Prevalence and Predictors of Type 2 Diabetes Mellitus in People With Bipolar Disorder:

A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This systematic review and meta-analysis assessed the prevalence and predictors of type 2 diabetes mellitus (T2DM) in people with bipolar disorder. We also compared the prevalence of T2DM in people with bipolar disorder versus age- and gender-matched healthy controls.

Data Sources: PubMed, EMBASE, PsycARTICLES, and CINAHL were searched from inception till October 23, 2014 using the medical subject headings terms *bipolar disorder* AND *diabetes* OR *glucose*. There was no language restriction. Observational studies including retrospective, cross-sectional, and prospective designs were eligible if they included participants with bipolar disorder diagnosed according to recognized diagnostic criteria (*DSM* or *ICD*).

Study Selection: Nineteen studies were included (n = 18,060; 54.8% male).

Data Extraction: Two independent authors extracted data in accordance with the meta-analysis of observational studies in epidemiology guidelines and PRISMA statement. A random effects meta-analysis was utilized.

Results: The overall prevalence of T2DM was 9.4% (95% CI, 6.5%–12.7%). Compared with age- and gender-matched controls (n = 783,049; 48.7% male), people with bipolar disorder (n = 6,595; 48.6% male) had double the risk of T2DM (relative risk = 1.98; 95% CI, 1.6–2.4, $P < .001$). No significant moderators were found. In an exploratory regression analysis, the variance in T2DM prevalence in the background population was associated with the variance in T2DM prevalence in people with bipolar disorder (5 studies, n = 4,983) ($r^2 = 0.85$, $t = 4.09$, $P = .03$).

Conclusions: T2DM is significantly more common in people with bipolar disorder than in healthy controls of similar age and sex. The current meta-analysis furthermore indicates that changes in food, built, and social environments are needed in order to curb the diabetes epidemic in this high-risk population.

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Increased rates of cardiovascular diseases (CVDs)[1,2] and associated premature mortality[3] have recently become a major concern in people with bipolar disorder. Underlying reasons for the development of CVD in those with bipolar disorder are complex and consist of genetic risk,[4] cardiometabolic side effects of psychotropic treatment,[5] and an unhealthy lifestyle. Unhealthy lifestyle factors include a sedentary lifestyle,[6] high prevalence of smoking,[7] and high rates of alcohol abuse.[8] To compound this, patients with bipolar disorder experience inequalities in the provision of medical health care.[9,10]

Type 2 diabetes mellitus (T2DM) is an established risk factor for CVD. It confers approximately a 2-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes.[11] With its increasing prevalence in the general population,[12] T2DM now rivals other important risk factors for CVD such as physical inactivity, cigarette smoking, hypertension, and lipid abnormalities.[13] Because of the cardiovascular complications of T2DM, its prevention and treatment demand careful consideration in clinical practice, particularly in populations with an increased risk for CVD and associated premature mortality, such as people with bipolar disorder.[14] Yet screening for cardiometabolic risk is suboptimal in patients with severe mental illness, even when compared to those with diabetes itself.[15]

To our knowledge, only one narrative review[16] has investigated, almost one decade ago, T2DM prevalence in people with bipolar disorder. This review[16] demonstrated a heightened risk of T2DM rates in people with bipolar disorder compared with the general population. The authors[16] did not, however, look at possible moderators (eg, mood states, psychotropic medication use, duration of illness) for this increased risk. A meta-analysis comparing T2DM estimates in people with bipolar disorder is also lacking. A meta-analysis pooling the relative risk for T2DM in people with bipolar disorder will provide rigorous up-to-date risk profile evidence to researchers, health care professionals, and decision makers. It is also a clinical imperative to understand whether the T2DM risk profile is the same depending on gender, age, illness duration, diagnostic subgroup, and educational level since it may help clinicians to detect high-risk subgroups that require screening and treatment. Similarly, it remains unclear whether T2DM estimates in people with bipolar disorder differ between treatment settings and medication regimens.

Given the uncertainties outlined above, we conducted a systematic review and meta-analysis aiming to clarify the prevalence of T2DM in people with bipolar disorder, taking into account variations in geographical region, gender, age, illness duration, education level, treatment setting, medication use, diabetes assessment method, and diagnostic subgroups. Our secondary aim was to evaluate studies comparing the prevalence of T2DM in people with bipolar disorder and age- and gender-matched comparison controls.

Clinical Points

- A rigorous up-to-date risk profile for diabetes in people with bipolar disorder is currently lacking.
- In patients with diabetes, fasting blood glucose and hemoglobin A_{1c} should be measured approximately every 3 to 6 months.

METHOD

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[17] and reported in accordance with the PRISMA statement[18] following a predetermined but unpublished protocol.

Inclusion and Exclusion Criteria

Observational studies including retrospective, cross-sectional, and prospective designs were eligible if they included participants with bipolar disorder diagnosed according to recognized (clinician-based) diagnostic criteria (*DSM* or *ICD*). We included comparative studies (those with a control group) and noncomparative studies without a control group. When we encountered studies containing groups of mixed participants (eg, psychotic disorders) or studies lacking data on age and gender, we contacted the authors up to 2 times over a 4-week period to ascertain the variables of interest in the group of people with bipolar disorder. If the data were not available, the study was excluded. We did not place any restriction on the method of T2DM assessment or language restriction upon our searches. If we encountered studies that reported data from the same sample at different time points, we used the data with the most rigorous diabetes assessment method (eg, American Diabetes Association criteria). We excluded (1) studies that had insufficient data for extraction of T2DM proportions; (2) studies that were restricted to participants with known CVD, which may cause selection bias; and (3) conference abstracts, case reports, and reviews.

Search Strategy

Two reviewers (D.V., B.S.) independently conducted searches on PubMed, EMBASE (major focus strategy), PsycARTICLES, and CINAHL from inception until October 23, 2014 using the medical subject heading terms *bipolar disorder* AND *diabetes* OR *glucose*. In addition, the reference lists of all eligible articles and reviews of the literature were screened to assess eligibility of additional studies.

Study Selection

After removal of duplicates, 2 independent reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full-text articles was developed through consensus. The 2 reviewers then considered the full texts of these articles, and a final list of included articles was reached through consensus.

