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

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

RESEARCH DESIGN AND METHODS—In this prospective cohort study of 3,145 adults from the Whitehall II Study (23.5% women, aged 60.6 ± 5.9 years), baseline examination included fasting glucose and insulin level, the homeostasis model assessment of insulin resistance (HOMA2-%IR), and the homeostasis model assessment of β-cell insulin secretion (HOMA2-%B). DepS (Center for Epidemiologic Studies Depression Scale ≥16 or use of antidepressive drugs) were assessed at baseline and at 5-year follow-up.

RESULTS—Over the 5-year follow-up, DepS developed in 142 men and 84 women. 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 than 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 measures were not associated with new-onset DepS in either sex.

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

Diabetes Care 36:928–934, 2013

Type 2 diabetes (T2D) is associated with depression (1,2). Plausible mechanisms underlying this association include the depressogenic effect of the treatment and management of T2D (3–6) and of the influence of the T2D diagnosis itself because it can be viewed as a stressful life event (7,8). Recently, the hypothesis that the link between diabetes and depression results 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 (HPA) 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 level and depression are mixed. Some investigations found that impaired fasting glucose (11) and high glycated hemoglobin (12) are associated with increased DepS, but others failed to observe this association (4,13–15) or suggested that the association varies by sex (16,17). Similarly, associations between hyperinsulinemia, insulin resistance, and depression showed conflicting results with findings from six 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 and 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 levels of glucose and 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. To minimize the depressogenic effects of T2D diagnosis and treatment, analyses took into account T2D status at study baseline and repeated in a subgroup of nondiabetic participants. We tested the strength of the findings by controlling for a wide range of potential confounders and mediators, including sociodemographic characteristics; health behaviors; inflammatory markers; cortisol; and health factors, such as cardiovascular and cerebrovascular diseases.

RESEARCH DESIGN AND METHODS

Population and study design

Data were from the Whitehall II Study (27), a large-scale prospective cohort

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Received 3 February 2012 and accepted 30 September 2012.
DOI: 10.2337/dc12-0239
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0239/-/DC1.

study of 10,308 civil servants (6,895 men and 3,413 women) aged 35–55 years at the start of the study (phase 1 1985–1988). Since phase 1, follow-up examinations have taken place approximately every 5 years, as follows: phase 3 (1991–1993) n = 8,104, phase 5 (1997–1999) n = 7,263, phase 7 (2003–2004) n = 6,943, and phase 9 (2008–2009) n = 6,354. After a 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 flowchart (Supplementary Fig. 1), 3,145 participants (2,406 men and 739 women) of the 4,978 participants free from DepS at phase 7 were included in the analysis. Compared with those excluded, included participants 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 to develop DepS at phase 9 ($P = 0.03$) and had 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 h of fasting or after ≥5 h 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 h. Plasma or serum was immediately removed from the monovette tubes and moved into microtubes and stored at −70°C. Blood glucose level was measured with the glucose oxidase method on YSI model 2300 STAT Plus analyzer (YSI Corporation, Yellow Springs, OH), and serum insulin was measured with an insulin enzyme-linked immunosorbent assay kit (DakoCytomation Ltd, Ely, U.K.) following standard procedures detailed elsewhere (28). Based on updated homeostasis model assessment (HOMA) methods, HOMA insulin resistance (HOMA2-%IR) and HOMA β-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 level of ≥7.0 mmol/L or a 2-h postload glucose level of ≥11.1 mmol/L during a 75-g oral glucose tolerance test (8) assessed at phases 3, 5, and 7; use of antidiabetic drugs; or self-report of a physician's diagnosis.

Assessment of DepS at phases 7 and 9. At both phases, DepS was defined by either a score ≥16 on the CES-D or the use of antidepressants. After excluding participants with prevalent or unknown DepS at phase 7 (n = 1,965), incident DepS over the 5-year follow-up was defined by the presence of DepS at phase 9.

Assessment of covariates at phase 7. Sociodemographic variables comprised sex, age, ethnicity (white, South Asian, black), marital status (married, cohabiting/single, divorced, widowed), and civil service employment grade (three 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 the following measures: prevalence of coronary heart disease (CHD) based on clinically verified nonfatal myocardial infarction or definite angina; self-reported stroke or transient ischemic attack; hypertension (systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, or use of hypertensive drugs); HDL cholesterol and use of lipid-lowering drugs; smoking status (non-, former, or current smoker); central obesity (waist circumference >102 cm in men and >88 cm in women); and cognitive impairment defined as a score ≤27 on the Mini-Mental State Examination.

