Cardiometabolic disease and features of depression and bipolar disorder: population-based, cross-sectional study of 145,991 UK Biobank participants.

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Abstract

Background: The relative contribution of demographic, lifestyle and medication factors to the association between affective disorders and cardiometabolic diseases is poorly understood.

Methods: Cross-sectional study of 145,991 UK Biobank participants: multivariate analyses of associations between features of depression or bipolar disorder and five cardiometabolic outcomes, adjusting for confounding factors.

Results: There were significant associations between mood disorder features and 'any cardiovascular disease' (depression OR=1.15, 95%CI=1.12-1.18; bipolar OR=1.28, 95%CI=1.14-1.43) and with hypertension (depression OR=1.15, 95%CI=1.12–1.1; bipolar OR=1.26, 95%CI=1.12-1.42). Individuals with features of mood disorder taking psychotropic medication were significantly more likely than controls to report MI (depression OR=1.47, 95%CI=1.24-1.73; bipolar OR=2.23, 95%CI=1.53–3.57) and stroke (depression OR=2.46, 95%CI=2.10-2.80; bipolar OR=2.31, 95%CI=1.39–3.85).

Conclusion: Associations between features of depression or bipolar disorder and cardiovascular diseases outcomes were statistically independent of demographic, lifestyle and medication confounders. Psychotropic medication may also be a risk factor for cardiometabolic disease in individuals without a clear history of mood disorder.

Keywords

Depression, bipolar disorder, cardiovascular disease, diabetes, stroke, psychotropic medication.

Background

Bipolar disorder and major depression are common affective disorders, affecting approximately 2% (1) and 16% (2) of the population, respectively. In addition to significant psychiatric morbidity, they also impact adversely on social and occupational functioning, quality of life and physical health (3-8), and often co-exist with cardiovascular and metabolic diseases (9). Specifically, both bipolar disorder and major depression are associated with coronary heart disease, stroke and peripheral arterial disease and there is evidence that these relationships are bidirectional (9-14).

Although psychotropic medications alter cardiovascular risk profiles (through weight gain, hypertension, dyslipidaemia and glucose dysregulation), their use is also associated with a range of demographic and lifestyle factors, including social deprivation, smoking and alcohol use (15). To date, there has been no large-scale population-based study in the UK which has assessed associations between a lifetime history of depressive or bipolar features and adverse cardiometabolic outcomes while also taking account of a wide range of potential confounding factors, including psychotropic medications.

Beyond the UK, there have been a number of large-scale reports assessing the association between mood disorders and cardiometabolic disease, including the National Comorbidity Study Replication (2) and the World Mental Health Survey (7). Although very informative, these studies did not assess the wide range of covariates we have been able to include in our analyses.

The landmark UK Biobank cohort (16), comprising over half a million adults in middle age, represents a unique opportunity to explore these associations at a population level (both cross-sectionally and prospectively) and has the potential to inform future mechanistic studies and the development of population-level interventions.

Here we assess relationships between five cardiometabolic diseases (myocardial infarction (MI), angina, hypertension, diabetes and stroke) and lifetime features of affective disorder (bipolar disorder and major depression) within UK Biobank, taking account of demographic,lifestyle and psychotropic medication factors. In additional sub-analyses we also assess the effect of current psychotropic medication and mood group status on cardiometabolic disease.

Methods

Data source

UK Biobank is a large, prospective cohort of more than 500,000 residents of the United Kingdom, aged between 40 and 70years (17). It is one of the largest resources worldwide for studying the genetic, environmental, medication and lifestyle factors that cause or prevent disease in middle and older age. Recruitment was undertaken over a four year period, from 2006 to 2010.

In the final two years of UK Biobank recruitment, 172,751 participants were assessed in detail with respect to lifetime features of bipolar disorder and major depression. Eligibility for inclusion in our study was restricted to the 145,991 participants who provided complete data on lifetime features of mood disorder and complete data on self-reported cardiometabolic disease status (3).

Data collection and ethical approval

Participants attended one of 22 assessment centres located across Great Britain. They completed a touchscreen questionnaire which collected information on demographics (including age, sex, ethnicity and postcode), health-related behaviours (including smoking status and alcohol consumption), and a self-report of physician-diagnosed medical conditions, including diabetes, hypertension, myocardial infarction, angina and stroke. Current medication was recorded with assistance from a member of trained clinic staff, who also used standard operating procedures to measure height and weight for body mass index (BMI) calculation.

This study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 17th June 2011, Ref 11/NW/0382) and full written informed consent was gained from participants at the point of data collection.

Definitions

Criteria for a lifetime history of clinically-significant features of bipolar disorder or depression were based on responses to questions within the baseline touchscreen questionnaire (Appendix 1, Appendix 2). Although not diagnostic of bipolar disorder or major depressive disorder, these questions were

similar to questions assessing mood disorders within structured diagnostic assessment instruments. To some extent the validity of these questions have been supported internally within this dataset by comparisons of gender distribution, socioeconomic status, self-reported health rating, current depressive symptoms and smoking status (17). For the purposes of this study, participants were categorised into three groups (Figure 1): those with a positive lifetime history of bipolar disorder features, those with features of major depression and a control group(17, 19). 'Any cardiovascular disease' was defined as the self-report of a previous physician diagnosis of hypertension, MI, angina and/or stroke. Diabetes was also defined by self-report. BMI was determined though anthropometric measurements carried out at the assessment centre and categorised into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class I obese (30.0-34.9 kg/m^2), class II obese (35.0-39.9 kg/m^2) and class III obese (≥40 kg/m^2)(20).Smoking status, frequency of alcohol consumption and ethnic group were self-reported on the touchscreen questionnaire. Smoking status was classified as 'current smoker', 'previous smoker' or 'never smoked' and alcohol use was classified as 'daily/almost daily', '3-4 times per week', '1-2 times per week', '1-3 times/month', 'special occasions only' or 'never'. Ethnicity was categorised as: 'white', 'mixed', 'Asian/Asian British', 'black/black British', 'Chinese', and 'other'. The Townsend deprivation index - an area-based measure of socioeconomic status derived from information collected in the census on car ownership, overcrowding, owner-occupation and unemployment - includes both positive and negative values, with positive values indicating higher levels of deprivation(20). Townsend scores were divided into quintiles (within the study population) to facilitate comparisons. The use of current medication (including psychotropics) was self-reported by participants and a comprehensive list of commonly used psychotropics was identified (Appendix 3). Participants were classified as using psychotropic medication if they reported currently taking any of these medications.

Statistical analyses

Differences in baseline characteristics between the three groups (control, depressive features and bipolar features) were analysed using the chi-squared test for categorical data, and the chi-squared test for trend for ordinal data.We used separate logistic regression models to examine the associations between mood group (independent variable) and cardiometabolic disease categories ('any cardiovascular disease' (not including diabetes), diabetes, hypertension, myocardial infarction, angina or stroke) (dependent variable),with controls as the referent group. Models were initially adjusted for age, sex, socioeconomic deprivation and ethnicity (the partially adjusted model) and then repeated

including additional covariates: smoking status, frequency of alcohol use, BMI and the use of psychotropic medication (fully adjusted model). Interaction tests for sex were undertaken and sub-group analyses carried out as appropriate.

In order to explore the relative contribution of psychotropic medication to cardiometabolic risk across the mood spectrum, we carried out a sub analysis to assess the effect of current psychotropic medication and mood group status on cardiometabolic disease across the mood spectrum. Six groups were created: individuals with no mood disorder features and not currently taking psychotropic medication (our referent group); individuals with no mood disorder features but currently taking one or more psychotropic medications; individuals with depressive features *not* currently taking psychotropic medication; individuals with depressive features currently taking one or more psychotropic medications; individuals with features of bipolar disorder *not* currently taking any psychotropic medication; and individuals with features of bipolar disorder currently taking psychotropic medication.
Differences in cardiometabolic outcomes between different mood and medication status groups were reported as prevalences and then analysed using the chi-squared test for categorical data. We again used separate logistic regression models to examine associations between medication and mood disorder group with cardiometabolic disease (diabetes, myocardial infarction, angina, hypertension or stroke). As noted above, controls who were not currently taking psychotropic medication were chosen as the most appropriate referent group. These models were adjusted for age, sex, socio-economic deprivation and ethnicity, smoking, alcohol and BMI.

All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined conservatively as $p<0.001$.

Results

Group characteristics: bipolar features, depression features and controls

A total of 172,751 UK Biobank participants were assessed at baseline with respect to lifetime history of depressive and bipolar features. Of these, complete data on mood disorder features and cardiometabolic disease status were available for 145,991 (84.5%). From this sample, according to our criteria within Figure 1, 1,557 (1.06%) had features of bipolar disorder, 30,991 (21.23%) had features of major depression and 113,447 (77.71%) had no significant features of mood disorder (controls) (Table 1).