Data Extraction

Two authors independently conducted data extraction using a predetermined format. The data collected from each article included study design (retrospective cohort or not); geographic location (Europe, Asia, North America, South America, Africa, Australia, and New Zealand); bipolar disorder and control sample characteristics, if available (number, percentage of male subjects, percentage of white subjects, mean age, smoking rates, illness duration); bipolar diagnosis method (*DSM* or *ICD*); bipolar subgroup characteristics (bipolar I disorder, bipolar II disorder, or mixed/unspecified); psychotropic medication (individual prescribed antipsychotics, antidepressants, mood stabilizers, lithium, if monotherapy); method of T2DM assessment (self-report, databases/files/claims, antidiabetic medication use, or international criteria); and the prevalence of diabetes in people with bipolar disorder and in controls.

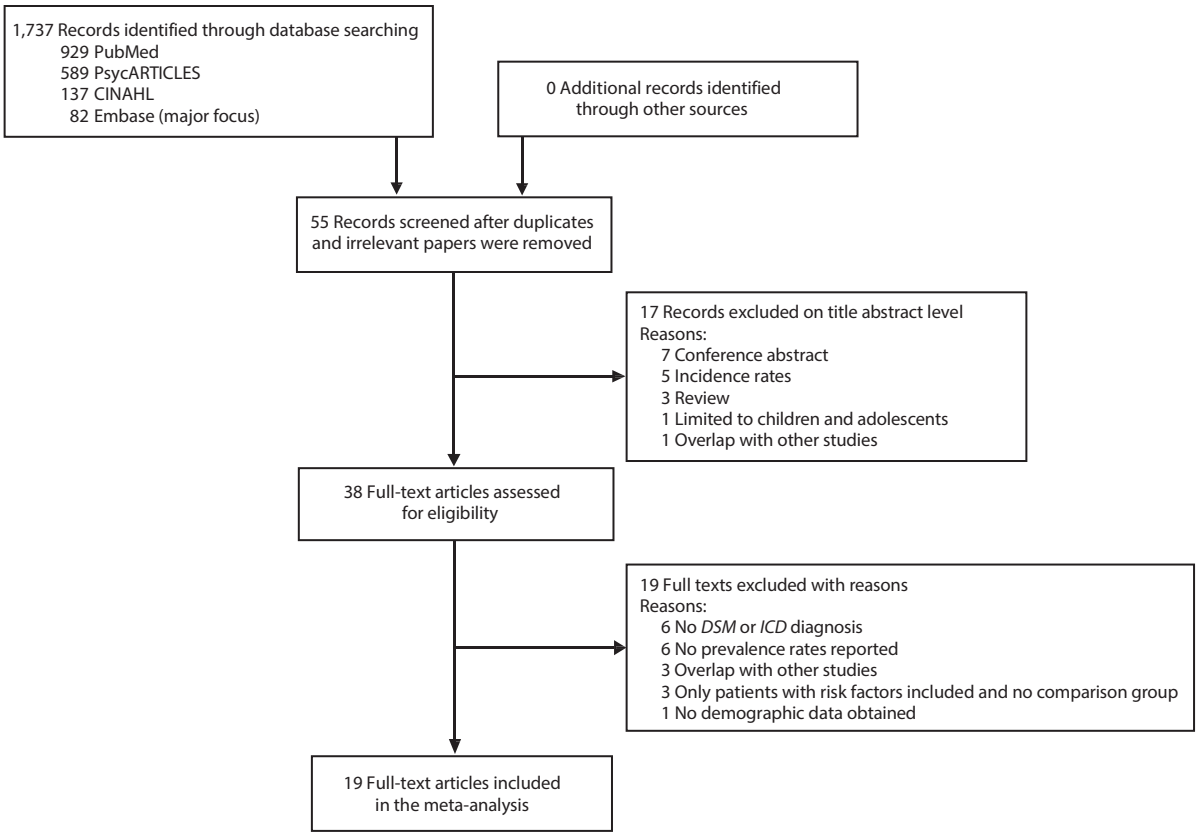
Methodological Quality Assessment

Two independent authors completed methodological quality assessment of included articles using the Newcastle Ottawa Scale (NOS).[19] Studies without a control group were considered as case-control studies for the purposes of methodological assessment in accordance with previous reviews.[20,21] The NOS[19] is utilized to assess the methodological quality of nonrandomized trials and has acceptable validity and reliability. The assessment tool focuses on 3 main methodological features: (1) the selection of the groups, (2) the comparability of the groups, and (3) the ascertainment of the outcome of interest. The NOS can be modified, and we adapted the NOS[19] to take into account age and gender as comparability measure and considered diabetes assessment in the exposure category. A diagnosis based on international criteria, eg, the American Diabetes Association criteria[22] or World Health Organization criteria,[23] was considered as the most objective. Studies are given a score from 0 to 9, with a score of 5 or greater being indicative of satisfactory methodological quality. We anticipated studies without a control group would score below this value and present their results with due consideration.

Statistical Analyses

We pooled individual study data using DerSimonian-Laird proportion method.[24] Our predetermined protocol stipulated that heterogeneity would be assessed with the Cochran *Q*

Figure 1. Flow Diagram for the Search Strategy



statistic. To reduce the heterogeneity, wherever possible, male and female participants and diagnostic subgroups (bipolar I or II disorder or bipolar disorder mixed/unspecified) were analyzed separately. Data on participants with known CVD were included only in the comparison analyses. Since we still found significant heterogeneity (Cochran $Q_{20} = 635.4$, $P < .001$), a random-effects meta-analysis was employed using StatsDirect. We calculated the relative risk (RR) to investigate the differences in T2DM prevalence between those with bipolar disorder and members of the general population (if ≥ 3 studies). To investigate sources of heterogeneity, we conducted moderator analyses (if ≥ 3 studies) with mean age (years), mean illness duration (years), percentage of male participants, race (percentage white), level of education (years), medication use (individual prescribed antipsychotics, antidepressants, mood stabilizers, lithium), smoking rate (percentage), percentage of people with diabetes in the background population, region (Europe, North America, Asia, Australia), NOS score,[19] study design (retrospective or cross-sectional), and the method of T2DM assessment (following international standards, self-report, clinician report, or medical records or based on antidiabetic medication use). We assessed publication bias with a visual inspection of funnel plots, yet gave priority to quantitative testing through the Begg-Mazumdar Kendall τ[25] and Egger bias test.[26] Finally, a regression analysis was performed (if ≥ 3 studies) to determine whether the T2DM prevalence in people with bipolar disorder could be predicted from the T2DM prevalence in the background population.

