Glycemia, Insulin Resistance, Insulin Secretion, and Risk of Depressive Symptoms in Middle Age.

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Running Title: Glycemia, insulin secretion & depressive symptoms

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ABSTRACT

Objective: The extent to which abnormal glucose metabolism increases the risk of depression remains unclear. In this study we investigated prospective associations of fasting glucose, fasting insulin and indices of insulin resistance and secretion with subsequent new-onset depressive symptoms (DepS).

Research Design and Methods: Prospective cohort study of 3145 adults from the Whitehall II Study (23.5% women, 60.6±5.9 years). Baseline examination included fasting glucose and insulin, homoeostasis model assessment insulin resistance (HOMA2-%IR) and HOMA beta-cell insulin secretion (HOMA2-%B). DepS (Center for Epidemiologic-Studies-Depression-Scale ≥16 or use of anti-depressive drugs) were assessed at baseline and at 5-year follow-up.

Results: Over the 5-year follow-up, 142 men and 84 women developed DepS. Women in the lowest quintile of insulin secretion (HOMA2-%B ≤55.3 %) had 2.18 (95%CI: 1.25-3.78) times higher odds of developing DepS compared to those with higher insulin secretion. This association was not accounted for by inflammatory markers, cortisol secretion, or menopausal status and hormone replacement therapy. Fasting insulin measures were not associated with DepS in men and fasting glucose was not associated with new-onset DepS in either sex.

Conclusion: Low insulin secretion appears to constitute a risk factor for DepS in middle-aged women, although further work is required to confirm this finding.

Type 2 diabetes (T2D) is associated with depression (1, 2). Plausible mechanisms underlying this association include the depressogenic effect of treatment and management of T2D (3-6) and influence of the T2D diagnosis itself, as it can be viewed as a stressful life event (7, 8). Recently, the hypothesis that the link between diabetes and depression may also result from a direct biological impact of diabetes-related biological changes has raised particular interest. More specifically, it has been proposed that hyperglycemia and hyperinsulinemia may alter hypothalamic-pituitary-adrenal axis function, which, in turn, increases the risk of depressive symptoms (DepS) (9, 10).

To date, the results from observational studies investigating the association between fasting glucose and depression are mixed. Some investigations found that impaired fasting glucose (11) and high glycated haemoglobin (12) were associated with increased DepS, but others failed to observe this association (4, 13-15) or suggested that the association varied by sex (16, 17). Similarly, evidence of an association between hyperinsulinemia, insulin resistance and depression is equivocal with findings from 6 studies showing a positive association between insulin resistance and DepS (17-23), two reporting a null effect (24, 25), and one suggesting that insulin resistance is inversely associated with DepS (26). Methodological limitations, such as cross-sectional study design and small sample size, may have contributed to these inconsistencies. Furthermore, the possibility of a nonlinear relationship between levels of fasting glucose (7) or insulin and DepS may explain these inconsistencies.

To dissect the effect of T2D diagnosis/treatment from the influences of biomarkers, it is crucial to examine associations prospectively between insulin and glucose levels and DepS and controlling for T2D status. It is also crucial to take into account the wide range of factors that could act as confounders. For example, the associations between glucose, insulin and

DepS may be explained by common causes, such as obesity, low socioeconomic status, or stroke.

In the present large-scale longitudinal study, we examined whether measures of glucose and insulin were prospectively associated with new-onset DepS over 5 years of follow-up. In order to minimize the depressogenic effects of T2D diagnosis/treatment, analyses were performed taking into account T2D status at study baseline and repeated in a subgroup of non-diabetic participants. We tested the strength of the findings by controlling for a wide range of potential confounders and mediators, including socio-demographic characteristics, health behaviors, inflammatory markers, cortisol, and health factors, such as cardio- and cerebrovascular diseases.

RESEARCH DESIGN AND METHODS

Population and Study Design

Data were from the Whitehall II Study(27), a large-scale prospective cohort study of 10308 civil servants (6895 men and 3413 women) aged 35 to 55 years at the start of the study (phase 1: 1985–1988). Since phase 1, follow-up examinations have taken place approximately every 5 years: phase 3 (1991–1993), n=8104; phase 5 (1997–1999), n=7263; phase 7 (2003–2004), n=6943, and phase 9 (2008–2009), n=6354. After complete description of the study to the subjects, written informed consent was obtained; the University College London ethics committee approved the study.

