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DOI:
10.1016/j.biopsych.2009.09.019

Document Version
Peer reviewed version

Citation for published version (Harvard):
Gale, CR, Kivimaki, M, Lawlor, DA, Carroll, D, Phillips, A & Batty, GD 2010, 'Fasting Glucose, Diagnosis of Type 2 Diabetes, and Depression: The Vietnam Experience Study', *Biological Psychiatry*, vol. 67, no. 2, pp. 189-192. https://doi.org/10.1016/j.biopsych.2009.09.019

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Fasting glucose, diagnosis of type 2 diabetes and depression: the Vietnam Experience Study

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Revised text word count = 1495
Abstract word count=199
No of tables = 2
Key words: Major depression, depressive symptoms, type 2 diabetes, fasting glucose, diagnosis

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Abstract

Background: Recent findings suggest that both low and very high fasting blood glucose concentrations may be linked with depression, though whether type 2 diabetes is associated with depression may depend on awareness of the diagnosis. We explored the association between fasting glucose and type 2 diabetes (undiagnosed and diagnosed) and depression in middle-aged men.

Methods: Participants were 4293 US veterans who underwent an examination during which fasting blood glucose was measured, major depression diagnosed using DSM-III criteria, and depressive symptoms assessed with Minnesota Multiphasic Personality Inventory (MMPI) Clinical Scale for Depression.

Results: Compared to those with normal fasting glucose, men with undiagnosed type 2 diabetes had nearly double the prevalence of major depression, odds ratio (95% confidence interval 1.80 (1.01, 3.22), and men with diagnosed diabetes had triple the prevalence of major depression, 3.82 (1.68, 8.70), after adjustment for confounding variables. Men with undiagnosed or diagnosed diabetes had higher MMPI depression scores. There was no curvilinear association between fasting glucose and depression ($p>0.45$).

Conclusions: These findings do not support a 'U'-shaped association between fasting glucose and depression. They suggest that the positive association between type 2 diabetes and depression extends beyond those who are aware they have the disease.

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Introduction

The relationship between glycaemia and depression is unclear.(1) Findings that the risk of depression is increased in people receiving medication for type 2 diabetes, but not in those whose diabetes is being managed without drugs or is as yet undiagnosed, (2-4) suggest that the stresses of managing the disease may play a greater role in influencing mood than the degree of hyperglycaemia. A recent study reported that depressive symptoms may be more prevalent not only among individuals with very high fasting glucose, but also in those with low glucose levels.(5) These observations merit further investigation.

We examined the cross-sectional association of fasting blood glucose and type 2 diabetes (undiagnosed and diagnosed) with two measures of depression using data from the Vietnam Experience Study in which participants underwent a particularly detailed assessment of psychological and physical health.

Methods

The Vietnam Experience Study has been described in detail previously.(6-9) In brief, 18,313 former military personnel were drawn randomly from records of US army veterans; 15,288 participated in a telephone survey when they provided information about medical history, medication use, socioeconomic position and lifestyle, and a random sample were invited to a medical examination in 1986; 4462 attended (69.3% of those invited). Information on intelligence at enlistment(7) and ethnicity was extracted from army records.

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At the medical examination, blood samples were taken in the morning; participants had fasted from 7 pm the previous day. Levels of triglycerides and cholesterol fractions were ascertained using a Kodak Ektachem 700 autoanalyzer.(9) Serum glucose level was determined with a standard adaptation of the glucose oxidase-peroxidase-chromogen-coupled system for glucose determination in biologic fluids.(9) Cortisol level was measured from blood using a double-antibody radioimmunoassay (Leeco Diagnostics).(9) Blood pressure, height and weight were assessed.(9) Body mass index (BMI kg/m^2) was calculated.

Participants' psychological health was first assessed with the Diagnostic Interview Schedule (DIS)(10) to assess the prevalence of psychiatric conditions according to the DSM-III (11) criteria of the American Psychiatric Association. Secondly, participants completed the Minnesota Multiphasic Personality Inventory (MMPI), which consists of 566 true-false statements and measures 10 clinical psychopathology scales.(12) The DIS and the MMPI were administered by psychology technicians under the supervision of a clinical psychologist. We used DIS data on the prevalence of major depression in the 12 months prior to examination and the MMPI Clinical Scale for Depression. Higher scores on the latter indicate greater depression.