RESULTS

Search Results and Included Participants

The initial electronic database search resulted in 55 valid hits. From candidate publications following exclusions, our search generated 19 studies[27–45] (17 for the pooled analyses and 2 extra for the comparison analyses excluded from the pooled analyses due to selection bias) fulfilling the inclusion criteria (see Figure 1 for search results and reasons for exclusion). Two research groups provided additional data (see acknowledgments), and one research group did not respond to our request (see eAppendix 1 at PSYCHIATRIST.COM).

The dataset comprised 18,060 unique individuals with a *DSM* or *ICD* diagnosis of bipolar disorder (mean age range, 38–58 years). Published studies involved sample sizes that ranged from 53[29] to 4,310[31] participants. Details on the included studies are presented in Table 1. Five studies[27–29,35,44] were conducted among inpatients (n = 1,418), another 5[34,36,39–41] in outpatient settings (n = 4,549), and 9[30–33,37,38,42,43,45] in mixed settings (n = 12,093). Four studies[29,35,36,41] focused on only patients with bipolar I disorder; none focused on only patients with bipolar II disorder. Four[32,36,40,45] of the 17 studies (n = 772) included in the pooled analyses reported smoking rates, and 48.9%

Table 1. Characteristics of the Included Studies

Study	Location and Design	Bipolar Diagnosis	Participant Characteristics[a]	Diabetes Assessment	Diabetes Prevalence	Newcastle Ottawa Scale Score
Lilliker,[27] 1980	United States Retrospective	*DSM-II*	203 (79 males) Inpatients 95% White Age, range, 28–77 y	Medical records	Male = 5% (n = 4), female = 13% (n = 16) vs 2% in the background population	4
Cassidy et al,[28] 1999	United States Retrospective	*DSM-III-R*	357 (172 males) Inpatients 59.4% White Age, range, 20–74 y	Medical records	Male = 8.1% (n = 14), female = 11.9% (n = 22) vs 3.4% in the background population	5
Regenold et al,[29] 2002	United States Retrospective	*DSM-IV* (SCID)	53 (18 males) Inpatients with bipolar I disorder 55% White Age, range, 50–74 y BMI = 27.2	Medical records	26.4% (n = 14) vs 13% in the background population	4
McElroy et al,[30] 2002	International Prospective, pretreatment, baseline	*DSM-IV* (SCID)	644 (279 males) Inpatients and outpatients Age, range,18–82 y BMI = 27.3 ± 6.4	Clinician and/or self-report	3.1% (n = 20) vs 16.49% in the background population	2
Kilbourne et al,[31] 2004	United States Retrospective	*ICD-9*	4,310 (3,879 males) Inpatients and outpatients Age, 53 ± 13 y	VA National Patient Care Database	17% (n = 733) vs 15.6% in the background population	6
Birkenaes et al,[32] 2007	Norway Cross-sectional	*DSM-IV* (SCID)	110 (43 males) Inpatients and outpatients Age, 39 ± 12 y BMI = 23.6 ± 5.0	Medical records	Male = 0% (n = 0), female = 8.1% (n = 5) vs 2.2% in age-matched, but not gender-matched, controls	4
van Winkel et al,[33] 2008	Belgium Cross-sectional	*DSM-IV-TR*[b]	60 (26 males) Inpatients and outpatients 100% Caucasian Age, 45 ± 13 y BMI = 24.4 ± 4.2	OGTT + ADA criteria	6.7% (n = 20) vs 16.4% in the background population	3
Fiedorowicz et al,[34] 2008	United States Retrospective	*DSM-IV*[b]	217 (80 males) Outpatients 85% White Age, 46 ± 15 y 59% Bipolar I disorder 34% Bipolar II disorder	Medical records	9% (n = 20)	2
Kim et al,[35] 2009	South Korea Baseline, pretreatment	*DSM-IV*	184 (88 males) Inpatients with bipolar I disorder Age, 38 ± 13 y	Antidiabetic medication	Male = 2.7% (n = 5), female = 1.6% (n = 3)	2
Tsai et al,[36] 2009	Taiwan Retrospective	*DSM-IV* (SCID)	59 (20 males) Outpatients with bipolar I disorder Age, 71.1 ± 5.9 y	Medical records	27.1% (n = 16) vs 13.6% (n = 8) in 59 age-, gender-, and education level–matched controls	7
Chien et al,[37] 2010	Taiwan Retrospective	*ICD-9*	1,848 (806 males) Inpatients and outpatients Age, ≥ 18 y	Claims database	Male = 10.2% (n = 82), female = 11.2% (n = 117) vs male = 5.7% (n = 21,341), female = 5.4% (n = 21,257) in age- and gender-matched controls	6
Hseih et al,[38] 2012[c]	Taiwan Cross-sectional	*ICD-9*	4,067 (1,878 males) Inpatients and outpatients	Claims database	10.33% (n = 420) vs 4.11% (n = 501) in age- and gender-matched controls	6
Magalhães et al,[39] 2012	United States Prospective, pretreatment, baseline	*DSM-IV* (MINI)	3,811 (1,639 males) Outpatients Age, 39 ± 13 y	Medical records	2.9% (n = 109)[b]	2
Calkin et al,[40] 2014	Canada Prospective, baseline	*DSM-IV-TR*	121 (40 males) Outpatients Age, range,19–85 y 69.9% Bipolar I disorder 30.1% Bipolar II disorder	OGTT + ADA criteria	21.5% (n = 26)	3
Depp et al,[41] 2014	United States Cross-sectional follow-up	*DSM-IV*	341 (164 males) Outpatients with bipolar I disorder Age, 48.3 ± 12.9 y BMI = 28.2 ± 6.1	Antidiabetic medication	7.3% (n = 25)	2
Foley et al,[42] 2014	Australia Cross-sectional	*ICD-10*	225 (101 males) Inpatients and outpatients with psychotic features Age, 40.6 ± 10.66 y	OGTT + ADA criteria	10.7% (n = 24)	3
Perugi et al,[43] 2014	Italy Retrospective	*DSM-IV-TR* (SCID)	347 (129 males) Inpatients and outpatients 59.7% bipolar I disorder Age, 47.7 ± 14.3 y	Medical records	8.6% (n = 30)	2
Schoepf and Heun,[44] 2014[c]	United Kingdom Retrospective	*ICD-10*	621(255 males) Inpatients Age, 47.3 ± 0.7 y 81.3% Caucasian	Medical records	12.6% (n = 78) vs 8% (n = 499) in age- and gender-matched controls	6
Sylvia et al,[45] 2014	United States Cross-sectional	*DSM-IV-TR*	482 (199 males) Inpatients and outpatients 72.2% White 68.3% Bipolar I disorder 31.7% Bipolar II disorder	Clinical interviews	6.2% (n = 30)	2