Phase 7, when DepS were first measured using the Center for Epidemiologic Studies Depression Scale (CES-D), serves as the baseline for the current analysis. As described in the study flow-chart (Appendix- Figure A), 3145 participants (2406 men, and 739 women) of the 4978 participants free from DepS at phase 7, were included in the analysis. Compared to those excluded, participants included were younger, less likely to be women and from the lowest occupational grades (all p<0.001). They were also less likely to have prevalent T2D (p<0.001) and less likely to develop DepS at phase 9 (p=0.03), in addition to having lower levels of fasting glucose, fasting insulin, insulin secretion and insulin resistance (all p<0.001) at Phase 7.

Data Collection

Measurement of fasting glucose and fasting insulin at phase 7 (baseline) and phase 9 (follow-up). Blood samples were taken in the morning from participants after ≥8 hours of fasting or after ≥5 hours if afternoon sampling was done. Glucose samples were drawn into fluoride monovette tubes and insulin samples into native tubes, which were centrifuged on site within 1 hour. Plasma or serum was immediately removed from the monovette tubes, and

moved into microtubes and stored at −70°C. Blood glucose was measured with the glucose

oxidase method on YSI model 2300 STAT PLUS analyzer (YSI Corporation, Yellow Springs,

OH, USA), and serum insulin was measured with a DAKO insulin ELISA kit

(DakoCytomation Ltd, Ely, UK) following standard procedures detailed elsewhere[28]. Based

on the updated homoeostasis model assessment (HOMA) methods, HOMA insulin resistance

(HOMA2-%IR) and HOMA beta-cell insulin secretion (HOMA2-%B) were calculated by the

HOMA2 calculator version 2.2 (http://www.dtu.ox.ac.uk/homacalculator/index.php)[29].

Prevalent cases of T2D at phase 7. Diabetes was defined by a fasting glucose

≥7.0mmol/L or a 2h postload glucose ≥11.1 mmol/L during a 75g oral glucose tolerance test

[8] assessed at phase 3, 5 and 7, use of anti-diabetic drugs, or self report of a doctor's

diagnosis.

Assessment of DepS at phases 7 and 9. At both waves, participants with DepS were

defined either by a score ≥16 on the CES-D scale or the use of antidepressants. After

excluding participants with prevalent or unknown DepS at phase 7 (n=1965), incident DepS

over the 5-year follow-up was defined by the presence of DepS at phase 9.

Assessment of covariates at phase 7. Socio-demographic variables consisted of sex,

age, ethnicity (White/ South Asian/ Black), marital status (married, cohabiting / single,

divorced, widowed), civil service employment grade (3 levels with grade 1 representing the

highest level and grade 3 the lowest in terms of salary, social status and level of

responsibility). Health status was ascertained using a number of measures: prevalence of

Coronary Heart Disease (CHD) based on clinically verified non-fatal myocardial infarction or

definite angina; self-reported stroke or transient ischemic attack; hypertension (systolic or

diastolic blood pressure ≥140 or ≥90 mm Hg respectively or use of hypertensive drugs); high

density lipoprotein (HDL) cholesterol and use of lipid-lowering drugs; smoking status (non /

former/ current smoker); central obesity (a waist circumference >102 cm in men and >88 cm

in women); and cognitive impairment defined by a score ≤27 in the Mini Mental State Examination (MMSE).

At phase 7, we additionally assessed inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) (30) and cortisol secretion (31), as previously described. Women's health factors included menstruation status (still menstruating versus natural menopause) and, for women with natural menopause, use of hormone replacement therapy (HRT) (never/past/current use).

