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## Accepted Manuscript

Title: Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials

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**Title:**

Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials

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## **Highlights**

- We perform a meta-analysis of diabetes treatment effects on depression
- We also test for correlates of response: glycaemia, insulin resistance & inflammation
- Pioglitazone consistently improves depressive symptoms, most strongly in women
- Metformin has no overall benefit on depressive symptoms compared to controls
- Elevated inflammation is implicated in the anti-depressant effects of pioglitazone

## **Abstract**

Depression is a common comorbidity in diabetes but conventional anti-depressant treatments do not consistently improve outcomes. We tested whether established diabetes treatments can also improve depressive symptoms and additionally examined biological correlates of response. We performed a multi-database systematic search of all clinical trials, which measured the effect of licensed diabetes treatments on depressive symptoms using a validated questionnaire. Results of randomised controlled trials (RCT's) were pooled for meta-analysis. Data were also collected on insulin resistance (HOMA-IR), C-reactive protein (CRP) and fasting blood glucose (FBG) as correlates of response. Nineteen studies (n=3369 patients) were included in the qualitative synthesis, 9 testing thiazolidenediones, 5 metformin, 2 thiazolidenediones against metformin, 2 incretin-based therapies and 1 insulin. Most studies were of good quality. In random-effects meta-analysis of RCT's, pioglitazone improved depressive symptoms compared to controls (pooled effect size = -0.68 (95% C.I. -1.12 to -0.24),  $p=0.003$ ,  $N_{\text{studies}}=8$ ,  $I^2=83.2\%$ ). Conversely, metformin was comparable to controls overall (pooled effect size = +0.32 (95% C.I. -0.23 to 0.88),  $p=0.25$ ,  $N_{\text{studies}}=6$ ,  $I^2=94.2\%$ ), although inferior to active controls (pooled effect size = +1.32 (95% C.I. 0.31 to 2.34),  $p<0.001$ ,  $N_{\text{studies}}=3$ ,  $I^2=90.1\%$ ). In random-effects meta-regression, female sex ( $\beta=-0.023$ , (95% C.I. -0.041 to -0.0041),  $p=0.016$ ,  $N_{\text{studies}}=8$ ) predicted reduction in depressive symptoms with pioglitazone, but baseline HOMA-IR, FBG and severity of depressive symptoms did not. In conclusion, pioglitazone was associated with improvement in depressive symptoms, an effect more marked in women and poorly explained by effects on glycaemia and insulin resistance. Metformin had no consistent benefit on depressive symptoms. Larger trials are needed, stratified by sex and including serial measures of innate inflammation.

## **1. Introduction**

Depressive symptoms are twice as common in people with type 2 diabetes compared to the general population and are associated with increased risk of diabetes complications and premature mortality (Anderson et al., 2001; Winkley et al., 2012). However, this association is inadequately explained by behavioural and psychological factors alone (Moulton et al., 2015). Conventional treatments for depressive symptoms in type 2 diabetes, such as anti-depressant medication and psychological therapies, are associated with high rates of treatment failure and frequent non-adherence to treatment (Rush et al., 2006; Sawada et al., 2009). Understanding the biological mechanisms underlying depressive symptoms in type 2 diabetes could lead to identifying new targets and development of novel treatments.

At least three potential (though not mutually exclusive) biological pathways have been implicated in the link between the two conditions. Firstly, increased concentrations of circulating inflammatory markers are seen in people with depressive symptoms and type 2 diabetes compared to people with type 2 diabetes alone (Hayashino et al., 2014; Laake et al., 2014). Secondly, higher insulin resistance is consistently associated with increased depressive symptoms in cross-sectional studies, even after adjustment for confounders (Kan et al., 2013), and insulin resistance is likewise associated with elevated inflammation (Donath, 2014). Thirdly, hyperglycaemia is associated with increased depressive symptoms in cross-sectional studies (Lustman et al., 2000), although the association is weaker when tested prospectively (Fisher et al., 2010b). Importantly, conventional antidepressants have inconsistent effects on glycaemic control, insulin resistance and inflammation (Katon et al., 2004; Kauffman et al., 2005), whereas many diabetes treatments have potent effects on these three pathways (Makdissi et al., 2012; Reynolds et al., 2007; Yki-Jarvinen, 2004). Meanwhile, many diabetes treatments, including metformin, glucagon-like peptide-1 (GLP-1) and thiazolidinediones, have been found to cross the blood-brain barrier (Heneka et al., 2005; Kastin et al., 2002; Labuzek et al., 2010). As well as reducing polypharmacy, this suggests that established diabetes treatments could be repurposed to improve both depressive symptoms and diabetes concurrently. In addition to possible central actions, such anti-depressant effects could be driven by the modification of biological pathways common to both depressive symptoms and diabetes. To date, however, the potential anti-depressant properties of diabetes treatments have not been systematically evaluated.

We have conducted a systematic review and meta-analysis of diabetes treatments and their effects upon depressive symptoms. Our primary aim was to test whether specific pharmacological classes of diabetes treatments are associated with improvements in depressive symptoms compared to controls. Our secondary aim was to test for potential correlates of treatment response, specifically inflammation, insulin resistance and glycaemic control.

## **2. Methods**

### **2.1. Design**

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, in which studies that meet review criteria are examined and those that were RCTs and with sufficient data pooled for meta-analysis.

### **2.2. Literature search**

We systematically searched PubMed, EMBASE and Web of Science from 1<sup>st</sup> January 1900 to 1<sup>st</sup> March 2018. A Boolean search was conducted, cross-referencing licensed pharmacological treatments of diabetes with depressive symptoms and related terms, with exclusion of non-human studies and limiting to clinical trials only. Notably, we included randomised- and non-randomised trials in the qualitative synthesis but only RCT's in the meta-analysis. The search strategy was as follows:

(sglt-2 inhibitor OR dapagliflozin OR canagliflozin OR empagliflozin OR metformin OR incretin OR dpp-iv inhibitor OR dpp-4 inhibitor OR linagliptin OR saxagliptin OR alogliptin OR sitagliptin OR nateglinide OR repaglinide OR albiglutide OR glp-1 OR dulaglutide OR exenatide OR liraglutide OR meglitinide OR pioglitazone OR rosiglitazone OR glipizide OR glyburide OR repaglinide OR acarbose OR insulin OR glimepiride OR gliclazide OR glipizide OR chlorpropamide OR tolazamide OR tolbutamide OR sulphonylurea) AND (mood OR depress\* OR dysthym\*) NOT (rat\* OR mouse OR mice).

A parallel search of potentially grey/unpublished literature (OpenGrey, DART-Europe, EThOS, clinicaltrials.gov and the WHO International Clinical Trials Registry Platform clinical trials databases) was also conducted.

Two authors (C.M. and C.H.) independently performed the literature search and resolved differences over inclusion through discussions and consensus. Titles were reviewed and then abstracts were reviewed for titles meeting inclusion criteria. From abstracts fulfilling inclusion criteria, full-text articles were reviewed and data extraction performed for studies still meeting inclusion criteria. The reference lists of included papers were checked for additional publications. Both published and unpublished articles were included, and authors were contacted where data were missing.