We defined diabetes by a fasting glucose ≥7.0 mmol/L,(13) or self-reported physician diagnosis of diabetes, or use of diabetes medication. We subdivided diabetics into undiagnosed or diagnosed according to self-reported physician diagnosis. In non-diabetic participants, we classified impaired fasting glucose (IFG) as fasting glucose between 5.6 and 6.9 mmol/L.

Gale, C.R., Kivmaki, M., Lawlor, D.A., Carroll, D., Phillips, A.C., & Batty, G.D. (2010). Fasting glucose, diagnosis for type 2 diabetes and depression: the Vietnam Experience Study. *Biological Psychiatry,* 67, 189-192.
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We used ANOVA, the χ^2 test and the Kruskal-Wallis test to examine participants' characteristics in relation to IFG and diabetes status. MMPI depression scores were transformed to normality using logarithms. We used linear and logistic regression to examine the associations of IFG and diabetes with logged MMPI depression scores and DIS diagnosis of major depression respectively. Models were adjusted for age, ethnicity, blood pressure, BMI, triglycerides, HDL cholesterol, cortisol, smoking, alcohol consumption, intelligence, education and household income. To test for a curvilinear trend, squared blood glucose was added to models containing the linear term.

Results

4293 men had complete data on diabetes status, depression measures and the covariates. Of these, 11.5% had IFG and 5.3% had type 2 diabetes; 79.8% of men with diabetes were undiagnosed. Mean (SD) fasting glucose was 5.23 (0.94), range 1.94 to 22.2 mmol/L.

Table 1 shows participant characteristics according to IFG and diabetes status. Compared to men with normal fasting glucose, those with IFG or diabetes tended to be older, non-white, have higher BMI, blood pressure, triglycerides and cortisol, and lower HDL cholesterol, IQ, and educational attainment. Men with undiagnosed diabetes were the least likely to smoke currently.

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Table 2 shows the relation between fasting glucose and diabetes status and the two measures of depression. Compared to men with normal fasting glucose, men with undiagnosed diabetes scored 4.99% higher (95% CI 1.71, 8.27) on the MMPI Depression Scale and men with diagnosed diabetes scored 11.1% (4.69, 17.6) higher, after adjustment for age and ethnicity. Additional adjustment for the other covariates had only slight attenuating effects on these associations. Men with IFG did not differ in depression scores from those with normal fasting glucose.

Compared to men with normal fasting glucose, men with diabetes were more likely to receive a diagnosis of major depression. After adjustment for age and ethnicity, the odds ratio (95% CI) for major depression was 1.67 (0.99, 2.81) in men with undiagnosed diabetes and 3.39 (1.54, 7.43) in those with diagnosed diabetes. Further adjustment for clinical characteristics strengthened these associations and they were only slightly attenuated by additional adjustment for IQ, educational attainment and household income: the fully-adjusted odds ratio was 1.80 (1.01, 3.22) in men with undiagnosed diabetes and 3.82 (1.68, 8.70) in those with diagnosed diabetes.

Men with IFG had a slightly lower prevalence of major depression than those with normal glucose tolerance. We tested for a curvilinear trend in the relations between fasting glucose concentration and the two measures of depression but there was no evidence of this (both $p>0.45$).

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Discussion

In this study of middle-aged men, the presence of type 2 diabetes was associated with higher scores on the MMPI Clinical Depression Scale and with an increased prevalence of major depression. This association was not confined to men who were aware that they had diabetes: men with undiagnosed diabetes were nearly twice as likely to have major depression as those with normal fasting glucose.

In contrast to a recent British study,(5) we found no evidence of a curvilinear association between fasting glucose and depressive symptoms. Sample sizes in each study were similar so the lack of such an association here is unlikely to be a Type 2 error. One explanation might be that the glucose tolerance test in the British study provided a more accurate measure of glycaemia than the single fasting sample used here.