Participants with features of bipolar disorder were younger and more likely to be female (Table 1). Current smoking was most common in the bipolar features group (21.3%), followed by the depressive features group (12.7%) and then the non-mood-disordered control group (8.8%) (Table 1). The proportions of different levels of socioeconomic deprivation were mixed between the groups, but of note was that 34.6% of the bipolar features group were in the most deprived quintile, compared to 22.4% for the depressive features group, and 19.2% for the control group. White ethnicity was most common in the depressive features group and least common in the bipolar features group (Table 1).

Patterns of alcohol use were similar between groups and obesity was more common in both the depressive features and bipolar features groups compared to controls. Rates of current psychotropic medication use were highest in the groups with bipolar (32.1%) and depressive (20.6%) features and lowest within the control group (3.4%).

Prevalence of Cardiometabolic Disease

The prevalence of 'any cardiovascular disease' was highest in the bipolar features group (34.5%), followed by the depressive features group (30.6%) and lowest in the control group (28.7%) (Table 1). Similar patterns were observed for hypertension, myocardial infarction, angina and stroke. Cardiometabolic disease frequencies were also calculated for men and women. Men had consistently higher rates of all cardiometabolic diseases and, in general, rates of cardiometabolic disease were highest in the bipolar features group, followed by the depressive features group and the control group (Table 1).

Partially adjusted model

On multivariate logistic regression (adjusting for age, sex, socio-economic deprivation and ethnicity) odds ratios (OR) for all cardiometabolic outcomes were significantly increased in the depressive features and the bipolar features group relative to controls (all p<0.001, Table 2). In general, the odds of each cardiometabolic outcome, as well as the odds of having 'any cardiovascular illness', increased across the two mood groups, in the depressive features group and the bipolar features group (Table 2). It should be noted, however, that findings for the bipolar features group with respect to diabetes and stroke were not statistically significant.

The highest odds ratios in the partially adjusted model for the combined male and female group were for MI (OR=1.90, p=0.001, 95%CI 1.44-2.51) and angina (OR=1.69, p=0.001, 95%CI 1.30-2.19) within the bipolar features group relative to controls, and for diabetes (OR=1.29, p<0.001, 95%CI 1.22-1.37) in the depressive features group relative to controls (Table 2).

There was a significant interaction between mood disorder and sex in predicting risk of having 'any cardiovascular illness' (p<0.001) and sub-group analyses by sex were subsequently carried out. Men with bipolar features had elevated odds ratios for myocardial infarction (2.02, 95%CI 1.50-2.72). Odds ratio for MI in women was not significantly elevated in the partially adjusted group (1.37 (0.65, 2.92) p=0.409). Women with bipolar features had slightly higher odds ratios for any cardiovascular disease (1.55 95%CI1.32-1.83 in women vs. 1.46 95%CI 1.25-1.69 in men) and for hypertension (1.46 95%CI 1.24, 1.73 in women vs. 1.42 95%CI 1.22-1.66 in men) (Table 2).

The odds ratios for specific conditions within the depressive features group were broadly similar for men and women. For angina in men this was OR=1.54 (95% CI = 1.40, 1.69) and OR=1.43 (95%CI = 1.27, 1.61) for women. Similarly, for diabetes the OR for men was 1.32 (95%CI = 1.23, 1.44) and for women the OR was 1.25 (95%CI = 1.15, 1.36). In women with depressive features, the odds ratio for stroke was 1.70 (95%CI = 1.47, 1.97) compared to 1.53 (95%CI = 1.33, 1.76) for men.

Fully adjusted model

On additional adjustment for smoking status, frequency of alcohol consumption, BMI and the use of psychotropic medication, the risk of having 'any cardiovascular illness' remained significantly elevated in both the depressive (OR=1.15 p<0.001, 95%CI 1.12–1.19) and the bipolar features groups (OR=1.28 p<0.001, 95%CI 1.14–1.43) (Table 2). This pattern was also largely present in a subgroup analysis by sex (Table 2). In the fully adjusted model, odds ratios for hypertension and myocardial infarction were also significantly elevated in the combined male and female groups (hypertension: depression: OR=1.15 p<0.001, 95%CI 1.12–1.13, bipolar: OR=1.26, p<0.001, 95%CI 1.12–1.42) (myocardial infarction: depression: OR=1.18, p<0.001, 95%CI 1.08–1.30) (Table 2).

Differences in odds ratios for angina and stroke within the fully adjusted, combined group analyses were not statistically significant. There were, however, significant elevations in odds of cardiovascular conditions within the depressive features group, most notably for stroke (OR=1.26, p<0.01, 95%CI 1.13-1.40) (Table 2). Associations with diabetes were not significant in the fully adjusted model in either the depressive features or bipolar features groups. Odds ratios were reduced by approximately a quarter for many of the outcome measures upon the additional adjustment for BMI, smoking, alcohol consumption and psychotropic medication.

Current use of any psychotropic medication

We carried out a sub-analysis to assess the contribution of current psychotropic medication use to cardiometabolic risk across the mood spectrum (from controls through depression and bipolar). 109,577 individuals without features of mood disorder who were not taking psychotropic medication were identified as a control group (Table 3). There were 3,867 individuals who did not meet the criteria for depressive or bipolar features but who reported taking one or more psychotropic medications (Table 3). Although the indication for these medications was not known, this group displayed higher prevalences of all cardiometabolic diseases compared to controls. Of particular note were elevated rates of diabetes (8.97%), angina (5.87%), hypertension (36.07%) and stroke (3.98%) (Table 3).

Compared to the control group, individuals with depressive features who reported no current psychotropic use showed similar rates of diabetes, myocardial infarction, angina, hypertension and stroke and those with depressive features taking psychotropic medication had higher rates of all cardiometabolic diseases, with rates of diabetes (8.31%) and MI (3.52%) notably higher than controls

(Table 3). It should be noted however that, with the exception of MI, rates of cardiometabolic disease in this group were not significantly elevated relative to controls currently on psychotropic medication.

Rates of cardiometabolic disease in individuals with bipolar features but who were *not* taking psychotropic medication (n=1057) were elevated compared to controls. Rates of diabetes (5.68%), MI (2.84%), angina (3.69%), hypertension (30.18%) and stroke (1.70%) in this group were all higher than controls (Table 3).Cardiometabolic diseases were most common for individuals with bipolar features who were also taking psychotropic medication (diabetes (9.60%), MI (5.00%) and stroke (3.20%)) (Table 3).

Fully adjusted medication analyses

To assess the relative contribution of current psychotropic medication use in cardiometabolic disease across the mood spectrum we carried out a multivariate logistic regression adjusting for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI (Table 4, Figures 2a-2e). In general, odds ratios for most cardiometabolic diseases remained significantly elevated in each of the mood and medication groups relative to controls (Table 4 and figures 2a-2e). Exceptions were for diabetes in the depressive features group not taking psychotropic medication, the bipolar features group not taking psychotropic medication, and the bipolar group currently taking psychotropic medication. Increases in odds ratios in the bipolar features not on psychotropic medication group were also not significantly elevated for angina (OR, 1.58 95%CI 1.22, 2.06, $p < 0.001$) and stroke (OR 1.70, 95%CI 1.20, 2.41, $p = 0.003$).

Furthermore, odds ratios for angina and stroke were not significantly elevated for both the bipolar features groups (those currently not taking psychotropic medication, as well as those taking psychotropic medication) (Table 4, Figures 2a-2e).

In general, however, the odds of reporting a history of an adverse cardiometabolic outcome were associated with both psychotropic medication use and with mood disorder (Table 4, figures 2a-2e) and the size of these associations increased with mood disorder severity (from depression to bipolar).

Discussion

We found that in a very large population sample of adults with lifetime features of depression and bipolar disorder, there was an increased risk of comorbid cardiovascular disorders, even after adjusting for a wide range of confounding factors. In general, these associations were more pronounced for individuals withfeatures of bipolar disorder than for features of depression. Perhaps unsurprisingly, we also identified an association between current use of psychotropic medication and risk of cardiometabolic disease in individuals with a history of depressive and bipolar features. It is, however notable that this association also occurred in individuals with no definite history of mood disorder who were currently taking psychotropic medication.

Both the bipolar features and depressive features groups had significantly higher odds ratios for 'any cardiovascular disease' relative to controls, within partially and fully adjusted models. Given the broad range of common confounding variables that were adjusted for, this suggests an independent association between mood disorder and cardiometabolic diseases.