### **2.3. Study selection**

The search was restricted to clinical trials, including controlled and uncontrolled trials. Specific inclusion criteria were: (1) study was a clinical trial testing a licensed diabetes treatment at licensed dose and route; (2) depressive symptoms were measured pre- and post-treatment using a validated depression scale either as primary or secondary outcome; (3) a minimum of 5 patients were recruited; and (4) the sample consisted of adults (18 years of age or more). Exclusion criteria were (1) study was an observational study; (2) study was a case report, case series or review article presenting no original data; (3) study was not published in English; (4) the measure of depressive symptoms was a sub-score of a general quality-of-life measure; and (5) patients with depression were specifically excluded from the study. Figure 1 shows the PRISMA flow diagram of the search.

[Figure 1 here]

### **2.4. Data extraction**

Studies were stratified into those selecting only patients with depression at baseline and those which did not specifically select for depression. Studies in which depression was specifically excluded were not included in our synthesis. For each study, we extracted the following data: study design; baseline depressive symptoms; baseline diabetes status; sample size; sex; neuropsychiatric comorbidity of the sample; type, dose, route and duration of intervention and control treatment; measure of depressive symptoms; mean (SD) change in depressive symptoms for each group; and significant adverse effects. In order to test for potential

correlates of change in depressive symptoms, we also extracted data on glycaemic control (fasting blood glucose (FBG) and HbA<sub>1c</sub>), insulin resistance and inflammatory markers, including baseline measures and their mean (SD) change following treatment. We also searched for duplicate publications for each trial to extract further data. Where raw values of insulin resistance were not presented but FBG and fasting insulin were available, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula was used to derive insulin resistance (Matthews et al., 1985). Where the SD was not presented for change in depressive symptoms, FBG, insulin resistance or inflammation, we estimated this by assuming that the true SDs at baseline and follow-up were constant and the correlation between patient's baseline and follow-up values was moderately positive ( $r=0.5$ ). If a study reported several follow-up time points, the longest follow-up interval was used. For studies with multiple arms, data were extracted only for pharmacological treatments or placebo. For studies testing a treatment at different doses, the mean score and SD was calculated, weighted according to numbers in each group.

## **2.5. Quality assessment**

We assessed quality using the Cochrane Common Mental Disorders Depression Anxiety & Neurosis Group (CCDAN) instrument (19). This was chosen because it was specifically developed for trials of treatments for depression and can be used for both randomised- and non-randomised trials (Cipriani et al., 2007; Moncrieff J, 2001). The scale consists of 23 items, each scored 0-2 and each contributing equally to a final score between 0-46, higher scores indicating higher quality. The CCDAN covers aspects of both internal validity (or control of bias) and external validity. A cut-off score of more than 20 has been suggested to identify high-quality studies (Cipriani et al., 2007).

## **2.6. Statistical analysis**

Using the `metan` command in STATA 11.0, we performed meta-analysis for any drug class tested in at least 5 RCTs. For each study, effect-size estimates were calculated using the standardized mean difference (SMD) in change in depressive symptoms following treatment. This was calculated by dividing the mean difference by the pooled SD of the change scores within the group (equivalent to Cohen's  $d$ ). SMD is an appropriate measure of effect estimate when studies assess the same variable but measure it using different questionnaires (Egger et al.). The standard error (SE) of each study's group sizes was calculated according to a formula provided by Cooper and Hedges (Cooper and Hedges, 1994).



Next, studies were weighted using an inverse-variance method, such that studies with larger precision were given greater weight. Pooled effect estimates were calculated using a random-effects model, which allows for heterogeneity between studies by permitting the true effects estimated by the studies to differ between studies. The combined effect thus represents the mean of the population of true effects and is appropriate where effects may vary between populations (Borenstein M, 2009). This is expected in this meta-analysis where there is variation in dose, treatment duration, severity of depressive symptoms and metabolic status at baseline. In addition to presenting an overall effect size, Forest plots were stratified into studies using placebo controls and active controls (e.g. other diabetes treatments). Heterogeneity between studies was quantified by calculating the  $I^2$  statistic, which represents the fraction of variation between studies attributable to heterogeneity. Values for  $I^2$  range between 0% and 100% with values of 25%, 50% and 75% suggesting low, moderate and high heterogeneity respectively (Higgins et al., 2003). Using all studies in the meta-analysis, we assessed potential publication bias by using the non-parametric Trim and fill test and Egger's test of small study effects (Egger et al., 1997). Because fewer than 10 studies were included in the meta-analysis, a Funnel plot was not presented (Sterne et al., 2011).

For any drug class tested in meta-analysis, we performed random-effects meta-regression using the following covariates in turn, which were selected *a priori*: age, sex (percentage male), baseline severity of depressive symptoms (% of maximum score on the questionnaire used), baseline FBG, baseline HOMA-IR and baseline C-reactive protein (CRP). Data were insufficient to test changes over time in FBG, HOMA-IR or CRP as covariates. Because of the small number of studies, we firstly used the Monte Carlo permutation test for meta-regression, which calculates a moment-based estimate of between-study variance and provides robust p-values and standard error (SE) associated with each covariate (Harbord RM, 2008). To ensure sufficient precision, 10000 permutations were used for each covariate (Manly, 2006). This technique reduces the chance of false-positive findings in meta-regression analyses (Higgins and Thompson, 2004). The effect size of any significant covariate was then quantified using the restricted maximum likelihood estimate of between-study variance, in order to quantify its effect size and effect on overall heterogeneity.

### **3. Results**

A total of 2490 titles were reviewed, of which 154 abstracts were read and 59 manuscripts carried forward for full-text extraction. From these, 19 were included in the qualitative synthesis and 12 included in meta-analysis. Of the 19 included studies, 9 tested thiazolidenediones, 5 tested metformin, 2 thiazolidenediones versus metformin, 2 incretin-based therapies and 1 insulin. The total number of patients included was 3369 with mean age 49.89 years. Fourteen studies were RCTs, 1 was a non-randomised controlled trial and 4 were pre-post open label studies. All RCTs were of good quality, whereas quality of open-label non randomised studies was poorer overall (Table 1). The full breakdown in CCDAN scoring for each study is included as supplementary material (Supplementary Table 1).

### **3.1. Qualitative synthesis**

#### *3.1.1. Thiazolidenediones*

##### 3.1.1.1. Randomised controlled trials

Of the 8 RCTs testing pioglitazone, 6 were placebo-controlled (Calabrese, 2017; Lin et al., 2015; Roohafza et al., 2014; Sepanjnia et al., 2012; Simuni T., 2015; Zeinoddini et al., 2015) and two used metformin as a control (Hu et al., 2015; Kashani et al., 2013). Apart from one study (Lin et al., 2015), all RCTs selecting depressed patients at baseline reported significant reduction in depressive symptoms compared to controls. There was population heterogeneity in terms of comorbidity, age and sex (Table 1). Where measured, improvement in depressive symptoms was not accompanied by significant change in FBG or insulin resistance. There was no correlation between change in insulin resistance and change in depressive symptoms where reported (Kashani et al., 2013). In the one RCT in which CRP was reported, positive effects on depressive symptoms were paralleled by significant reduction in CRP (Roohafza et al., 2014) (Table 2).

