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Hyperglycaemia, Type 2 Diabetes and Depressive Symptoms: The British Whitehall II Study

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ABSTRACT

OBJECTIVE—The recent suggestion that impaired fasting glucose may protect against depression, whereas a diagnosis of diabetes might then result in depression, warrants further examination.

RESEARCH DESIGN AND METHODS—Cross-sectional analysis of 4228 adults (mean age 60.7 years, 73.0% male) who underwent oral glucose tolerance testing and completed the Center for Epidemiologic Studies Depression (CES-D) scale.

RESULTS—After adjustment for demographic factors, health behaviours and clinical measurements (BMI, waist circumference, lipid profile and blood pressure), there was a 'U'-shaped association between fasting glucose and depression (Pcurve=0.001), with elevated CES-D at low and very high glucose levels. This finding was replicable with 2-hour postload glucose (p=0.11) and HbA1c (p=0.007).

CONCLUSION—The 'U'-shaped association between blood glucose and CES-D, with the lowest depression risk seen amongst those in the normoglycaemic range of HbA1c did not support the hypothesized protective effect of hyperglycaemia.

The association between type 2 diabetes and depression, both major public health challenges, remains unclear (1-8). In a recent U. S. report, people with type 2 diabetes had an increased risk of depressive symptoms, whereas, conversely, in non-diabetic individuals higher impaired fasting glucose (IFG) appeared to confer protection against depression (7). While an increased prevalence of depression in people receiving a diagnosis of a pernicious chronic disease such as type 2 diabetes is perhaps unsurprising, the apparent counter-intuitive protective effect of IFG warrants further scrutiny. In the Whitehall II study we were able to explore the relationship between depression and a greater range of glycaemia measures [fasting and postload glucose, glycated haemoglobin 1c (HbA1c)] than has previously been possible.

RESEARCH DESIGN AND METHODS—In 2003/04 data collection phase of the Whitehall II study (described in detail elsewhere)(9), 4228 men and women aged 50 to 74 years completed a depression questionnaire and, if without known diabetes, underwent an oral glucose tolerance test (OGTT). Venous blood samples were taken after at least 8 hours of fasting, before OGTT, and at 2-hour post administration of a 75g glucose solution. Blood glucose was measured using the glucose oxidase method (10) on a YSI MODEL 2300 STAT PLUS Analyzer (YSI Corporation, Yellow Springs, OH, USA) (mean coefficient of variation (CV): 1.4%-3.1%)(11). Diabetes was defined by a fasting glucose ≥7.0 mmol/L or a 2-hour postload glucose ≥11.1 mmol/L or reported doctor diagnosed diabetes or use of diabetes medication (12). In non-diabetic participants, we classified moderate hyperglycaemia as IFG (fasting glucose between 5.6 to 6.9 mmol/L) and Impaired Glucose Tolerance (IGT, 2-hour

postload glucose between 7.8 and 11.0 mmol/L)(12). HbA1c was measured on whole blood

with a calibrated HPLC system (CV: 0.8%).

Depressive symptoms were assessed with the Center for Epidemiologic Studies

Depression scale (CES-D) summary score (13), a measure that has been validated among

diabetic patients (14). Ethnicity (white or non-white), body mass index [weight (kg) per height

squared (m^2)], waist circumference (cm), systolic and diastolic blood pressure (mm Hg),

HDL- and LDL-cholesterol (mmol/L), triglycerides (mmol/L), current smoking (yes/no),

alcohol consumption (none, 1 to 3 units per day, >3 units per day) and physical inactivity

(<2.5 hrs moderate and <1 hr vigorous exercise per week) were measured according to

standardised protocols.

Statistical methods

All 4228 participants had adequate data on CES-D and diabetes status, but there were some

missing data for some of the different glucose parameters. Thus, our different analyses are

based on between 3945 (93.3% of the 4228) and 4228 (100%) of the eligible participants.

Values for triglycerides were log-transformed prior to analyses due to skewed distribution. We

used linear regression analysis to model the associations of IFG and IGT with the CES-D

score. The shape of the associations between fasting glucose, postload glucose, HbA1c and

CES-D were studied by treating all these measures as continuous variables. To test for

curvilinear trends a squared term of the glycaemic measures was added to an equation

containing the linear term. The models were adjusted for age, sex, ethnicity and clinical

characteristics (BMI, waist, systolic and diastolic blood pressure, HDL- and LDL-cholesterol,

triglycerides, smoking, alcohol consumption, and physical activity). The statistical tests were performed with Stata version 10.1.