Within the partially adjusted (for age, sex, deprivation, ethnicity) versus fully adjusted models (additionally adjusted for BMI, smoking status, alcohol consumption and psychotropic medication), odds ratios for 'any cardiovascular disease' fell from 1.29 (partial) to 1.15 (full) within the depressive features group and from 1.50 (partial) to 1.28 (full) in the bipolar features group. Although depression has been considered a risk factor for cardiovascular disease for some time (21), there has been debate about the relative contribution of lifestyle factors for this group of patients. We have been able to control for some of these lifestyle factors.

Limitations

The strengths of this study include the general population design, breadth of coverage of confounding factors and the very large sample size.However, several limitations are acknowledged. Cardiometabolic disorders previously diagnosed by a physician were self-reported by the participants. Similarly, mood disorder features were self-reported, rather than assessed using a formal diagnostic interview, although a structured approach was used (Figure 1). Psychiatric diagnoses based on formal interviews were notpracticalwithin UK Biobank, so we tooka pragmatic approach to mood disorder groupings. It is possible that our criteria for mood disorder are less stringent than formal diagnostic criteria.

It should be noted, however, that we are reporting features of mood disorders at a population level, rather than formal clinical diagnoses and we were unable to validate diagnoses due to lack of availability of definitive diagnostic information. This has implications in terms of the likely sensitivity and specificity of our groupings, which are based on self-report.Linkage to routine hospital and general practice health records will be available in the future and will allow validation of our groupings.
There is however some evidence for the validity of these groupings using internal variables (21), for example, the sex distributions of approximately 1:1 for bipolar disorder and approximately 2:1 (women: men) for depression are consistent with a large body of epidemiological research on lifetime rates of mood disorder in men and women (22, 23). Furthermore, the lifetime prevalence rates for bipolar disorder (1.1%) and recurrent major depressive disorder (21.2%) are consistent with other population-based lifetime estimates (17). In the future, linkage of UK Biobank participants to routine health records will be possible and will help to address some of these limitations.
Although we are reasonably confident that members of the control group did not have significant features of depression or bipolar disorder, it should be noted that a proportion may have fulfilled criteria for other mental illnesses, such as anxiety disorder or, less likely, schizophrenia, both of which have been associated with poor cardiometabolic health (24)(25)(26).

There are also limitations with our broad definition of "current psychotropic medication use", which groups together different classes of medication. In a sub-analysis of individuals on psychotropic monotherapy, we found that SSRIs, other antidepressants and sedatives/hypnotics were all associated with greater risk of MI relative to psychotropic-free controls (SSRIs OR 1.82, 95%CI 1.51-2.21; other antidepressants OR 1.50, 95%CI 1.20-1.87; and sedatives/hypnotics OR 2.53, 95%CI 1.76-3.66). It is therefore possible that adverse cardiovascular outcomes in depressive disorders are not limited to the use of antipsychotics but may also be a consequence of other classes of psychotropic medications.

It is also the case that a relatively low proportion of the mood disorders features groups reported taking psychotropic medication (bipolar features 32.1%, depressive features 20.6% and controls 3.4%) but, as noted above, the focus in this study was not clinically-diagnosed mood disordered groups but rather lifetime features of mood disorder at a population level. Compliance with medication is a major issue in the management of mental illness.

According to some estimates up to 50% of patients prescribed psychotropic medication do not comply with their proposed medication (27-29). Although compliance with physical medication may be slightly

better than this (30), it is likely that the factors which cause poor compliance with psychotropic medication may also lead to poor compliance with cardiovascular medications in this group. This might explain the proportionately worse cardiovascular outcomes in a less compliant mood disordered group compared to a more compliant non-mood disordered group. Due to the level of information on medication status which was collected at baseline, we were unable to assess the impact of duration of exposure to psychotropic medication on adverse cardiometabolic outcomes.

We included a range of possible confounding variables in the regression models but were unable to control for physical activity. The available data on physical activity was not collected in terms of standardised measures. Unfortunately, it was not possible to create a standardised measure, such as the Metabolic Equivalent of Task (MET).Similarly, we were unable to adjust for the potential confounding effects of diet. When considering appropriate variables to include as confounding variables, it is important to note that there is uncertainty as to the extent that these variables might represent confounders or mediators. For example, obesity may represent an important component of the pathophysiology for depression, bipolar disorder and coronary heart disease. A prospective cohort study is required to address these concerns and is planned as part of future work in this cohort.
Our analyses did not assess the additive effects of sociodemographic and lifestyle factors. Rather, given the large number of confounding factors involved, we took a broad approach, focussing on cardiovascular outcomes after partial and full adjustment for confounders.

Severity of mood disorder may have contributed to the associations we observed. We therefore conducted an additional analysis of the impact of illness severity on the cardiovascular disease outcomes. The depressive features group were divided into those who had a history of a probable single episode of major depression, versus those with a history of probable moderate recurrent depression and those with probable severe recurrent depression (figure 1). The bipolar group was also split into those with features of probable bipolar type one illness and those with features of probable bipolar type two illness (figure 1). In general, individuals in the more severe mood disorder groups had higher risk of adverse cardiovascular outcomes. For the bipolar type one group the OR of 'any cardiovascular illness' was 1.39 (95%CI 1.23-1.58), for the recurrent severe depression group the OR was 1.33 (95%CI 1.18-1.50) and for the bipolar type two group the OR was 1.21 (95%CI 1.09-1.32).

Findings in the context of previous work

Many studies have investigated the association between depressive illness and cardiovascular disease and the association is well established (31). Relatively fewer studies have examined the association between bipolar disorder and cardiovascular disease. Although reports in the literature support the association between bipolar disorder and cardiovascular disease(4)(32)(33)(34), these studies have not been able to adjust for the same variety of potential confounding factors as in our study.Relative to controls, women with features of bipolar disorder had a greater risk of 'any cardiovascular disease' than men with bipolar features (OR 1.36 versus 1.19). This finding may be particularly noteworthy given that men are known to have increased rates of cardiovascular disease within the general population. In their 2013 population study, Crump and colleagues (33) reported increased all-cause mortality for women with bipolar disorder compared to men with bipolar disorder (adjusted hazard ratio of 2.13 compared to 1.74). Furthermore, the same study reported higher hazard ratios of death from ischaemic heart disease for women with bipolar disorder compared to men with bipolar disorder (2.14 compared to 1.73). Our findings add to the evidence that women with bipolar disorder may be disproportionately affected by cardiovascular disease.Our findings also highlight other, more specific interactions between mood disorder and gender with respect to the association with cardiometabolic disease. In our fully adjusted model for individuals with depressive or bipolar features, men (but not women) had an increased risk of MI, and women (but not men) were at higher risk of stroke (Table 2). There are several possible explanations for this, including studies which have found that men are more likely to receive a diagnosis of MI than women (35) and that stroke is more commonly diagnosed in middle-aged women than in men (36). Differential rates of diagnosis of MI may in part be due to the use of troponin levels for diagnosis (troponin concentrations correlate with left ventricular mass (37, 38) which is greater in men (39). The increased risk of stroke in middle-aged women compared to men could be explained by several factors, including increased systolic blood pressure, increased total cholesterol and inadequate risk factor modification in women (36).

Possible mechanisms

Our study adds to the literature on the associations and covariates of increased cardiometabolic morbidity and mortality in mood disorder. There are numerous possible underlying mechanisms for

these associations, for example, shared behavioural factors, inequalities in treatment, shared genetic vulnerabilities and shared underlying pathophysiology.

Individuals with mood disorder may have difficulties in accessing preventative medical interventions as well as having higher rates of risky lifestyle factors(40). Such factors include including smoking, physical inactivity and reduced compliance with cardiovascular medications (41, 42). Individuals with depression tend to exercise less and have lower exercise capacity (52, 53, 54). Furthermore, rates of current smoking have also been found to be approximately double in those experiencing depressive symptoms compared to non-mood-disordered controls (50)(43). Individuals with depression and bipolar disorder are also at increased risk of obesity and the combination of sedentary lifestyle, smoking and obesity confers a significant additive risk for cardiovascular disease (50). Other relevant lifestyle factors include increased rates of drug and alcohol use in individuals with mood disorder (44, 45).

Inflammatory pathways are also likely to be relevant to the overlap between mood disorders and cardiometabolic disease. Proinflammatory cytokines are implicated in atherosclerosis (46, 47) and individuals with depression are known to have elevated serum levels of inflammatory markers (47). Additionally, a depressed mental state in patients receiving angioplasty has been shown to be positively correlated with serological markers of inflammation, furthering the case for a role of inflammation in the association between mood disorder and cardiovascular disease(48).

Oxidative stress is also thought to be relevant when considering potential mechanisms for the association. Markers of oxidative stress including superoxide dismutase and malondialdehyde have been reported as higher in depressed subjects and have also been shown to reduce upon pharmacological treatment of depression(49).

