

# THE MANAGEMENT OF CARDIOVASCULAR DISEASE RISK FACTORS IN BIPOLAR DISORDER PATIENTS IN PRIMARY HEALTHCARE SETTINGS\*

## EL MANEJO DE LOS FACTORES DE RIESGO DE LA ENFERMEDAD CARDIOVASCULAR EN PACIENTES CON EL TRASTORNO BIPOLAR EN CONTEXTOS DE SALUD PRIMARIA

Recibido: 18 de mayo de 2020 | Aceptado: 22 de octubre de 2020

Sandra I. Ralat<sup>1</sup>, Rossana I. Barrios<sup>2</sup>

<sup>1</sup>. Department of Psychiatry, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

<sup>2</sup>. Conrado F. Asenjo Library, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

### ABSTRACT

Accumulating evidence supports the association between cardiovascular disease (CVD) risk factors and bipolar disorder (BD). CVD is the leading cause of morbidity and mortality in patients with bipolar disorder. However, there is a need to study the management of the risk factors in the primary healthcare context. This narrative review aims to appraise the different approaches of care that have been used in the management of these patients to address CVD risk factors in primary care. We reviewed articles from PubMed, Science Direct and other studies cited in the articles found. The keywords used for this review included "bipolar," "bipolar disorder," "cardiovascular" or "metabolic syndrome," "screening," "primary care," and "integrative" or "integrated care model" or "collaborative care model." This review includes studies published over a period of 48 months (January 2016 through December 2019). We identified 128 articles, removing two duplicates. From them, 115 articles are excluded based on the inclusion/exclusion criteria leaving eleven relevant articles. Upon full-text review, six studies were excluded. The final studies included are five. We used the study-quality assessment tools from the National Heart, Lung, and Blood Institute to assess the quality of the articles found. CVD risk factors in patients with BD and forms of other severe mental illness (SMI) are often underdetected. Primary healthcare providers need to identify these risk factors in the management of these patients to determine and recommend appropriate strategies.

**KEYWORDS:** Bipolar disorder, cardiovascular disease, risk factors, collaborative care model, primary healthcare

### RESUMEN

La evidencia acumulada apoya la asociación entre los factores de riesgo de la enfermedad cardiovascular (ECV) y el desorden bipolar (DB). La ECV es la causa principal de morbilidad y mortalidad en pacientes con el DB. Sin embargo, existe la necesidad de estudiar el manejo de estos factores de riesgo en contextos de atención primaria. Esta revisión narrativa tiene como objetivo evaluar los diferentes enfoques de atención que se han utilizado en el manejo de estos pacientes para abordar los factores de riesgo de ECV en la atención primaria. Revisamos artículos de PubMed, Science Direct y otros estudios citados en los artículos encontrados. Las palabras claves utilizadas para esta revisión incluyeron "bipolar", "trastorno bipolar", "síndrome metabólico" o "cardiovascular", "detección", "atención primaria" y "modelo de atención integrada" o "integrativo" o "modelo de atención colaborativa". Esta revisión incluye estudios publicados durante un período de 48 meses (enero de 2016 a diciembre de 2019). Identificamos 128 artículos, eliminando dos duplicados. De éstos, se excluyen 115 artículos a base de los criterios de inclusión / exclusión dejando 11 artículos relevantes. Tras la revisión del texto completo, se excluyeron seis estudios. Los estudios finales incluidos fueron cinco. Utilizamos las herramientas de evaluación de la calidad de los estudios del Instituto Nacional del Corazón, los Pulmones y la Sangre para evaluar la calidad de los artículos encontrados. Los factores de riesgo de ECV en pacientes con el DB y otras enfermedades mentales graves (EMG) a menudo no se detectan correctamente. Los proveedores de atención primaria de la salud deben identificar estos factores de riesgo en el tratamiento de estos pacientes para determinar y recomendar estrategias adecuadas.

**PALABRAS CLAVE:** Atención primaria, factores de riesgo, enfermedad cardiovascular, modelo de atención colaborativa, desorden bipolar

\* Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health, Award Number #R25MD007607 and U54MD007600. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Correspondence concerning this article should be addressed to Sandra I. Ralat, Department of Psychiatry, School of Medicine, PO Box 365067, San Juan, PR 00936-5067. Email: sandra.ralat@upr.edu 787-758-2525, Ext 3431

Several published studies have described patients with severe mental illness (SMI), including bipolar disorder (BD), in whom the risk factors for cardiovascular disease (CVD), but not the disease, itself, were present. In a past qualitative research experience using focus groups (Ralat et al., 2018) we found that if one asks a patient, a family member of a patient, or, in some cases, a healthcare provider about the relationship between BD and CVD risk factors, frequently the answer is that they do not have any knowledge of such a relationship or said relationship might be a secondary effect of the medication. BD patients tend to receive inadequate care for their medical conditions (when such are present and including CVD) from their primary healthcare systems (Ayerbe, Forgnone, Addo et al., 2018). The studies of Hayes et al. (2017), Nielsen et al. (2019), Ritchie and Muldoon (2017) have found that disparities between SMI patients (including those more specifically suffering from BD) and the general population exist in terms of preventive care services for CVD. Additionally, only half of BD patients typically receive adequate monitoring for the CVD risk factors associated with atypical antipsychotic use (Kilbourne et al., 2008).

These risk factors tend to be under-recognized and poorly treated, also exerting harmful effects on BD patients (Damegunta & Gundugurti, 2017). This article is a narrative review of the current research regarding the management of CVD risk factors in the care of bipolar patients in primary care settings.

Background of bipolar disorder and medical comorbidity

#### *Bipolar Disorder and Cardiovascular Disease*

BD, also known as manic-depressive illness, is a chronic disease that causes unusual shifts in a person's mood polarity, energy, and ability to function, causing that individual to display symptoms that are severe and disabling (Czepielewski et al., 2013; Emilien et al., 2007). It is a psychiatric disease of significant public health importance that affects about 60

million people worldwide (WHO, 2017). It is considered a Severe Mental Illness (SMI). The lifetime prevalence of BD usually reported in U.S. is 1% or 2%, but when subthreshold cases are included, higher rates of up to 6.4% are established (Judd & Akiskal, 2003; Kessler & Wang, 2008). In Puerto Rico, the prevalence of BD is 3.4% (Behavioral Sciences Research Institute, 2016). BD is the sixth leading cause of disability, which means an impairment in social and occupational functioning, frequent relapses, and medical comorbidity ("Burden of Mental Illness," CDC, 2013). It is one of the costliest mental diseases after schizophrenia (SCZ) in the US (Russo & Andrews, 2006). Healthcare cost is high, but there are also other intangible costs such as family burden and impaired health-related quality of life (Maina et al., 2013). Furthermore, the bipolar patient is at higher risk of committing suicide (Ferrari et al., 2014).

BD subtypes include bipolar disorder I (BD-I) and bipolar disorder II (BD-II). Patients with BD-I experience one or more manic episodes and experience major depressive and hypomanic episodes. BD-II is characterized by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (2013).

