Bipolar disorders, type 2 diabetes mellitus, and the brain

Tomas Hajek[a,b], *Roger McIntyre*[c], *and Martin Alda*[a,b]

Purpose of review
Type 2 diabetes mellitus (T2DM) negatively affects brain structure and function. Meta-analytical data show that relative to age and sex matched non-psychiatric controls, patients with bipolar disorders have double the risk of T2DM. We review the evidence for association between T2DM and adverse clinical and brain imaging changes in bipolar disorders and summarize studies investigating effects of diabetes treatment on psychiatric and brain outcomes.

Recent findings
Participants with bipolar disorders and T2DM or insulin resistance demonstrate greater morbidity, chronicity and disability, and lower treatment response to Li. Bipolar disorders complicated by insulin resistance/T2DM are associated with smaller hippocampal and cortical gray matter volumes and lower prefrontal N-acetyl aspartate (neuronal marker). Treatment of T2DM yields preservation of brain gray matter and insulin sensitizers, such as pioglitazone, improve symptoms of depression in unipolar or bipolar disorders.

Summary
T2DM or insulin resistance frequently cooccur with bipolar disorders and are associated with negative psychiatric clinical outcomes and compromised brain health. This is clinically concerning, as patients with bipolar disorders have an increased risk of metabolic syndrome and yet often receive suboptimal medical care. At the same time treatment of T2DM and insulin resistance has positive effects on psychiatric and brain outcomes. These findings create a rich agenda for future research, which could enhance psychiatric pharmacopeia and directly impact patient care.

Keywords
bipolar disorders, hippocampus, insulin resistance, lithium, pioglitazone, type 2 diabetes mellitus

INTRODUCTION

Neuroanatomical alterations have been replicated in bipolar disorders, but are not found in all studies. Meta-analyses of neuroimaging findings in bipolar disorders typically show nonsignificant pooled effect sizes in the presence of significant between group differences in some individual investigations [1]. This statistical heterogeneity suggests that changes in brain structure may not be related to the diagnosis of bipolar disorders as such, but may be secondary to the presence of certain clinical variables [2▪–4▪]. Yet, the specific clinical factors associated with these secondary changes remain unknown. One potential and understudied source of heterogeneity in psychiatric neuroimaging is the comorbidity with medical conditions known to affect the brain. Perhaps, certain neuroimaging alterations in bipolar disorders are associated with the presence of certain medical comorbidities. This could explain why neuroimaging changes are not found in all patients with bipolar disorders. In addition, studying comorbidities could identify preventable risk factors for brain changes in bipolar disorders, provide insight into mechanisms underlying these alterations, and yield new treatment targets. Type 2 diabetes mellitus (T2DM) is a medical condition that frequently cooccurs with bipolar disorders and is associated with brain abnormalities similar to those observed in bipolar disorders.

[a]Department of Psychiatry, Dalhousie University, Halifax, Canada, [b]National Institute of Mental Health, Klecany, Czech Republic and [c]Department of Psychiatry, University of Toronto, Toronto, Canada

Correspondence to Tomas Hajek, MD, PhD, Department of Psychiatry, Dalhousie University, QEII HSC, A.J. Lane Bldg., Room 3093, 5909 Veteran's Memorial Lane, Halifax, NS B3H 2E2, Canada. Tel: +902 473 8299; fax: +902 473 1583; e-mail: tomas.hajek@dal.ca

Curr Opin Psychiatry 2016, 29:1–6
DOI:10.1097/YCO.0000000000000215

KEY POINTS

- Patients with bipolar disorders and T2DM or insulin resistance show greater morbidity, lower treatment response, greater chronicity and disability, as well as lower hippocampal and cortical gray matter volumes.
- These negative clinical and brain outcomes are present in bipolar patients with insulin resistance to a similar extent as in those with fully developed T2DM.
- Treatment of diabetes or insulin resistance might alleviate some of these negative psychiatric and brain outcomes.