RESULTS—Of the 4228 participants, 2038 (73.0%) were men and 3895 (92.1%) Caucasian. Mean±SD age was 60.7±6.0 years and the levels of clinical characteristics were 128±17/74±10 mm Hg for systolic/diastolic blood pressure, 1.6±0.4 mmol/L for HDL-cholesterol, 3.58±1.9 mmol/L for LDL-cholesterol, 26.7±4.4 kg/m^2 for BMI, and 94.2±10.7 (men) and 84.3±13.0 cm (women) for waist circumference. For triglycerides, median±IQR was 1.2±0.9 mmol/L. Of the participants, 7.9% were current smokers, 16.0% were physically inactive, 17.8% consumed more than 3 units alcohol per day and 16.2% did not consume alcohol regularly. Overall CESD-mean score was 9.9±6.6.

      Fasting glucose—Mean±SD was 5.55±1.51 mmol/L. Compared to participants with normal fasting glucose [n=3038, mean+SD CES-D=9.9+6.7], those with IFG (n=735) showed a marginally reduced CES-D score [Mean+ SD=9.0+ 6.1, P=0.05], while those with diabetes (n=455) showed an elevated CES-D score [Mean+ SD=11.2+ 7.0, P=0.002] after taking into account age, sex and ethnicity. As shown in Figure 1-Panel A, there was a U-shaped association between fasting glucose and CES-D (Pcurve=0.001 after adjustment for age, sex and ethnicity, n=3986), with elevated CES-D values at glucose levels <4.5 mmol/L and >9.0 mmol/L. The curvilinear trend was robust to additional adjustment for clinical characteristics (P=0.001).

      Postload glucose—Mean±SD was 6.38±2.09 mmol/L. IGT [n=423, CES-D mean±SD=9.49±6.58] and isolated IGT (n=284) were not associated with CES-D (P>=0.53). However, there was a U-shaped association between postload glucose and CES-D (Figure 1-

Panel B, n=3455, P_{curve}=0.05 after adjustment for age, sex and ethnicity; P_{curve}=0.11 after additional adjustment for clinical characteristics).

HbA1c—Mean±SD was 5.36±0.73%. Again, a curvilinear association with CES-D was evident (p=0.04, n=4160), Figure 1-Panel C. The lowest CES-D scores were between HbA1c levels 4.0% to 5.5% (nadir 4.4% in age, sex and ethnicity adjusted model) and this was also seen in raw data (Appendix). The curvilinear trend remained after additional adjustment for all clinical characteristics (P=0.007).

CONCLUSIONS—We examined the associations of various glycaemic measures, including fasting and postload glucose and HbA1c with symptoms of depression. Our results show slightly lower levels of depressive symptoms among non-diabetic individuals with IFG (7). However, this finding was generated by a 'U'-shaped association between fasting glucose and CES-D with elevated depression scores seen at both ends of the glucose distribution, a finding which was replicated for 2-hour postload glucose and HbA1c. While low depression scores were observed both at normal and prediabetic ranges of fasting and postload glucose, findings from long-term glucose levels (HbA1c) clearly demonstrated that normoglycaemic individuals had the lowest depression risk.

In summary, our results do not support the protective effect of long-term hyperglycaemia but they are in agreement with the recommendation that clinicians consider screening for depression among patients with diabetes. Future research should determine explanatory mechanisms for increased depressive symptoms among non-diabetic individuals with low glucose levels.