##### 3.1.1.2. Non-randomised trials

Of the three open-label studies, two testing pioglitazone and one rosiglitazone (Kemp et al., 2012; Kemp et al., 2014; Rasgon et al., 2010), all reported significant reduction in depressive symptoms as primary outcome. However, all were small in size (Table 1). The two open-label trials of pioglitazone reported significant pre-post effects on depressive symptoms,

glycaemic control, insulin resistance and inflammation (Kemp et al., 2012; Kemp et al., 2014). Whereas one of these reported a significant correlation between change in depressive symptoms and HOMA-IR (Kemp et al., 2012), the other reported a similar for interleukin-6 (Kemp et al., 2014) (Table 2).

[Table 1 here]

[Table 2 here]

### 3.1.2. *Metformin*

#### 3.1.2.1. Randomised controlled trials

Three trials of metformin used placebo controls. In an RCT selecting patients with depression at baseline, 24 weeks of metformin treatment in patients with type 2 diabetes led to significant reduction in depressive symptoms compared to placebo (Guo et al., 2014), which was paralleled by improvement in FBG. However, correlation between FBG change and change in depressive symptoms was not reported, nor were data on insulin resistance or inflammation. In an unpublished 16-week trial of metformin in overweight people with depression all receiving sertraline, metformin performed similarly to placebo, although significance values have not been reported (Lustman, 2018). In the 1-year diabetes prevention study of people with impaired glucose tolerance (IGT), metformin significantly reduced CRP and fasting glucose, yet was not associated with reduction in the Beck Depression Inventory (BDI) score (a secondary outcome) compared to placebo (Ackermann et al., 2009). However, the baseline BDI score was very low, limiting scope for potential effects (Table 1, Table 2).

Three trials of metformin used active controls. In the two aforementioned RCT's against pioglitazone, metformin was inferior in reducing depressive symptoms in patients with depression (Hu et al., 2015; Kashani et al., 2013). In a 12-week trial of women with polycystic ovarian syndrome, myo-inositol was marginally superior to metformin in reducing depressive symptoms. The population was not selected for depression at baseline and data on FBG, insulin resistance or inflammation were not reported (Jamilian et al., 2017).

### 3.1.2.2. Non-randomised trials

In a non-randomised trial of a sample including people with type 2 diabetes and IGT, metformin was associated with greater reduction in BDI score compared to treatment-as-usual (Krysiak et al., 2017). FBG, insulin resistance and inflammation were not reported (Table 1, Table 2).

### 3.1.3. Incretin-based therapies

#### 3.1.3.1. Randomised controlled trials

In a 6-month study of insulin-dependent type 2 diabetes patients, the GLP-1 receptor agonist liraglutide was associated with non-significant improvement in BDI score – a secondary outcome – compared to usual care (de Wit et al., 2014). FBG improved compared to controls, but insulin resistance and inflammation were not measured (Table 1, Table 2).

#### 3.1.3.2. Non-randomised trials

In a 4-week open label study of patients with comorbid depression and below-average cognitive performance, liraglutide was associated with significant reduction in depressive symptoms (Mansur et al., 2017), as a secondary outcome. However, this did not correlate with reduction in FBG or insulin resistance, and inflammation was not measured (Table 1, Table 2).

### 3.1.4. Insulin

In a 3-arm randomised trial of 57 patients with poorly controlled type 2 diabetes, insulin was not associated with any change in depressive symptoms (Hendra and Taylor, 2004). There was no difference in change in glycaemic control between treatment arms, whilst insulin resistance and inflammation were not reported (Table 1, Table 2).

## 3.2. Tolerability

Gastro-intestinal side-effects were commonly seen in studies of metformin and incretin-based therapies. Increased appetite and/or weight gain were reported at significant frequency for insulin and for the open-label studies of thiazolidenediones, whereas 6 out of 8 RCT's of thiazolidenediones reported no significant adverse effects (Table 1).

## 3.3. Statistical analysis

### 3.3.1. Meta-analysis of pioglitazone

Meta-analysis was performed for the 8 RCT's (n=611 patients) of pioglitazone. In random-effects meta-analysis, there was a significant overall treatment effect on depressive symptoms (pooled effect size = -0.68, 95% C.I. -1.12 to -0.24,  $p=0.003$ ,  $I^2=83.2\%$ ), which remained for placebo-controlled studies alone (pooled effect size = -0.41 (95% C.I. -0.75 to -0.07),  $p=0.018$ ,  $I^2=60.5\%$ ,  $N_{\text{studies}}=6$ ). The trim and fill test produced no changes to the results, whilst Egger's test likewise showed no evidence of publication bias ( $t=-1.70$ ,  $p=0.14$ ). Of note, one metformin-controlled study (Kashani et al., 2013) reported a markedly larger effect of pioglitazone than the others. Using the metainf command, the significant effect for pioglitazone remained even following removal of this study (pooled effect size = -0.42, 95% C.I. -0.71 to -0.14).

[Figure 2 here]

### 3.3.2. Meta-regression for pioglitazone

To help explain the high overall heterogeneity of  $I^2=83.2\%$ , a meta-regression was performed for all RCT's studies testing pioglitazone. Of the covariates selected, data on age and sex were available for all studies; data on FBG and baseline severity of depressive symptoms were available for 7 studies and data on baseline HOMA-IR were available for 6 studies. Data on CRP were insufficient for meta-regression. In the Monte Carlo permutation test, female sex ( $p=0.035$ ) was significantly associated with reduction in depressive symptoms across studies. In the random-effects estimate of between-study variance, the effect size was significant for proportion of women ( $\beta=-0.023$  (95% C.I. -0.041 to -0.0041),  $p=0.016$ ) and residual  $I^2$  heterogeneity was reduced to 72.5%. Conversely, age ( $p=0.15$ ), baseline severity of depressive symptoms ( $p=0.58$ ), baseline HOMA-IR ( $p=1.0$ ) and baseline fasting glucose ( $p=0.92$ ) showed no association with change in depressive symptoms in Monte-Carlo permutation tests, and further meta-regression analyses were therefore not performed.

### 3.3.3. Meta-analysis of metformin

Meta-analysis was performed for the 6 RCT's of metformin, comprising pooled data from 2638 patients. Overall, metformin was comparable to controls in its effect on depressive

symptoms (pooled effect size = +0.32 (95% C.I. -0.23 to 0.88),  $p=0.25$ ), although heterogeneity was high ( $I^2=94.2\%$ ). When stratified by type of controls (placebo or active), metformin was non-significantly superior to placebo (pooled effect size -0.49 (95% C.I. -1.04 to 0.074),  $p=0.089$ ,  $I^2=92.3\%$ ) but was inferior to active controls (pooled effect size 1.32 (95% C.I. 0.31 to 2.34),  $p<0.001$ ,  $I^2=90.1\%$ ). The trim and fill test produced no changes to the results, whilst Egger's test likewise showed no evidence of publication bias ( $t=0.74$ ,  $p=0.50$ ). Two studies appeared to be outliers: Guo et al. (favouring metformin) and Kashani et al. (very strongly favouring controls). Using the `metainf` command for all studies, removal of Guo et al. changed the overall effect in favour of controls (pooled effect size = 0.65, 95% C.I. 0.12 to 1.18). Removal of Kashani et al. did not change the overall effect (pooled effect size = -0.02, 95% C.I. -0.49 to 0.45).