Previous studies found that while a prior diagnosis of diabetes was associated with higher scores on self-rated depression scales, undiagnosed diabetes was not.(4,14) In one cohort, diabetes that was treated with medication was associated with prevalent and incident depressive symptoms, but people whose diabetes was being managed without medication were no more likely to be depressed than those with normal fasting glucose.(2,3) These observations suggest that it is the stress of managing diabetes that leads to depression. However, although we found that diagnosed diabetes was more strongly linked to depression than undiagnosed diabetes, the increased risk of major depression and higher MMPI depression scores in men who were unaware that they had diabetes does not support this interpretation.

The cross-sectional nature of these data mean it is not possible to establish direction of effect, but a recent meta-analysis suggests that depression may be a stronger predictor of subsequent type 2 diabetes than vice versa.(1) Depression is associated with poorer health behaviours, such as smoking and physical inactivity, that may increase risk of diabetes. Activation of the hypothalamic-pituitary-adrenal axis has been linked with both depression and the development of type 2 diabetes. However, although cortisol was linked with both glucose levels and depression, as shown in a previous study using these data,(15) adjustment for this together with a range of clinical characteristics and health behaviours had little or no attenuating effect on risk estimates. We were, however, unable to explore the role of other stress hormones or inflammatory responses.

Our study has some limitations. Findings in this male sample may not apply to women: evidence suggests that the association between depression and diabetes is weaker in women. (1) On average, age at onset of type 2 diabetes tends to be older than the mean age of our participants, so our cases may not be representative. Numbers with a prior diagnosis of diabetes were small. For this reason, the observation that they appeared to have slightly higher levels of depression than those with undiagnosed diabetes needs to be treated with caution. We were also unable to assess accurately whether men whose diabetes was being treated with medication had a higher risk of depression than those who were not on medication, although crude comparisons suggest that the prevalence of major depression was high in both groups (16% and 25% respectively). Classification of diabetes status depended on self-reports or a single fasting blood sample so some men may have been misclassified. The strengths of the study are the availability of data on a range of potential

confounding variables, and the comprehensive assessment of depression, which, in contrast to the majority of previous studies, included a diagnostic measure.

In conclusion, our results do not support the existence of a curvilinear association between fasting glucose and depressive symptoms, but they confirm that the presence of type 2 diabetes is associated with a higher prevalence of depression, and suggest that this is so even in those people who are unaware that they have diabetes.

Acknowledgments

The Centre for Cognitive Ageing and Cognitive Epidemiology is funded by the Biotechnology Sciences Research Council, the Engineering and Physical Sciences Research Council, the Economic and Social Research Council, the Medical Research Council and the University of Edinburgh as part of the cross-council Lifelong Health and Wellbeing initiative. Mika Kivimaki is supported by the BUPA Foundation Specialist Grant, UK, and the Academy of Finland. David Batty is a Wellcome Trust Fellow (WBS U.1300.00.006.00012.01).

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Gale, C.R., Kivmaki, M., Lawlor, D.A., Carroll, D., Phillips, A.C., & Batty, G.D. (2010). Fasting glucose, diagnosis for type 2 diabetes and depression: the Vietnam Experience Study. *Biological Psychiatry,* 67, 189-192. http://dx.doi.org/10.1016/j.biopsych.2009.09.019

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Table 1: Characteristics of the participants by impaired fasting glucose and type 2 diabetes status (n=4293)