CVD is the leading cause of morbidity and mortality among patients with BD (García-Portilla et al., 2009; Kalelioğlu et al., 2018; Wiener et al., 2011). The mortality rates for these patients are approximately two times higher than are those of the general population according to several authors (Bobes et al., 2008; Druss et al., 2011; Walker et al., 2014; Wiener et al., 2011). A study from Sweden taking into consideration the 1987 – 2010 years found 3-fold mortality compared to the general population (Osby et al., 2016). These authors found a trend in people with bipolar disorder where the rate ratio increased for coronary heart disease. Goldstein et al. (2015) found that BD patients have

significantly increased risk to develop CVD over the course of three years compared to Major Depression Disorder.

#### The risk factors for CVD in BD

Not only CVD prevalence rates but also the prevalence rates for the risk factors for CVD are about twice as high in BD patients as they are in the general population (Birkenaes et al., 2007; Vancampfort et al., 2013). Individuals with BD are vulnerable to a variety of physical conditions considered as risk factors for CVD, such as hypertension, hyperlipidemia, type 2 diabetes, abdominal obesity, and metabolic syndrome, among other medical conditions. These risk factors might appear in BD patients from four to 20 years earlier than they do in the general population (Goodrich et al., 2012). Lifespan can be reduced anywhere from eight to 25 years (Carliner et al., 2014). The appearance of these risk factors in bipolar patients has been reported to be related to *psychiatric symptoms, unhealthy behaviors, psychiatric medications, and disparities in health services*.

#### *CVD risk factors and psychiatric symptoms in BD*

Mortality in bipolar patients during the 19th and 20th centuries was associated with collapse from acute mental illness (Derby, 1933). These patients got little food and sleep and functioned with such constant restlessness and anxiety that they were at risk not only of getting CVD but also of suffering sudden death (Wiener et al., 2011). In the 1930s, physicians began to recognize cardiovascular disturbance as having been the cause of death in many manic-depressive patients (Murray et al., 2009). Even when the CVD risk is not specific to BD patients and can be related to SCZ or major depression, the literature indicates there to be greater CVD mortality in BD patients compared to what is seen in those with major depression (Martin et al., 2016).

It is well known that extreme mood swings can exacerbate both CVD and its attendant risk factors. However, in studies of the

relationship of manic, hypomanic, and depressive episodes with CVD or cardiovascular risk factors, different results have been obtained (Fiedorowicz et al., 2009, 2014; Ramsey, et al., 2010; Slomka et al., 2012).

Mood symptoms in BD patients speeds up vascular mortality. Moreover, psychiatric illness is associated with changes in the pathophysiologic processes that promote heart disease (Vuksan-Cusa et al., 2009).

#### *CVD risk factors and unhealthy behaviors in BD*

Unhealthy behaviors such as smoking, having a poor diet, consuming alcohol, having a sedentary lifestyle, and not adhering to treatment are behavioral mechanisms that could induce CVD in BD patients. People with a mental illness (including BD) are more than twice as likely to smoke cigarettes and 50% more likely to be overweight/obese than people without a mental illness are (Compton et al., 2006). Environmental factors such as diet and lack of exercise are well-established causal factors (Bauer et al., 2016; Firth et al., 2019). Several studies suggested a relationship between an unhealthy diet and BD (Lopresti & Jacka, 2015). Having a poor diet was found to influence symptom severity. Healthy eating plays a role in preventing or minimizing the adverse effects of CVD risk factors. A sedentary lifestyle is an independent predictor of CVD (Vancampfort et al., 2016). Nonadherence to medication and other unhealthy behaviors as well influence these risk factors.

#### *CVD risk factors and psychiatric medications*

Several medications used to treat bipolar patients can contribute to cardiovascular risk factors. For example, lithium is considered the gold-standard treatment in BD. However, it has been associated with weight gain, and it may also negatively affect cardiac conduction, although, in general, it can safely be used in cardiac patients (Vuksan-Cusa et al., 2009). However, compared to quetiapine, lithium is less severe, because with quetiapine, there

are more severe effects, such as obesity and diabetes (McIntyre et al., 2009). There are other effective treatments for BD patients that include anticonvulsant mood stabilizers. The second generation of antipsychotics is associated with hyperlipidemia, insulin resistance or increased risk of diabetes mellitus, and weight gain. It is important to emphasize the appropriate monitoring of the patient (Vuksan-Cusa et al., 2009).

Although CVD risk factors have been associated with psychiatric medications, several authors found that CVD mortality was excessive in BD patients even before the advent of atypical antipsychotics and prior to the use of tricyclic antidepressants and lithium (Goldstein et al., 2009; Wiener et al., 2011). BD itself appears to confer risk for CVD, independent of treatments used to manage the disorder (Swartz et al., 2012). Weight gain seems prevalent in affective disorders and is caused by both the effects of the illness as well as to those of a given treatment (Shrivastava et al., 2010). Nevertheless, treatment with medication requires that BD patients be rigorously monitored for CVD and its risk factors.

#### *CVD risk factors, health disparities, and the Latino population in the US*

International studies have revealed inequities between people with SMI (among them, BD patients) and the general population in the provision of preventive care services for CVD. There is a lack of care being provided to patients with physical health conditions in psychiatric settings; much room for improvement exists (Ritchie & Muldoon, 2017). Inadequate access to quality care and health disparities in minorities lead to fewer people seeking help and prevent the distribution of adequate treatment for mental health and medical conditions.

Low access to preventive health services, financial and structural barriers to high-quality medical care, disease-related unhealthy lifestyle choices, and the belief that patients are unable to achieve physical health and

wellness are among the several reasons for the marked morbidity and mortality of CVD (Carliner et al., 2014). In the US, for example, a systematic review and meta-analysis regarding health disparities in patients with psychiatric disorders (Ayerbe, Forgnone, Foguet-Boreu et al., 2018) found evidence that suggests that patients with BD or SCZ tend to receive poorer care for hypertension than do individuals in the general population.

Higher rates of CVD and shorter life expectancies are found in Latinos, which could be considered a double burden of risk, associated with both being of a certain race/ethnicity and having psychiatric diagnosis (Carliner et al., 2014; Ralat et al., 2018). A high proportion of CVD risk factors and the presence of three or more adverse CVD risk factors were found in men and women of Puerto Rican background with low education levels (Daviglius et al., 2014).

Substantial barriers to the efficacious coordination of health care exist and include suboptimal outcomes, undertreatment, and, critically, the fragmentation of mental and medical care (Ayerbe, Forgnone, Foguet-Boreu et al., 2018). The result? The quality of care for BD patients in primary care settings is often inferior (Cerimele & Skern, 2017; Kilbourne et al., 2018).

#### *Development of collaborative care model (CCM)*

During the nineties, the chronic care model emerged for the primary care of patients with chronic physical illness; this model recognized that such illness was inadequately treated (Bauer et al., 2006; Bodenheimer et al., 2002). Also known as the collaborative care model (CCM), it is a treatment model that focuses on enhancing existing services within a given treatment setting to improve the management of chronic medical illness in primary care patients. The evidence concerning the effectiveness of collaborative care applied to the mental health context was derived, initially, from the care of depression and anxiety patients (Cerimele & Skern, 2017). However, primary care providers have had



patients with other psychiatric disorders that are considered to be an SMI (e.g., BD and SCZ). Six components are part of the CCM: patient self-management support, delivery-system redesign, use of clinical information systems, provider decision support, linkage to community resources, and healthcare-organization support (Woltmann et al., 2012). In 2000, several investigators adapted this model to work with individuals with BD (Bauer et al., 2006).

