surveys in the time of COVID-19.

Deenik, J., Czosnek, L., Teasdale, S.B., Stubbs, B., Firth, J., Schuch, F.B., Tenback, D.E., Van Harten, P.N., Tak, E.C., Lederman, O., 2020. From impact factors to real impact: translating evidence on lifestyle interventions into routine mental health care. Translational behavioural medicine 10, 1070–1073.

Fagiolini, A., Coluccia, A., Maina, G., Forgione, R.N., Goracci, A., Cuomo, A., Young, A.H., 2015. Diagnosis, epidemiology and management of mixed states in bipolar disorder. CNS drugs 29, 725–740.

Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A.F., 2019a. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry 6, 675–712.

Firth, J., Solmi, M., Wootton, R.E., Vancampfort, D., Schuch, F.B., Hoare, E., Gilbody, S., Torous, J., Teasdale, S.B., Jackson, S.E., 2020. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry 19, 360–380.

Firth, J., Ward, P.B., Stubbs, B., 2019b. Lifestyle psychiatry. Frontiers in psychiatry 10, 597.

Gillis, A.J., 1997. The Adolescent Lifestyle Questionnaire: Development and Psychometric Testing. Canadian Journal of Nursing Research Archive 29–46.

Hu, Z., Lin, X., Kaminga, A.C., Xu, H., 2020. Impact of the COVID-19 epidemic on lifestyle behaviours and their association with subjective well-being among the general population in mainland China: cross-sectional study. Journal of medical Internet research 22, e21176.

Huang, J., Yuan, C.M., Xu, X.R., Wang, Yong, Hong, W., Wang, Z.W., song Su, Y., Hu, Y.Y., Cao, L., Wang, Yu, 2018. The relationship between lifestyle factors and clinical symptoms of bipolar disorder patients in a Chinese population. Psychiatry Research 266, 97–102.

Jensen, L.W., Decker, L., Andersen, M.M., 2006. Depression and Health-Promoting Lifestyles of Persons with Mental Illnesses. Issues in Mental Health Nursing 27, 617–634. https://doi.org/10.1080/01612840600642919

Kapczinski, N.S., Mwangi, B., Cassidy, R.M., Librenza-Garcia, D., Bermudez, M.B., Kauer-Sant'anna, M., Kapczinski, F., Passos, I.C., 2017. Neuroprogression and illness trajectories in bipolar disorder. Expert review of neurotherapeutics 17, 277–285.

Karantonis, J.A., Rossell, S.L., Berk, M., Van Rheenen, T.E., 2021. The mental health and lifestyle impacts of COVID-19 on bipolar disorder. Journal of affective disorders 282, 442–447.

Kasper, S.F., 2004. Living with bipolar disorder. Expert Review of Neurotherapeutics 4, S9–S15. https://doi.org/10.1586/14737175.4.6.S9

Kroenke, K., Spitzer, R.L., Williams, J.B., 2003. The Patient Health Questionnaire-2: validity of a two-item depression screener. Medical care 1284–1292.

Kuan, G., Kueh, Y.C., Abdullah, N., Tai, E.L.M., 2019. Psychometric properties of the health-promoting lifestyle profile II: cross-cultural validation of the Malay language version. BMC public health 19, 1–10.

Lopresti, A.L., Hood, S.D., Drummond, P.D., 2013. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. Journal of Affective Disorders 148, 12–27. https://doi.org/10.1016/j.jad.2013.01.014

Manger, S., 2019. Lifestyle interventions for mental health. Aust J Gen Pract 48, 670–673. https://doi.org/10.31128/AJGP-06-19-4964

Merrill, D.A., Small, G.W., 2011. Prevention in psychiatry: effects of healthy lifestyle on cognition. Psychiatric Clinics 34, 249–261.

Noordsy, D.L., 2019. Lifestyle psychiatry. American Psychiatric Pub.

Pinar, R., Celik, R., Bahcecik, N., 2009. Reliability and construct validity of the health-promoting lifestyle profile II in an adult Turkish population. Nursing research 58, 184–193.

Safaie, N., Ketabi, S., Kia, N., Mirmohammadkhani, M., Moonesan, M.R., Paknazar, F., 2020. Exploration of mental health problems in association with health-promoting lifestyle profile in Iranian medical students: A cross-sectional study. J Educ Health Promot 9, 84. https://doi.org/10.4103/jehp.jehp_582_19

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, Shna, Mohammadi, M., Rasoulpoor, Shabnam, Khaledi-Paveh, B., 2020. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Globalization and health 16, 1–11.

Scott, D., Happell, B., 2011. The High Prevalence of Poor Physical Health and Unhealthy Lifestyle Behaviours in Individuals with Severe Mental Illness. Issues in mental health nursing 32, 589–97. https://doi.org/10.3109/01612840.2011.569846

Shatte, A.B., Hutchinson, D.M., Teague, S.J., 2019. Machine learning in mental health: a scoping review of methods and applications. Psychological medicine 49, 1426–1448.

Spitzer, R.L., Kroenke, K., Williams, J.B., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine 166, 1092–1097.

Tanjani, P.T., Azadbakht, M., Garmaroudi, G., Sahaf, R., Fekrizadeh, Z., 2016. Validity and reliability of health promoting lifestyle profile II in the Iranian elderly. International journal of preventive medicine 7.

Veldhuis, C.B., Nesoff, E.D., McKowen, A.L.W., Rice, D.R., Ghoneima, H., Wootton, A.R., Papautsky, E.L., Arigo, D., Goldberg, S., Anderson, J.C., 2021. Addressing the critical need for long-term mental health data during the COVID-19 pandemic: Changes in mental health from April to September 2020. Preventive Medicine 146, 106465.

Vermeulen-Smit, E., Ten Have, M., Van Laar, M., De Graaf, R., 2015. Clustering of health risk behaviours and the relationship with mental disorders. Journal of affective disorders 171, 111–119.

Walker, S.N., Sechrist, K.R., Pender, N.J., 1995. Health promotion model-instruments to measure health promoting lifestyle: Health-promoting lifestyle profile [HPLP II](Adult version).

Walker, S.N., Sechrist, K.R., Pender, N.J., 1987. The Health-Promoting Lifestyle Profile: development and psychometric characteristics. Nurs Res 36, 76–81.

Walsh, R., 2011. Lifestyle and mental health. American Psychologist 66, 579.

World Health Organization and Calouste Gulbenkian Foundation, 2014. Social Determinants of Mental Health.

Xiong, J., Lipsitz, O., Nasri, F., Lui, L.M., Gill, H., Phan, L., Chen-Li, D., Iacobucci, M., Ho, R., Majeed, A., 2020. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. Journal of affective disorders.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry 133, 429–435.

Zhang, H., Wisniewski, S.R., Bauer, M.S., Sachs, G.S., Thase, M.E., 2006. Comparisons of perceived quality of life across clinical states in bipolar disorder: data from the first 2000 Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants. Comprehensive Psychiatry 47, 161–168. https://doi.org/10.1016/j.comppsych.2005.08.001