	Fasting glucose		Type 2 Diabetes		
	Normal (n=3573)	**Impaired (n=492)**	**Undiagnosed (n=182)**	**Diagnosed (n=46)**	**P value for difference**
Age (yr), mean (SD)	38.2 (2.51)	38.6 (2.47)	39.1 (2.42)	39.6 (2.48)	<0.001
Ethnicity, no (%)					
White	2962 (82.9)	404 (81.3)	128 (70.3)	26 (56.5)	<0.001
Black	400 (11.2)	55 (11.2)	33 (18.1)	14 (30.4)	
Other	211 (5.9)	37 (7.52)	21 (11.5)	6 (13.0)	
IQ at enlistment, mean (SD)	101.6 (15.1)	99.4 (15.1)	98.3 (15.5)	95.3 (18.6)	<0.001
Education (grade completed), mean (SD)	13.4 (2.31)	12.9 (2.14)	13.1 (2.38)	12.8 (2.29)	0.002
Household income (US$ per yr), no (%)					
<20,000	997 (27.9)	145 (29.5)	59 (32.4)	17 (37.0)	0.612
-40,000	1790 (50.1)	248 (50.4)	87 (47.8)	20 (43.5)	
>40,000	786 (22.0)	99 (20.1)	36 (19.8)	9 (19.6)	
BMI, mean (SD), kg/m^2	26.4 (4.15)	28.7 (4.98)	30.1 (5.55)	29.5 (6.53)	<0.001
Systolic blood pressure (mm Hg), mean (SD)	121.9 (11.4)	127.5 (12.7)	130.3 (13.9)	128.2 (16.6)	<0.001
Diastolic blood pressure (mm Hg), mean (SD)	83.3 (9.10)	87.3 (9.46)	89.8 (11.0)	86.9 (10.9)	<0.001
Smoking status, no (%)					
Never	900 (25.2)	129 (26.2)	52 (28.6)	11 (23.9)	0.006
Former	986 (27.6)	155 (31.5)	70 (38.5)	13 (28.3)	
Current	1687 (47.2)	208 (42.3)	60 (33.0)	22 (47.8)	
Alcohol intake (units per wk), median (IQR)	2 (0-9)	2 (0-11)	2 (0-9)	1 (0-4)	0.397
Triglycerides (mg/dL), median (IQR)	86 (60-127)	106 (73-158)	149 (96-231)	105 (66-188)	<0.001
HDL cholesterol (mg/dL), mean (SD)	45.0 (12.3)	44.0 (12.5)	41.1 (13.6)	41.4 (15.3)	<0.001
Cortisol (mg/dL), median (IQR)	17.1 (14-20.8)	19.9 (15.7-23.9)	20.0 (16.1-25.5)	18.5 (15.4-21.7)	<0.001

SD, standard deviation; IQR, inter-quartile range

Gale, C.R., Kivmaki, M., Lawlor, D.A., Carroll, D., Phillips, A.C., & Batty, G.D. (2010). Fasting glucose, diagnosis for type 2 diabetes and depression: the Vietnam Experience Study. *Biological Psychiatry*, 67, 189-192. http://dx.doi.org/10.1016/j.biopsych.2009.09.019

Table 2: Percent difference (95% CI) in logged MMPI Clinical Scale for Depression scores, and odds ratios (95% CI) for major depression, according to fasting glucose and type 2 diabetes status

Measure of depression	Adjustments	Fasting glucose		Type 2 diabetes		
		Normal (n=3573)	Impaired (n=492)	Undiagnosed (n=182)	Diagnosed (n=46)	P for linear trend
MMPI Clinical Scale for Depression		**Percent difference (95% CI)**				
	Age & ethnicity	0 (Reference)	2.03 (-0.04, 4.10)	4.99 (1.71, 8.27)	11.1 (4.69, 17.5)	<0.001
	Age, ethnicity, clinical characteristics & health behaviours[a]	0 (Reference)	1.68 (-0.43, 3.79)	4.55 (1.16, 7.93)	11.2 (4.82, 17.7)	<0.001
	Fully adjusted[b]	0 (Reference)	1.23 (-0.86, 3.31)	3.81 (0.49, 7.13)	10.1 (3.89, 16.4)	<0.001
DIS diagnosis of major depression		**Odds ratio (95% CI)**				
		(227 cases)	**(25 cases)**	**(16 cases)**	**(8 cases)**	
	Age & ethnicity	1 (Reference)	0.82 (0.54, 1.26)	1.67 (0.99, 2.81)	3.39 (1.54, 7.43)	0.016
	Age, ethnicity, clinical characteristics & health behaviours[1]	1 (Reference)	0.90 (0.58, 1.40)	1.80 (1.01, 3.19)	3.83 (1.72, 8.54)	0.005
	Fully adjusted[2]	1 (Reference)	0.90 (0.58, 1.40)	1.80 (1.01, 3.22)	3.82 (1.68, 8.70)	0.007

[a] BMI, triglycerides, HDL cholesterol, cortisol, systolic and diastolic blood pressure, smoking status and alcohol consumption.
[b] Further adjusted for intelligence, educational attainment and household income