Based on the chronic care model, the bipolar collaborative chronic care model was developed to improve mental health outcomes in patients with BD (Bauer et al., 2006). Nevertheless, no linkage to medical care providers was established. Another adaptation was the bipolar disorder medical care model (BCM), developed in 2005 and implemented in March 2006 (Kilbourne et al., 2008). This model was adapted from the previous one and included three of the following components: patient self-management support, care management, and guideline dissemination focused on medical treatment in BD. Both the medical and the psychiatric outcomes for the BCM group improved compared with those of the usual care group in one study (Kilbourne et al., 2008). Two specific research questions are raised after having obtained this information: (1) Are there other collaborative or integrated models of primary healthcare for bipolar patients? (2) What approaches to primary healthcare have been tested for the management of the CVD risk factors during 2016-2019?

This review article aims to report on the state of knowledge about the different approaches of care that have been used to address these medical conditions and unhealthy lifestyle choices through collaborative care models and other integrative care models.

## METHOD

Our review has an emphasis on the management of CVD risk factors in BD

patients in the primary healthcare context. The literature examined from January 2016 through December 2019 compared “treatment as usual” and other specific models of care in primary healthcare settings for people with severe mental illness, including bipolar patients. The search was limited to studies published in that period of time in order to obtain the most recent scientific articles. Inclusion criteria comprised the management of CVD risk factors in a primary healthcare context through several integrated care models. The keywords used were “bipolar,” “bipolar disorder,” “cardiovascular” or “metabolic syndrome,” “screening,” “primary care,” and “integrated” or “integrative care model” or “collaborative care model.” We used the PRISMA guidelines (Moher et al., 2009) for the process of the literature search (Figure A). As part of the inclusion criteria were studies that have used a care model in primary healthcare to intervene with medical conditions related to CVD risk factors in patients with bipolar disorder. All in the English language. We included articles in which the sample was composed of SMI patients that comprise bipolar patients. Those articles that were only research proposals or those that were not management approaches for these risk factors were excluded. The assessment of quality and risk of bias due to flaws in the study design was made using the quality assessment of controlled intervention studies tool, and the quality assessment tool for before-after (pre-post) studies with no control group from the National Heart, Lung, and Blood Institute (NHLBI, 2016). These quality assessment tools are important for critical appraisal of the internal validity of a study. The ratings of the studies will be between good, fair or poor quality. A good study is a research with the least risk of bias.

The authors assessed the studies independently. Then, both authors met to explore coincidences and disagreements in their assessments of each study. In moments of disagreement, the authors discussed the relevant item to resolve the disagreement. For an overview of the characteristics of the included studies, see Table 1.

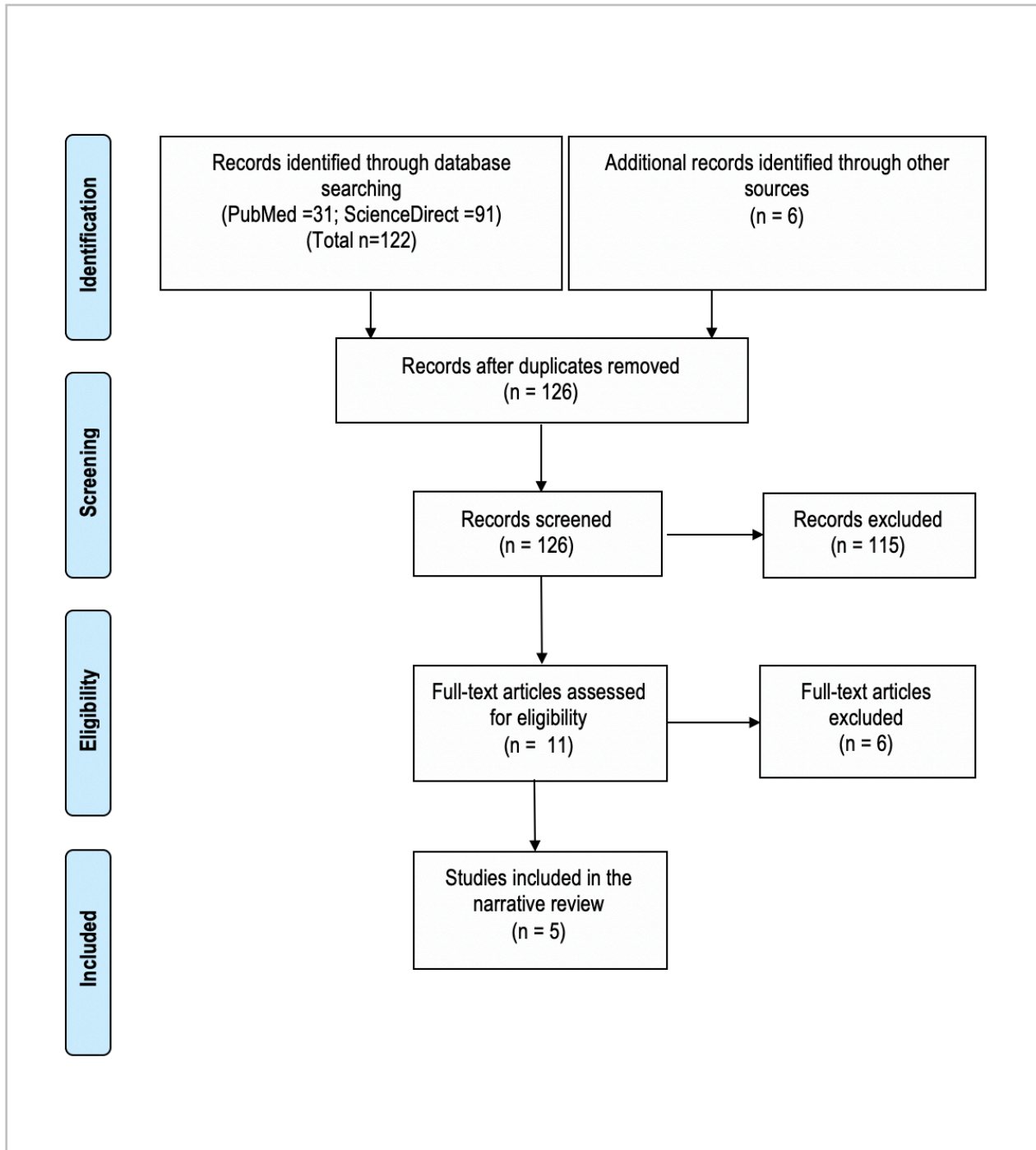


FIGURE A.  
Flow Diagram (PRISMA)

TABLE 1.  
An overview of the characteristics of the included studies.