The role of the hypothalamic pituitary axis (HPA) is also relevant. HPA axis abnormalities are associated with a variety of cardiometabolic diseases including ischaemic heart disease, stroke and type 2 diabetes(50). Moreover, there is some evidence that individuals with severe depression or bipolar disorder may have significantly elevated rates of HPA axis dysfunction(51, 52)(53).

Endothelial dysfunction should also be considered as a potential underlying mechanism for the association between mood disorder and cardiometabolic disease. There are reports in the literature that both depression and bipolar disorder (54) are linked to endothelial dysfunction. Endothelial

dysfunction has been proposed as a potential cause for a variety of cardiometabolic diseases including hypertension, hypercholesterolemia, obesity and type 2 diabetes (54)(55).

Although both depression and coronary heart disease are known to be influenced by genetic factors (56-58), there has been relatively little work investigating shared genetic risk factors between the two disorders (57). Scherrer and colleagues reported on the associations between hypertension and coronary heart disease in 6,903 male-male twins from the Vietnam Era Twin Registry (57) and found significant genetic correlations between depressive symptoms and both hypertension and coronary heart disease(57). In addition, there has been work on a possible genetic link between bipolar disorder and type 2 diabetes- one genome wide association study found that bipolar disorder and type 2 diabetes shared 68 single nucleotide polymorphisms (SNPs) (59). In our study with respect to diabetes, odds ratios for individuals with depression were significantly higher in the partially adjusted model but not in the fully adjusted model, perhaps because of the association between diabetes and both obesity (60) and psychotropic medications (61, 62).

It is also appropriate to consider the effect of psychological stress on haemodynamic reactivity and systolic blood pressure (63). Our findings that the odds ratios for hypertension were increased in both depressive features and bipolar features relative to controls could possibly be related to differences in haemodynamic reactivity. Heightened cardiovascular reactivity seen in chronic stress may also be associated with the triggering of acute coronary events and the development of atherosclerosis (63).

The effects of psychotropic medication should also be considered. The metabolic effects of psychotropic medications are known to increase cardiometabolic risk by various mechanisms including weight gain (64), and impaired glucose tolerance (65).Psychotropic medication (appendix 3) was associated with cardiometabolic disease (even in the absence of mood disorder features) and that this effect increased across the mood disorder spectrum, from depressive features to features of bipolar disorder.

Given that our analyses were conducted on the basis of current use of any psychotropic medication, it is perhaps noteworthy that adverse cardiometbolic effects may not be limited to antipsychotics. There are reports in the literature of other psychotropic medications used in the treatment of mood disorder, such as antidepressants, lithium and valproic acid, having adverse metabolic effects(66-68). Our finding that psychotropic medication is an important factor in the development of cardiometabolic disease in the depressive features and the control group adds weight to this.

Future work

There remain several unanswered questions and opportunities for further research. To date, very few studies have tested specific genetic associations between lifestyle-related risk factors for cardiometabolic disease and the broad spectrum of mood disorders. There is a need for longitudinal and mechanistic studies in this area to better understand causal pathways (69). In addition, further mechanistic studies examining genetic and epigenetic factors as well as oxidative stress, endothelial dysfunction and HPA axis abnormalities, are essential to better understand the associations between mood disorder and cardiometabolic disease.

Conclusions

Overall, within a large, representative population cohort of UK adults in middle age, we identified associations between lifetime features of mood disorders and cardiovascular diseases which in general were more pronounced for features of bipolar disorder than for features of major depression. These findings persisted even after adjusting for several confounding factors, including current psychotropic medication use, which also increased risk for cardiometabolic disease in individuals without a clear history of mood disorder.

Author's Contributions

DJM carried out the analyses with input from ZUH. DJM and DJS drafted the initial manuscript and all other authors contributed to subsequent drafts. All authors read and approved the final manuscript.

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Figure 1.Criteria for lifetime features of bipolar disorder and depression.

Bipolar disorder features:

1. Features of bipolar disorder, type I: Ever 'manic or hyper' for at least 2 days OR ever 'irritable/argumentative' for 2 days; *plus* at least 3 features from 'more active', 'more talkative', 'needed less sleep' and 'more creative/more ideas'; *plus* duration of a week or more; *plus* **'**needed treatment or caused problems at work'.

2. Features of bipolar disorder, type II: Ever 'manic or hyper' for at least 2 days OR ever 'irritable/argumentative' for 2 days; *plus* at least 3 features from 'more active', 'more talkative', 'needed less sleep' and 'more creative/more ideas'; *plus* duration of a week or more.

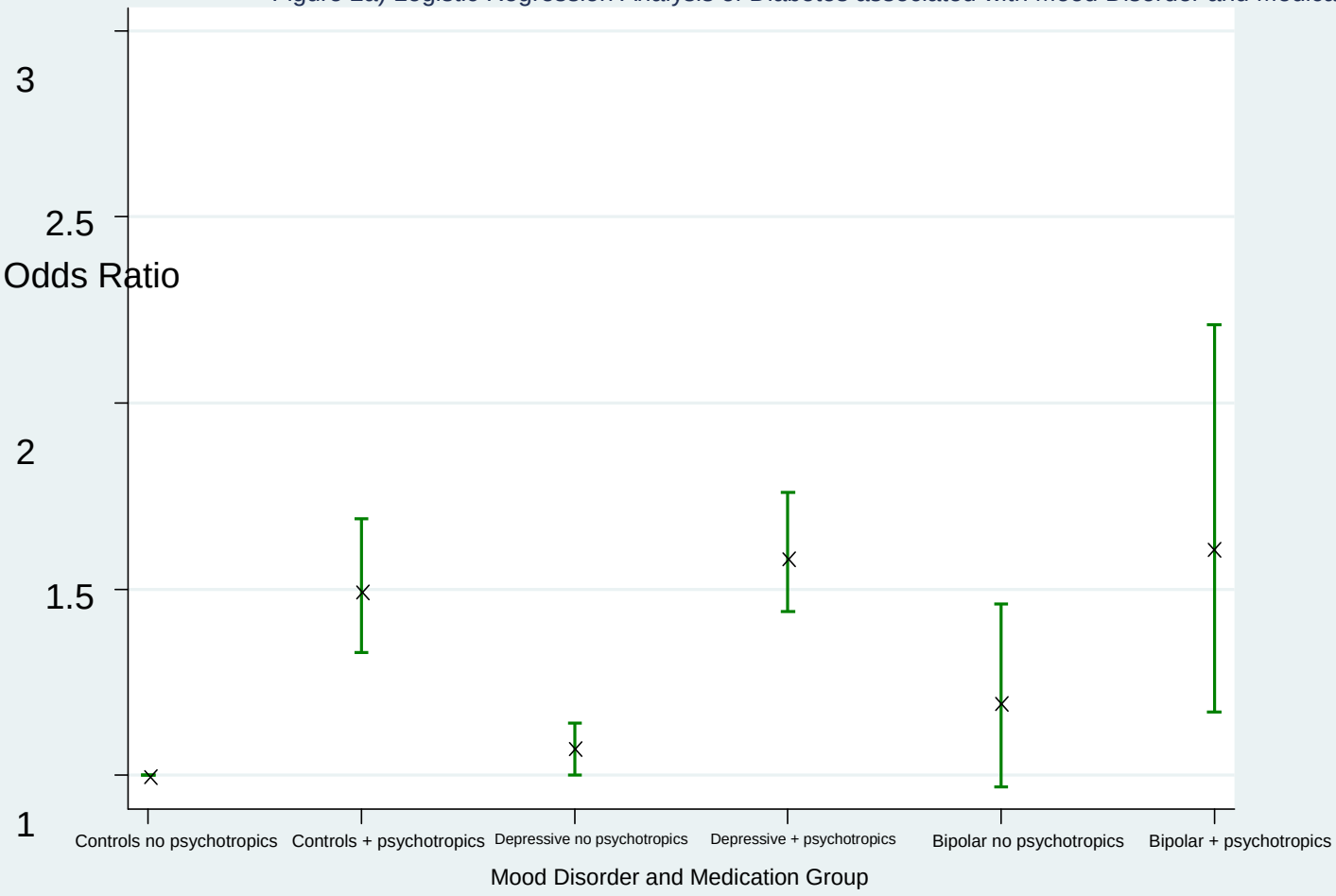
Major depression features:

1. Features of single episode major depression: Ever depressed/down for a whole week; *plus* at least two weeks duration; *plus* only one episode; *plus* ever seen a GP or a psychiatrist for 'nerves, anxiety, depression' OR ever anhedonic (unenthusiasm/uninterest) for a whole week; *plus* at least two weeks duration; *plus* only one episode; *plus* ever seen a GP or a psychiatrist for 'nerves, anxiety, depression'.