Diabetes mellitus and bipolar disorders

The largest available meta-analysis showed that bipolar patients had roughly double the risk of T2DM relative to nonpsychiatric controls of comparable age and sex (relative risk= 1.98; 95% CI, 1.6–2.4) [5▪▪]. The overall risk is likely to be even higher, as T2DM remains markedly under diagnosed in bipolar disorders [6,7▪]. A recent cross sectional study among 121 adults with bipolar disorders found that 13% of participants self-reported a personal history of T2DM. After systematic testing, this number increased to 21%, indicating that in 40% of cases, psychiatrists were the first to make the diagnosis of T2DM [8▪]. Moreover, an additional 32.2% of subjects suffered from prediabetes (insulin resistance or glucose intolerance) and none of the participants knew about these conditions. Taken together, upon systematic assessment, 40% of all patients in this sample had previously unidentified metabolic disturbance [8▪]. These findings are concerning and clinically relevant.

Pathoplastic effects of type 2 diabetes mellitus on bipolar disorders

High rates of T2DM in bipolar disorders may contribute to the disproportionately high cardiovascular mortality reported in bipolar disorders [9▪,10▪] and to the fact that bipolar disorders is considered a tier II moderate risk condition for cardiovascular disease even among youth [11▪]. Interestingly, the presence of T2DM or insulin resistance affects not only somatic but also psychiatric outcomes. Bipolar disorders complicated by T2DM is associated with greater morbidity, lower treatment response, and poorer outcome with greater chronicity and disability [8▪,12,13]. In a recent cross sectional study, whereas most patients with excellent Li response were euglycaemic, most of the subjects with T2DM showed poor or no response to Li. Importantly, already insulin resistance was associated with these adverse clinical outcomes. The proportion of Li responders in euglycaemic participants was significantly higher than among patients with insulin resistance, who had comparably low rates of response to Li as participants with manifest T2DM [8▪]. Participants with insulin resistance typically show a combination of normal fasting plasma glucose and disproportionately elevated insulin level. Therefore, the standard clinical measures, which rely only on fasting glucose, would not detect this important correlate of poor response.

Is it possible, that these pathoplastic effects of T2DM or insulin resistance on psychiatric outcomes are related to the negative effects of impaired glucose metabolism on the brain? This is a viable hypothesis, as brain is one of the targets for diabetic end-organ damage [14,15].

Diabetes and the brain

Participants with T2DM typically show smaller hippocampal and frontal lobe volumes relative to euglycaemic subjects. In keeping with these structural alterations, patients with T2DM often suffer from impairments in verbal memory or executive functions [14,15,16▪,17▪], which show a replicated significant, albeit weak association with measures of glucose metabolism or insulin resistance [18▪]. Similarly, hyperglycaemia and insulin resistance even without clinically diagnosed T2DM have been related to poorer cognitive and brain measures, particularly memory impairment and hippocampal atrophy [16▪,19,20,21▪].

These changes resemble the most frequently reported brain imaging and cognitive impairments in bipolar disorders. They may also explain why T2DM is a risk factor for mild cognitive impairment or dementia [22▪,23▪]. Studying the effects of insulin resistance/T2DM on brain structure and cognitive functions may provide insight into molecular mechanisms, which contribute to these brain structural and functional impairments.

Why does type 2 diabetes mellitus damage the brain?

Some of the negative effects of T2DM may be mediated by macrovascular/microvascular disease. However, studies have shown that measures of glucose or insulin are a better predictor of brain and cognitive changes in patients with T2DM than vascular risk factors and the negative association between T2DM/insulin resistance and brain structure occurs already in the absence of cerebrovascular diseases [16▪,19,24▪,25]. It is generally thought that neuronal

damage/loss seen in T2DM is mediated principally by mechanisms other than hemodynamic causes, such as withdrawal of trophic factors, inhibition of insulin-responsive gene expression, neuroinflammation, and impaired mitochondrial energy metabolism, which causes oxidative stress through increased production of reactive oxygen species [6,26]. The combination of these factors may lead to pathological and clinical signs of Alzheimer's dementia, which has been termed diabetes of the brain or type 3 diabetes.

