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Greater variation in affect is associated with lower fasting plasma glucose[#]

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Abstract

Background: Depression and bipolar illness are associated with a 2–3 fold increase in the prevalence of diabetes. However, it is unknown whether variation in mood affects glucose metabolism. The aim of this study was to assess whether changes in affect were related to fasting plasma glucose and glycated haemoglobin.

Methods: 379 men and 441 women who took part in the 2003 Health Survey for England and had valid data for GHQ12 and fasting blood glucose were included. Mood variability was assessed by the General Health Questionnaire 12 (GHQ12). Fasting plasma glucose and glycated haemoglobin (HbA_{1c}) were measured by standard laboratory methodology and their relationship to variability assessed using linear regression.

Results: There was a significant inverse relationship between fasting blood glucose, but not HbA_{1c}, and variability score ($R^2 = 0.327$, $p = 0.02$) after adjusting for sociodemographic factors, anthropometric measurements, lifestyle, and use of medication.

Conclusion: This study has shown an inverse association between changes in affect and fasting plasma glucose. This unexpected finding suggests that the association between affect and glucose is more complex than previously thought. Fasting blood glucose may reflect the operation of homeostatic mechanisms that are disturbed in certain mental states and are associated, therefore, with altered risk

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of diabetes and related metabolic conditions. This may have implications for the management of those with such conditions and with mental disorders.

Keywords: Medicine

1. Introduction

The prevalence of depression and depressive symptoms is approximately two-fold higher in people with diabetes while epidemiological studies have demonstrated that this association is bi-directional (Holt et al., 2014). A meta-analysis of 11 studies found that adults with depression had a 37% increased risk of developing type 2 diabetes (Knol et al., 2006) while two further meta-analyses indicated that incident depression was increased by 15–24% in people with diabetes (Mezuk et al., 2008; Nouwen et al., 2010). The mechanisms and pathogenesis underlying the association are unclear but a variety of explanatory theoretical models have been proposed, including a psychological response to the diagnosis and treatment demands, common biological and environmental pathways and possible treatment effects.

Variability of mood which leads to mood instability ("lability") is an important and clinically significant symptom (Marwaha et al., 2013). For example, studies suggest that there is greater positive affect during the day and greater diurnal mood variation in negative affect in people with major depression compared to matched controls (Marwaha et al., 2013). Mood instability, when assessed by the question "Do you have a lot of sudden mood changes?", increased the odds of experiencing non-psychotic symptoms by nearly 10 fold (Marwaha et al., 2013). Lability or mood instability is also associated with a number of psychiatric conditions including attention deficit disorders (Stringaris and Goodman, 2008; Marwaha et al., 2013), borderline personality disorder and bipolar disorder (Marwaha et al., 2014), and major depression (Marwaha et al., 2013).

Few studies have examined variability of mood in relation to glucose metabolism. Kotani et al. (2007) found a significant positive relationship between "mood change tendency" and fasting blood glucose in a group of healthy people. Skaff et al. (2009) looked at the daily emotional "ups and downs" in a group of participants with type 2 diabetes. After adjusting for sociodemographic characteristics, BMI, time with diabetes, medicines and indices of depression, they found that, in men, when negative affect was greater than the individual's own average level on one day, the fasting glucose was higher than the mean value the next morning.

The aim of the present study was to examine the relationship between mood variability, assessed using the GHQ12 (Goldberg and Williams, 1988), and fasting blood glucose in a general population sample in which it was possible to control for

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potential confounders. As mood variability predisposes to depression and a number of other psychiatric illnesses which are associated with increased rates of diabetes, we hypothesised that mood variability would be associated with increased glucose concentration.

2. Method

2.1. Participants

The Health Survey for England is a national survey carried out each year on a fresh sample of the population of England living in private households. The sample is chosen using a stratified, random sampling technique and is representative of the population from which it is drawn. Since 1993 it has included participants aged 2 years upwards, and in 2003 there were 14,836 participants who were aged 16 or over (mean age 46 yrs: see Table 1). 6602 were men and 8234 were women. Ethical approval for the Survey was granted by the London Multi-Centre Research Ethics Committee (MREC) and informed consent obtained from all participants, which in the case of blood samples was in writing (Sproston and Primatesta, 2004).

2.2. Measures

The 2003 Survey focused on cardiovascular disease and its risk factors, and included the General Health Questionnaire (GHQ12) as well as questions on smoking, alcohol intake, diet and physical activity, relevant medical history and medication (Sproston and Primatesta, 2004). The questionnaires, including the GHQ12, were administered during an initial interview.