2. Features of recurrent major depression (moderate): Ever depressed/down for a whole week; *plus* at least two weeks duration; *plus* at least two episodes; *plus* ever seen a GP (but not a psychiatrist) for 'nerves, anxiety, depression' OR ever anhedonic (unenthusiasm/uninterest) for a whole week; *plus* at least two weeks duration; *plus* at least two episodes; *plus* ever seen a GP (but not a psychiatrist) for 'nerves, anxiety, depression'.

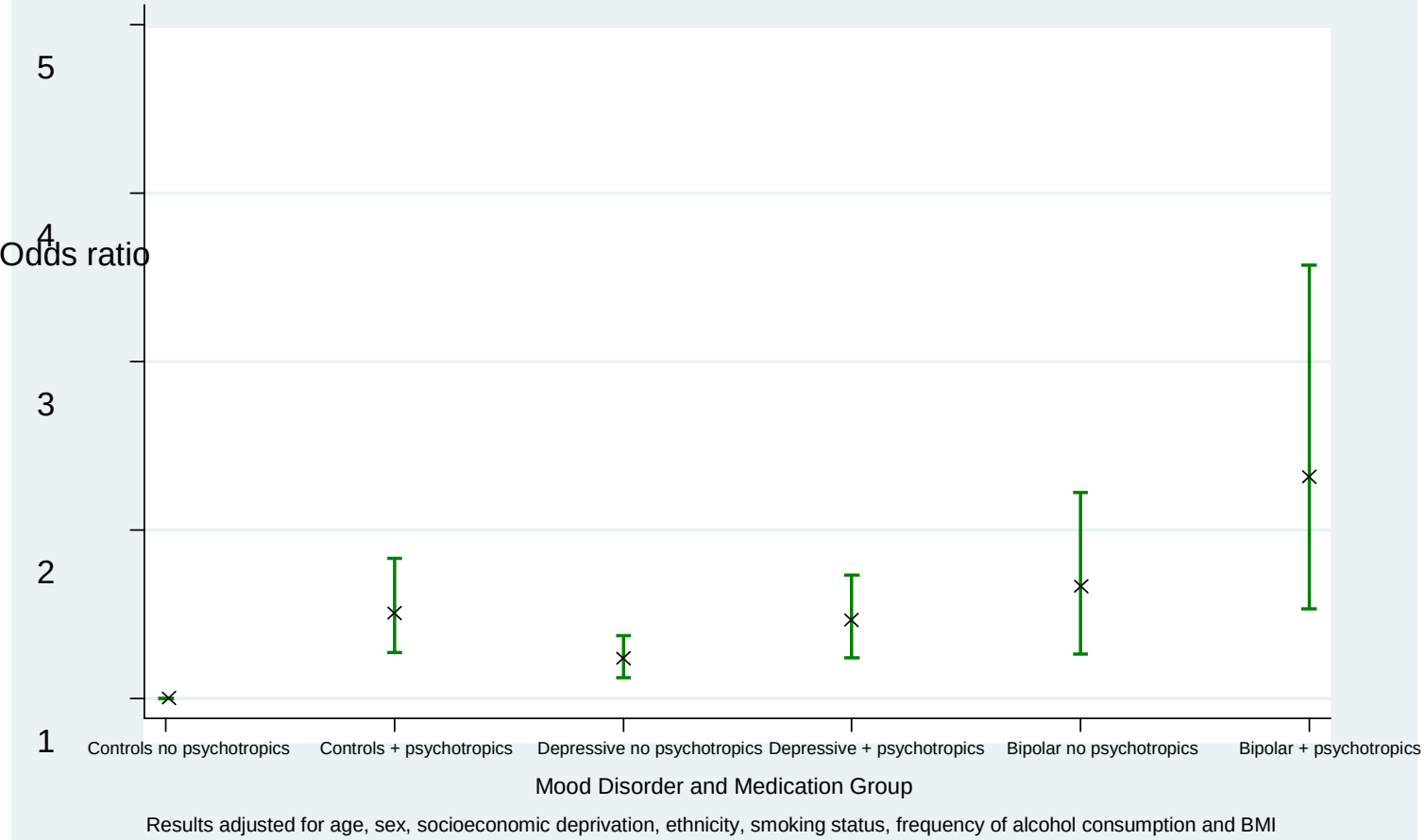
3. Features of recurrent major depression (severe): Ever depressed/down for a whole week; *plus* at least two weeks duration; *plus* at least two episodes; *plus* ever seen a psychiatrist for 'nerves, anxiety, depression' OR ever anhedonic (unenthusiasm/uninterest) for a whole week; *plus* at least two weeks duration; *plus* at least two episodes; *plus* ever seen a psychiatrist for 'nerves, anxiety, depression'.

Figure 2a) Logistic Regression Analysis of Diabetes associated with Mood Disorder and Medication Status



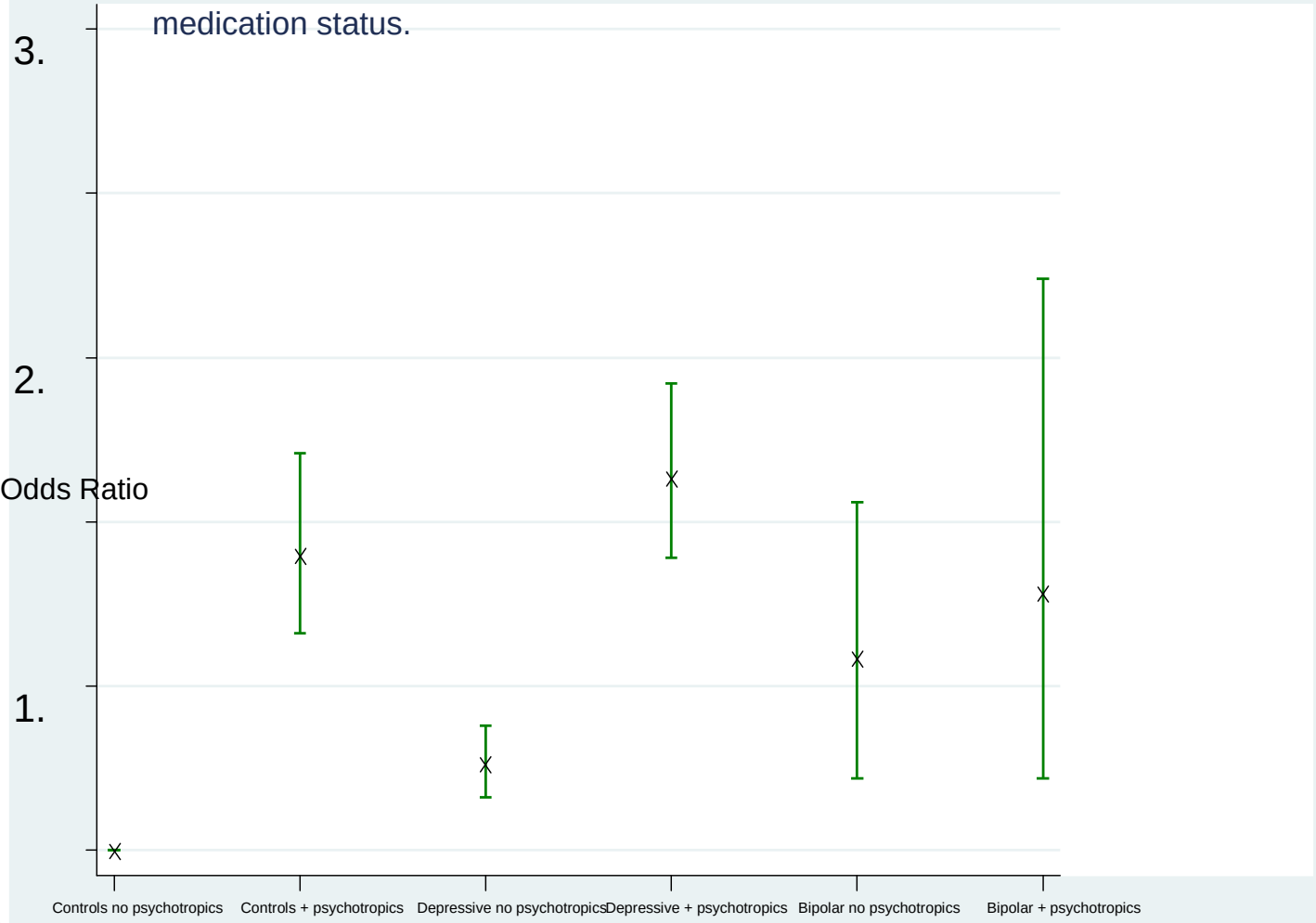
Results adjusted for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI

Figure 2b) Logistic regression analysis of MI associated with mood disorder and medication status