Impaired energy metabolism/oxidative stress are particularly damaging to neurons, which have limited energy storage and a limited capacity to counter oxidative damage. In keeping with this, oxidative stress with resulting lipid peroxidation and nitrosative damage plays an important role in diabetes-related neuronal injury [26,27▪] and contributes to the overlap between T2DM and neurodegenerative disorders [26]. Although T2DM is the prototypical disorder of impaired mitochondrial energy metabolism/oxidative stress, similar mechanisms may play a role in the pathophysiology of bipolar disorders. Patients with bipolar disorders show evidence of oxidative stress, including increased lipid peroxidation and nitrosative damage [28▪▪], and these measures negatively correlate with structural brain changes [29▪▪]. Considering all these overlaps, it is logical to ask whether T2DM or insulin resistance could be modifiable risk factors for brain changes in bipolar disorders.

Type 2 diabetes mellitus, brain, and bipolar disorders

The first evidence for association between metabolic alterations and brain structure in bipolar disorders came from a recent study [30,31▪▪]. In a sample of participants shortly after the first episode of mania, Bond *et al.* showed that increased BMI was associated with decreased white matter and temporal lobe volumes. Consequently, obese/overweight participants with bipolar disorders had smaller white matter and temporal lobe volume than normal weight patients [30]. Subsequently the authors performed exploratory voxel-based analyses, which demonstrated that elevated BMI in patients was significantly associated with reduced gray matter volume in the right superior, middle, and inferior temporal gyri and uncus and with reduced white matter in the right frontal and temporal lobes and subcortical white matter [31▪▪]. It is of note that these weight-related volume reductions were detectable in people with only modestly elevated BMI and overlapped with regions frequently associated with bipolar disorders.

To further investigate the association between metabolic factors and brain structure in bipolar disorders, we systematically measured glucose and insulin levels and obtained brain scans in bipolar participants and controls [2▪,4▪]. In keeping with our a-priori hypotheses, participants with bipolar disorders and impaired glucose metabolism (insulin resistance, glucose intolerance, or T2DM) showed lower N-acetyl aspartate (NAA), creatine levels and smaller hippocampal, cortical gray matter volumes than euglycaemic subjects with bipolar disorders, who had comparable NAA, creatine levels, and hippocampal, cortical gray matter volumes to euglycaemic, nonpsychiatric controls. Similar to the clinical data, these adverse effects were seen already in participants with insulin resistance. Although we found the largest changes among the diabetic participants, even subjects with insulin resistance/glucose intolerance showed lower NAA, creatine levels and smaller hippocampal volumes than euglycaeimc controls. These neuroimaging alterations were associated with impaired psychosocial functioning, which was lower among dysglycaemic relative to euglycaemic participants. The changes remained essentially unchanged, when we controlled for BMI.

Our results extend the findings of Bond *et al.* [30,31▪▪], to show that impaired glucose metabolism in bipolar disorders may contribute to the brain changes observed in overweight subjects. The concomitant decrease in levels of NAA, which is synthesized in mitochondria and creatine, one of the main energy metabolites and markers of cellular energy status, suggests that the observed changes may indicate impaired mitochondrial energy metabolism in neurons. This is supported by the fact, that we found alterations already at the level of insulin resistance, when patients displayed a combination of euglycaemia and disproportionately elevated insulin levels. Consequently, hyperglycaemia-related effects, such as elevation in advanced glycation end products or microangiopathy, may not be necessary for these brain changes to occur. If T2DM or insulin resistance are associated with brain changes, does treatment of the metabolic disorder alleviate some of these brain alterations?

Effects of diabetes treatments on brain outcomes

Observational evidence suggests that although T2DM is a strong risk factor for development of dementia, treatment of T2DM may decrease this risk [32]. Diabetes may even be among the largest potentially modifiable risk factors for dementia [23▪]. These conclusions from observational studies are in part supported by intervention studies.

The Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes trial, which is by far the largest intervention study on brain changes in diabetes mellitus ($N = 503$), showed that intensive glycaemic lowering treatment over 40 months yielded a significant, but small preservation of total brain volume relative to regular glycaemic control. The preservation of gray matter predominantly happened around the Sylvian fissure as well in the medial–frontal cortex. The regions that showed longitudinal alterations were mostly adjacent to regions displaying significant cross-sectional relationship with diabetes duration. Based on these observations the authors concluded that intensive glycaemic control slowed the spatial spreading of the T2DM-related cortical changes [33▪▪,34]. However, there was no benefit of the intensive treatment on cognitive functioning and this approach was in fact associated with increased mortality and no overall benefit on cardiovascular disease events [34].

Perhaps the lack of effects of diabetes treatment on cognition could be related to short follow-up. Perhaps the cognitive outcome measures may not have been sensitive enough to diabetes-related changes. Also, treatment emergent issues, such as hypoglycaemia might have compromised any benefits of the intensive glucose lowering regimen on cognition. Most importantly, as elderly patients with long standing diabetes were recruited, the interventions might have occurred too late, after a pathway of irreversible neuronal/cognitive damage had started [34]. Late-life treatment of chronic disease may be less effective than preventive strategies aimed at younger individuals or those earlier in the course of the illness. Therefore, intervening earlier, focusing primarily on insulin resistance, or selecting more sensitive brain outcomes, such as depressive symptoms, might have yielded different results.

Effects of diabetes treatment on psychiatric outcomes

There is a growing pharmacopeia of treatments targeting insulin resistance, so called insulin sensitizers. The synthetic peroxisome proliferator-activated receptor gamma agonists, the thiazolidinediones, such as pioglitazone, are particularly interesting. Pioglitazone shows not only insulin-sensitizing properties, but is also antiapoptotic and antiinflammatory [35▪]. Several recent trials have shown that treatment with insulin sensitizers was effective in alleviating depressive symptoms, which we consider a particularly sensitive brain outcome.

Two proof of concept studies demonstrated that 8–12 weeks of treatment with pioglitazone in patients with unipolar or bipolar depression and metabolic syndrome reduced depressive symptoms across both clinician and patient-rated assessments. Additionally, pioglitazone was associated with improvement in inflammation, fasting glucose, triglycerides, and total body insulin resistance [35▪,36].

Two double blind, placebo controlled trials showed greater reductions of depressive symptoms when pioglitazone was added to citalopram in unipolar or to Li in bipolar depression. These improvements started already at week 2 of treatment and were present even among patients without metabolic syndrome [37,38▪▪].

These recent studies add to the emerging body of evidence showing that treatments targeting glucose regulation, such as insulin, metformin, and glucagon-like peptide-1 agonists (liraglutide, exenatide) have positive effects on brain-related outcomes [39▪].

T2DM, brain and bipolar disorders – implications

Taken together, these studies strongly suggest that metabolic alterations, including obesity, insulin resistance or T2DM are associated with adverse psychiatric outcomes and brain structural alterations in bipolar disorders. This is clinically concerning, as patients with bipolar disorders have an increased risk of metabolic syndrome and yet often receive suboptimal medical care. At the same time these metabolic alterations are preventable and even treatable. Simply improving the screening for and treatment of insulin resistance/T2DM in bipolar disorders could minimize the neuroprogressive changes in these patients. Increasing the awareness of the adverse effects of T2DM on clinical and neuroimaging outcomes in bipolar disorders could help bridge the translation gap and improve the unfortunately low standard of diabetes care among psychiatric patients.