Statistical Analyses

Logistic regression models were performed to assess the association between quintiles of fasting glucose and fasting insulin at phase 7 and new-onset DepS at phase 9. The statistical evidence of sex differences in the insulin-DepS association led us to conduct all these analyses separately in men and women (p for sex interaction=0.004). Odds ratios were sequentially adjusted for age and ethnicity (Model 1), T2D status at phase 7 (Model 2), occupational grade, marital status, smoking behavior, stroke, CHD, hypertension, use of lipid lowering drugs, decreased HDL-cholesterol, central obesity and cognitive impairment (MMSE) (Model 3). Similar logistic regression models were performed to assess the association between indices of insulin resistance (HOMA2-%IR) and insulin secretion (HOMA2-%B) categorized in quintiles at phase 7 and new-onset DepS at phase 9. To assess the extent to which the associations were driven by biological processes involved in T2D or the depressogenic effect of treatment and management of T2D, analyses were repeated after excluding participants with T2D at phase 7.

To examine the robustness of the associations studied and to obtain information on potential mechanisms which could mediate the observed associations, we conducted several

sets of supplementary analyses which were adjusted successively for inflammatory markers, women's health measures and cortisol secretion variables.

All analyses were conducted using SAS software, version 9 (SAS Institute, Cary, NC, USA).

RESULTS

Over the 5-year follow-up, 142 men (5.9%) and 84 women (11.4%) developed DepS.

Table 1 presents the characteristics of participants as a function of new-onset DepS separately

for men and women. Means (SD) of fasting insulin and fasting glucose were significantly

higher in men (insulin: 9.26 (6.27) uIU/mL, glucose: 5.45 (0.76) mmol/L) compared to

women (insulin: 8.51 (5.38) uIU/mL, glucose: 5.19 (0.60) mmol/L).

Analyses of the associations of quintiles of fasting glucose and fasting insulin with

new-onset of DepS over the 5-year follow-up were performed separately for men (Appendix-

Table A1) and women (Appendix-Table A2). No association between fasting glucose and

onset of DepS was observed before or after taking into account T2D status and other

covariates at baseline.

Women in the lowest quintile of the insulin distribution tended to show higher odds of

new onset of DepS compared to those in other quintiles although the overall heterogeneity

between quintiles did not reach statistical significance (p = 0.09). Compared to women in the

first insulin quintile, the fully-adjusted odds of developing DepS was reduced by 51%, 56%,

43% and 62% for women in the 2nd, 3rd, 4th and 5th quintiles, respectively (Appendix-Table

A2, Model 3). Similar analyses carried out in 2929 non-diabetic participants showed that

while the direction and magnitude of associations were similar, the results in the non-diabetic

women were attenuated. No significant association between insulin and DepS was observed

in men (Appendix-Table A1).

To further examine insulin metabolism in women, we analyzed the associations of

insulin resistance (assessed by HOMA2-%IR) and insulin secretion (assessed by HOMA2-

%B) with new-onset of DepS in women (Figure 1). The first quintile of HOMA2 -%IR (i.e.

women with lower level of insulin resistance or higher level of insulin sensitivity) tended to

be associated with an increased odds of new-onset DepS although this association did not

reach statistical significance. In contrast, women in the first quintile of HOMA2-%B (i.e. women with lower levels of insulin secretion) showed significantly increased odds of developing DepS compared to those in the other quintiles (Figure 1). This association was not attenuated after adjustment for T2D and other potential confounders or when analyses were confined to non-diabetic women only. Figure 1 also shows that the odds of developing DepS did not differ significantly between women with insulin secretion in the 2nd, 3rd, 4th or 5th quintile, suggesting that low insulin secretion may be a risk factor for DepS in women.

To examine the robustness of this finding, we performed a set of logistic regression models comparing risk of DepS between women in the lowest insulin secretion group (HOMA2-%B ≤ 55.3%) with those with higher insulin secretion levels (HOMA2-%B >55.3 %)(Table 2). Even after adjustment for socio-demographic, health behavior and health status factors, women with low insulin secretion had a 2-fold increased odds of developing DepS over the 5-year follow-up, compared to those with higher insulin secretion levels (Models A and B). This association was not accounted for by the inflammatory markers IL6 and CRP (Model C); HPA axis related indicators, such as diurnal slope of cortisol secretion and waking cortisol (Model D); or women's health factors, such as menopausal status and use of HRT (Model E). Supplementary analyses showed that women in the first quintile of insulin secretion (HOMA2-%B ≤ 55.3%) were more likely to have higher fasting glucose and insulin sensitivity and a lower level of insulin than other women (results not shown, but available upon request).