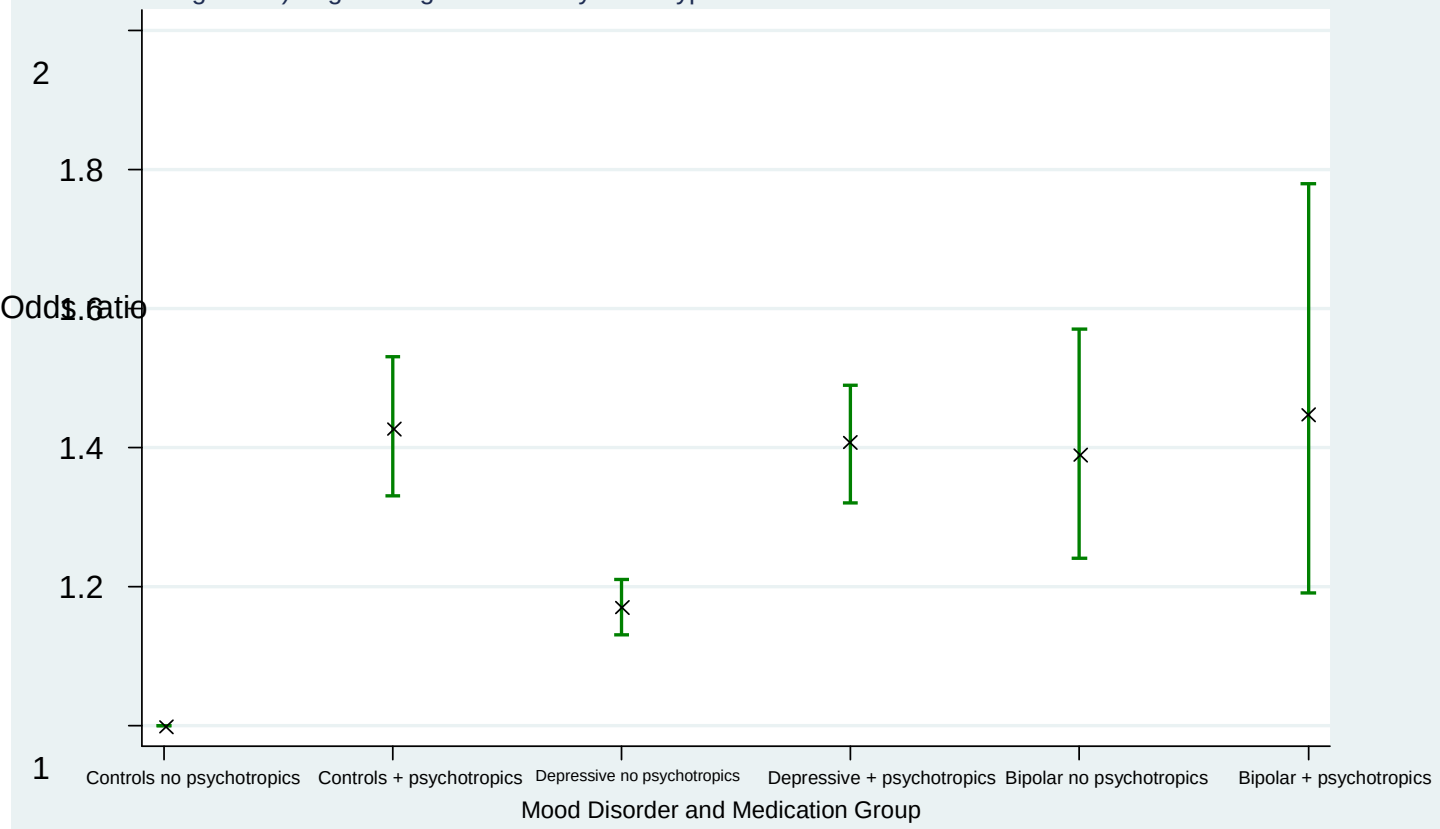
Results adjusted for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI

Figure 2c)Logistic regression analysis of angina associated with mood disorder and medication status.



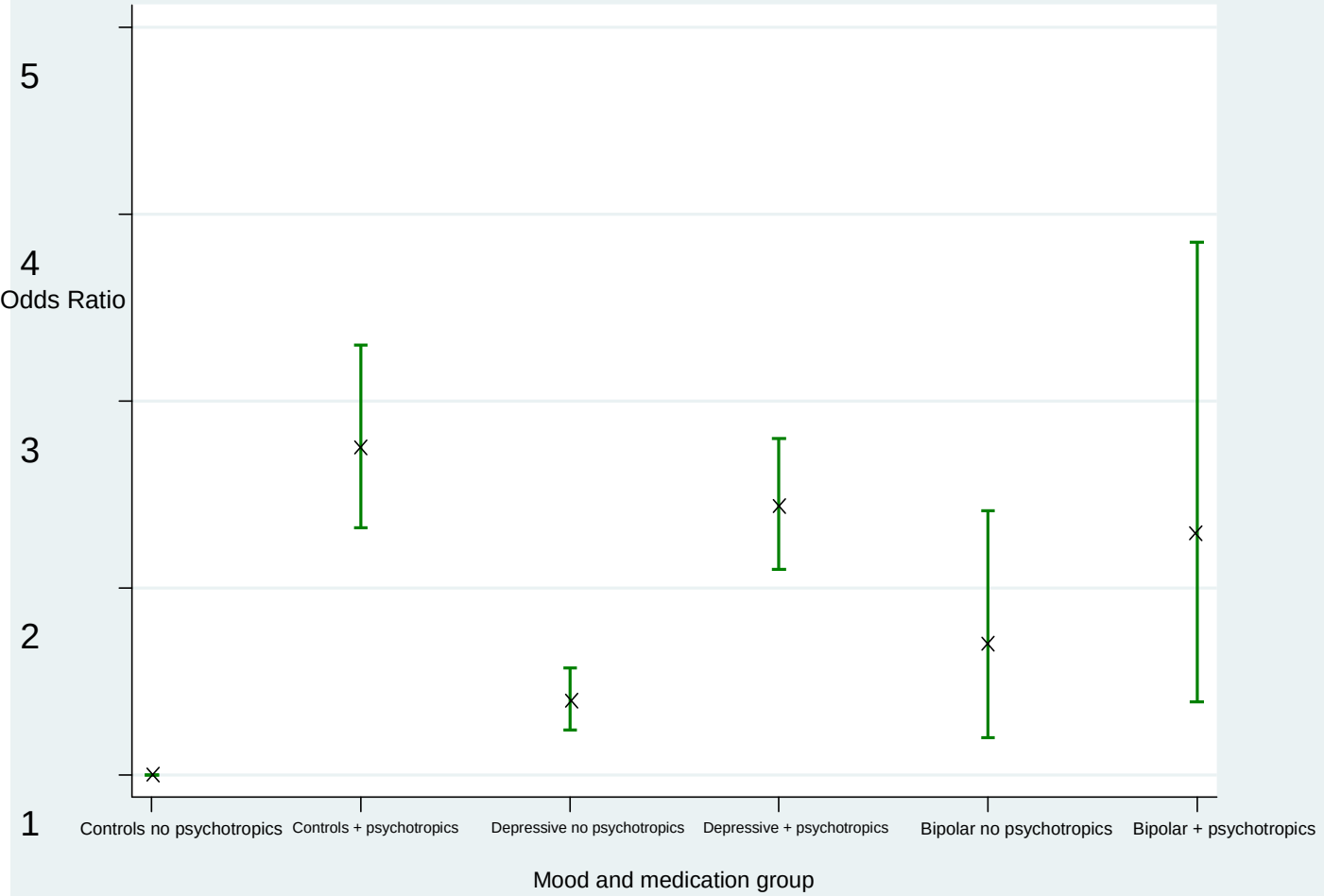
Results adjusted for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI

Figure 2d) Logistic regression analysis of hypertension associated with mood disorder and medication status



Results adjusted for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI

Figure 2d) Logistic regression analysis of stroke associated with mood disorder and medication status.



