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# Association of insulin resistance with depression: cross sectional findings from the British women's heart and health study

Debbie A Lawlor, George Davey Smith, Shah Ebrahim

A large cohort study of nearly 15 000 individuals found that indicators of insulin sensitivity were associated with increased risk of suicide.<sup>1</sup> The authors assumed that insulin resistance was the key factor responsible. Insulin resistance is a determinant of free fatty acids in the blood, which are in turn important in tryptophan metabolism and brain serotonin concentrations.<sup>2,3</sup> Individuals who are insulin resistant may therefore have higher serotonin concentrations and as a result be less likely to be depressed.<sup>1</sup> We know of no previous study that has assessed the association between insulin resistance and depression in humans.

## Participants, methods and results

We assessed this association in a cross sectional analysis of 4286 women aged 60-79 who were randomly selected from general practitioners' lists in 23 British towns.<sup>4</sup> We used the homoeostasis model assessment method (HOMA score), derived from fasting insulin and glucose concentrations to assess insulin resistance.<sup>4</sup> We used three indicators of depression: current use of antidepressant medication, self report of ever having received a diagnosis of depression from a doctor, and the EQ5D mood question of the EuroQOL.<sup>5</sup> Participants brought all of their medications to an interview with a nurse. We used the *British National Formulary* ([www.bnf.org/](http://www.bnf.org/)) to code medications; "antidepressants" included any medication in section 4.3. Participants whose response to the EQ5D mood question was that they were "today feeling either moderately or extremely anxious and/or depressed" were coded as currently anxious or depressed.

We categorised women without diabetes into quarters of HOMA score and added a fifth category of women with diabetes. We estimated proportions of women with depression for each of these HOMA score and diabetes categories. We used multiple logistic regression to assess the effect of insulin resistance on depression, with adjustment for potential confounding factors. In all analyses we used robust standard errors, allowing for potential clustering between women from the same town, to calculate confidence intervals and P values.

The prevalence of depression decreased linearly with increasing insulin resistance among women without diabetes and then increased among women with diabetes (figure). The age adjusted odds ratio (95% confidence interval) of current antidepressant use per increase in one category (quarters of the distribution) of HOMA score among non-diabetic women was 0.86 (0.76 to 0.96,  $P=0.01$ ). Similar results for ever being diagnosed with depression and reporting feeling anxious or depressed were 0.84 (0.74 to 0.97,  $P=0.006$ ) and 0.89 (0.79 to 0.99,  $P=0.04$ ). None of these associations was altered by further adjustment for waist:hip ratio, body mass index, smoking, alcohol

consumption, physical activity, and social class during adulthood and childhood.

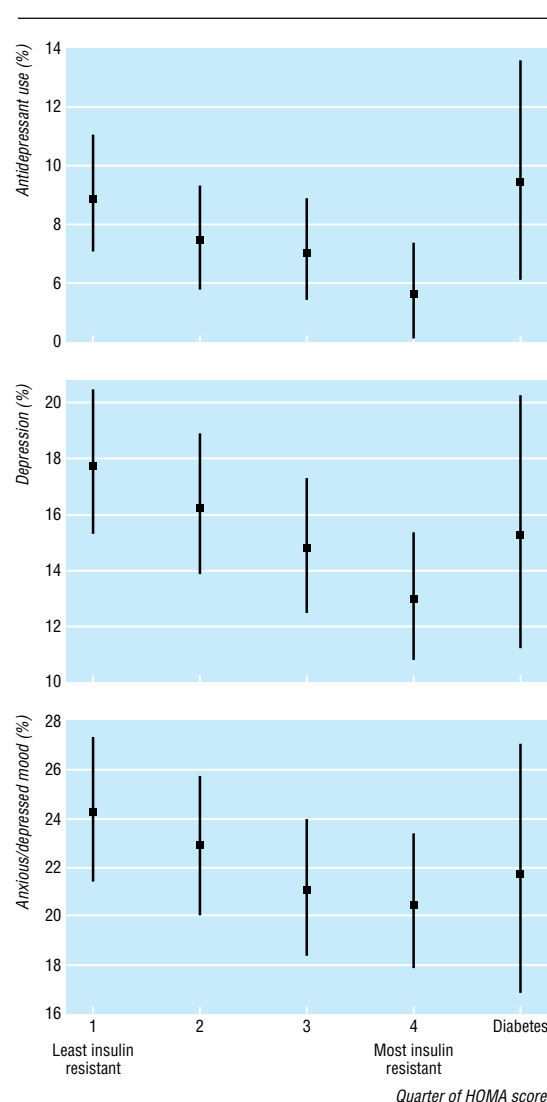
## Comment

Insulin resistance is inversely associated with depression. Our results are consistent with a large prospective