After more than 50 years of modulating mono amines, the study of metabolic comorbidities might provide new molecular targets for treatment of mood disorders. Targets, which unlike most other treatments in psychiatry would emerge from research, not serendipity. In other fields of medicine, such as oncology, new molecular targets have led to marked advancements, the likes of which have not been achieved in psychiatry. It would be particularly important to test whether insulin sensitizer could alleviate brain changes in bipolar disorders. This would allow us to expand the fairly limited psychiatric pharmacopoeia, as well as focus the treatment of bipolar disorders on biological outcome measures rather than just behavioural symptoms.

These studies also suggest a potential blind spot in clinical practice. The adverse clinical and brain outcomes were associated with insulin resistance, which is currently not monitored for. However, as association does not imply causation, we need prospective studies to test the direction of the association between insulin resistance and clinical outcomes.

Last but not least, advancing our knowledge about the effects of insulin resistance/T2DM on brains of our patients could allow for a more rational, personalized treatment approach and might help bring neuroimaging research from bench to the bedside. Treatment of insulin resistance/T2DM might also prove beneficial for the impaired cognitive and psychosocial functioning, which were associated with the brain alterations.

The negative association between insulin resistance or T2DM and brain structure/function and the disproportionate rates of insulin resistance and T2DM in bipolar disorders have implications for interpretation of neuroimaging studies. Without adequate screening for these conditions, it is impossible to ascertain whether neuroimaging findings are related to the presence of bipolar disorders or whether they are confounded by higher rates of insulin resistance or T2DM among patients with bipolar disorders. Even in research of cognitive ageing, less than 10% of studies excluded subjects with T2DM and only 12% of studies screened for T2DM using laboratory testing [40▪].

CONCLUSION

There is replicated and meta-analytical evidence that T2DM and especially insulin resistance are very frequent in bipolar disorders. The comorbidity with dysglycaemia is associated with negative clinical outcomes, poor response to Li as well as compromised brain health. At the same time these metabolic disorders are under diagnosed and poorly treated in bipolar disorders. Preclinical research has identified a number of mechanisms through which insulin dysregulation damages the brain. Some of these could prove fruitful targets for treatment of certain dimensions of psychiatric morbidity. Indeed, seminal treatment studies have shown that strict glycaemic control has positive effect on brain health and insulin sensitizers treat depressive symptoms. These findings create a rich agenda for future research, which could enhance psychiatric pharmacopeia and have direct clinical implications for our patients.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by NARSAD Independent Investigator Award to Dr Hajek and by funding from the Canadian Institutes of Health Research grant (341717).

Dr McIntyre is a consultant/speaker/received research grant support from Johnson & Johnson, Astra-Zeneca, Eli-Lilly, Purdue, Shire, Allergan, Lundbeck, Pfizer.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Kempton MJ, Geddes JR, Ettinger U, *et al.* Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry 2008; 65:1017–1032.
2. ▪ Hajek T, Calkin C, Blagdon R, *et al.* Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. Neuropsychopharmacology 2014; 39:2910–2918.

The first study to demonstrate association between T2DM or insulin resistance and structural brain changes in bipolar disorders.

3. ▪ Hajek T, Bauer M, Simhandl C, *et al.* Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med 2014; 44:507–517.

The study systematically investigated the interplay between exposure to Li, treatment response, and brain structure.

4. ▪ Hajek T, Calkin C, Blagdon R, *et al.* Type 2 diabetes mellitus: a potentially modifiable risk factor for neurochemical brain changes in bipolar disorders. Biol Psychiatry 2015; 77:295–303.

The first study to demonstrate association between T2DM or insulin resistance and neurochemical brain changes in bipolar disorders.

5. ▪▪ Vancampfort D, Mitchell AJ, De Hert M, *et al.* Prevalence and predictors of type 2 diabetes mellitus in people with bipolar disorder: a systematic review and meta-analysis. J Clin Psychiatry 2015. [Epub ahead of print]

The largest meta-analysis (19 studies and 18 060 participants), showing that bipolar patients had roughly double the risk of diabetes compared with nonpsychiatric controls of comparable age and sex.