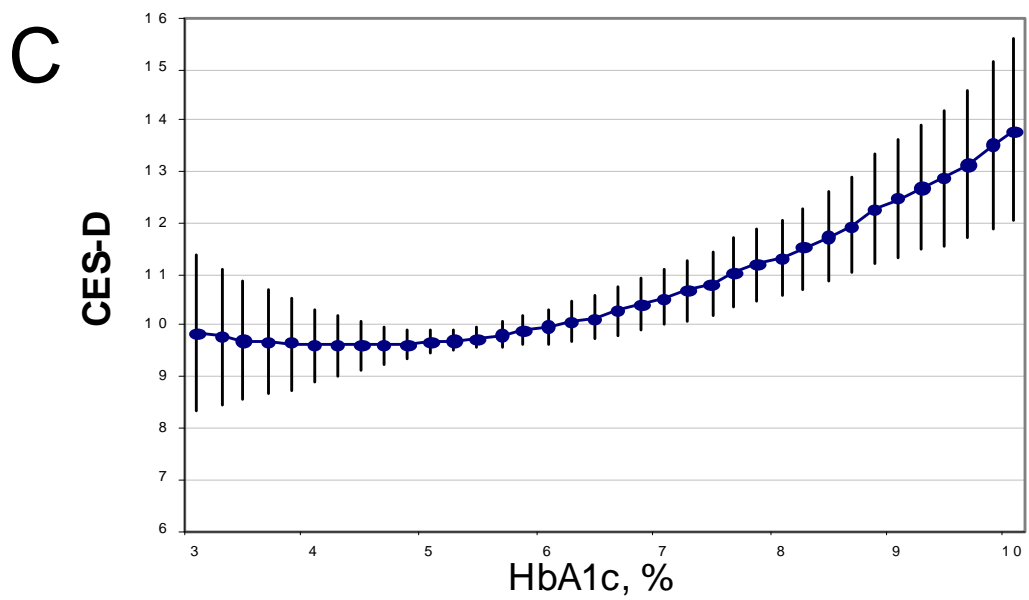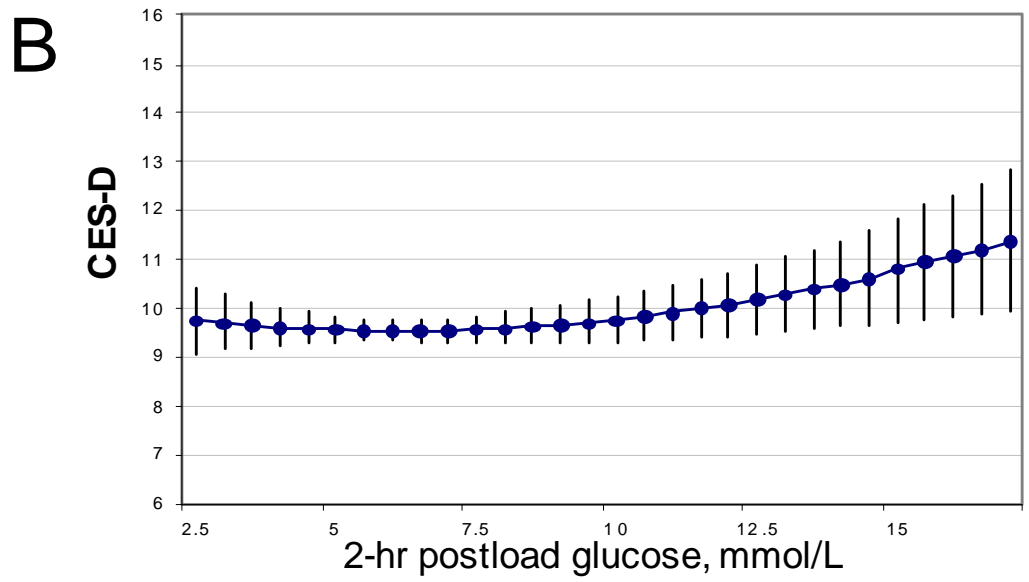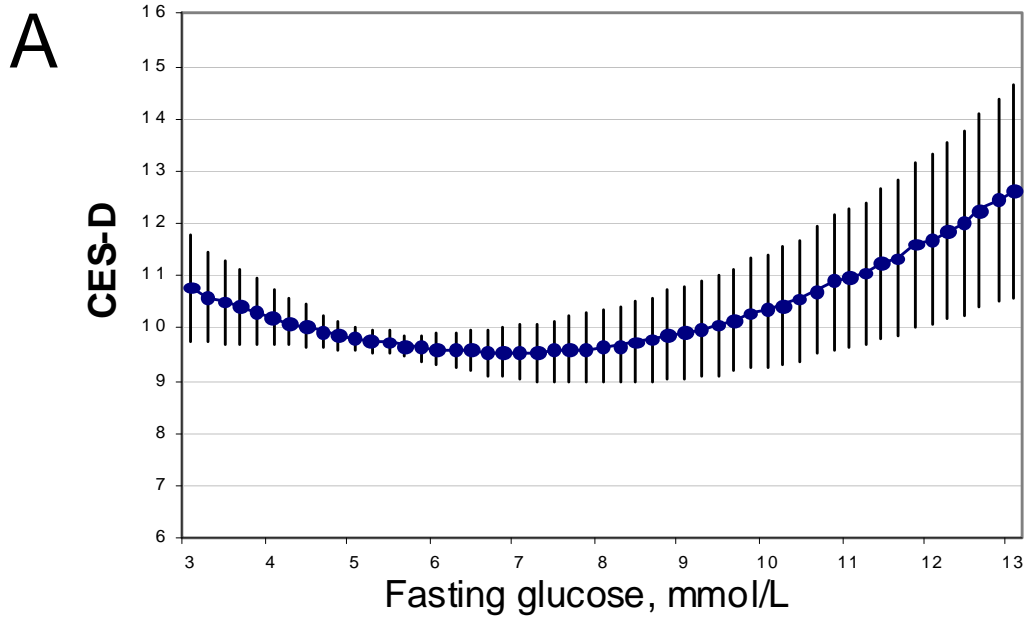**Disclosure:** No conflict of interest to disclose.

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FIGURE LEGENDS

Figure 1. Age, Sex and Etnicity/Race Adjusted Associations of Fasting Glucose (A), 2-hour Postload Glucose (B) and Glycated Hemoglobin (C) with Depression Assessed by the Center for Epidemiologic Studies Depression scale (CES-D).

Appendix: Lowess Smoother Curve Based on Raw Data on HbA1c and CES-D