[Figure 3 here]

#### 3.3.4. Meta-regression for metformin

To help explain the high overall heterogeneity of  $I^2=94.2\%$ , a meta-regression was performed for studies testing metformin. Data on age, sex and baseline depression severity were available for all 6 studies, whereas available data on HOMA-IR (2 studies) and FBG (3 studies) were insufficient for meta-regression. In the Monte Carlo permutation test, older age ( $p=0.082$ ), male sex ( $p=0.078$ ) and baseline depression severity ( $p=0.81$ ) were not associated with reduction in depressive symptoms across studies. Due to non-significance and therefore risk of false-positive findings, further meta-regression was not performed.

## **4. Discussion**

In this systematic review, we firstly tested whether individual classes of diabetes drugs were associated with improvement in depressive symptoms and secondly examined for biological correlates of treatment response. In meta-analysis, pioglitazone had a positive overall effect on depressive symptoms, although significant heterogeneity between studies was observed. Conversely, metformin had a neutral overall effect on depressive symptoms and was inferior to active controls, mostly pioglitazone. In random-effects meta-regression, female sex was associated with treatment response to pioglitazone, whereas insulin resistance and glycaemic control were not. There was some evidence that reduction in inflammation may parallel

reduction in depressive symptoms, although data were insufficient to test this statistically. Incretin-based therapies showed promise in improving depressive symptoms, but data were insufficient for meta-analysis.

#### **4.1. Comparison with other studies**

##### *4.1.1. Effects of diabetes treatments on depressive symptoms*

One previous meta-analysis has tested the effects on diabetes treatments of depressive symptoms (Colle et al., 2017). This analysis focussed on pioglitazone only and included 4 papers in its meta-analysis. Our calculated  $I^2$  heterogeneity was slightly higher than their reported value of 71%. Compared to the previous meta-analysis, our study was enhanced by including a greater number of studies – including an unpublished study – and broader range of covariates, enabling more detailed analysis of candidate mechanisms and better powered meta-regression. There has been no previous meta-analysis testing the effects of metformin on depressive symptoms.

Despite promising findings from individual studies, clinical trial data for incretin-based therapies were not sufficient for meta-analysis in our review. Nevertheless, there is observational evidence from previous studies that would support such trials in future. In a secondary analysis of the SOUL-D study, patients prescribed incretin-based therapies reported improvement in depressive symptoms over 1 year compared to those receiving other diabetes treatments (Moulton et al., 2016). Conversely, previous supporting observational data for metformin have been fewer and have focussed on small non-diabetes samples (Hahn et al., 2006). For insulin, any supporting observational data have been limited to 1-item depressed mood measures (Ascher-Svanum et al., 2015), whilst more recent trials of intranasal insulin have shown disappointing effects on mood (Cha et al., 2017).

##### *4.1.2. Correlates of treatment response*

In previous interventional studies, treatment of depressive symptoms in isolation has not translated consistently into improvements in glycaemic control (Katon et al., 2004; Petrak et al., 2015). This has led to a challenge of the behavioural model for the adverse effects of depressive symptoms on diabetes outcomes (Moulton et al., 2015). As a possible alternative or additional explanation, depressive symptoms and type 2 diabetes may be linked by shared biological mechanisms. If this was the case, then this may partly explain why depressive

symptoms in type 2 diabetes are less responsive to conventional anti-depressant treatments (Moulton et al., 2015; Strawbridge et al., 2015; Uher et al., 2014). In this paper we focussed on three candidate mechanisms: insulin resistance, hyperglycaemia and inflammation.

Elevated insulin resistance may increase the risk of incident depressive symptoms (Ford et al., 2015). If true, patients with elevated insulin resistance may be expected to experience more marked reduction in depressive symptoms following insulin sensitization. However, we did not observe these effects for pioglitazone, a potent insulin sensitizer. For glycaemic control, studies have more often tested the effects of treating depressive symptoms on hyperglycaemia rather than vice versa. In meta-regression, we found that differences in elevated blood glucose between studies likewise did not predict improvement in depressive symptoms. This is corroborated by observational findings that glycaemia itself does not predict worsening in depressive symptoms over time (Fisher et al., 2010a). Collectively, this implicates mechanisms other than glycaemia and insulin resistance in the anti-depressant effects of pioglitazone.

In our review, we found promising isolated findings to support reduction in inflammation as a correlate of improvement in depressive symptoms, although data were insufficient for meta-regression. In previous research, elevated inflammation has been found in people with comorbid depressive symptoms and type 2 diabetes (Hayashino et al., 2014; Laake et al., 2014) and predicts incident depressive symptoms in the general population (Valkanova et al., 2013). Moreover, in a secondary analysis of an incident cohort of type 2 diabetes, improved depressive symptoms in people receiving incretin-based therapies correlated with reduction in CRP but not HbA1c (Moulton et al., 2016). In mechanistic studies, both incretin-based therapies have been found to have potent anti-inflammatory effects, as have thiazolidinediones (Kapadia et al., 2008; Makdissi et al., 2012).

#### **4.2. Interpretation**

Our findings suggest that repositioning of diabetes treatments could present novel opportunities for treating depressive symptoms. Although the best evidence to date supports pioglitazone, this is cautioned by high between-study heterogeneity, a lack of large trials and the insufficiency of studies for some other drug classes. This highlights the need both for larger clinical trials of pioglitazone and trials of other diabetes treatments, such as incretin-based therapies, targeted at patients with depressive symptoms. Metformin shows little



promise in improving depressive symptoms and further trials are not supported by our meta-analysis.

Mechanistically, neither insulin resistance nor FBG was found to predict treatment response to pioglitazone in our analysis. It is noteworthy that female sex predicted treatment response to pioglitazone. Although speculative, this finding is consistent with an inflammatory hypothesis, as female sex is associated with increased inflammation and added susceptibility to the effects of inflammation on depressive symptoms (Derry et al., 2015). An alternative explanation is that the anti-depressant properties of pioglitazone occur through direct central effects; although only a minority of pioglitazone is thought to cross the blood-brain barrier (Heneka et al., 2005), PPAR $\gamma$  receptors are widely expressed in the brain, including in areas implicated in depression, such as the hippocampus (Drew et al., 2006). In parallel with further mechanistic research, sex-stratified clinical trials are now needed to test whether reduction in inflammation is a cause or consequence of improvement in depressive symptoms in people with type 2 diabetes.