2.2.1. Lifestyle questions

Alcohol consumption was assessed by answers to the question "Whether drinks nowadays", smoking by answers to the question "Whether smokes cigarettes nowadays", dietary salt intake by answers to the question "Salt added when cooking?" and consumption of cakes, chocolates, crisps, nuts or biscuits by answers to questions "How often eat cakes?" and "How often eat chocolate, crisps or biscuits?".

Fruit and vegetable intake was assessed by portions of fruit (including orange juice) and vegetables yesterday. Physical activity level was coded as low, medium or high depending on the responses to questions about specific forms of physical activity-including sports, walking, manual work, and housework.

2.2.2. GHQ12 questionnaire

The GHQ12 questionnaire was completed by all those aged 13 years and above. The GHQ12 is intended to detect possible mental illness in the general population

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Table 1. Comparing gender, age and prevalence of doctor-diagnosed diabetes amongst those with valid values of fasting glucose, HbA_{1c} and variability of mood with the total sample aged 35 (or 16) and over in the 2003 Health Survey for England.

	35 and over with valid values for GHQ12 and fasting glucose	All 35 and over	16 and over with valid values for GHQ12 and HbA_{1c}	All 16 and over
% Males	46%	44%	46%	45%
Mean age	55 yrs	56 yrs	49 yrs	49 yrs
% with doctor-diagnosed diabetes	3.0%	5.4%	3.4%	4.1%
n	820	10,890	7872	14,836

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(Goldberg and Williams, 1988), and within community or non-psychiatric clinical settings such as primary care or general medical out-patients.

There are six "negative" questions with responses ranging from "Not at all", "No more than usual;" "Rather more than usual" to "Much more than usual". The GHQ12 also includes "positive" questions, with possible responses including "Better than usual", "Same as usual", "Less than usual", and "Much less than usual". In conventional scoring methods, the first two answers to positive questions are usually collapsed so that improvements in positive affect do not contribute to the score (cf. Huppert and Whittington, 2003; Ploubidis et al., 2007).

The GHQ was originally developed on the premise that it focused on breaks in normal function rather than on lifetime traits and therefore may underestimate the prevalence of chronic illness (Goodchild and Duncan-Jones, 1985). We used the measures of *change* in normal function to our advantage. In order to assess variability in mood, any participant who responded "Rather more than usual" or "Much more than usual" to one of the negative items received a score of "1" for that question. If they responded "Better than usual", "Less than usual", or "Much less than usual" to one of the positive questions they received a score of 1 for that question.

We considered using a scale of 0, 1 and 2 to differentiate the size of the change but this would have incorrectly implied that the categories were equidistant from one another (e.g. that the difference between "Rather more than usual" and "Much more than usual" was the same as that between "Rather more than usual" and "No more than usual"), and so we chose a simple bimodal scale of 0 or 1 instead.

Scores thus reflected *change* whether in response to a negative question or a positive one, and in the case of the latter regardless of whether it represented an increase or a decrease of positive affect. The total change score was defined as "variability" and any participant could obtain a score of between 0 and 12.

2.2.3. Anthropometry and blood test

A number of anthropometric measurements were also taken, including weight, height and waist and hip circumference to calculate the waist-hip ratio.

A blood sample for HbA_{1c} was obtained from those aged 16 years or above at a second, nurse visit. A fasting blood glucose sample was also taken in those aged 35 years or above by a nurse. The average interval between the interviewer visit, at which the self-completion booklet containing the GHQ12 was administered, and the nurse visit at which the fasting blood sample was taken was 31 $\pm$ 24 days.

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2.3. Statistics

Data are reported as mean ± SD. The data were analysed with IBM SPSS Statistics 19 using a linear regression analysis in which fasting plasma glucose was the dependent variable and variability of mood the independent variable. The regression was then repeated with the following additional variables included as covariates:

- Age
- Gender
- Medication for central nervous system (CNS), cardiovascular or endocrine disease
- Alcohol
- Smoking
- Diet
  - Addition of salt to cooking
  - Consumption of cakes, chocolate, crisps, nuts or biscuits
  - Fruit and vegetables intake
  - Fat intake
- Physical activity
- Waist-hip ratio
- Doctor diagnosed diabetes (excluding gestational diabetes)

A separate regression analysis was carried out with mood variability as the independent variable and HbA_{1c} as the dependent variable, restricting the analysis to those aged 16 or over as HbA_{1c} was only carried out on those in this age range.