[a]Values with ± symbol are mean ± SD. [b]Information obtained from the authors. [c]Study only included in the comparison analysis.
Abbreviations: ADA = American Diabetes Association, BMI = body mass index, MINI = Mini-International Neuropsychiatric Interview, OGTT = oral glucose tolerance test, SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders, VA = Veterans Administration.

of people with bipolar disorder in these studies were smokers. In 5 studies,[27–29,31,33] the prevalence of T2DM in the background population was reported (range, 2%–15.6%). There was variation in how T2DM was ascertained across the studies. Three studies[33,40,42] reported T2DM in accordance with American Diabetes Association criteria.[22] Twelve studies[27–29,31,32,34,36–39,43,44] utilized medical records/claims databases, 2[35,41] relied on antidiabetic medication prescriptions, and 2[30,45] used physician or self-report. Studies in people with bipolar disorder on monotherapy were lacking in the literature.

Publication Bias

The funnel plot of the 22 prevalence estimates included in our pooled meta-analysis of 17 articles[26–37,39–43,45] was broadly symmetrical (Figure 2). Both the Egger test (2.689 [95% CI, −0.502 to 5.88] $P = .09$) and the Begg-Mazumdar test (Kendall $\tau = 0.125541$, $P = .43$) showed no evidence of publication bias.

Methodological Quality

Overall, the methodological quality of the included articles was low to moderate, and the mean NOS score was 3.7 (range, 2–7). The NOS summary scores are presented in Table 1.

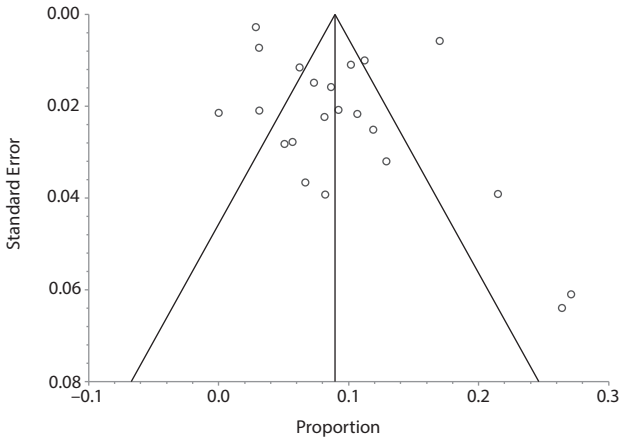
Pooled Prevalence of T2DM

The overall pooled prevalence of T2DM calculated from 22 prevalence estimates in 17 articles[26–37,39–43,45] (n = 13,365) was 9.4% (95% CI, 6.5%–12.7%) ($Q_{21} = 643.78$, $P < .001$). The forest plot is presented in Figure 3. The pooled prevalence of T2DM among people with bipolar I disorder was 12.1% (95% CI, 5.2%–21.4%) ($Q_4 = 33.97$, $P < .001$, n = 637) and 8.7% among people with mixed diagnoses (bipolar I and II disorder) (95% CI, 5.6%–12.4%) ($Q_{16} = 609.76$, $P < .001$, n = 12,728).

Moderating Variables of T2DM

Type 2 diabetes mellitus was not significantly associated with study design (b1 [b = unstandardized coefficient] = −30.0, $z = -0.000092$, $P > .99$), median study period (b2 = −20.2, $z = -0.000086$, $P > .99$), NOS score (b3 = 11.4, $z = 0.000043$, $P > .99$), country of origin (b4 = −1.2, $z = -0.000012$, $P > .99$), geographic region (b5 = −10.7, $z = -0.000082$, $P > .99$), treatment setting (b6 = 19.8, $z = 0.000063$, $P > .99$), mean age (b7 = 1.4, $z = 0.000045$, $P > .99$), percentage of male participants (b8 = −63.1, $z = -0.00046$, $P = .99$), or T2DM assessment method (b9 = 113.8, $z = 0.000258$, $P = .99$). There was also no significant difference in pooled T2DM prevalence in female (11.4%; 95% CI, 9.8%–13.1%) (4 studies; n = 1,412) and male (8.9%; 95% CI, 7.4%–10.7%) (4 studies; n = 1,099) estimates (RR = 1.38, $P = .13$; Cochran $Q_3 = 4.32$, $P = .23$). In contrast, in an exploratory regression analysis, the variance in T2DM prevalence in people with bipolar disorder (5 studies, n = 4,983) was moderated by the variance in prevalence of T2DM in the background population ($r^2 = 0.85$, coefficient = 0.52, standard error = 0.13, $t = 4.09$, $P = .03$). There were insufficient data to investigate the role of ethnicity, medication use (monotherapy antidepressants, mood stabilizers, and antipsychotics), and diagnostic subgroups.

Figure 2. Funnel Plot of 22 Prevalence Estimates



Comparison of T2DM Prevalence in Bipolar Disorder With Age- and Gender-Matched Controls

Four studies[36–38,44] compared individuals with bipolar disorder (n = 6,595; 48.6% male) with age- and gender-matched control subjects or cohorts (n = 783,049; 48.7% male). There was no evidence of publication bias in this analysis (Begg-Mazumdar: Kendall $\tau = -0.4$, $P = .23$; Egger: bias = −2.45 [95% CI, −9.5 to 4.6], $P = .07$). Compared with the respective general population groups, patients with bipolar disorder had a significantly greater risk of diabetes when data from the individual studies were pooled (RR = 1.98; 95% CI, 1.6–2.4; $P < .001$). The relative risk forest plot (random effects) is presented in Figure 4.

