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Insulin resistance and depressive symptoms in middle aged men: findings from the Caerphilly prospective cohort study

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Insulin resistance may protect against depression, possibly through an effect on circulating free fatty acid concentrations and brain serotonin concentration,[1 2] although a recent study contradicted these findings.[3] Studies to date have either used indirect measures of insulin resistance,[1] or they have been cross sectional.[2 3] We assessed the association of insulin resistance with depressive symptoms in a prospective cohort.

Participants, methods, and results

The Caerphilly cohort study has been described in detail before.[4] In phase I (1979-83), 2512 (89% of eligible) men aged 45-59 years from Caerphilly in Wales provided fasting blood samples. Insulin resistance (homoeostasis model assessment (HOMA) score) was derived from fasting insulin and glucose.[5] HOMA scores were not calculated for men with diabetes or high fasting glucose (≥ 7.0 mmol/l).

In phases II (1984-88), III (1989-93), and IV (1993-7), depressive symptoms were measured by the 30 item general household questionnaire (GHQ). This was validated at phase II in a subgroup (n=97) by comparison with a clinical interview schedule given by a psychiatrist blinded to the GHQ score.[4] Based on receiver operating characteristics, we defined men scoring five or above as having mild to moderate psychological distress.[4]

At phase I, 2203 (88%) of the men had assessment of insulin resistance or diabetes status. Of the surviving men, the numbers with GHQ data at phases II, III, and IV were 1619/2025 (80%), 1236/1845 (67%), and 1088/1675 (65%).

Insulin resistance and high GHQ score were not associated at any phase of follow up (table). Diabetes at baseline was associated with a tendency to reduced odds of high GHQ at follow up, but, owing to small numbers, these estimates are imprecise. Additional adjustment for smoking, physical activity, alcohol consumption, and adult and childhood social class did not substantively alter any of the findings.

Insulin resistance and GHQ scores were not associated in linear regression models with GHQ as a continuous outcome (all P values >0.2). When fasting insulin was used there was no evidence of an association with GHQ. In cross sectional analyses (exposures and outcomes measured at phase II) there was no association between any HOMA scores, fasting insulin, or diabetes and GHQ score. We also found no associations between body mass index, systolic blood pressure, high density lipoprotein cholesterol, or (logged) triglyceride concentration and GHQ in either prospective or cross sectional analyses (all P values >0.3).

Comment

Insulin resistance was not associated with reduced depressive symptoms in a prospective study of middle aged men. This contradicts our earlier findings in a cross sectional study of older women, in which there was an inverse association with both clinically diagnosed depression and use of antidepressant drugs,[2] and the findings of a second cross sectional study which found a positive association between insulin resistance and depression assessed using the Beck's depression inventory.[3] These contradictory findings may be due to the cross sectional nature of the earlier studies. A large prospective study, in which reverse causality would be unlikely, found that indicators of insulin sensitivity were associated with suicide risk.[1] Taken together these findings indicate that insulin resistance may protect against only severe depression.

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Insulin resistance and diabetes at baseline (1979-83) and GHQ score (indicative of depressive symptoms) at different phases of follow up in middle aged men in the Caerphilly prospective cohort study

	Phase of follow up			High GHQ* at all three follow up phases
	II	III	IV	
Median no of years from baseline	5	10	14	14
No with GHQ data	1619	1236	1088	944
No with high GHQ	362	289	271	63
Age and time of blood sampling adjusted prevalence of high GHQ score by insulin resistance or diabetes (% (95% CI)):				
Lowest fourth HOMA	22.9 (19.1 to 27.2)	21.7 (17.4 to 26.7)	24.1 (19.5 to 29.4)	7.9 (5.1 to 12.0)
2nd fourth HOMA	21.4 (17.7 to 25.7)	22.2 (18.0 to 27.2)	21.6 (17.0 to 27.0)	4.3 (2.4 to 7.6)
3rd fourth HOMA	24.6 (20.6 to 29.1)	23.7 (19.2 to 28.9)	27.0 (21.9 to 32.7)	6.7 (4.1 to 10.7)
Highest fourth HOMA	20.5 (16.7 to 25.0)	26.9 (22.1 to 32.4)	28.8 (23.4 to 34.9)	7.3 (4.4 to 11.9)
Diabetes or high fasting glucose	19.5 (11.1 to 31.9)	16.3 (7.5 to 31.8)	12.3 (4.7 to 28.5)	4.0 (0.6 to 2.3)
Age and time of sampling adjusted odds ratio (95% CI) per increase of one quarter HOMA distribution†	0.97 (0.87 to 1.08)	1.09 (0.96 to 1.22)	1.09 (0.96 to 1.23)	0.97 (0.77 to 1.23)
Age and time of sampling adjusted odds ratio (95% CI) comparing those with diabetes or high glucose to those without‡	0.64 (0.30 to 1.38)	0.62 (0.25 to 1.50)	0.40 (0.14 to 1.18)	0.59 (0.08 to 4.39)
Age and time of sampling adjusted odds ratio (95% CI) comparing those with clinical diagnosis of diabetes to those without§	0.84 (0.61 to 1.14)	1.02 (0.83 to 1.22)	0.88 (0.68 to 1.14)	0.61 (0.16 to 2.38)

GHQ=general household questionnaire; HOMA=homoeostasis model assessment

*To calculate adjusted prevalence of high GHQ scores we used logistic regression models with the covariates age and time of blood sampling included as continuous variables centred around their mean values (that is, age in years minus mean age in years for the sample and time of sampling in 10 minute intervals minus mean time for the sample. Blood samples were taken between 8 am and 7 pm).

†Odds ratio of high GHQ per increase in one fourth of HOMA distribution among only those with no evidence (diagnosis or high fasting glucose ≥7.0 mmol/l) of diabetes.

‡Odds ratio comparing those with either a clinical diagnosis of diabetes or high fasting glucose (≥7.0 mmol/l) with all others.

§Odds ratio comparing those with a clinical diagnosis of diabetes with all others (irrespective of fasting glucose level).

Our assessment of depression was based on GHQ rather than clinical assessment, and if insulin resistance is only protective against severe depression then this measure may be inadequate to detect an association. Also, any measurement error in our assessment of depression would tend to dilute the results. We validated the score, however, against a clinical interview in a subgroup.[4]

The contradictory results concerning the association of insulin resistance with depression and suicide warrant further research. Future studies might include trials of the effects on insulin resistance of treating depression. Observational studies should ideally use standardised diagnostic criteria for depression and prospectively assess the association of insulin resistance with differing severities.

What is already known on this topic

Cross sectional studies and those using indirect measurements indicate that insulin resistance may protect against depression

What this study adds

Insulin resistance was not associated with reduced depressive symptoms in a prospective study of middle aged men

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Contributors: YB-S, GDS, SE, and DAL developed the study idea. SAS validated the GHQ data. JY initiated the Caerphilly study, and YB-S, JEJG, and JWGY are responsible for the continued management of the study. DAL did the analysis and wrote the first draft of the paper, and all authors contributed to the final version. DAL and YB-S are guarantors.

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