Study	Hypothesis/Objective	Methods/Design	Sample	Conclusion
Druss et al. (2017) <i>Randomized Trial of an Integrated Behavioral Health Home: The Health Outcomes Management and Evaluation (HOME) Study</i>	Compare quality and outcomes of care between patients at an integrated behavioral health home and those receiving usual care (UC).	Single blind randomized trial of the patient care received at a behavioral health home compared with the UC received by patients at a community mental health center.	The sample consisted of 447 patients with SMI and one or more cardiometabolic risk factors, randomly assigned to either a behavioral health home or UC, for 12 months.	The behavioral health home was associated with significant benefits to the quality of general medical care and cardiometabolic care as well as concordance with the chronic care model. However, there was not a significant effect on cardiometabolic risk factors.
Kilbourne et al. (2017) <i>Improving physical health in patients with chronic mental disorders: 12-month results from a randomized controlled collaborative care trial</i>	Patients receiving LG-CC (Life Goals Collaborative Care) compared to those in UC will have improved physical health-related quality of life and improvements in CVD symptom-specific measures.	Single-blind randomized controlled trial. This intervention trial was done with adult patients diagnosed with chronic mental disorders and with at least one CVD risk factor who received care at a VA outpatient health clinic.	A total of 304 persons agreed to participate and were enrolled. Eleven dropped out prior to the randomization, resulting in a sample size of 293. The age range was 28 to 75 years.	Patients with chronic mental disorders and one cardiovascular (CVD) risk factor who received the LG-CC had a greater improvement in physical health-related quality of life after 12 months than did patients that received UC. The effect size was moderate. However, the authors did not observe improvements in the secondary outcomes related to CVD risk factors, with the exception of LDL levels.
Lambert et al. (2018) <i>Comorbidity of chronic somatic diseases in patients with psychotic disorders and their influence on 4-year outcomes of integrated care treatment (ACCESS II Study).</i>	Assess the prevalence of somatic comorbidity in general and of specific comorbidity according to ICD- 10 (German version) in people with psychotic disorders.  Evaluate if somatic comorbidity at baseline influences the long-term outcome of the mental disorder.	Prospective, single-center, long-term study to assess the effectiveness and efficiency of ACCESS based in the "Hamburg Model of Integrated Care" for severe psychotic disorders.	From 312 patients identified, 187 patients completed the interventions and assessments.	An average of over two chronic somatic illnesses was found in 80% of the ACCESS patients. They found 55 different diseases from 15 different ICD-10 disease areas. Both groups (with and without comorbidity) received the ACCESS intervention and displayed statistically and clinically significant improvements.
Osborn et al. (2018) <i>Clinical and cost-effectiveness of an intervention for reducing cholesterol and cardiovascular risk for people with severe mental illness in English primary care: a cluster randomized controlled trial</i>	Compare the clinical effectiveness and cost-effectiveness of the intervention (Primrose) versus "treatment as usual" for people with SMI. A pragmatic intervention was developed to reduce CVD risk factors in SMI patients in primary care in England.	Cluster randomized trial with general practices from across England as the unit of cluster.	Forty or more patients with SMI, aged 30 to 75 years with SCZ (schizophrenia), BD (bipolar disorder), or psychosis. The participants had high cholesterol concentrations or HDL or one or more modifiable CVD risk factor.	Total cholesterol concentration at 12 months did not differ between the Primrose group and the UC group. However, the Primrose intervention was associated with fewer psychiatric admissions, with potential cost-effectiveness. All the participants received screening for CVD risk factors and feedback, which is not customary in primary care settings.
Tepper et al. (2017) <i>Mind the gap: Developing an integrated behavioral health home to address health disparities in serious mental illness</i>	Evaluate a defined behavioral health home (BHH) program implemented in a safety-net institution for adults with BD or SCZ.  BHH will reduce emergency department visits and general medical and psychiatric admissions and will increase preventive health screening.  The secondary hypothesis was that BHH would impact secondary metabolic outcomes.	Quasi-experimental methods were used to compare outcomes (before and after) in patients at an integrated BHH patients and a control group.	The sample consisted of 1,945 participants. Of them, 1,331 were people with a diagnosis of SCZ, schizoaffective disorder, and other psychotic disorders. BD patients numbered 614, all with one or more visits for mental or general medical care before and after the intervention. Mean age was 48 years for the patients in the BHH group and 50 years for the members of the control group.	A safety-net BHH program for adults with SMI reduced rates of psychiatric hospitalization and emergency department (ED) utilization. Additionally, increased HbA1c screening. However, the BHH had no effect on rates of general medical hospitalization or LDL screening or on values of metabolic parameters for diabetic patients over the 12-month study period.

RESULTS

Overall, 122 studies were identified through PubMed (31) and Science Direct (91). Six studies cited in the papers that were selected were also included and reviewed for a total of 128. Two duplicates were removed. Some 115 articles were excluded because the title and abstract were out of the scope based on the inclusion/exclusion criteria leaving eleven relevant articles. Upon full-text review, six studies were excluded. The final studies included were five (Figure A). We found five studies in which four different models of care

that had been explored and tested. There were randomized clinical trials (RCTs) and intervention studies; and a before-after (pre-post) study with no control group. Table 2 through Table 3 present the results of the quality assessments, according to the study design. The qualitative tools used in this study assessed the risk of bias due to flaws in the study design or its implementation, so studies could vary in their strengths and weaknesses (National Heart, Lung, and Blood Institute [NHLBI], 2016). In general, we found studies of good quality, meaning that a good study had the least risk of bias.

TABLE 2.  
Quality Assessment of Controlled Intervention Studies.

Criteria for Assessment	Osborn et al. (2018)	Druss et al. (2017)	Tepper et al. (2017)	Kilbourne et al. (2017)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial or an RCT?	Yes	Yes	No	Yes
2. Was the method of randomization adequate?	Yes	Yes	Yes (Propensity score methods)	Yes
3. Was the treatment allocation concealed?	Yes	Yes	No	Yes
4. Were study participants and providers blinded to treatment group assignment?	Yes	No* (Single blind)	N/A	Yes
5. Were the people assessing the outcomes blinded to the participants' group assignments?	Yes	No	No	Yes
6. Were the group similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Yes	Yes	Yes	Yes
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes	Yes	Yes	Yes
8. Was the differential drop-out rate (between tx groups) at endpoint 15 % points or lower?	Cannot Determine	No	Yes	Yes
9. Was there high prevalence to the intervention protocols for each tx group?	Yes	Cannot Determine	Cannot Determine	Yes
10. Were other interventions avoided or similar in the groups?	Yes	Yes	Cannot Determine	Yes
11. Were the outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes	Yes
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Yes	Yes Authors reported a large Cohen'd value of large effect.	Yes	Yes
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Yes	Yes	Yes	Yes
14. Were all randomized participants analyzed in the group to which they were originally assigned, e.i., did they use an ITT analysis?	Yes	Yes	Yes	Yes
QUALITY (total number of positive items)	13/14	10/14	8/14	14/14

RCTs, Intervention Studies (Table 2)

A study conducted in England, used the Primrose model in their study (Osborn et al.,

2018). Primrose is a five years research program for the prediction and management of cardiovascular disease risk for people with severe mental illnesses (UCL, 2020). Consist



of several stages. The first was the elaboration of a risk score tool. A cardiovascular risk prediction tool for SMI patients was developed and validated. The second was the development of an intervention and training program. The third was a clinical trial in primary care. This model is based on eight strategies that healthcare professionals could use to help decrease cardiovascular risk. This intervention was associated with fewer admissions for mental health issues (in terms of adverse events) and significantly lower costs for those admissions. The conclusion was that the Primrose intervention was acceptable to participants and general practices, but in terms of improving medical outcomes, this model resulted in no differences with the “treatment as usual,” in England. The authors stated that the number of participants with 12-month follow-up data surpassed the requirements of the original sample size calculation. However, the significant result was related to medical-cost savings and reduced admissions. This study had a good quality, overall, in terms of compliance, with a score of 13 out of 14 in the quality assessment of controlled intervention studies from NIHBL (2016).