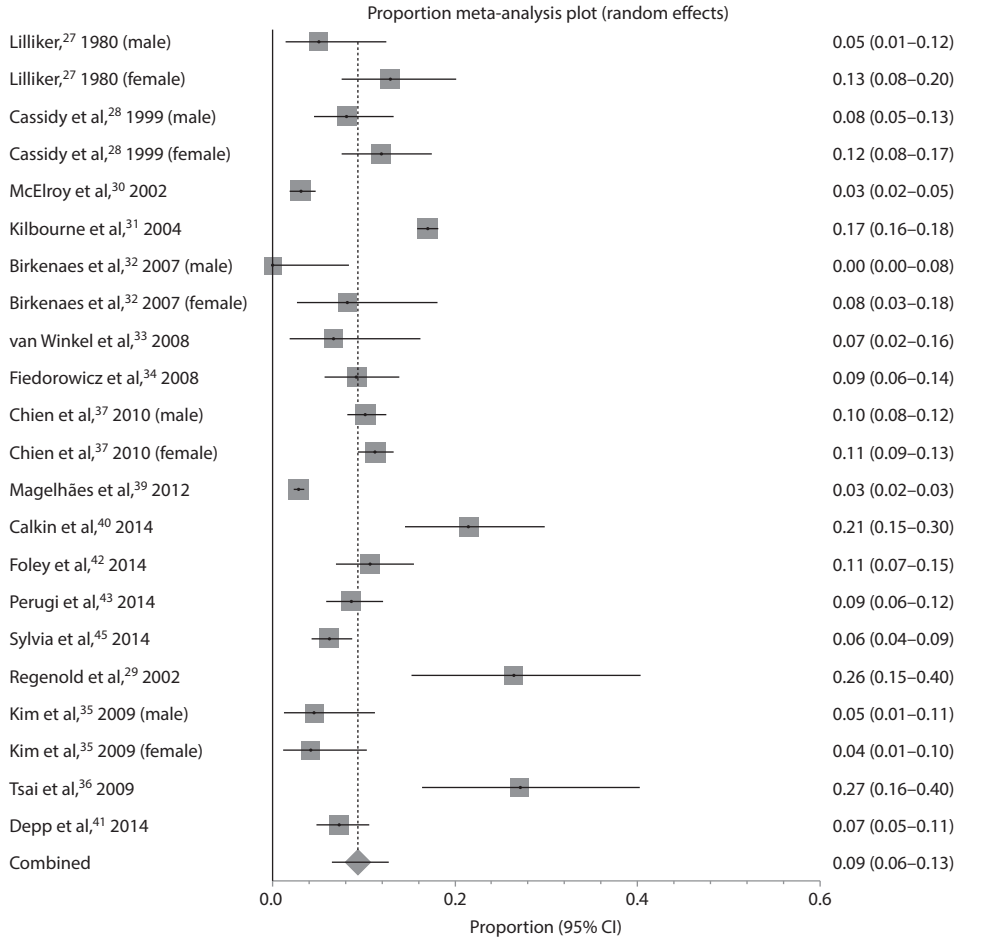
DISCUSSION

General Findings

To the authors' knowledge, this is the first meta-analysis of the proportion of T2DM in people with bipolar disorders. We found 19 publications including 18,060 persons with a *DSM* or *ICD* diagnosis of bipolar disorder. The current meta-analytic data demonstrate that approximately 10% (9.4%; 95% CI, 6.5%–12.7%) of individuals with bipolar disorder had clear evidence of T2DM. In reality, without systematic rigorous testing, the true prevalence rates could be higher given that up to half of all cases of T2DM may be undiagnosed.[46] Yet, even taken at face value, our meta-analysis adds to the current literature by showing that the relative risk for T2DM is 2 times higher for people with bipolar disorder compared with age- and gender-matched general population controls.

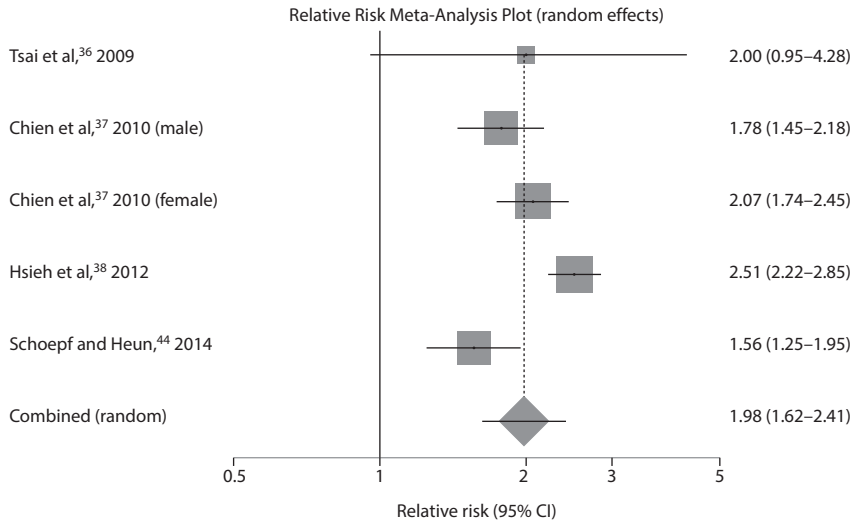
Identifying those who currently have or are at high-risk for T2DM is a clinical imperative. This is particularly true for people with severe mental illness, since in this population, T2DM is associated with a reduced quality of life,[47] a 3- to

Figure 3. Forest Plot of Pooled Prevalence of Type 2 Diabetes Mellitus in Bipolar Disorder



4-fold higher risk of death than the general population,[48] and significantly increased medical costs.[30] We were not able, however, to identify any significant demographic or clinical variables that moderated the heterogeneity in T2DM prevalence at study level. The fact that increasing age was not a significant moderator, as could have been expected, might be due to the limited mean age range at study level (38–58 years). In contrast, the variance of T2DM prevalence in the background population contributed largely to the variance in diabetes prevalence in people with bipolar disorder. This may suggest that national initiatives to improve health and prevent obesity and cardiometabolic risk are just as relevant to people with bipolar disorder as they are to those in the general population. Accumulating evidence,[49] for example, strongly demonstrates that the majority of T2DM cases can be prevented through diet and lifestyle modification. For example, compared with an active lifestyle following health recommendations, a sedentary behavior is associated with a 112% increase in the RR of diabetes (RR = 2.12; credible interval [CrI], 1.61–2.78), a 147% increase in the RR of cardiovascular events (RR = 2.47; 95% CrI, 1.44–4.24), a 90% increase in the risk of cardiovascular mortality (HR = 1.90; 95% CrI, 1.36–2.66), and a 49% increase in the risk of all-cause mortality (HR = 1.49; 95% CrI, 1.14–2.03).[50] However, very few studies have examined lifestyle modification in people with bipolar disorder. One study[51] recruited 58 patients with bipolar disorder to 4 self-management sessions over 6 months and found a change on the 12-Item Short-Form Health Survey (SF-12) subscale for physical health ($t_{173} = 2.01$, $P = .04$) relative to the usual care group. Another pilot study[52] in 5 overweight patients with bipolar disorder indicated that weight, cholesterol, triglycerides, and the number of daily calories and sugar intake decreased while weekly exercise duration more than tripled following an 18-session, 20-week cognitive-behavioral therapy–based lifestyle modification program. However, T2DM has not, as yet, been studied as an outcome of interest. The finding that the prevalence of T2DM in people with bipolar disorder is related to the background population indicates that the adoption of a healthy lifestyle requires not only individual behavioral changes in persons with bipolar disorder but also societal changes in our food, built, and social environments. Public health strategies that target the obesogenic environment are likely to be critical. Previous research[53,54] in people with severe mental illness has already demonstrated that the built environment strongly influences lifestyle behaviors in this vulnerable population. Built environments are the totality of places built