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(a) Prevalence % (95% confidence interval) of use of antidepressant medication against quarters of HOMA score (insulin resistance) and diabetes among British women aged 60-79. (b) Prevalence % (95% confidence interval) of a self report of ever being diagnosed by a doctor with depression against quarters of HOMA score (insulin resistance) and diabetes among British women aged 60-79. (c) Prevalence % (95% confidence interval) of a self report of feeling depressed or anxious against quarters of HOMA score (insulin resistance) and diabetes among British women aged 60-79

study in which indicators of insulin sensitivity were associated with suicide risk.<sup>1</sup> The explanation for the reverse J shaped association seen when diabetes was included as a fifth category alongside insulin resistance may be due to patients with a clinical diagnosis of diabetes developing depression as a result of this diagnosis.

We based our assessment of depression on current use of medication and self reports of past diagnoses and current mood rather than clinical assessment with international diagnostic criteria. However, the consistency of our findings across the three different assessments supports a causal association, and any measurement error in our assessment of depression would tend to dilute the results. Insulin resistance is positively associated with diabetes and cardiovascular disease, and we do not believe that our results should be used to discourage appropriate interventions to prevent and treat insulin resistance. Further, these are novel findings and need to be replicated in other studies. However, if our findings are confirmed there may be an indication for assessing depressive symptoms among individuals receiving treatments that affect insulin resistance, since depressive symptoms are often disabling and could affect compliance with treatment and quality of life.

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Ethical approval: Ethics committee approvals were obtained for the British Women's Heart and Health Study.

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## Drug points

### Pulmonary embolism possibly associated with olanzapine treatment

Inger Marie Waage, Ane Gedde-Dahl

Antipsychotic drugs have been associated with an increased risk of venous thromboembolism.<sup>1</sup> We report for the first time the case of a patient who developed a pulmonary embolism after starting treatment with olanzapine.

A 28 year old man was admitted to hospital due to a psychotic disorder. Treatment with olanzapine (10 mg/day) was started, and the dose was gradually increased to 30 mg/day. He also received levomepromazine (50 mg/day), oxazepam (10 mg/day), and flunitrazepam (1 mg/day). After 10 weeks, the patient complained of respiratory pain and he had two episodes of haemoptysis. Clinical examination showed no auscultatory findings, no dyspnoea, no tachypnoea, no fever, and normal blood pressure and heart rate. Blood analysis showed raised concentrations of C reactive protein (113 mg/l (normal range <10 mg/l)), fibrinogen (6 g/l (2-4 g/l)), and D-dimer (0.89 mg/l (<0.50 mg/l)). Spiral computed tomography showed a pulmonary embolism in the left lower lobe. Standard anticoagulant treatment was started, and the patient recovered. Olanzapine was discontinued, and his medication changed to quetiapine.

Recent reports suggest an association between clozapine and venous thromboembolic events.<sup>2-5</sup> However, thromboembolic complications have not previously been described in patients taking olanzapine. The sedating effects as well as the weight gain associated with this antipsychotic treatment can lead to a more sedentary lifestyle,

thus creating predisposing conditions for venous thrombosis. In this case, the patient was overweight (body mass index 28.5), but his weight had not substantially changed since starting to take olanzapine. He was otherwise healthy, and his level of physical activity was normal. Tests for possible coagulation disorders—including tests for antiphospholipid antibodies (immunoglobulin lupus anticoagulants and anticardiolipin antibodies), mutation of the methylenetetrahydrofolate reductase C677T thermolabile variant, prothrombin G20210A mutation, activated protein C resistance, protein C, protein S, antithrombin III, and homocysteine—did not show any underlying risk factors. This leaves the question of the medication's possible direct causal effect.

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