#### **4.3. Strengths and limitations**

Our review is strengthened by its systematic literature search, combined data collection on depression-specific questionnaires and biological correlates, the use of random-effects meta-analysis to account for heterogeneity, and inclusion of published- and unpublished literature. The review was further enhanced by meta-regression analysis, which including a wide range of covariates selected *a priori* and use of Monte Carlo permutation analysis to reduce the risk of false-positive associations. We were also able to perform the first meta-analysis of metformin for depressive symptoms, which is important because of its widespread use in clinical practice. Limitations of our review included the variable quality of included studies, several of which tested depressive symptoms as a secondary outcome, but this was necessary when hypotheses are being generated by modelling and pilot data. Inclusion of studies that did not specifically recruit depressed patients may have led to underestimation of treatment effects. Because of the relatively small number of studies, the meta-regression analysis may have been underpowered, and others (such as inflammation) were too infrequently reported to be tested as a covariate. Finally, the use of averages of patient characteristics instead of individual patient data may have further limited power to detect relationships and assumes that the relationship with patient averages across trials is the same as the relationship for patients within trials (Thompson and Higgins, 2002).

#### **4.4. Summary**

Repositioning of diabetes treatments shows promise for treating comorbid depressive symptoms. In particular, thiazolidenediones and incretin-based therapies may improve depressive symptoms, although there are limited studies on the latter. Conversely, metformin shows little benefit. Anti-depressant effects of pioglitazone appear not to be explained by improvements in glycaemic control and insulin resistance. Larger, mechanistically informed trials are now needed, testing different classes of diabetes treatments, stratified by sex and including longitudinal measures of innate inflammation.

#### **Author contributions**

C.M. and K.I. conceived the manuscript. C.H. and C.M. performed the literature search and data extraction. C.M. and D.S. performed the statistical analyses. C.M. wrote the first draft. K.I., C.H. and D.S. revised the manuscript for important intellectual content.

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#### **Duality of interest**

None

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**Figure Legends****Figure 1**

PRISMA flow diagram of literature search

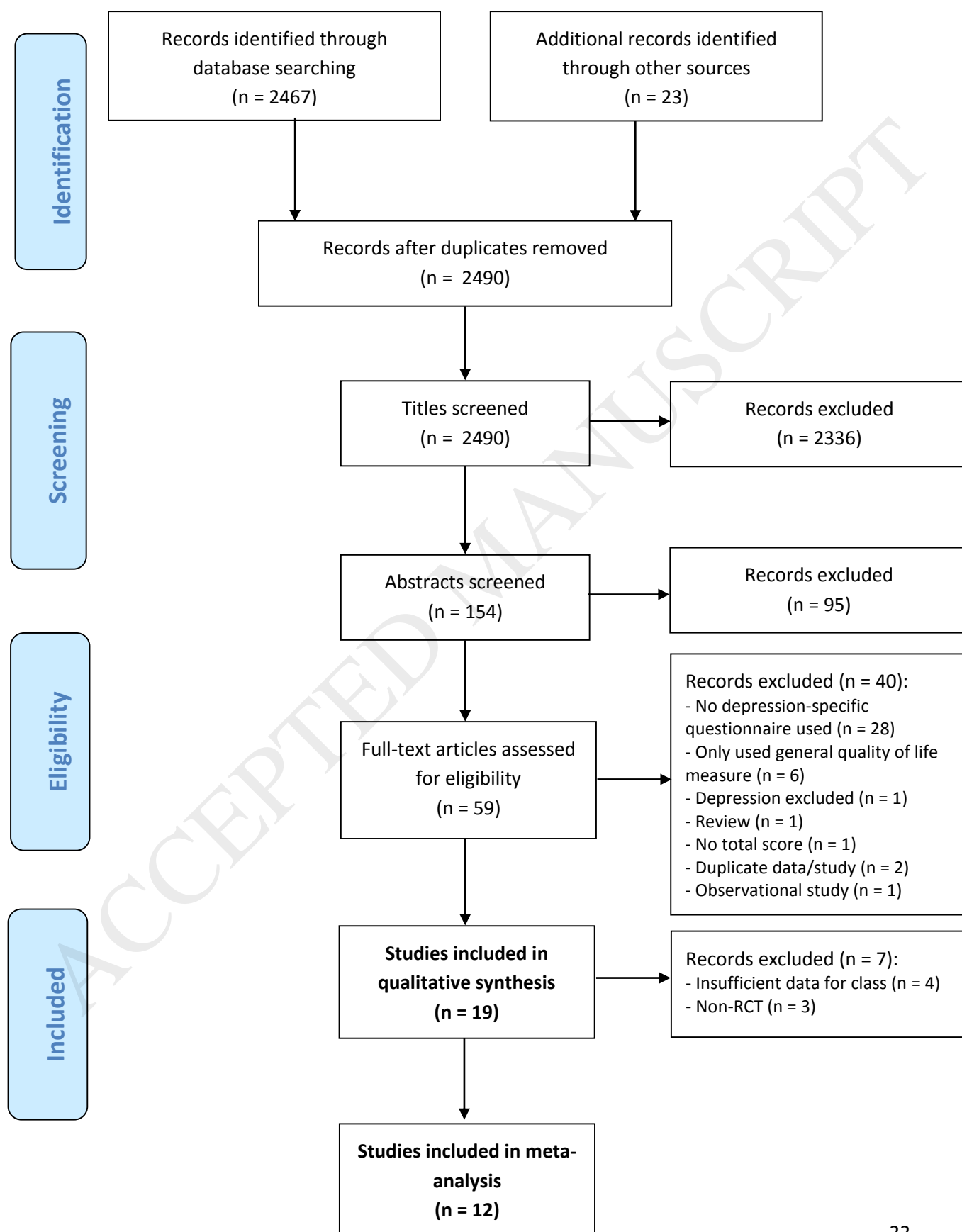
**Figure 2**

Random-effects meta-analysis of standardised mean difference in depressive symptoms for pioglitazone group compared to controls

**Figure 3**

Random-effects meta-analysis of standardised mean difference in depressive symptoms for metformin group compared to controls