To examine the robustness of our findings, we repeated analyses 1) after defining DepS by a CES-D score ≥23 or use of anti-depressive drugs, a measure indicating more severe DepS, 2) after excluding participants who had DepS at phase 3 or phase 5 (i.e. prior to study baseline), as assessed by the use of anti-depressive drugs or a score ≥4 on the four-item

depression subscale of the 30-item General Health Questionnaire (GHQ) (32). The results

changed little in these sensitivity analyses (results not shown but available upon request).

No associations of indices of insulin resistance and insulin secretion with new-onset

DepS were observed in men (results not shown).

DISCUSSION

In the present report we investigated the prospective association between glucose metabolism and DepS in a large cohort of pre-elderly participants. While no longitudinal association was found between fasting glucose and DepS in either sex, we found that women with low insulin secretion (HOMA2-%B ≤ 55.3%) had a 2-fold increased odds of developing DepS over the 5-year follow-up compared to those with higher insulin secretion (HOMA2-%B >55.3%). This association was independent of TD2 status and associated common metabolic disorders, coronary heart disease and cognitive impairment. The association was also robust to adjustment for inflammatory markers, cortisol secretion profiles, menopausal status and hormone replace therapy.

Some previous studies have suggested that disturbed glucose homeostasis *per se* is an implausible cause of DepS (3, 4). One investigation found an increased prevalence of DepS among participants aware of their T2D status but not among undiagnosed diabetic subjects (4). Another study provided evidence that treated T2D patients but not untreated participants with impaired fasting glucose had a higher incidence of DepS, suggesting that DepS may be a consequence of the treatment regime (3). The lack of evidence supporting an association between fasting glucose and DepS in our findings accords with these studies and suggests that the process linking T2D to depression may not involve a direct path between hyperglycemia and related glucose transport alteration and depression risk.

Previous findings on the association between insulin levels, indices of insulin resistance and DepS are mixed and mostly come from cross-sectional studies (17-26). By investigating these associations prospectively in a large pre-elderly population including both men and women, our analyses make a contribution to this area of research. Women with low insulin secretion and low insulin resistance appeared to have an increased risk of developing DepS. These women, compared to other women, had a slightly elevated fasting glucose. From

our understanding of the trajectories of insulin secretion leading to T2D development (7), the biomarker profile of these women - characterized by a decrease in insulin secretion together with an increase in glucose levels - could actually correspond to women in the non-diabetic range but very close to the onset of T2D and thus unable to increase their insulin secretion in response to increasing glucose levels.

Our finding is in accordance with the cross-sectional data from the British Women's Heart and Health Study in which prevalence of depression was inversely associated with insulin resistance in 4286 women aged 60-79 years(26). Our results are also in agreement with a prospective study reporting that accumulation of factors related to high insulin sensitivity was associated with an increased risk of suicide in a Finnish population (33).

The reason why this association was found in women only remains unclear. To study whether this sex difference might reflect sex-specific characteristics of insulin metabolism, we performed additional analyses in which menopausal status and HRT were taken into account. We found no evidence to suggest that menopausal status or HRT mediate the association between insulin secretion and DepS, making these factors an unlikely explanation of our results. A further possible explanation, although untestable with the present dataset, is that the instrument we used to assess DepS may be less sensitive to male depression; it has been suggested that the CES-D scale may measure different phenomena in men and women (34, 35). Further prospective studies using clinical interview or other sensitive measures to detect depression both in men and women are needed to understand the underpinning of these sex differences.

The present analysis took into account a large range of clinical characteristics and health behaviors. Inflammatory markers, such as CRP and IL6, and activation of the HPA axis have previously been linked with both development of T2D (11, 36) and DepS (11, 37) and may confound the studied association. However, we found no evidence to suggest that the

inflammatory factors measured, CRP and IL6, or diurnal cortisol patterns were driving the observed association between insulin metabolism and DepS.