In the U.S., the development of several integrative services has been tested. Several authors carried out a randomized trial of an integrated Behavioral Health Home (BHH) study (Druss et al., 2017). This model, the BHH, consisted of a medical health home that was located in a community mental health center; its purpose was to improve outcomes and the experience of care, as well as control costs. The study evaluated the impact of a BHH on the quality and outcomes of care in a sample of patients with comorbid SMI and cardiometabolic risk factors. The results showed that the patients in the BHH group exhibited significant improvements in terms of their diabetes and hypertension care. Additionally, they received care of a significantly higher quality compared with those in the usual care. The overall score was 10 out of 14 in the quality assessment of controlled intervention studies tool.

In another study, the BHH was used to address health disparities in patients with SMI (Tepper et al., 2017). This study was a quasi-experimental research in which they compared outcomes (before and after the BHH intervention) between ambulatory patients and a control group that received “treatment as usual.” The contribution of this study was that it evaluated a defined BHH program for use by adults with SCZ or BD. The results showed that the BHH program decreased rates of psychiatric hospitalization, emergency department (ED) visits; and the patients underwent HbA1c screening with greater frequency. They discovered, over the course of the 12-month study period, the rates of both general medical hospitalization and LDL screening remained unaffected by the BHH experience, as did the values of the metabolic parameters of the diabetic patients. However, they stated that sample size of BD patients was relatively small for the primary outcomes. The overall score was 8 out of 14.

In U.S. several authors examined the physical health in patients with SMI in an RCT that explored collaborative care (Kilbourne et al., 2017). Specifically, they wanted to determine if Life Goals Collaborative Care (LG-CC), contrasted with usual care (UC), improved physical and mental results in a 12-month period in patients with chronic mental disorders who were at risk of CVD. LG-CC had initially been tested with bipolar patients in previous studies (Kilbourne et al., 2013). In the Kilbourne et al. (2017) study, the authors wanted to test the model's effectiveness at working with patients with other severe psychiatric illnesses. The sample size was of 240 participants that enabled a .80 power to detect a small to moderate effect at a significance level of .05 on the primary outcome. The results were that the LG-CC produced a modest improvement in physical health-related quality of life, related to LDL levels. The outcomes were suboptimal for persons with chronic mental disease. The study had a good quality overall compliance of 14 out of 14.

TABLE 3.  
Quality Assessment Tool for Before-After (Pre-Post) Studies, No Control Group.

Criteria for Assessment	Lambert et al. (2018)
1. Was the study question or objective clearly stated?	Yes
2. Were eligibility/selection criteria for the study population pre-specified and clearly described?	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings? (Effect size reported).	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Not reported
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)? Only baseline measures, during and after the interventions were taken.	No
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes
QUALITY (total number of positive items)	9/12

Before-after (pre-post) studies, no control group (Table 3)

ACCESS II is a prospective, single-center, long-term study for people with severe psychotic disorders that included SCZ, BD, and other diagnoses (Lambert et al., 2018). ACCESS is based on the Hamburg Model of Integrated Care. The intervention is a collaborative care network and integrated care model that includes three aspects from the Therapeutic Assertive Community Treatment (TACT). This model is from Germany. ACCESS I was used during 2006. ACCESS II continued. The model was adapted to include first-episode and adolescent patients with psychotic disorders 12 years and above. Detection and treatment of somatic comorbidities include (i) standardized assessment, including physical and neurological examination, blood test, ECG, EEG, cerebral MRI and lumbar puncture for the cases of early psychosis; (ii)

standardized documentation of somatic disorders according to ICD 10- German version; (iii) access to all somatic diagnostic and treatment institutions as part of integrated care; (iv) psychiatrists of the TACT team should coordinate and monitor somatic health in collaboration with primary and specialized healthcare services; (v) support and monitoring of adherence to medications. They used two groups (one with somatic comorbidity and other without somatic comorbidity). A mixed model repeated measures (MMRM) was used to evaluate baseline, and changes at week 6, months 3, 6, 12, 18, 24, 30, 36, 42, and 48. An analysis was made of the interaction between time and presence of any baseline comorbid somatic disorder. The authors reported the main effects, significance levels, confidence intervals, and effect size. The results showed two or more chronic somatic disorders in patients. The authors identified 55 different ICD-10 disease areas. The finding highlights

that severe and persistent mental illness patients had different chronic somatic disorders, but not only those related to psychotropic medications. The overall score was 9 out of 12.

## DISCUSSION

Answering our two questions, we found four collaborative and integrated models, not only for bipolar patients but also for SMI patients. We did not find a model that only takes into consideration bipolar patients as in the past CCMs discussed in the introduction that was adapted to work with bipolar patients. Through the past 48 months (2016-2019), different integrated and collaborative care models with particular goals have evolved. We found good quality studies investigating the management of CVD risk factors in SMI patients, including bipolar patients through primary healthcare settings using different models of care. The top ratings in the quality assessment tools were the Primrose and LG-CC. Primrose is from England and LG-CC is from the U.S. Three of the five studies found had more than one risk of bias in the quality assessment tool from NHLBI: the two studies of BHH (from the U.S.) and ACCESS II (from Germany). We found that the results of all studies included for this narrative review were different. The Primrose model achieved fewer admissions and lower costs for admissions, and all the participants received screening for CVD risk factors and feedback. While LG-CC found improvements in physical health-related quality of life related to the LDL levels of the patients. In the studies of BHH model improvement in diabetes and hypertension were found; and also decrease rates of psychiatric hospitalization, fewer emergency department visits, and more screening for HbA1c were found. And, the ACCESS II model found two or more somatic diseases in severe and persistent mental illness patients that were not only related to psychotropic medications.

The different results raise the question to us about how we could have a model that gathers the positive results of these studies.

In the articles we studied, the authors agreed that there was a need for interventions to manage the CVD risk factors in SMI patients and that an integrated treatment should address both psychiatric and physical symptoms. Several authors concluded that there was a need for establishing a guideline for consistent screening in SMI patients (Pérez-Piñar et al., 2016). Ritchie & Muldoon (2017) mentioned the importance of determining mechanisms by which primary care practices would be able to work with community resources in an integrated manner, with the purpose of caring for people with different needs.

The CCM and the other integrated models work, but more research is needed to continue identifying how these models can be improved. It is important to replicate these studies in other contexts to ensure if there are similar results. We agreed that in working with BD patients (in fact, with any patient with an SMI), using a personalized model is critical: "One size fits all" interventions do not address the particular needs of a given patient.

Thus, in the development and implementation of a CCM or other integrated model, a given intervention should be tailored to a given patient. Moreover, it is important to improve quality of care, by working in groups, receiving training, coordinating with different providers, and engaging the community, among other strategies (Kilbourne et al., 2018). In the case of the Primrose model, nurses and healthcare assistants were trained to provide the intervention in a collaborative manner. In the BHH study, the clinic staff included a part-time nurse care manager and a full-time nurse who offered health education for lifestyle factors and logistical support. The nurses attended weekly meetings at the CMHC to make possible the integration with the mental health team. There also were psychiatrists and master-level therapists

among others. The LG-CC was designed as a shorter intervention focus on self-management skills among existing teams of providers. The team was composed of psychiatrists, psychologists, or clinical social workers among other medical care providers.