Results adjusted for age, sex, socioeconomic deprivation, ethnicity, smoking status, frequency of alcohol consumption and BMI

Table 1 Demographic, lifestyle and clinical characteristics

	Control, N (%)	Depression, N (%)	Bipolar, N (%)	*P-value* [a]
Participants, *n = 145,991*	113,444 (77.7)	30,990 (21.2)	1,557 (1.1)	
Demographic and lifestyle characteristics				
Sex				
Female	57,082 (50.3)	20,004 (64.6)	766 (49.2)	<0.001
Male	56,362 (46.7)	10,986 (35.5)	791 (50.8)	
Age (years)				
39-49	25,215 (22.2)	8,027 (25.9)	492 (31.6)	<0.001
50-60	40,012 (35.3)	12,351 (39.9)	624 (40.1)	
61-72	48,217 (42.5)	10,612 (34.3)	441 (28.3)	
BMI category				
Underweight	552 (0.5)	159 (0.5)	15 (1.0)	<0.001
Normal-weight	37,613 (33.2)	9,783 (31.6)	451 (29.0)	
Overweight	48,835 (43.1)	12,578 (40.6)	614 (39.4)	
Class I obese	19,473 (17.2)	5,708 (18.4)	328 (21.1)	
Class II obese	5,186 (4.5)	1,888 (6.1)	108 (6.9)	
Class III obese	1,785 (1.6)	874 (2.8)	41 (2.6)	
Townsend score quintile				
1 (least deprived)	19,541 (17.2)	4,802 (15.5)	169 (10.9)	<0.001
2	23,102 (20.4)	5,781 (18.7)	205 (13.2)	
3	23,659 (20.9)	6,270 (20.2)	260 (16.7)	
4	25,414 (22.4)	7,197 (23.2)	384 (24.7)	
5 (most deprived)	21,728 (19.2)	6,940 (22.4)	539 (34.6)	
Ethnicity				
White	103,786 (91.5)	29,295 (94.5)	1,385 (89.0)	<0.001
Mixed	777 (0.7)	264 (0.9)	25 (1.6)	
Asian/Asian British	3,811 (3.4)	564 (1.8)	65 (4.2)	
Black/Black British	3,248 (2.9)	522 (1.7)	50 (3.2)	
Chinese	471 (0.4)	49 (0.2)	6 (0.4)	
Other	1,351 (1.2)	296 (1.0)	26 (1.7)	
Alcohol consumption				
Daily/Almost Daily	23,377 (21.0)	6,134 (19.8)	318 (20.4)	<0.001
3-4 times/week	26,571 (23.4)	6,588 (21.3)	263 (16.9)	
1-2 times/week	29,107 (25.7)	7,467 (24.1)	337 (21.6)	

1-3 times/month	12,317 (10.9)	3,943 (12.7)	196 (12.6)	
Special occasions only	12,737 (11.2)	4,091 (13.2)	231 (14.8)	
Never	8,935 (7.9)	2,767 (8.9)	212 (13.6)	
Smoking status				
Never	65,154 (57.4)	15,647 (50.5)	667 (42.8)	<0.001
Previous	38,320 (33.4)	11,412 (36.8)	559 (35.9)	
Current	9,970 (8.8)	3,931 (12.7)	331 (21.3)	
Psychotropic medication				
No	109,577 (96.6)	24,603 (79.4)	1,057 (67.9)	<0.001
Yes	3,867 (3.4)	6,387 (20.6)	500 (32.1)	
Clinical Characteristics				
CVD any				
No	80,854 (71.3)	21,516 (69.4)	1,020 (65.5)	<0.001
Yes	32,590 (28.7)	9,474 (30.6)	537 (34.5)	
Diabetes				
No	107,457 (94.7)	29,260 (94.4)	1,449 (93.1)	0.002
Yes	5,987 (5.3)	1,730 (5.6)	108 (6.9)	
Hypertension				
No	83,762 (73.8)	23,316 (72.0)	1,073 (68.9)	<0.001
Yes	29,682 (26.2)	8,674 (28.0)	484 (31.1)	
Myocardial infarction				
No	111,046 (97.9)	30,314 (97.8)	1,502 (96.5)	0.001
Yes	2,398 (2.1)	6,76 (2.2)	55 (3.5)	
Angina				
No	110,296 (97.2)	29,979 (96.7)	1,494 (96.0)	<0.001
Yes	3,148 (2.8)	1,011 (3.3)	63 (4.1)	
Stroke				
No	111,974 (98.7)	30,428 (98.2)	1,523 (97.8)	<0.001
Yes	1,470 (1.3)	562 (1.8)	34 (2.2)	

CVD, cardiovascular disease

[a] χ^2 tests.

Table 2.Logistic regression analysis of cardiometabolic disease associated with mood disorder.

	Overall				Female				Male			
	Partially adjusted[a]		Fully adjusted[b]		Partially adjusted[a]		Fully adjusted[b]		Partially adjusted[a]		Fully adjusted[b]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CVD any												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.29 (1.25, 1.33)	<0.001	1.15 (1.12, 1.19)	<0.001	1.21 (1.17, 1.26)	<0.001	1.08 (1.03, 1.12)	<0.001	1.40 (1.34, 1.46)	<0.001	1.26 (1.20, 1.32)	<0.001
Bipolar	1.50 (1.34, 1.68)	<0.001	1.28 (1.14, 1.43)	<0.001	1.55 (1.32, 1.83)	<0.001	1.36 (1.15, 1.62)	<0.001	1.46 (1.25, 1.69)	<0.001	1.19 (1.02, 1.40)	0.027
Diabetes												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.29 (1.22, 1.37)	<0.001	1.07 (1.03, 1.13)	0.038	1.25 (1.15, 1.36)	<0.001	1.03 (0.94, 1.12)	0.554	1.32 (1.23, 1.44)	<0.001	1.10 (1.01, 1.20)	0.023
Bipolar	1.37 (1.15, 1.67)	0.002	1.01 (0.81, 1.24)	0.960	1.17 (0.82, 1.66)	0.399	0.88 (0.61, 1.28)	0.506	1.48 (1.16, 190)	0.002	1.09 (0.84, 1.41)	0.527
Hypertension												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.27 (1.23, 1.31)	<0.001	1.15 (1.13, 1.18)	<0.001	1.19 (1.14, 1.24)	<0.001	1.07 (1.03, 1.12)	0.002	1.39 (1.32, 1.45)	<0.001	1.27 (1.21, 1.34)	<0.001
Bipolar	1.44 (1.29, 1.61)	<0.001	1.26 (1.12, 1.42)	<0.001	1.46 (1.24, 1.73)	<0.001	1.32 (1.11, 1.57)	<0.001	1.42 (1.22, 1.66)	<0.001	1.20 (1.03, 1.41)	0.022
MI												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.38 (1.26, 1.51)	<0.001	1.18 (1.08, 1.30)	<0.001	1.29 (1.08, 1.55)	0.005	1.05 (0.87, 1.27)	0.580	1.41 (1.27, 1.56)	<0.001	1.23 (1.11, 1.37)	<0.001
Bipolar	1.90 (1.44, 2.51)	<0.001	1.45 (1.09, 1.92)	0.011	1.37 (0.65, 2.92)	0.409	0.93 (0.43, 2.00)	0.855	2.02 (1.50, 2.72)	<0.001	1.59 (1.17, 2.16)	0.003
Angina												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.49 (1.39, 1.61)	<0.001	1.23 (1.14, 1.33)	<0.001	1.43 (1.27, 1.61)	<0.001	1.17 (1.03, 1.32)	0.018	1.54 (1.40, 1.69)	<0.001	1.28 (1.16, 1.41)	<0.001
Bipolar	1.69 (1.30, 2.19)	<0.001	1.21 (0.93, 1.58)	0.154	1.17 (1.30, 2.90)	0.008	1.33 (0.84, 2.11)	0.231	1.62 (1.18, 2.22)	0.003	1.17 (0.54, 1.61)	0.351
Stroke												
Control	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Depression	1.61 (1.46, 1.78)	<0.001	1.26 (1.13, 1.40)	<0.001	1.70 (1.47, 1.97)	<0.001	1.38 (1.18, 1.61)	<0.001	1.53 (1.33, 1.76)	<0.001	1.15 (1.00, 1.34)	0.058
Bipolar	1.80 (1.27, 2.54)	0.001	1.17 (0.82, 1.67)	0.373	2.73 (1.69, 4.41)	<0.001	1.85 (1.14, 3.02)	0.013	1.29 (0.78, 2.13)	0.317	0.81 (0.48, 1.34)	0.317

CI; Confidence Interval, CVD, cardiovascular disease; MI, Myocardial Infarction; OR, Odds Ratio

[a]partially adjusted; age, sex, deprivation and ethnicity

[b]fully adjusted; age, sex, deprivation, ethnicity, BMI, smoking status, alcohol consumption and psychotropic medication.