3. Results

3.1. Participant characteristics

854 participants had valid fasting blood glucose measurements (5.2 ± 1.0 mmol/L range: 3.0–17.5 mmol/L). 14,490 participants had valid values for mood variability (1.7 ± 2.5, range 0–12).

There were 379 men and 441 women for whom data were available for both GHQ12 and fasting blood glucose (Age: 55.1 ± 13.0 yrs; range: 35–89). Table 1 below compares this sample with the overall sample of those aged 35 or over in the 2003 Health Survey.

8199 participants had valid HbA_{1c} measurements (mean ± SD = 5.3% ± 0.7%; 34 mmol/mol. ± 8 mmol/mol). 3614 men and 4258 women had valid values for both GHQ12 and HbA_{1c} (Age: 49.25 ±17.1 yrs; range:16–98).

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Table 1 shows how this sample compares with the overall sample of those aged 16 or over in the 2003 Health Survey.

3.2. Relationship between fasting glucose, HbA_{1c} and variability score

There was a significant inverse relationship between fasting blood glucose and variability score ($p = 0.013$; $t = -2.477$; $R = 0.086$; R square = 0.007) in the bivariate analysis.

In the multivariate analysis, age and a diagnosis of diabetes were significantly related to fasting glucose (age: $p = 0.001$; doctor diagnosed diabetes: $p < 0.001$). The association between mood variability and fasting glucose remained after adjustment for all covariates ($p = 0.02$; R square = 0.327) (Table 2).

By contrast there was no significant association between variability of mood and $HbA_{1c.}$

Table 2. Ordinary least squares (OLS) regression of fasting blood glucose on mood variability and potential confounders (* $p < 0.05$; ** $p < 0.01$).

Explanatory variables	Coefficients	Standard errors
Mood variability	-0.033*	0.014
Age	0.011**	0.003
Gender	0.100	0.093
Taking CNS medicine	-0.075	0.098
Taking cardiovascular medicine	0.110	0.092
Taking endocrine medicine	-0.007	0.114
Doctor diagnosed diabetes	-2.329**	0.211
Drink alcohol	-0.220	0.118
Current smoker	-0.010	0.082
Salt added in cooking	-0.020	0.069
Cakes often eaten	0.061	0.040
Chocolate, crisps, nuts or biscuits often eaten	0.017	0.039
Portions of fruit and vegetables eaten the previous day	0.003	0.016
Fat intake score	0.008	0.005
Physical activity level	-0.002	0.046
Waist/hip ratio	1.088	0.570
Constant	7.854	0.818
Adjusted r^2	0.306	
F(16,503)	15.277**	

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4. Discussion

Although set up primarily to monitor the health of the country (Gupta, 1994), the Health Survey for England also has considerable potential to be used as a research tool. This afforded us the opportunity to examine a general population sample, representative of those living in private households in England in 2003. Amongst this group, contrary to our initial hypothesis, there was a significant inverse relationship between mood change scores (variability) and subsequent fasting blood glucose. By contrast, there was no relationship between variability and HbA_{1c} which reflects the average plasma glucose concentration over a longer period of 6–8 weeks, as opposed to fasting glucose, which largely reflects hepatic glucose output.

Variability of mood to a degree that leads to mood instability ("lability") is an important and common clinically significant symptom. The present study used the 12 item GHQ12 questionnaire which has been shown to be valid and reliable in many different countries and cultures (e.g. see Piccinelli et al., 1993). The scoring method used in this study has not, to our knowledge, been used in this way before but the method has face and construct validity. However, further research will be needed to determine whether mood variability as assessed in this way is a stable, enduring trait, and also to replicate the findings of the present study.

In the light of the associations between type 2 diabetes and psychiatric disorder, we had hypothesised that *increased* variability of mood (which may be a marker of increased emotional/behavioural reactivity and a predictor of psychiatric illness) would be associated with increased fasting plasma glucose. We were therefore surprised to find the opposite. However, this finding is not unprecedented. For example, a US study (Golden et al., 2008) found evidence that obesity and insulin resistance might be associated with a *lower* risk of developing depression and they confirmed that individuals with impaired fasting glucose had a reduced risk of incident depressive symptoms. On the other hand, a later paper from the Whitehall Study (Kivimaki et al., 2009) found a U-shaped association between fasting glucose and depression with the lowest depression risk seen among those in the normoglycemic range of HbA_{1c}.