While we want to explore more about health disparities during the search, only one study included the term health disparities in the title (Tepper et al., 2017). However, although the other studies did not include formally the concept, mental health is considered part of the definition of the Healthy People 2020. It is “a particular type of health difference that is closely linked with economic, social or environmental disadvantage” (U.S. Department of Health and Human Services, 2008, p. 46). We observed in the study of Tepper et al. (2017) these differences in the sociodemographic characteristics of the sample used. However, a specific discussion about it is not presented. In the study of Druss et al. (2017) the Hispanic sample were included. It would be interesting to include analyses considering the variables related with health disparities for future studies.

A limitation of this narrative review is that the search was done mainly on two sites' search. Most of the collaborative care studies were conducted before 2016, thus fewer studies qualified for this analysis. The articles reviewed failed to provide a common definition for the term “collaborative care.” Other relevant studies could not be included in the review as they were not published in English language. The quality assessment tools do not have a cut-off point for the classification of good, fair, and poor. They explain that it is only for the purpose of examining to the risk of bias due to flaws in the study design or implementation. A good study has the least risk of bias. A fair study is susceptible to some bias but not necessarily sufficient to invalidate its results. In some studies, you can observe that was reported “cannot determine” or “not reported” as part of the possible answer. Therefore, we recommend that for future use of these quality assessment tools contact the

corresponding authors for exploring that information that is missing the article or to confirm if, in fact, the study has this type of flaws.

#### Conclusion

This narrative review focuses on the need for screening for CVD risk factors in BD patients at primary healthcare centers. Five studies, performed from January 2016 through December 2019, were identified by our search. There was no consensus about the definition of CCM or integrated healthcare, but the articles concurred that there was a need to offer BD and other SMI patients' services aimed at ameliorating such mental and physical conditions and disorders from which they might be suffering and, in so doing, improve the quality of care of those patients. The healthcare provider in a given primary care setting should have a good grasp of the risk factors for CVD that BD patients face. More (and good quality) research in primary healthcare settings is needed to determine the efficacy of the CCM or integrated healthcare. To optimize outcomes and minimize costs, medical health and mental health care must be integrated, with the relevant healthcare professionals collaborating to provide multidisciplinary and complementary healthcare to BD and SMI patients (Goldstein et al., 2009).

The studies found among January 2016 through December 2019 showed the importance of working with physical illness comorbidities and emphasized that the patient with SMI should receive an integrated service with teamwork that helps the patient identify and treat CVD risk factors. Unlike several studies prior to 2016, no study was found that made the distinction between bipolar disorder and other SMI for managing the risks of cardiovascular disease. It would appear that comorbidities are similar in SMI patients. Primary healthcare providers need to identify these risk factors to determine and recommend appropriate management strategies for these patients.

Compliance with Ethics Standards in Research

**Funding:** Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health, Award Number #R25MD007607 and U54MD007600. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Conflict of interests:** The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

**Approval of the Institutional Board for the Protection of Human Beings in Research:** N/A.

**Informed Consent or Assent:** N/A

#### REFERENCES

- Ayerbe, L., Forgnone, I., Addo, J., Siguero, A., Gelati, S., Ayis, S. (2018). Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis. *Journal of Affective Disorders, 225*, 665-670.  
<https://doi.org/10.1016/j.jad.2017.09.002>
- Ayerbe, L., Forgnone, I., Foguet-Boreu, Q., González, E., Addo, J., Ayis, S. (2018). Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis. *Psychological Medicine, 48*(16), 2693-2701.  
<https://doi.org/10.1017/S0033291718000302>
- Bauer, I.E., Gálvez, J.F., Hamilton, J.E., Balanzá-Martínez, V., Zunta-Soares, G.B. & Meyer, T.D. (2016). Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *Journal of Psychiatric Research, 74*, 1-7.  
<https://doi.org/10.1016/j.jpsychires.2015.12.006>
- Bauer, M.S., McBride, L., Williford, W.O., Glick, H., Kinosian, B., Altshuler, L., Beresford, T., Kilbourne, A.M., & Sajatovic, M. (2006). Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. *Psychiatric Services, 57*(7):927-936.  
<https://doi.org/10.1176/ps.2006.57.7.927>
- Behavioral Sciences Research Institute (2016). Need Assessment Study of Mental Health and Substance Use Disorders and Service Utilization among Adult Population of Puerto Rico.  
<http://www.assmca.pr.gov/BibliotecaVirtual/Estudios/Need%20Assessment%20Study%20of%20Mental%20Health%20and%20Substance%20of%20Puerto%20Rico%202016.pdf>
- Birkenaes, A.B., Opjordsmoen, S., Brunborg, C., Engh, J.A., Jonsdottir, H., Ringen, P.A., Simonsen, C., Vaskinn, A., Birkeland, K.I., Friis, S., Sundet, K. & Andreassen, O.A. (2007). The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. *Journal of Clinical Psychiatry, 68*(6), 917-23.  
<https://doi.org/10.4088/jcp.v68n0614>
- Bobes, J., Sáiz-Ruiz, J., Montes, J.M., Mostaza, J., Rico-Villademoros, F. & Vieta, E. (2008). Spanish consensus on physical health of patients with bipolar disorder. Spanish Consensus on Physical Health of Patients with Bipolar Disorder. *Revista de Psiquiatría y Salud Mental, 1*, 26-37.  
[https://doi.org/10.1016/S2173-5050\(08\)70056-6](https://doi.org/10.1016/S2173-5050(08)70056-6)
- Bodenheimer, T., Wagner, E.H. & Grumbach, K. (2002). Improving primary care for patients with chronic illness. *JAMA-Journal of American Medical Association, 288*(14), 1775-79.  
<https://doi.org/10.1001/jama.288.14.1775>
- Carliner H., Collins, P.Y., Cabassa, L.J., McNallen, A., Joestl, S.S., Lewis-Fernández, R. (2014). Prevalence of cardiovascular risk factors among racial and ethnic minorities with schizophrenia spectrum and bipolar disorders: a critical literature review. *Comprehensive*