Further investigations are needed to better understand the mechanism underlying the low insulin secretion-DepS association. In particular, we suggest that future research should consider the possible physiologic pathway between inadequate insulin action and and DepS via increased central serotonin production, proposed by Golomb et al. (33). Briefly, as insulin action may suppress postprandial mobilization of non-esterified fatty acids from adipose tissue, lower postprandial free fatty acid levels are expected in a state of low insulin secretion. This would translate into lower availability of the free fraction of tryptophan, which is a rate limiting substrate of serotonin production and is associated with mood disorders, as illustrated in Appendix-Figure B.

Limitations of the present findings include, first, the use of the CES-D scale to assess depressive symptoms, as it is not a measure of clinically recognized psychiatric disorder. Although the CES-D scale has been validated in epidemiological studies carried out in the general population, it does not indicate the severity or the chronicity of depression. Furthermore, as the recall period for CES-D symptoms is over the past week, with only two measures over a 5-year period, it is difficult to provide accurate information on incidence of DepS. However, this is unlikely to cause a major bias in our results given that a similar pattern of insulin secretion-DepS association was observed after excluding DepS cases identified using the General Health Questionnaire over a 10-year period before the study baseline.

A further limitation relates to HOMA models as measures of insulin resistance and insulin secretion. As HOMA2-%IR and HOMA2-%B uses the same fasting values for estimation, we were unable to calculate the disposition index which is a measure of insulin secretion accounting for the underlying degree of insulin resistance (38). We therefore

interpret our findings cautiously. In the present study, the group of non-diabetic women with low HOMA2-%B and increased risk of developing depressive symptoms tend to have low HOMA2-%IR and elevated fasting glucose values. This suggests that these women were in prediabetic state, although at this stage we do not have data to confirm this hypothesis.

A further drawback is related to the fact that participants of the Whitehall II study are mainly office-based civil servants who are not fully representative of the British population. This may limit the generalizability of our findings. We cannot exclude the possibility that we observed the higher odds of DepS found in women with the lowest insulin and insulin secretion levels by chance. In addition, with observational data the possibility remains that unmeasured confounders may explain the observed association. However, the robustness of the association between insulin levels and depressive symptoms after taking into account a wide range of potential confounders and mediators including socio-demographic characteristics, health behavior, health factors such as chronic diseases, inflammatory factors and cognitive performance, makes less probable that the observed association between insulin secretion and onset of depressive symptoms was an artifact.

In conclusion, our findings suggest that low insulin secretion is associated with an increased risk of DepS in middle-aged women after taking into account potential confounders, such as common cardio metabolic disorders, cognitive impairment, inflammatory markers, cortisol secretion profiles, menopausal status and hormone replacement therpy. This study
supports the hypothesis of a direct impact of insulin secretion on new-onset depression risk in women. It does not exclude the possibility that depressive symptoms relate to type 2 diabetes as in longstanding type 2 diabetes insulin secretion is decreasing. However, additional arguments are needed to establish the exact biological mechanisms linking insulin metabolism and depression risk and to clarify reasons for the observed gender differences.

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FIGURE 1: Association between indices of insulin resistance, insulin secretion and new onset of CES-D depression over the 5-year follow-up in women

Figure 1 footnotes:

OR, Odds ratio for new onset of CES-D depression; HOMA, homeostasis model assessment; Q, quintile.

Median and range for HOMA2 insulin resistance quintiles were for Q1: 0.45 (0.34- 0.52), Q2: 0.62 (0.53- 0.70), Q3 : 0.83 (0.71- 0.95), Q4: 1.12 (0.96- 1.35) and Q5: 1.87 (1.36- 7.69)

Median and range (%) for HOMA2 insulin secretion quintiles were: 48.8 (13.8- 55.3), Q2: 61.1 (55.4- 67.4), Q3 : 73.7 (67.5- 80.7), Q4: 89.6 (80.8- 100.7) and Q5: 122.9 (100.8- 416.5)

Model 1: Model adjusted for age and ethnicity

Model 2: Model 1 additionally adjusted for type 2 diabetes prevalence at baseline.

Model 3: Model 2 additionally adjusted for occupational grade, marital status, smoking, stroke, coronary heart disease, hypertension, low HDL-cholesterol, use of lipid-lowering drugs, central obesity, and cognitive impairment

* All P-values are for tests of heterogeneity in odds ratios of new-onset depressive symptoms.