6. Calkin CV, Gardner DM, Ransom T, Alda M. The relationship between bipolar disorder and type 2 diabetes: more than just co-morbid disorders. Ann Med 2013; 45:171–181.
7. ▪ McGinty EE, Baller J, Azrin ST, *et al.* Quality of medical care for persons with serious mental illness: a comprehensive review. Schizophr Res 2015; 165:227–235.

The study documents the disparity in medical care for some populations of patients with serious mental illness and reviews the factors associated with variation in medical care.

8. ▪ Calkin CV, Ruzickova M, Uher R, *et al.* Insulin resistance and outcome in bipolar disorder. Br J Psychiatry 2015; 206:52–57.

The study showed a negative association between T2DM or insulin resistance and response to Li and suggests that insulin resistance is an important prognostic factor for adverse clinical outcomes in bipolar disorders.

9. ▪ Hayes JF, Miles J, Walters K, *et al.* A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand 2015; 131:417–425.

The study demonstrates the strength and robustness of the evidence for elevated mortality in bipolar disorders.

10. ▪ Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. J Affect Disord 2015; 180:142–147.

A population study among 5.4 million people showing that bipolar disorders is associated with lower life expectancy and that natural causes of death are the main reason for lost life years.

11. ▪ Goldstein BI, Carnethon MR, Matthews KA, *et al.* Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2015; 132:965–986.

A position paper demonstrating that bipolar disorder among youth meets criteria for Expert Panel tier II moderate-risk condition for cardiovascular morbidity.

12. Hajek T, Slaney C, Garnham J, *et al.* Clinical correlates of current level of functioning in primary care-treated bipolar patients. Bipolar Disord 2005; 7:286–291.
13. Kemp DE, Gao K, Chan PK, *et al.* Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord 2010; 12:404–413.
14. Jones N, Riby LM, Mitchell RL, Smith MA. Type 2 diabetes and memory: using neuroimaging to understand the mechanisms. Curr Diabetes Rev 2014; 10:118–123.
15. Lee JH, Choi Y, Jun C, *et al.* Neurocognitive changes and their neural correlates in patients with type 2 diabetes mellitus. Endocrinol Metab (Seoul) 2014; 29:112–121.
16. ■ Weinstein G, Maillard P, Himali JJ, *et al.* Glucose indices are associated with cognitive and structural brain measures in young adults. Neurology 2015; 84:2329–2337.

The negative association between diabetes and brain structure/cognitive functioning occurs already in young adults and middle-aged persons.

17. ■ Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? Diabetes 2014; 63:2244–2252.

One of the few comprehensive reviews of interplay between neuroimaging and cognitive changes in patients with T2DM.

18. ■ Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol 2015; 3:75–89.

Unlike other reviews, this study focuses not on differences between patients with and without diabetes, but rather on association between measures of glycaemia and cognitive outcomes.

19. Willette AA, Xu G, Johnson SC, *et al.* Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. Diabetes Care 2013; 36:443–449.
20. Kerti L, Witte AV, Winkler A, *et al.* Higher glucose levels associated with lower memory and reduced hippocampal microstructure. Neurology 2013; 81:1746–1752.
21. ■ Frazier DT, Bettcher BM, Dutt S, *et al.* Relationship between insulin-resistance processing speed and specific executive function profiles in neurologically intact older adults. J Int Neuropsychol Soc 2015; 21:1–8.

Insulin resistance is associated with cognitive functioning in neurologically intact participants even after controlling for vascular risk factors, adiposity, and cerebrovascular injury.

22. ■ Huang CC, Chung CM, Leu HB, *et al.* Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. PLoS One 2014; 9:e87095.

This large, population study demonstrates an association between T2DM and future development of Alzheimer disease, especially in patients with longer duration of T2DM.

23. ■ Cooper A, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. Am J Psychiatry 2015; 172:323–334.

The largest meta-analysis demonstrating that diabetes or prediabetes are among the strongest risk factors for conversion from mild cognitive impairment to dementia.

24. ■ Friedman JI, Tang CY, de Haas HJ, *et al.* Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. JACC Cardiovasc Imaging 2014; 7:1039–1053.