- Psychiatry*, 55, 233-47.  
<https://doi.org/10.1016/j.comppsy.2013.09.009>
- Cerimele, J.M., Skern, J.S. (2017). Bipolar disorder in primary care: integrated care experiences. *Focus: The Journal of Lifelong Learning in Psychiatry*, 15(3), 244-248.  
<https://doi.org/10.1176/appi.focus.20170005>
- Compton, M.T., Daumit, G.L., Druss, B.G. (2006). Cigarette smoking and overweight/obesity among individuals with serious mental illness: a preventive perspective. *Harvard Review of Psychiatry*, 14(4), 212-22.  
<https://doi.org/10.1080/10673220600889256>
- Czepielewski, L., Filho, L.D., Brietzke, E., Grassi-Oliveira, R. (2013). Bipolar disorder and metabolic syndrome: a systematic review. *Brazilian Journal of Psychiatry*, 35(1), 88-92.  
<https://doi.org/10.1016/j.rbp.2012.07.004>
- Damegunta, S.R., Gundugurti, P.R. (2017). A cross-sectional study to estimate cardiovascular risk factors in patients with bipolar disorder. *Indian Journal of Psychological Medicine*, 39(5), 634-640.  
[https://doi.org/10.4103/IJPSYM.IJPSYM\\_369\\_17](https://doi.org/10.4103/IJPSYM.IJPSYM_369_17)
- Daviglus, M.L., Pirzala, A., Talavera, G.A. (2014). Cardiovascular disease risk factors in the Hispanic/Latino population: lessons from the Hispanic community health study/Study of Latinos (HCHS/SOL). *Progress in Cardiovascular Diseases*, 57, 230-236.  
<https://doi.org/10.1016/j.pcad.2014.07.006>
- Derby IM. (1933). Manic-depressive "exhaustion" deaths: an analysis of "exhaustion" case histories. *Psychiatric Quarterly*, 7, 436-49.
- Druss, B.G., Zhao, L., Esenwein, S.V., Morrato, E.H., Marcus, S.C. (2011). Understanding excess mortality in persons with mental illness: 17-year follow up of a nationally representative US survey. *Medical Care*. 2011; 49:6, 599-604.
- Druss, B.G., von Esenwein, S.A., Glick, G.E., Deubler, E., Lally, C., Ward, M.C. & Rask, K.J. (2017). Randomized trial of an integrated behavioral health home: the health outcomes management and evaluation (HOME) study. *American Journal of Psychiatry*, 174(3), 246-255.  
<https://doi.org/10.1176/appi.ajp.2016.16050507>
- Emilien, G., Septien, L., Brisard, C., Corruble, E., Bourin, M. (2007). Bipolar disorder: How far are we from a rigorous definition and effective management? *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 31(5), 975-996.
- Ferrari, A.J., Norman, R.E., Freedman, G., Baxter, A.J., Pirkis, J.E., Harris, M.G., Page, A., Carnahan, E., Degenhardt, L., Vos, T. & Whiteford, H.A. (2014). The Burden Attributable to Mental and Substance Use Disorders as Risk Factors for Suicide: Findings from the Global Burden of Disease Study 2010. *PLoS ONE*, 9(4).  
<https://doi.org/10.1371/journal.pone.0091936>
- Fiedorowicz, J.G., Jancic, D., Potash, J.B., Butcher, B., & Coryell, W.H. (2014). Vascular mortality in participants of a bipolar genomics study. *Psychosomatics*, 55(5), 485-90.  
<https://doi.org/10.1016/j.psym.2014.02.001>
- Fiedorowicz, J.G., Solomon, D.A., Endicott, J., Leon, A.C., Li, C., Rice, J.P. & Coryell, W.H. (2009). Manic/Hypomanic symptom burden and cardiovascular mortality in bipolar disorder. *Psychosomatic Medicine*, 71(6), 98-606.  
<https://doi.org/10.1097/PSY.0b013e3181acee26>
- Firth, J., Veronese, N., Cotter, J., Shivappa, N., Hebert, J.R., Ee, C., Smith, L., Stubbs, B., Jackson, S.E. & Sarris, J. (2019). What is the role of dietary inflammation in severe mental illness? A review of observational and experimental findings. *Frontiers in Psychiatry*, 10, 1-9.  
<https://doi.org/10.3389/fpsy.2019.00350>

- García-Portilla, M., Saiz, P., Bascaran, MT, Martínez, S., Benabarre, A., Sierra, P., Torres, P., Montes, J.M., Bousoño, M. & Bobes, J. (2009). Cardiovascular risk in patients with bipolar disorder. *Journal of Affective Disorders*, 115, 302-308. <https://doi.org/10.1016/j.jad.2008.09.008>
- Goldstein, B.I., Fagiolini, A., Houck, P. & Kupfer, D. (2009). Cardiovascular disease and hypertension among adults with bipolar disorder in the United States. *Bipolar Disorders An International Journal of Psychiatry and Neurosciences*, 11(6), 657-662.
- Goldstein, B.I., Schaffer, A., Wang, S., Blanco, C. (2015). Excessive and Premature New-Onset Cardiovascular Disease Among Adults with Bipolar Disorder in the US NESARC Cohort. *Journal of Clinical Psychiatry*, 76(2):163-9. <https://doi.org/10.4088/JCP.14m09300>
- Goodrich, D.E., Kilbourne, A.M., Lai, Z., Post, E.P., Bowersox, N.W., Mezuk, B., Schumacher, K., Bramlet, M., Welsh, D.E. & Bauer, M.S. (2012). Design and rationale of a randomized controlled trial to reduce cardiovascular disease risk for patients with bipolar disorder. *Contemporary Clinical Trials*, 33(4), 666-678. <https://doi.org/10.1016/j.cct.2012.02.010>
- Hayes, J.F., Marston, L., Walters, K., King, M.B., Osborn, D.P.J. (2017). Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *British Journal of Psychiatry*, 211(3), 175-181. <https://doi.org/10.1192/bjp.bp.117.202606>
- Kalelioğlu, T., Ünalın, P., Kök B., Sözen, S., Yüksel, Ö., Akkuş, M., Cihnioglu, R., Karamustafalioglu, N. (2018). Atherogenic index of plasma as a cardiovascular risk marker in manic, depressive and euthymic stages of bipolar disorder. *Archives of the Turkish Society of Cardiology*, 46(1), 32-38. <https://doi.org/10.5543/tkda.2017.23350>
- Kilbourne, A.M., Post, E.P., Nossek, A., Sonel, E., Drill, L.J., Cooley, S. & Baer, M.S. (2008). Service delivery in older patients with bipolar disorder: a review and development of a medical care model. *Bipolar Disorders An International Journal of Psychiatry and Neurosciences*, 10, 672-683. <https://doi.org/10.1111/j.1399-5618.2008.00602.x>
- Kilbourne, A.M., Goodrich D.E., Lai, Z., Post, E.P., Schumacher, K., Nord, K.M., Bramlet, M. Chermack, S., Bialy, D & Bauer, M.S. (2013). Randomized controlled trial to assess reduction of cardiovascular disease risk in patients with bipolar disorder: The Self-Management Addressing Heart Risk Trial (SMAHRT). *Journal of Clinical Psychiatry*, 74(7), 655-662. <https://doi.org/10.4088/JCP.12m08082>
- Kilbourne, A.M., Barbaresso, M.M., Lai, Z., Nord, K.M., Bramlet, M., Goodrich, D.E., Post, E.P., Almirall, D. & Bauer, M.S. (2017). Improving physical health in patients with chronic mental disorders: 12-month results from a randomized controlled collaborative care trial. *Journal of Clinical Psychiatry*, 78(1), 129-137. <https://doi.org/10.4088/JCP.15m10301>
- Kilbourne, A.M., Beck, K., Spaeth-Ruble, B., Ramanuj, P., O'Brien, R.W., Tomoyasu, N. & Pincus, H.A. (2018). Measuring and improving the quality of mental health care: a global perspective. *World Psychiatry*, 17, 30-38. <https://doi.org/10.1002/wps.20482>
- Lambert, M. Ruppelt, F., Siem, A.K., Rohenkohl, A.C., Kraft, V., Luedecke, D., Sengutta, M., Schroter, R., Daubmann, A., Correll, C.U., Gallinat, J., Karow, A., Wiedemann, K. & Schottle, D. (2018). Comorbidity of chronic somatic diseases in patients with psychotic disorders and their influence on 4-year outcomes of integrated care treatment (ACCESS II Study). *Schizophrenia Research*, 193, 377-383. <https://doi.org/10.1016/j.schres.2017.07.036>
- Lopresti, A.L. & Jacka, F.N. (2015). Diet and