Figure 4. Relative Risk of Type 2 Diabetes Mellitus in Bipolar Disorder Versus Age- and Sex-Matched Controls



or designed, including buildings, grounds around buildings, layout of communities, transportation infrastructure, and parks and trails.[53,54] Translating the current findings into daily practice requires therefore fundamental shifts in public policies and mental and physical health care systems.[55] For example, public policies should target safe walk/bike trails to community mental health care settings, shared-use agreements for recreational facility use between inpatient and outpatient settings on the one hand and the private sector or public communities on the other.

Clinical Implications

Next to the fact that primary prevention should be a public health policy priority, the current meta-analysis has also a number of clinical implications for the care of people with bipolar disorder. The American Diabetes Association[22] recommends earlier screening and more frequent monitoring of high-risk patients. Our data clearly demonstrate that people with bipolar disorder should be considered a high-risk group that needs to be proactively screened for T2DM. Psychiatrists may be best placed to coordinate this risk assessment and management if patients are under their care, but, for other patients, general practitioners may also have this responsibility. Screening could also form part of shared care arrangements with general and specialist health care services working together.[11] It is particularly important to establish baseline diabetes risk at initial presentation so that any subsequent change during treatment can be monitored. The medical history and examination should, at a minimum, include (1) history of previous CVD, T2DM, or other related diseases; (2) family history of premature CVD, T2DM, or other related diseases; (3) smoking, dietary, and lifestyle habits; (4) weight and height (to calculate body mass index) and waist circumference; (5) fasting blood glucose and/or hemoglobin A_{1c} (HbA_{1c}); (6) blood pressure (measured twice and average taken); and (7) past medication history.[56] It is recommended that fasting blood glucose measurements should also be taken before the first prescription of psychotropic medication. The frequency of testing will depend on the patient's medical history and the prevalence of baseline risk factors. For patients with normal baseline tests, it is recommended that measurements are repeated at 6 weeks and 12 weeks after initiation of treatment and at least annually thereafter.[56] During the initial phase of treatment, it is important to measure weight weekly to identify those individuals who gain weight rapidly with psychotropic treatment. In patients with T2DM (and those with prediabetes), fasting blood glucose and HbA_{1c} should be measured regularly (approximately every 3–6 months).[56,57] An annual examination should include measurement of CVD risk factors; urinary albumin excretion and serum creatinine; an eye examination, ideally including fundus photography; and foot examination to diagnose early signs of complications.[56] Despite the imperative to screen for T2DM, screening for T2DM and cardiometabolic disease and risk factors is suboptimal, with only slight improvement over the last decade.[58] The low screening rates might reflect both patient and professional barriers. People with bipolar disorder might be less likely than the general population to take opportunities for health screening.[59] Professional barriers to screening within mental health settings include lack of clarity about whose responsibility screening is, lack of understanding about what should be measured and when, lack of confidence in interpreting results, and lack of access to necessary equipment.[60] Although there are screening recommendations following initiation of antipsychotic medication,[61] such guidelines are currently not available for all psychotropic medications. Without systematic screening following detailed recommendations and using acceptable and accurate diagnostic tests, the true prevalence of T2DM in patients with bipolar disorder and other mental illnesses will remain unknown and underestimated.

Further, research has shown that even after an established diagnosis of diabetes is made, many of those with mental ill health are not offered timely treatment.[62,63] Thus, routine screening is only the first step. Psychiatric centers should cooperate with diabetes centers to establish shared care pathways for people with mental illness and T2DM. Those with diagnosed T2DM should also be seen by a multidisciplinary team including physicians, diabetes nurses, physical therapists, and dietitians regularly to advise on not just diabetes but other risk factors (such as smoking) and other medical comorbidities. When T2DM is detected, people with bipolar disorder are likely to require additional pharmacologic management, but this therapy is unlikely to be significantly different from the general population, for which guidelines are available from the European Society of Cardiology and European Association for the Study of Diabetes[64] and the American Diabetes Association.[22] Insulin treatment should be initiated and monitored by health care professionals with expertise in the management of diabetes.

Limitations

We wish to acknowledge several limitations in the primary data and this meta-analysis. First, there was considerable methodological heterogeneity across studies. This heterogeneity may be attributable to the differences in study design, sample size, participant characteristics (including, age, gender, illness duration, ethnicity, levels of education, bipolar disorder subgroups, medication regimens), and different methods for assessing T2DM. Second, we also observed that the obtained NOS scores in the current meta-analysis were remarkably lower than in comparable recent meta-analyses[20,21] investigating medical comorbidities in people with severe mental illness. A possible reason might be the lack of accurate assessment of T2DM in the current literature. Only 3 studies[34,40,42] assessed T2DM using an oral glucose tolerance test and following the American Diabetes Association criteria.[22] There are inherent problems with using chart reviews of inpatients in relation to selection bias and to the reliability and validity of the diabetes diagnosis. It has been previously shown that a large proportion of T2DM cases remains undetected when people with severe mental illness are not actively screened for these abnormalities,[65] which might imply (as mentioned above) that the actual prevalence of T2DM could even be higher than the rate reported in our pooled analysis. Third, there was marked variation in the quantity and quality of analyzable studies, some of which had limited sample sizes and with a reliance largely on retrospective studies. Fourth, moderator variables were not often reported, reducing the power for these analyses. In particular, duration of treatment, specific medication use, and lifestyle behaviors, all relevant variables for T2DM, were recorded insufficiently, precluding the meta-analytic assessment of these factors as moderating or mediating variables. In particular, data were too limited regarding individual prescribed antidepressants, mood stabilizers, and antipsychotics. Without this information, we were not able to assess the risk-moderating effects of specific medications. Fourth, our findings are based on patient populations. In order to generate more accurate estimates of T2DM in bipolar disorder, well-designed epidemiologic studies that carefully assess large general population samples for both bipolar disorder and T2DM are needed. Nevertheless, allowing for the above-mentioned caveats, this is the largest study of T2DM proportions and its moderators in people with bipolar disorder and the first formal meta-analysis of this important topic.