Table 1: Characteristics of participants according to onset of CES-D depression between phase 7 and phase 9

Baseline characteristic		Men (n=2406)			Women (n=739)		
		Onset of CES-D depression			Onset of CES-D depression		
		No*	Yes*	*P*	No*	Yes*	*P*
		n=2264	n=142		n=655	n=84	
Age (years)		60.6 (5.8)	61.7 (6.5)	0.04	60.5 (5.9)	60.2 (5.4)	0.62
Employment grade	High	59.8	47.2	0.01	29.6	29.8	0.98
	Intermediate	37.7	50.0		49.8	48.8	
	Low	2.5	2.8		20.6	21.4	
Ethnicity	White	96.8	89.4	<0.001	91.9	95.2	0.39
	South Asian	2.4	9.1		3.8	3.6	
	Black	1.4	0.8		4.3	1.2	
Marital status	Married	86.0	77.5	0.005	59.8	64.3	0.43
Smoking status	Non	48.9	45.8	0.31	58.5	54.8	0.09
	Former	45.0	45.1		33.9	42.9	
	Current	6.0	9.1		7.6	2.4	
History of CHD	yes	5.7	11.3	0.007	4.0	9.5	0.02
Self reported stroke	Yes	2.1	4.9	0.03	1.7	2.4	0.64
T2D	Yes	6.7	9.1	0.25	7.2	5.9	0.68
Hypertension	Yes	36.0	38.0	0.46	36.0	25.0	0.04
HDL-cholesterol (mmol/L)		1.46(0.36)	1.48(0.39)	0.70	1.84 (0.49)	1.91(0.45)	0.23
Lipid lowering drugs	Use	10.2	15.6	0.04	8.7	9.5	0.80
Central obesity	Yes	23.6	20.4	0.39	46.3	42.9	0.56
Cognitive Impairment	Yes	10.7	11.3	0.84	13.74	7.1	0.10

For each characteristic the % (for categorical variable) or mean (SD) (for continuous variable) are presented.

Table 2: Association between being in the low insulin secretion group and new onset of depressive symptoms in non diabetic women (n=687)

	Odds of developing CES-D depression for low vs. high insulin secretion *		
	OR	95% CI	*p*
Model A: Adjusted for age and ethnicity (79 cases / n=687)	2.18	1.25;3.78	*<0.001*
Model B: Model A + additional adjustment for socio-demographic, health behavior and health status factors (79 cases / n=687)	2.14	1.18;3.89	*0.01*
Model C: Model A + additional adjustment for inflammatory markers **			
CRP and IL6 (79 cases / n=684)	2.17	1.23;3.82	*0.007*
Model D: Model A + additional adjustment for diurnal cortisol patterns†			
Waking cortisol (47 cases / n=423)	2.91	1.47;5.76	*0.002*
Slope across the day (47 cases / n=427)	2.74	1.40;5.42	*0.004*
Model E: Model A + additional adjustment for women's health variables‡			
Menopause status (56 cases / n=486)	2.44	1.29;4.62	*0.006*
Use of HRT (45 cases / n=418)	2.46	1.20;5.06	*0.01*

Abbreviations: Confidence interval, CI; CRP, C-reactive protein; HRT, Hormone replacement therapy; IL6, Interleukin 6; odds ratio, OR.

*Odds ratio for depressive symptoms in women with low insulin secretion (defined as having HOMA2-% B in the 1st quintile (HOMA2-%B ≤55.3 %) compared to those with higher insulin secretion (HOMA2-%B>55.3 %).

Model A odds ratio in subgroups:

** 2.16, 95% CI: 1.24-3.76 in the 684 women with data on inflammatory markers,

† 2.89, 95% CI: 1.46-5.70 in the 423 women with data on waking cortisol and 2.80, 95% CI: 1.42-5.51 in the 427 women with data on cortisol slope.

‡ 2.48, 95% CI: 1.31-4.67 in the 486 women with data on menopausal status and 2.54, 95% CI: 1.24-5.19 in the 418 women with data on HRT.