- bipolar disorder: a review of its relationship and potential therapeutic mechanisms of action. *Journal of Alternative and Complementary Medicine*, 21(2), 733-9. <https://doi.org/10.1089/acm.2015.0125>
- Maina, G, Bechon, E, Rigardetto, S & Salvi, V (2013). General Medical Conditions are associated with delay to treatment in patients with bipolar disorder. *Psychosomatics*, 54, 437- 442. <https://doi.org/10.1016/j.psych.2012.10.011>
- Martin, D.J., Ul-Haq, Z., Nicholl, B.I., Cullen, B., Evans, J., Gill, J.M., Roberts, B., Gallacher, J., Mackay, D., McIntosh, A., Hotopf, M., Craddock, N., Deary, I.J., Pell, J.P. & Smith, D.J. (2016). Cardiometabolic disease and features of depression and bipolar disorder: population-based, cross-sectional study. *The British Journal of Psychiatry*, 208(4), 343-51.
- McIntyre, R.S. (2009). Understanding needs, interactions, treatment, and expectations among individuals affected by bipolar disorder or schizophrenia: the UNITE global survey. *Journal of Clinical Psychiatry*, 70(3), 5-11.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* 6(6). <https://doi.org/10.1371/journal.pmed1000097>
- Murray, D.P., Weiner, M., Prabhakar, M. & Fiedorowicz, J. (2009). Mania and mortality: why the excess cardiovascular risk in bipolar disorder? *Current Psychiatry Report*, 11(6), 475-480. <https://doi.org/10.1007/s11920-009-0072-3>
- National Heart, Lung, and Blood Institute. (2016.) Study Quality Assessment Tools. <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.
- Nielsen, R.N., Kugathasan, P.K., Straszek, S., Jensen, S.E., Licht, R.W. (2019). Why are somatic diseases in bipolar disorder insufficiently treated? *International Journal of Bipolar Disorders*, 7(12), 1-7. <https://doi.org/10.1186/s40345-019-0147-y>
- Osborn, D., Burton, A., Hunter, R., Marston, L., Atkins, L., Barnes, T., Blackburn, R., Craig, T., Gilbert, H., Heinkel, S., Holt, R., King, M., Michie, S., Morris, R., Morris, S., Nazareth, I., Omar, R., Petersen, I., Peveler, R., Pinfold, V. & Walters, K. (2018). Clinical and cost-effectiveness of an intervention for reducing cholesterol and cardiovascular risk for people with severe mental illness in English primary care: a cluster randomized controlled trial. *The Lancet Psychiatry*, 5, 145-154.
- Ösby, U., Westman, J., Hallgren, J. & Gissler, M. (2016). Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987-2010. *The European Journal of Public Health*, 26(5), 867-871. <https://doi.org/10.1093/eurpub/ckv245>
- Pérez-Piñar, M, Mathur, R, Foguet, Q, Ayis, S, Robson, J, Ayerbe, L. (2016). Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. *European Psychiatry*, 35, 8-15.
- Ralat, S.I., Depp, C.A., Bernal, G. (2018). Reasons for nonadherence to psychiatric medication and cardiovascular risk factors treatment among latino bipolar disorder patients living in Puerto Rico: a qualitative study. *Community Mental Health Journal*, 54(6), 707-716.
- Ramsey, C.M., Leoutsakos, J.M., Mayer, L.S., Eaton, W.W. & Lee, H.B. (2010). History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 follow-up from the Baltimore Epidemiologic Catchment Area Study. *Journal of Affective Disorders*, 125(1-3), 35-41.
- Ritchie, S., Muldoon, L. (2017). Cardiovascular preventive care for patients with serious mental illness. *Canadian Family Physician*, 63, 483-487.

- Russo, C.A., Andrews, R.M. (2006). *The national hospital bill: the most expensive conditions, by payer, 2004*. Agency for Healthcare Research and Quality. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb13.pdf>
- Shrivastava, A., Johnston, M.E. (2010). Weight-gain in psychiatric treatment: risks, implications, and strategies for prevention and management. *Mens Sana Monographs*, 8(1), 53-68.
- Slomka, J.M., Piette, J.D., Post, E.P., Krein, S.L., Zongshan, L., Goodrich, D.E. & Kilbourne, A.M. (2012). Mood disorder symptoms and elevated cardiovascular disease risk in patients with bipolar disorder. *Journal of Affective Disorders*, 138, 405-408. <https://doi.org/10.1016/j.jad.2012.01.005>
- Swartz, H.A., Fagiolini, A. (2012). Cardiovascular disease and bipolar disorder: risk and clinical implications. *Journal of Clinical Psychiatry*, 73(2), 1563-5.
- Tepper, M.C., Cohen, A.M., Progovac, A.M., Ault-Brubus, A., Leff, H.S., Mullin, B., Chunningham, C.M. & Cook, B.L. (2017). Mind the gap: developing an integrated behavioral health home to address health disparities in serious mental illness. *Psychiatric Services*, 68(12), 1217-24.
- UCL Psychiatry (2020). The PRIMROSE Programme of Research. <https://www.ucl.ac.uk/psychiatry/research/epidemiology-and-applied-clinical-research-department/primrose-programme-research/about>
- U.S. Department of Health and Human Services. (2008). The Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020. Phase I report: Recommendations for the framework and format of Healthy People 2020. [http://www.healthypeople.gov/sites/default/files/PhaseI\\_0.pdf](http://www.healthypeople.gov/sites/default/files/PhaseI_0.pdf).
- Vancampfort, D., Vansteelandt, K., Correll, C.U., Mitchell, A.J., De Hert, A., Sienaert, P., Probst, M. & De Hert, M. (2013). Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *American Journal of Psychiatry*, 170(3), 265-274. <https://doi.org/10.1176/appi.ajp.2012.12050620>
- Vancampfort, D., Firth, J. & Schuch, F. (2016). Physical activity and sedentary behavior in people with bipolar disorder: a systematic review and meta-analysis. *Journal of Affective Disorders*, 201, 145-152. <https://doi.org/10.1016/j.jad.2016.05.020>
- Vuksan-Cusa, B., Marcinko, D., Sagud, M., Jakovljevic, M. (2009). The comorbidity of bipolar disorder and cardiovascular diseases from pharmacotherapy perspective. *Psychiatria Danubina*, 21(3), 382-385.
- Walkers, E.R., McGee, R.E., Druss, B.G. (2015). Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*, 72(4), 334-341. <https://doi.org/10.1001/jamapsychiatry.2014.2502>
- Wiener, M., Warren, L., Fiedorowicz, J.G. (2011). Cardiovascular morbidity and mortality in bipolar disorder. *Annals of Clinical Psychiatry*, 23(1), 40-47.
- Woltmann, E., Grogan-Kaylor, A., Perron, B., Georges, H., Kilbourne, A.M. & Bauer, M.S. (2012). Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis. *American Journal of Psychiatry*, 169(8), 790-804.