Future Research

An overview of the current literature shows that, unlike research in people with schizophrenia,[66,67] no study has been conducted in drug-naive persons with bipolar disorder to test the hypothesis that T2DM can be found more frequently in treated compared with untreated or never treated individuals with bipolar disorder. However, a recent pilot study[68] in 7 drug-naive patients with *DSM-IV-TR* bipolar I disorder who underwent an oral glucose tolerance test suggests that bipolar disorder may be highly associated with abnormal glucose metabolism, even if unmedicated. The authors found an impaired glucose tolerance in 6 of 7 patients, suggesting that glucose abnormalities are linked to the diagnosis of bipolar disorder before the effects of pharmacotherapy and other confounders had taken place. Future studies should therefore investigate to which extent risk for T2DM in drug-naive and untreated persons with bipolar disorder is lower than in those treated with specific pharmacologic regimens. Second, since antipsychotic medications are increasingly prescribed as frontline treatment for bipolar disorder,[69] research on the effect of these medications on T2DM risk in people with bipolar disorder is urgently needed. Third, future studies should investigate whether there are differences in T2DM risk between people with bipolar I or II disorder. Since individuals with bipolar II disorder experience a higher burden of depressive symptoms than those with bipolar I disorder, it might be hypothesized that the T2DM risk is higher in patients with bipolar II disorder. Fourth, the pathophysiology that underlies the association between bipolar disorder and T2DM is complex and not well understood and should be a research priority. Emerging evidence[70–72] suggests that both have shared pathophysiologic features, including hypothalamic–pituitary–adrenal axis and mitochondrial dysfunction, neuroinflammation, common genetic links, and epigenetic interactions. Fifth, future studies should examine whether there is an underlying genetic risk for the development of T2DM after pharmacotherapy initiation. Examining whether metabolic outcomes are moderated by genetic factors as well as clinical characteristics and background lifestyle risk factors or whether they are mediated by individual treatments should become a clinical research priority. Sixth, interventions that target T2DM risk in bipolar disorder should be evaluated. Seventh, future research should undertake a comprehensive assessment of the value of regular screening for T2DM risk factors following recommended monitoring guidelines to evaluate how much screening helps, particularly when linked with follow-up

care. Last, long-term follow-up studies are required in order to accurately document the emergence of some more distal outcomes, including not only CVD and medical costs but also premature mortality, that may be particularly linked with T2DM in people with bipolar disorder.

In conclusion, the current meta-analysis demonstrates that T2DM is significantly more common in people with bipolar disorder than in age- and gender-matched general population controls. Overall, from the available data it appears that approximately 10% of people with bipolar disorder are currently affected by T2DM, but it is likely many are undiagnosed. We recommend that treating mental health professionals, general practitioners, and medical specialists should all be responsible for giving preventive and proactive lifestyle advice (in particular reducing sedentary behavior), implementing the necessary screening assessments following international standards, and orchestrating or conducting the appropriate timely treatment of clinically relevant, abnormal findings. Next to this, changes in health promotion, lifestyle and dietary advice, and food, built, and social environments are essential in order to curb what appears to be an epidemic of T2DM in this high-risk population.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Prevalence and Predictors of Type 2 Diabetes Mellitus in People With Bipolar Disorder: A Systematic Review and Meta-Analysis

Authors: Davy Vancampfort, PhD; Alex J. Mitchell, MD; Marc De Hert, PhD, MD; Pascal Sienaert, PhD, MD; Michel Probst, PhD; Roselien Buys, PhD; and Brendon Stubbs, PhD

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List of Supplementary Material for the article

1. eAppendix 1 List of the excluded studies

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1. List of the excluded studies

Nr.	Reference	Reason for exclusion
1.	Bai YM, Su TP, Chen MH, Chen TJ, Chang WH. Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: a 10-year nationwide population-based prospective cohort study. J Affect Disord 2013;150(1):57-62.	Incidence rates
2.	Calkin C, Ruzickova M, Slaney C, Garnham J, Ransom T, Alda M. Are comorbid insulin resistance and type II diabetes risk factors for refractory bipolar illness? Eur Neuropsychopharmacol 2013; 2: S366-367.	Overlap with Calkin 2014 + conference paper
3.	Chen MH, Li CT, Lin WC, Wei HT, Chang WH, Chen TJ, Pan TL, Su TP, Bai YM. A predisposition for allergies predicts subsequent hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder: A nationwide longitudinal study. Schizophr Res 2014; 159(1):171-175.	Only at risk patients included
4.	Gomes FA, Almeida KM, Magalhães PV, Caetano SC, Kauer-Sant'Anna M, Lafer B, Kapczinski F. Cardiovascular risk factors in outpatients with bipolar disorder: a report from the Brazilian Research Network in Bipolar Disorder. Rev Bras Psiquiatr 2013; 35(2): 126-130.	Only at risk patients included
5.	Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. Neuropsychopharmacol 2014; 39(12): 2910-2918.	Overlap with Calkin 2014
6.	Nair RR. Assessment of diabetes mellitus and dyslipidaemia among patients with bipolar affective disorder: A hospital based cross-sectional study Ind J Psychiatry 2013; 55: 35	No prevalence rates obtained
7.	Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med 2013; 11: 263.	No DSM or ICD diagnosis
8.	Enger C, Jones ME, Kryzhanovskaya L, Doherty M, McAfee AT. Risk of developing diabetes and dyslipidemia among adolescents with bipolar disorder or schizophrenia. Int J Adolesc Med Health 2013; 25(1): 3-11.	Incidence rates
9.	Garcia-Rizo C, Kirkpatrick B, Fernandez-Egea E, Oliveira C, Grande I, Undurraga J, Vieta E, Bernardo M. Glucose abnormalities in newly diagnosed, medication-naïve patients with bipolar disorder, mania, and psychosis. Eur Neuropsychopharmacol 2013; 23: S95-S96.	Conference abstract
10.	Chauvet-Gélinier JC, Gaubil I, Kaladjian A, Bonin B. Bipolar disorders and somatic comorbidities: A focus on metablolic syndrome, diabetes and cardiovascular disease. Encephale 2012; 38(4): S167-172.	Review