ACCEPTED MANUSCRIPT

**Figure 1**



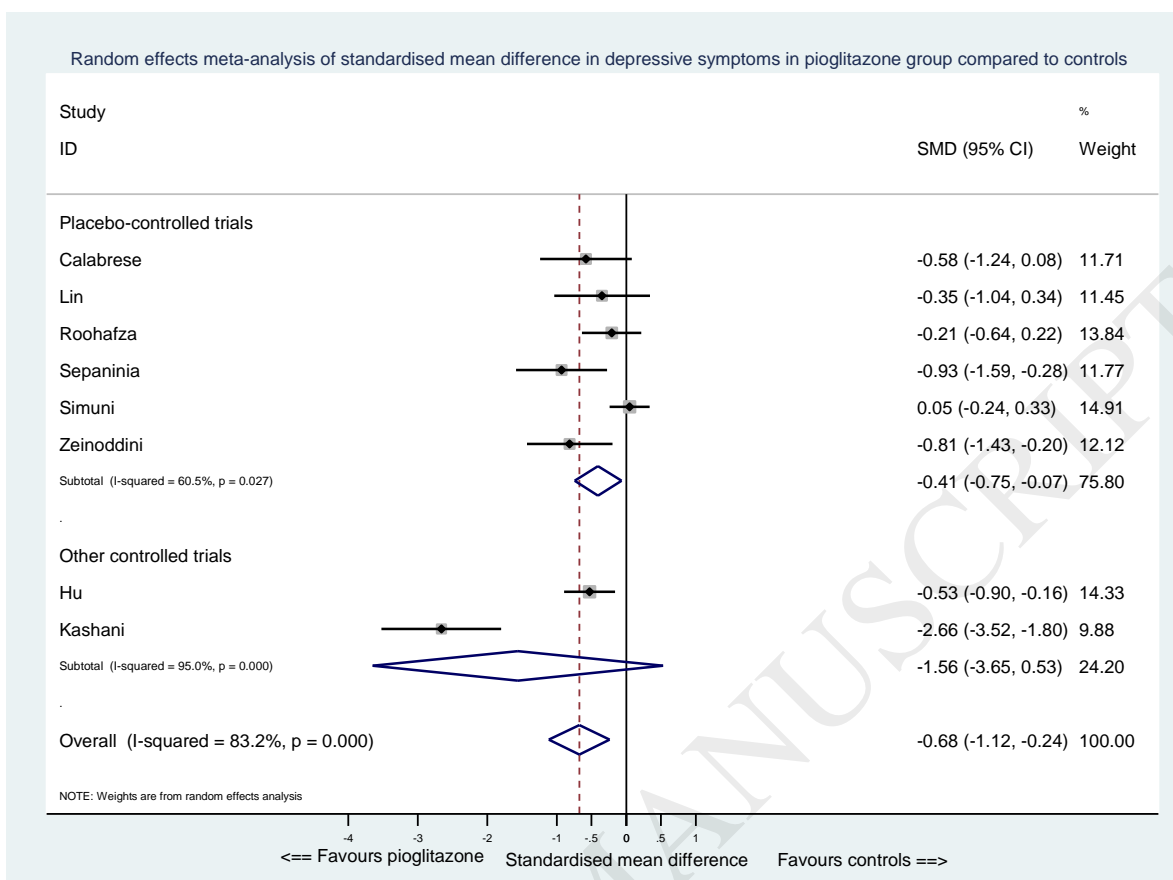
**Figure 2**

Figure 3

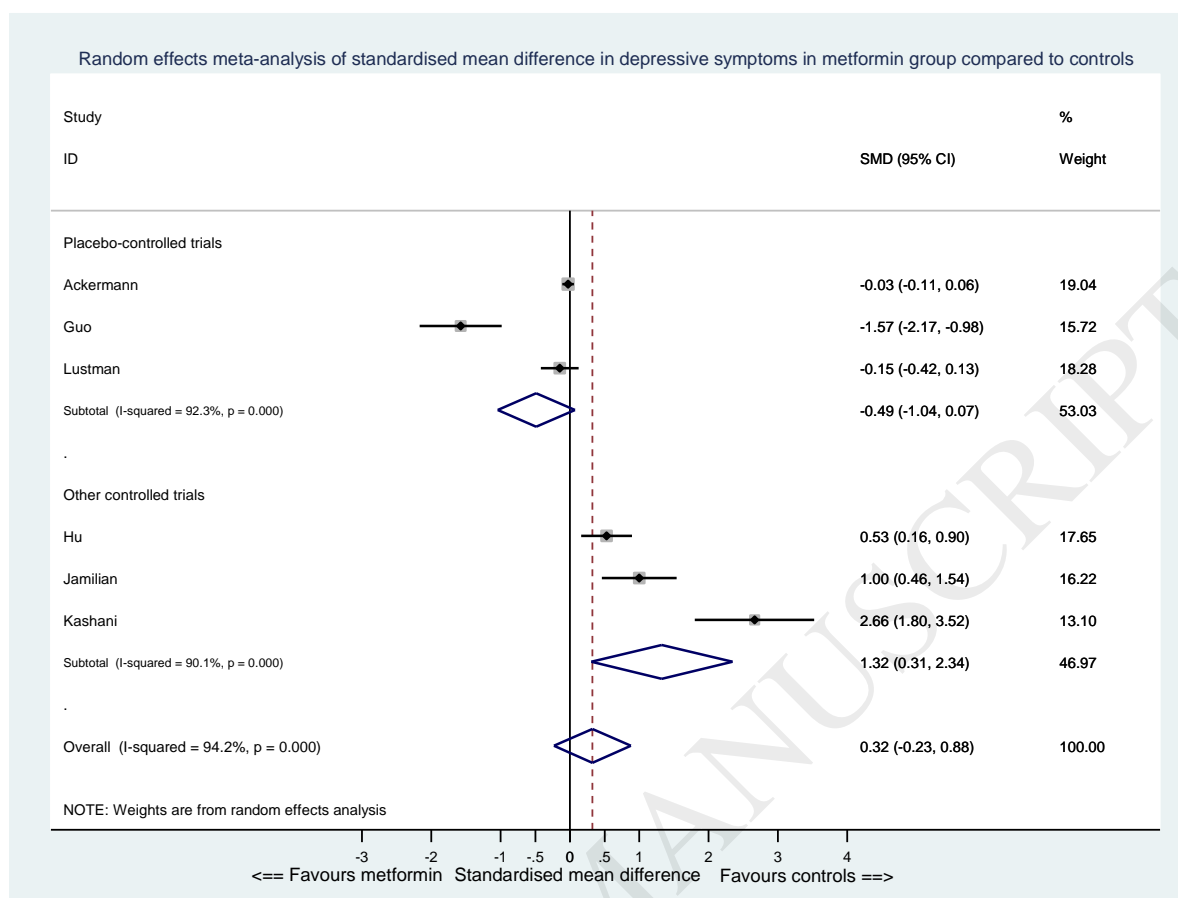


Table 1: Data extraction for included studies

First author, year, country	Study type	Baseline diabetes status	No. patients (male), mean age±SD	Neuro-psychiatric comorbidity	Intervention (number of patients)	Control therapy (number of patients)	Study duration	Mean (SD) baseline depressive symptoms; primary or secondary outcome	Mean (SD) change in depressive symptoms (treatment group)	Mean (SD) change in depressive symptoms (controls)	p-value treatment vs controls	Adverse effects <sup>a</sup>	CCDAN Quality score /46 (% of max score)
<b>a) Studies recruiting only patients with depression at baseline</b>													
<b>Metformin</b>													
Guo, 2014, China	Double-blind RCT	T2D only	59 (36) 54±7.3	Nil	Metformin 1-2g/day (n=29)	Placebo (n=29)	24 weeks	MADRS 24.0 (3.7), HDRS-17 20.3 (2.7)	-8.3 (4.1)	-2.0 (3.9)	<b>p&lt;0.001</b>	Gastro-intestinal upset	21 (45.7%)
Lustman, 2018, USA	Double-blind RCT	Not selected but BMI >28.7	206 (35) 42.9 (N/S)	Nil	Metformin 2g/day plus sertraline (n=104)	Placebo plus sertraline (n=102)	16 weeks	BDI 22.4 (7.86)	-18.82 (8.8)	-17.5 (7.9)	N/R	None	24 (52.2%)
<b>Thiazolidenediones</b>													
Calabrese, 2017, USA	Double-blind RCT	Non-diabetes	37 (13) 45.1±12.5	All bipolar disorder, not currently manic	Pioglitazone 15-45mg/day (n=17)	Placebo once per day (n=20)	8 weeks	IDS, baseline N/R	-31.4 (12.4)	-24.3 (12.1)	No p-value given	None	21 (45.6%)
Kemp, 2012, USA	Open-label study	Abdominal obesity or metabolic syndrome	23 (3) 44.6±10.2	56% history of alcohol use disorder	Pioglitazone average 32.7mg /day (n=23)	Nil	12 weeks	IDS 40.3 (8.6), QIDS 15.2 (3.8)	IDS -21.1 (8.6), QIDS -8.1 (3.8), both p<0.001	N/A	N/A	Appetite and weight gain	22 (47.8%)
Kemp, 2014, USA	Open-label study	Metabolic syndrome or insulin resistance	34 (15) 47.8±10.9	All bipolar disorder, not currently manic.	Pioglitazone average 27.4mg/day (n=34)	Nil	8 weeks	IDS 38.7 (8.2), QIDS 16.1 (3.4)	IDS -17.5 (8.7), QIDS -7.2 (4.3), both p<0.001	N/A	N/A	Increased appetite, peripheral oedema	22 (47.8%)
Lin, 2015, USA	Double-blind RCT	Non-diabetes	37 (8) 46.4±13.5	10.8% bipolar disorder	Pioglitazone 30mg/day (n=17)	Placebo (n=16)	12 weeks	HDRS-21 15.6 (4.9)	-4.1 (5.5)	-2.7 (4.0)	p=0.23	None	27 (58.9%)

Rasgon, 2010, USA	Open-label study	Nondiabetic insulin resistance	8 (1) 51.9±5.6	Nil	Rosiglitazone 8 mg/day (n=8)	Nil	12 weeks	HDRS 19.9 (5.0)	-7.8 (N/R), p=0.019	N/A	N/A	Weight gain	18 (39.1%)
Sepanjnia, 2012, Iran	Double-blind RCT	Non-diabetes	40 (11) 32.1±5.4	Nil	Pioglitazone 30mg/day (n=20)	Placebo (n=20)	6 weeks	HDRS-17 25.4 (3.5)	-16.7 (3.5)	-13.4 (3.5)	<b>p=0.005</b>	None	35 (76.1%)
Zeinoddini, 2015, Iran	Double-blind RCT	Non-diabetes	44 (29) 32.7±4.5	All bipolar I disorder, not currently manic	Pioglitazone 30mg/day (n=22)	Placebo (n=22)	6 weeks	HDRS-17 23.1 (1.8)	-14.0 (3.2)	-11.7 (2.3)	<b>p=0.006</b>	None	31 (67.4%)
<b>Metformin vs. thiazolidenediones</b>													