Table 3.Cardiometabolic disease in mood and medication groups

Mood Group	Diabetes (n, %)	MI (n, %)	Angina (n, %)	Hypertension (n, %)	Stroke (n, %)
Controls not on psychotropic medication (N=109,514)	5,640 (5.15)	2,262 (2.06)	2,921 (2.67)	28,287 (25.81)	1,316 (1.20)
Controls on psychotropic medication (N=3,867)	347 (8.97)	136 (3.51)	227 (5.87)	1,395 (36.07)	154 (3.98)
Depressive features not on psychotropic medication (N=24,603)	1,199 (4.87)	508 (2.06)	690 (2.80)	6,609 (26.86)	370 (1.50)
Depressive features on psychotropic medication (N=6,387)	531 (8.31)	168 (2.63)	321 (5.03)	2,065 (32.33)	192 (3.01)
Bipolar features not on psychotropic medication (N=1557)	108(6.94)	55(3.53)	63(4.05)	484(31.09)	34(2.18)
Bipolar symptoms on psychotropic medication (N=500)	48 (9.60)	25 (5.00)	24 (4.80)	165 (33.00)	16 (3.20)

Appendix 1. Unique Data Identifier (UDI) codes:

Features of bipolar disorder (type I):

Either: 4642 Ever manic/hyper for at least 2 days or 4653 Ever irritable/argumentative for at least 2 days, plus

At least 3 from 6156.01 (more active), 6156.02 (more talkative), 6156.03 (needed less sleep), and 6156.04 (more creative/more ideas), plus

5663 Duration of a week or more, plus

5674 Needed treatment or caused problems at work

Features of bipolar disorder (type II):

Either: 4642 Ever manic/hyper for at least 2 days or 4653 Ever irritable/argumentative for at least 2 days, plus

At least 3 from 6156.01 (more active), 6156.02 (more talkative), 6156.03 (needed less sleep), and 6156.04 (more creative/more ideas), plus

5663 Duration of a week or more

Single (probable) episode of major depression:

EITHER:

4598 Ever depressed/down for a whole week, plus

4609 At least two weeks duration, plus

4620 Only one episode, plus

2090 Ever seen a GP or 2100 a psychiatrist for nerves, anxiety, depression

OR:

4631 Ever anhedonic (unenthusiasm/uninterest) for a whole week, plus

5375 At least two weeks, plus

5386 Only one episode, plus

2090 Ever seen a GP or 2100 a psychiatrist for nerves, anxiety, depression

Probable recurrent major depression (moderate):

EITHER:

4598 Ever depressed/down for a whole week, plus

4609 At least two weeks duration, plus

4620 At least two episodes, plus

2090 Ever seen a GP (but not a psychiatrist) for nerves, anxiety, depression

OR:

4631 Ever anhedonic (unenthusiasm/uninterest) for a whole week, plus

5375 At least two weeks, plus

5386 At least two episodes, plus

2090 Ever seen a GP (but not a psychiatrist) for nerves, anxiety, depression

Probable recurrent major depression (severe):

EITHER:

4598 Ever depressed/down for a whole week, plus

4609 At least two weeks duration, plus

4620 At least two episodes, plus

2100 Ever seen a psychiatrist for nerves, anxiety, depression

OR:

4631 Ever anhedonic (unenthusiasm/uninterest) for a whole week, plus

5375 At least two weeks, plus

5386 At least two episodes, plus

2100 Ever seen a psychiatrist for nerves, anxiety, depression

Appendix 2 – Questions and answers used to assess mood disorder features

Bipolar Features Questions

1. Have you ever had a period of time lasting at least two days when you were feeling so good, "high", excited or "hyper" that other people thought you were not your normal self or you were so "hyper" that you got into trouble?" (4642) or “Have you ever had a period of time lasting at least two days when you were so irritable that you found yourself shouting at people or starting fights or arguments? (4653)"

Select: Yes No Don’t know Prefer not to answer

2. Please try to remember a period when you were in a “high” or “irritable” state and select which of the following apply

Select:

I was more active than usual (6156.01)

I was more talkative than usual (6156.02)

I needed less sleep than usual (6156.03)

I was more creative or had more ideas than usual (6156.04)

All of the above

None of the above

3. What is the longest time period that these "high" or "irritable" periods have lasted? (5663)
Select:

At least two days, but less than a week

Less than a week

A week or more

Do not know

Prefer not to answer

4. How much of a problem have these "high" or "irritable" periods caused you? (5674)
Select:

No Problems

Needed treatment or caused problems with work, relationships, finances, the law or other aspects of life.

Do not know

Prefer not to answer

Depressive Features Questions

1. Looking back over your life, have you ever had a time when you were feeling depressed or down for at least a whole week? (4598)

Select: Yes No Don't know Prefer not to answer

2. How many weeks was the longest period when you were feeling depressed or down? (4609)

Participants asked to enter the number of weeks on the touchscreen.

3. How many periods have you had when you were feeling depressed or down for at least a whole week?"

Participants asked to enter the number of periods on the touchscreen.

4. Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression? (2090) or Have you ever seen a psychiatrist for nerves, anxiety, tension or depression? (2100)

Yes No Don't know Prefer not to answer

Anhedonia:

1. Have you ever had a time when you were uninterested in things or unable to enjoy the things you used to for at least a whole week? (4631)

Yes No Don't know Prefer not to answer

2. How many weeks was the longest period when you were uninterested in things or unable to enjoy the things you used to?"

Participants asked to enter the number of weeks on the touchscreen.

3. How many periods have you had when you were uninterested in things or unable to enjoy the things you used to for at least a whole week?"

Participants asked to enter the number of periods on the touchscreen.

4. Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression? (2090) or Have you ever seen a psychiatrist for nerves, anxiety, tension or depression? (2100)

Yes No Don't know Prefer not to answer

Appendix 3 – list of psychotropic medications

1 Mood stabilisers	2 Antidepressant-SSRI	3 Antidepressant - Other
lithium product	paroxetine	mirtazapine
Priadel (lithium)	Seroxat (paroxetine)	Zispin (mirtazapine)
Camcolit (lithium)	fluoxetine	duloxetine
sodium valproate	Prozac (fluoxetine)	Cymbalta (duloxetine)
Epilim (sodium valproate)	citalopram	Yentreve (duloxetine)
Depakote (semisodium valproate)	Cipramil (citalopram)	venlafaxine
valproic acid	escitalopram	Efexor (venlafaxine)
carbamazepine product	Cipralex (escitalopram)	amitriptyline
carbamazepine	sertraline	Elavil (amitriptyline)
Tegretol (carbamazepine)	Lustral (sertraline)	Tryptizol (amitriptyline)
Teril (carbamazepine)	fluvoxamine	Lentizol (amitriptyline)
Teril retard (carbamazepine)		amitriptyline+perphenazine
Timonil retard (carbamazepine)		Triptafen (amitriptyline+perphenazine)
Epimaz (carbamazepine)		amitriptyline+chlordiazepoxide
		Limbitrol 10 (amitriptyline+chlordiazepoxide)
		Limbitrol-5 (amitriptyline+chlordiazepoxide)
		phenelzine
		maoi - phenelzine
		Nardil (phenelzine)
		moclobemide
		Manerix (moclobemide)
		imipramine
		Tofranil (imipramine)
		trimipramine
		Surmontil (trimipramine)
		dothiepin
		dosulepin
		Prothiaden (dosulepin)
		Thaden (dosulepin)
		clomipramine
		Anafranil (clomipramine)
		lofepramine
		Gamanil (lofepramine)
		Lomont (lofepramine)
		mianserin
		Bolvidon (mianserin)

		Norval (mianserin)
4 Antipsychotic - traditional	**5 Antipsychotic - second generation**	**6 Sedatives and hypnotics**
chlorpromazine	quetiapine	diazepam
cpz - chlorpromazine	Seroquel (quetiapine)	diazepam product
Largactil (chlorpromazine)	risperidone	Valium tablet (diazepam)
haloperidol	Risperdal (risperidone)	Valium syrup (diazepam)
Haldol (haloperidol)	olanzapine	Valiumsupp (diazepam)
Serenace (haloperidol)	Zyprexa (olanzapine)	temazepam
fluphenazinedecanoate	aripiprazole	Normison (temazepam)
fluphenazine	Abilify (aripiprazole)	Euhypnos (temazepam)
Modecate (fluphenazine)	amisulpride	zopiclone
Moditen tablet (fluphenazine)	Solian (amisulpride)	Zimovane (zopiclone)
Moditenenanthate (fluphenazine)	clozapine	zaleplon
flupentixol	Clozaril (clozapine)	Sonata (zaleplon)
Flupenthixol (flupentixol)		zolpidem
Depixol (flupentixol)		Stilnoct (zolpidem)
Fluanxol (flupentixol)		nitrazepam
zuclopenthixol		Mogadon (nitrazepam)
Clopixol (zuclopenthixol)		Nitrados (nitrazepam)
loxapine		Remnos (nitrazepam)
Loxapac (loxapine)		Somnite (nitrazepam)
droperidol		Noctesed (nitrazepam)
Droleptan (droperidol)		Surem (nitrazepam)
trifluoperazine		Unisomnia (nitrazepam)
Stelazine (trifluoperazine)		flunitrazepam
thioridazine		Rohypnol (flunitrazepam)
Melleril (thioridazine)		triazolam
		Halcion (triazolam)