Appendix 1. Continued

	Reference	Reason for exclusion
11.	Erickson SC, Le L, Zakharyan A, Stockl KM, Harada AS, Borson S, Ramsey SD, Curtis B. New-onset treatment-dependent diabetes mellitus and hyperlipidemia associated with atypical antipsychotic use in older adults without schizophrenia or bipolar disorder. J Am Geriatr Soc 2012; 60(3): 474-479.	Incidence rates
12.	Gencer AG, Kesebir S. Diabetes in first episode mania: Relations with clinical and the other endocrinological and metabolic parameters. Bipolar Disord 2012; 14(1): S90.	Conference abstract
13.	Kodesh A, Goldshtein I, Gelkopf M, Goren I, Chodick G, Shalev V. Epidemiology and comorbidity of severe mental illnesses in the community: findings from a computerized mental health registry in a large Israeli health organization. Soc Psychiatry Psychiatr Epidemiol 2012; 47(11): 1775-1782.	No prevalence rates available
14.	Slomka JM, Piette JD, Post EP, Krein SL, Lai Z, Goodrich DE, Kilbourne AM. Mood disorder symptoms and elevated cardiovascular disease risk in patients with bipolar disorder. J Affect Disord 2012; 138(3): 405-408.	Only at risk patients included
15.	Svendal G, Fasmer OB, Engeland A, Berk M, Lund A. Co-prescription of medication for bipolar disorder and diabetes mellitus: a nationwide population-based study with focus on gender differences. BMC Med 2012; 10: 148.	No DSM or ICD diagnosis
16.	Thakurathi N, Henderson DC. Atypical antipsychotics are associated with incident diabetes in older adults without schizophrenia or bipolar disorder. Evid Based Ment Health 2012; 15(3): 61.	Incidence rates
17.	Bai YM, Su TP, Tzeng-Ji C, Chen YC. Diabetes mellitus syndrome in bipolar disorder, schizophrenia compared with general population: A taiwan population based 8-year study. Int Clin Psychopharmacol 2011; 26: e6-e7.	Conference abstract
18.	Coclami T, Cross M. Psychiatric co-morbidity with type 1 and type 2 diabetes mellitus. East Mediterr Health J 2011; 17(10): 777-783.	No prevalence rates obtained
19.	Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res 2011; 70(2): 145-154.	No clinician-based diagnosis
20.	Kesebir S, Salkin G, Dereboy F. Diabetes and bipolar disorder: A case report with late onset and review of literature Yeni Symposium 2011; 49(2): 113-119.	Conference abstract + case report

Appendix 1. Continued

	Reference	Reason for exclusion
21.	Lee E, Leung CM. Clustering of hypertension, dyslipidemia and diabetes mellitus in bipolar disorder: A case-control study of Chinese patients. Eur Psychiatry 2011; 26(1): 875.	Conference abstract
22.	Schulte PF, Bocxe JT, Doodeman HJ, Cohen D, Van Haelst IM. Risk of new-onset diabetes after long-term treatment with clozapine in comparison to other antipsychotics in patients with schizophrenia. Bipolar Disord 2011; 13(1): S87.	Conference abstract + incidence rates
23.	Sit DKY, Luther J, Wisniewksi S, Wisner KL. Diabetes and obesity in pregnant women with unipolar and bipolar disorders: Adverse birth outcomes. Bipolar Disorders 2011; 13(1): S90-S91.	Conference abstract
24.	Callaghan RC, Khizar A. The incidence of cardiovascular morbidity among patients with bipolar disorder: a population-based longitudinal study in Ontario, Canada. J Affect Disord 2010; 122(1-2): 118-123.	Incidence rates
25.	Correll CU, Druss BG, Lombardo I, O'Gorman C, Harnett JP, Sanders KN, Alvir JM, Cuffel BJ. Findings of a U.S. national cardiometabolic screening program among 10,084 psychiatric outpatients. Psychiatr Serv 2010; 61(9): 892-898.	No DSM or ICD diagnosis
26.	Jerrell JM, McIntyre RS, Tripathi A. A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder J Clin Psychiatry 2010; 71(11): 1518-1525.	Limited to children and adolescents
27.	Rasgon NL, Kenna HA, Reynolds-May MF, Stemmle PG, Vemuri M, Marsh W, Wang P, Ketter TA. Metabolic dysfunction in women with bipolar disorder: the potential influence of family history of type 2 diabetes. Bipolar Disord 2010; 12(5): 504-513.	No prevalence rates available
28.	Castilla-Puentes R. Effects of psychotropics on glycosylated hemoglobin (HbA1c) in a cohort of bipolar patients. Bipolar Disord 2007; 9(7): 772-778.	Limited to non-diabetics
29.	Guo JJ, Keck PE Jr, Corey-Lisle PK, Li H, Jiang D, Jang R, L'Italien GJ. Risk of diabetes mellitus associated with atypical antipsychotic use among Medicaid patients with bipolar disorder: a nested case-control study. Pharmacotherapy 2007; 27(1): 27-35.	Incidence rates
30.	Harley C, Li H, Corey-Lisle P, L'Italien GJ, Carson W. Influence of medication choice and comorbid diabetes: the cost of bipolar disorder in a privately insured US population' published in Soc Psychiatry Psychiatr Epidemiol 2007; 42: 690-697.	No demographical data for the bipolar group obtained.
31.	Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics 2007; 48(5): 412-417.	Overlap with Kilbourne 2004

Appendix 1. Continued

	Reference	Reason for exclusion
32.	McIntyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. Ann Clin Psychiatry 2005; 17(2): 83-93.	Review
33.	Ruzickova, M, Slaney, C, Garnham, J, and Alda, M Clinical features of bipolar disorder with and without comorbid diabetes mellitus. Can J Psychiatry 2003; 48(7): 458-461.	Overlap with Calkin 2014
34.	Russell JD, Johnson GF. Affective disorders, diabetes mellitus and lithium. Aust N Z J Psychiatry 1981; 15(4): 349-353.	Review
35.	van der Velde CD, Gordon MW: Manic-depressive illness, diabetes mellitus, and lithium carbonate. Arch Gen Psychiatry 1969; 21: 478-485.	No DSM or ICD diagnosis
36.	Gildea EF, McLean VL, Man EB: Oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis. Arch Neurol Psychiatry 1943; 49: 852-859.	No DSM or ICD diagnosis