Hu, 2015, China	Unblinded RCT	T2D only	118 (67) 64.6±7.2	All 3 months post-stroke	Pioglitazone 30 mg/day (n=59)	Metformin 1g/day (n=59)	13 weeks	HDRS-21 29.1 (5.7)	-6.5 (3.6)	-3.1 (8.2)	<b>p&lt;0.05</b>	None	28 (60.9%)
Kashani, 2012, Iran	Double-blind RCT	Drug-dependent diabetes excluded	40 (0) 20.8±4.0	Nil	Pioglitazone 30mg/day (n=20)	Metformin 1.5g/day (n=20)	6 weeks	HDRS-17 15.1 (1.7)	-5.6 (2.1)	-1.3 (0.9)	<b>p&lt;0.001</b>	None	33 (71.7%)
<b>Incretin-based therapies</b>													
Mansur, 2017, Canada,	Open-label study	Drug-dependent diabetes excluded	19 (8) 38.2±7.8	All below-average cognitive performance	Liraglutide 1.8mg/day (n=19)	None	4 weeks	HDRS-17 12.6 (N/R)	-3.8 (5.5), p=0.022	N/A	N/A	Severe nausea	18 (39.1%)

**b) Studies not specifically selecting for depression at baseline**

<b>Metformin</b>													
Ackermann, 2009, USA	Double-blind RCT	Impaired glucose tolerance	2155 (698) 50.6±10.7	Nil	Metformin 1.7g/day (n=1073)	Placebo (n=1082)	52 weeks	BDI 4.6 (4.6)	-0.7 (4.0), p<0.001	-0.58 (4.5), p<0.001	N/R	Gastro-intestinal upset	36 (78.2%)
Jamilian, 2017, Iran	Double-blind RCT	No selection	60 (0) 28.1±4.1	Nil	Metformin 1.5g/day (n=30)	Myo-inositol 2g/day (n=30)	12 weeks	BDI 15.51 (4.6)	0.3 (0.7)	-1.0 (1.7)	<b>p=0.03</b>	Not reported	29 (63.0%)
Krysiak, 2017, Poland	Non-randomised, open-label study	T2D or prediabetes, HbA1c<9.5%	87 (0) 37.8±4.0	Nil	Metformin 1.7-3g/day (n=45)	Treatment as usual (n=42)	26 weeks	BDI-II 11.6 (3.3)	-1.2 (3.4)	+0.5 (3.35)	<b>p&lt;0.05</b>	None	22 (47.8%)
<b>Thiazolidenediones</b>													
Roohafza, 2014, Iran	Double-blind RCT	Non-diabetic metabolic syndrome	85 (35) 51.4±9.4	Nil	Pioglitazone 30mg/day (n=53)	Placebo (n=51)	24 weeks	HADS-D 5.8 (3.9)	-2.2 (3.3)	-1.5 (4.0)	<b>p=0.011</b>	None	28 (60.9%)

Simuni, 2015, USA	Double-blind RCT	Non-diabetes	210 (148) 59.7±9.9	All Parkinson's disease	Pioglitazone 15mg/day (n=72) or 45mg/day (n=67)	Placebo (n=71)	44 weeks	GDS-15 1.4 (1.6)	+0.3 (2.0)	+0.2 (2.3)	N/R	Weight gain	30 (65.2%)
<b>Insulin</b>													
Hendra, 2004, UK	Randomised 3-arm open label trial	T2D on oral therapy	57 (28) 69.9± 6.2	Nil	Insulin variable dose (n=38)	Continue tablets (n=19)	26 weeks	HADS 5.6 (3.4)	-0.9 (3.4)	+0.7 (3.5)	Non-significant	Weight gain	22 (47.8%)
<b>Incretin-based therapies</b>													
De Wit, 2014, Netherlands	Unblinded RCT	T2D on insulin	50 (31) 58±9.0	Nil	Liraglutide 1.8 mg/day (n=26)	Standard therapy (n=24)	26 weeks	BDI-II 9.5 (8.0)	-1 (2)	0 (1)	p=0.46	Nausea and vomiting	33 (71.7%)

**Significant effects are highlighted in bold (5%  $\alpha$ -level used).**

Key: BD, bipolar disorder; BDI, Beck Depression Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; HADS, hospital anxiety and depression scale; HDRS, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Symptomatology; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; N/R, not reported; OD once per day; PCOS, polycystic ovarian syndrome; PHQ-9, Patient Health Questionnaire-9; QIDS, Quick Inventory of Depressive Symptomatology; RCT, randomised controlled trial; SD, standard deviation; T2D, type 2 diabetes.