The review shows that diabetes is associated with brain imaging changes even in the absence of cardio or cerebrovascular end-organ damage.

25. van Elderen SG, de Roos A, de Craen AJ, *et al.* Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up. Neurology 2010; 75:997–1002.
26. Rosales-Corral S, Tan DX, Manchester L, Reiter RJ. Diabetes and Alzheimer disease, two overlapping pathologies with the same background: oxidative stress. Oxid Med Cell Longev 2015; 2015:985845.
27. ■ Rodriguez-Carrizalez AD, Castellanos-Gonzalez JA, Martinez-Romero EC, *et al.* Oxidants antioxidants and mitochondrial function in nonproliferative diabetic retinopathy. J Diabetes 2014; 6:167–175.

The study demonstrates an association between peripheral markers of oxidative stress and mitochondrial dysfunction and damage of the central nervous system neurons (retinopathy).

28. ■■ Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res 2014; 218:61–68.

The meta-analysis suggests that oxidative stress may play an important role in pathophysiology of bipolar disorders.

29. ■■ Versace A, Andreazza AC, Young LT, *et al.* Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry 2014; 19:200–208.

The first study to demonstrate an association between peripheral markers of oxidative stress and brain white matter structure.

30. Bond DJ, Lang DJ, Noronha MM, *et al.* The association of elevated body mass index with reduced brain volumes in first-episode mania. Biol Psychiatry 2011; 70:381–387.
31. ■■ Bond DJ, Ha TH, Lang DJ, *et al.* Body mass index-related regional gray and white matter volume reductions in first-episode mania patients. Biol Psychiatry 2014; 76:138–145.

One of the first studies to demonstrate association between obesity and structural brain changes in bipolar disorders.

32. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J Alzheimers Dis 2011; 24:485–493.
33. ■■ Erus G, Battapady H, Zhang T, *et al.* Spatial patterns of structural brain changes in type 2 diabetic patients and their longitudinal progression with intensive control of blood glucose. Diabetes Care 2015; 38:97–104.

The largest prospective study investigating the effects of diabetes treatment on brain structure.

34. Strachan MW, Price JF. Diabetes. Cognitive decline and T2DM: a disconnect in the evidence? Nat Rev Endocrinol 2014; 10:258–260.
35. ■ Kemp DE, Schinagle M, Gao K, *et al.* PPAR-gamma agonism as a modulator of mood: proof-of-concept for pioglitazone in bipolar depression. CNS Drugs 2014; 28:571–581.

The proof of concept study suggested that insulin sensitizers may treat psychiatric symptoms.

36. Kemp DE, Ismail-Beigi F, Ganocy SJ, *et al.* Use of insulin sensitizers for the treatment of major depressive disorder: a pilot study of pioglitazone for major depression accompanied by abdominal obesity. J Affect Disord 2012; 136:1164–1173.
37. Sepanjnia K, Modabbernia A, Ashrafi M, *et al.* Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. Neuropsychopharmacology 2012; 37:2093–2100.
38. ■■ Zeinoddini A, Sorayani M, Hassanzadeh E, *et al.* Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. Depress Anxiety 2015; 32:167–173.

The double blind, randomized study provides strong evidence for beneficial effects of pioglitazone in treatment of bipolar depression.

39. ■ Kim B, Feldman EL. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. Exp Mol Med 2015; 47:e149.

Among the many factors associated with metabolic syndrome, insulin resistance appears to be particularly relevant for cognitive decline.

40. ■ Meusel LA, Kansal N, Tchistiakova E, *et al.* A systematic review of type 2 diabetes mellitus and hypertension in imaging studies of cognitive aging: time to establish new norms. Front Aging Neurosci 2014; 6:148.

Without adequate screening, inclusion of individuals with T2DM may confound neuroimaging studies. Less than 10% of brain imaging studies excluded subjects with T2DM and only 12% of studies screened for T2DM using laboratory testing.