Possible explanations for the observed paradoxical inverse association between variability of mood and diabetes risk emerge when one considers the literature on atypical depression. People with bipolar disorder show greater short-term mood fluctuations when depressed than people with unipolar depression (e.g. Aheam and Carroll, 1996), while nearly three quarters of people with atypical major depression meet the criteria for bipolar disorders (Perugi et al., 1998). Thus, atypical depression appears to be associated with more labile and reactive mood. Atypical depression is associated with hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis, low

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cortisol concentration, less CRF, and reduced activation of noradrenergic pathways (Juruena and Cleare 2007; Lamers et al., 2013).

Another study of glucose disposal in depression showed that people with atypical depression had lower sympathoadrenal responses and higher insulin concentrations than healthy controls (Schweiger et al., 2008). Reduced sympathetic nervous system responsiveness and hyperinsulinaemia could lead to lower fasting blood glucose levels. Schweiger et al. (2008) suggest that overeating (a feature of atypical depression) may be a way of maintaining an adequate supply of glucose to the brain and that changes in eating behaviour in depression are secondary to alterations in brain glucose metabolism and glucose allocation. This has been found to be associated with abnormalities of cortisol regulation at certain points of the day (Thorn et al., 2011), and the diurnal physiology and metabolism of both blood pressure and blood glucose are known to be under the influence of circadian clocks (Singh et al., 2016).

Lability of mood may reflect the emotional reactivity of the individual to *psychosocial* stress. It has features in common with atypical depression and it is possible that it may also be associated with reduced activity of the HPA axis and/or of noradrenergic pathways. These in turn are involved in homeostatic mechanisms which come into operation in the fasting state in response to *physiological* stress. Insensitivity of such biological mechanisms could lead to lower levels of fasting glucose and hence explain the inverse relationship between the latter and variability of mood. HbA_{1c}, on the other hand, reflects average plasma glucose concentration over a longer period, rather than the short term response to the withdrawal of food, and this may explain why there is no association with variability of mood.

The present study does not permit conclusions about the direction of any causative pathway between mood variability and low fasting glucose. Nevertheless, it is interesting that Yehuda et al. (1990) found that the mean cortisol level in a post-traumatic stress disorder group was significantly lower, and the range narrower, than that observed in healthy volunteers (cf. Meewisse et al., 2007). They suggest that this is due to physiological adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress. It is possible, therefore, that increased emotional reactivity results in repeated activation of the HPA axis and the sympathetic nervous system which eventually leads to a state of physiological decompensation. The related atypical depression may be initially associated with lower levels of fasting glucose, but hyperphagia, inactivity and possibly reduced cortisol may over time lead to increased BMI, waist–hip ratio and inflammation (Lamers et al., 2013), which in turn could result in insulin resistance and type 2 diabetes. Thus, whilst elevated levels of catecholamines and cortisol may cause damage to the cardio- and

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cerebro-vascular system (Singh et al., 2012), abnormally low levels may also have pathological effects in the long term.

There are a number of limitations to the study. In the interests of confidentiality, the GHQ is self-administered rather than by a trained interviewer, and does not specifically ask about mood, though many of the questions are related to mood and we used it as a proxy measure of mood variability. The association between the latter and fasting glucose is small in real terms (and based on low numbers compared with those for HbA_{1c}). This may be because a general population sample was used, and a stronger relationship might emerge in clinical populations (with the *caveat*, that the relationships in clinical populations may not necessarily be the same as in non-clinical ones). The relationship is cross-sectional. Longitudinal studies could clarify the relationship. A further limitation is that fasting glucose was not measured at the same time as mood variability; however, this might also be considered a strength because it suggests that the relationship may not simply result from the direct impact of low glucose on mood (or vice versa), but rather both may be due to common underlying mechanisms. Glucose was measured at just one point in time when in fact there is also evidence for disorders which relate to the extent of *variability* of glucose (Singh et al., 2014). Some of the covariates (e.g. dietary measures) were based on self-report and it is conceivable, therefore, that they, or other variables, may have produced residual confounding of the results.

5. Conclusions

There is evidence from this study that variability of mood is associated with lower fasting glucose. There is considerable evidence for an association of psychiatric morbidity and metabolic disorders, and the results of this study may shed light on the relationship between them, and the mechanisms underlying these associations.

Declarations

Author contribution statement

Sunjai Gupta: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Robert Anderson: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Richard IG Holt: Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

Data associated with this study can be accessed at https://discover.ukdataservice.ac.uk/catalogue/?sn=5098

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