<sup>a</sup>Adverse effects presented where significantly more frequent in treatment group than controls, or for open-label studies where incidence is 10% or more.

**Table 2: Effects of treatments on glycaemia, insulin resistance and innate inflammation for included studies**

First author, year, country	Mean (SD) baseline fasting glucose (mg/dL) and HbA1c (%)	Mean (SD) change in fasting glucose (mg/dL) and HbA1c (%) for intervention vs controls, p-value	Mean (SD) baseline insulin resistance	Mean (SD) change in insulin resistance for intervention vs controls, p-value	Mean (SD) baseline hs-CRP (mg/L)	Mean (SD) change in hs-CRP (mg/L) for intervention vs controls, p-value	Correlation with depression
<b>a) Studies recruiting only patients with depression at baseline</b>							
<b>Biguanides</b>							
Guo, 2014, China	HbA1c 7.92 (0.7)	<b>HbA1c -1.52 (0.59) vs +0.19 (0.60), p&lt;0.001</b>	N/R	N/R	N/R	N/R	N/R
Lustman, 2018, USA	N/R	N/R	N/R	N/R	N/R	N/R	N/R
<b>Thiazolidenediones</b>							
Calabrese, 2017, USA	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Kemp, 2012, USA	FBG 98.85 (11.1)	<b>FBG -8.2 (13.3), p=0.01 (uncontrolled)</b>	Log-HOMA-IR 1.23 (0.62)	<b>Log-HOMA-IR -0.81 (0.75), p&lt;0.001</b>	Log-hs-CRP 1.99 (0.78)	<b>-0.87 (0.72), p&lt;0.001</b>	Reduction in HOMA-IR correlated with improvement in depression severity (r=0.46, p=0.048)
Kemp, 2014, USA	FBG 105.2 (24.5)	<b>FBG -7.7 (3.8), p=0.01 (uncontrolled)</b>	HOMA-IR 6.28 (3.67); ISI 1.90 (0.75)	<b>HOMA-IR -0.89 (4.83), p=0.27; ISI +0.98 (1.41), p&lt;0.001</b>	6.03 (6.68)	<b>-3.03 (2.14), p=0.01</b> and trend decrease in IL-6 (-0.42 (0.46), p=0.06)	<b>Significant correlation between change in IDS and change in IL-6 (r=0.44, p=0.01).</b>
Lin, 2015, USA	FBG 97.61 (11.53)	N/R	HOMA-IR 3.09 (1.78)	N/R	N/R	N/R	N/R
Rasgon, 2010, USA	FBG 101.2 (14.2)	N/R	Matsuda Index 2.37 (0.72)	+0.87 (0.96), p=0.053			
Sepanjnia, 2012, Iran	FBG 89.05 (12.03); HbA1c 5.65 (0.6)	N/R	HOMA-IR 1.43 (0.21)	N/R	N/R	N/R	N/R
<u>Zeinoddini</u> , 2015, Iran	FBG 88.0 (11.92)	FBG -1.7 (12.35) vs +0.4 (10.91), p=0.79; HbA1c +0.1 (0.6) vs +0.1 (0.652), p=0.58	N/R	N/R	N/R	N/R	N/R
<b>Metformin vs. Thiazolidenediones</b>							
Hu, 2015, China	FBG 166.86 (30.78); HbA1c 8.75 (1.60)	N/R	HOMA-IR 4.76 (no SD)	N/R	N/R	N/R	N/R

Kashani, 2012, Iran	FBG 100.57 (22.81)	FBG -4.3 (19.50) vs -4.5 (20.11), p=0.83	HOMA-IR 3.66 (0.95)	-0.16 (0.85) vs -0.14 (0.94), p=0.41	N/R	N/R	No correlation between HDRS change and HOMA-IR at end of the study (r=0.20, p=0.21)
<b>Incretin-based therapies</b>							
Mansur, 2017, Canada,	FBG 89.1 (9.0) HbA1c 5.28 (0.25)	<b>FBG -8.28 (8.1), p&lt;0.001</b>	HOMA2-IR 1.01 (0.53)	+0.11 (0.55), p=0.20	N/R	N/R	Non-significant correlations between change in HDRS and changes in glucose (r=0.096, p=0.72) and HOMA2-IR (r=0.11, p=0.69)
<b>b) Studies not specifically selecting for depression at baseline</b>							
<b>Biguanides</b>							
Ackermann, 2008, USA	FBG 106.5 (8.5); HbA1c 5.91 (0.5)	FBG -0.23 (0.65) vs +0.03 (0.65)	ISI 0.19 (0.13) HOMA-IR 7.0 (no SD)	Log ISI +0.11 ± 0.02 vs +0.041±0.02, p=0.51; HOMA-IR -1.2 vs +0.2 (no p-value)	3.34 (3.68)	<b>-0.35 (3.00) vs -0.12 (2.44), p&lt;0.05</b>	N/R
Krysiak, 2017, Poland	FBG 135.04 (12.58)	FBG -21.89 (no SD)	HOMA-IR 4.29 (1.24)	-2.23 (no SD)	N/R	N/R	N/R
Jamilian, 2017, Iran	N/R	N/R	N/R	N/R	N/R	N/R	N/R
<b>Thiazolidenediones</b>							
Roohafza, 2014, Iran	FBG 97.97 ± 12.92	FBG -0.19 (16.23) vs +1.02 (11.19), p=0.56	HOMA-IR 3.33 (1.39)	-1.02 (1.22) vs -0.24 (1.87) p=0.077	3.14 (2.03)	<b>-1.05 (1.61) vs +0.11 (1.34), p=0.04</b>	Change in HOMA-IR in pioglitazone group not correlated with change in HADS (??=0.14; p=0.15).
Simuni, 2015, USA	N/R	N/R	N/R	N/R	N/R	N/R	N/R
<b>Insulin</b>							
Hendra, 2004, UK	HbA1c 9.7 (1.7)	HbA1c -0.7 (1.5) vs -1.1 (1.6), no p-value	N/R	N/R	N/R	N/R	N/R
<b>Incretin-based therapies</b>							
De Wit, 2014, Netherlands	HbA1c 7.34 (0.7)	<b>HbA1c -0.77 (0.11) vs +0.01 (0.12), p&lt;0.001</b>	N/R	N/R	N/R	N/R	N/R

**Significant effects are highlighted in bold (5%  $\alpha$ -level used).**

FBG values are converted to mg/dL where reported in other units.

Key, N/R, not reported; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; HDRS, Hamilton Depression Rating Scale; HOMA-IR, Homeostasis Model of Insulin Resistance; IL-6, interleukin-6; ISI, Insulin Secretory Index; N/R, not reported.