At phase 7, we also assessed levels of inflammatory markers (interleukin [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, or 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 (ORs) were sequentially adjusted for age and ethnicity (model 1); T2D status at phase 7 (model 2); and occupational grade, marital status, smoking behavior, stroke, CHD, hypertension, use of lipid-lowering drugs, decreased HDL cholesterol, central obesity, and cognitive impairment (Mini-Mental State Examination) (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 that could mediate the observed associations, we conducted several sets of supplementary analyses that were adjusted successively for inflammatory markers, women's health measures, and cortisol secretion variables. All analyses were conducted with SAS version 9 (SAS Institute, Cary, NC) statistical software.

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. Mean (SD) fasting insulin and fasting glucose levels were significantly higher in men (insulin 9.26 (6.27) μIU/mL, glucose 5.45 (0.76) mmol/L) than in women (insulin 8.51 (5.38) μIU/mL, glucose 5.19 (0.60) mmol/L).

Analyses of the associations of quintiles of fasting glucose and fasting insulin with new-onset DepS over the 5-year follow-up were performed separately for men (Supplementary Table 1) and women (Supplementary Table 2). No association between fasting glucose level 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 DepS than those in other quintiles, although the overall heterogeneity between quintiles did not reach statistical significance (P = 0.09). Compared with women in the first insulin quintile, the fully adjusted

Table 1—*Characteristics of participants according to onset of DepS as measured by CES-D between phase 7 and phase 9*

	Onset of DepS					
	Men (*n* = 2,406)			Women (*n* = 739)		
Baseline characteristic	No (*n* = 2,264)	Yes (*n* = 142)	*P* value	No (*n* = 655)	Yes (*n* = 84)	*P* value
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						
Nonsmoker	48.9	45.8	0.31	58.5	54.8	0.09
Former smoker	45.0	45.1		33.9	42.9	
Current smoker	6.0	9.1		7.6	2.4	
History of CHD	5.7	11.3	0.007	4.0	9.5	0.02
Self-reported stroke	2.1	4.9	0.03	1.7	2.4	0.64
T2D	6.7	9.1	0.25	7.2	5.9	0.68
Hypertension	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	10.2	15.6	0.04	8.7	9.5	0.80
Central obesity	23.6	20.4	0.39	46.3	42.9	0.56
Cognitive impairment	10.7	11.3	0.84	13.74	7.1	0.10

Data are % for categorical variables and mean (SD) for continuous variables.

odds of developing DepS was reduced by 51, 56, 43, and 62% for women in the second, third, fourth, and fifth quintiles, respectively (Supplementary Table 2, model 3). Similar analyses carried out in 2,929 nondiabetic participants showed that although the direction and magnitude of associations were similar, the results in the nondiabetic women were attenuated. No significant association between insulin level and DepS was observed in men (Supplementary Table 1).

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 DepS (Fig. 1). The first quintile of HOMA2-%IR (i.e., women with a lower level of insulin resistance or higher level of insulin sensitivity) tended to be associated with 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 than those in the other quintiles (Fig. 1). This association was not attenuated after adjustment for T2D and other potential confounders or when analyses were confined to nondiabetic women only. Figure 1 also shows that the odds of developing DepS did not differ significantly among women with insulin secretion in the second, third, fourth, or fifth quintiles, suggesting that a low level of 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%) and women in the highest insulin secretion group (HOMA2-%B >55.3%) (Table 2). Even after adjustment for sociodemographic, health behavior, and health factors, women with low insulin secretion levels had a twofold increased odds of developing DepS over the 5-year follow-up compared with those with higher insulin secretion levels (models A and B). This association was not accounted for by the inflammatory markers IL-6 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 levels of fasting glucose and insulin sensitivity and a lower level of insulin than other women (data not shown but available upon request).

To examine the robustness of the findings, we repeated analyses after defining DepS by a CES-D score ≥23 or use of antidepressive drugs, a measure indicating more severe DepS, and after excluding participants who had DepS at phase 3 or phase 5 (i.e., before study baseline), as assessed by the use of antidepressive drugs or a score ≥4 on the four-item depression subscale of the 30-item General Health Questionnaire (32). The results changed little in these sensitivity analyses (data not shown but available upon request). No associations of indices of insulin resistance and insulin secretion with new-onset DepS were observed in men (data not shown).

CONCLUSIONS—We investigated the prospective association between glucose metabolism and DepS in a large cohort of pre-elderly participants. Although no longitudinal association was found between fasting glucose level and DepS in either sex, we found that women with low insulin secretion levels (HOMA2-%B ≤55.3%) had a twofold increased odds of developing DepS over the 5-year follow-up compared with those with higher insulin secretion levels (HOMA2-%B >55.3%). This association was independent of T2D status and associated common metabolic disorders, CHD, and cognitive impairment. The association was also robust when adjusted for inflammatory markers, cortisol secretion profiles, menopause status, and HRT.

Some previous studies 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

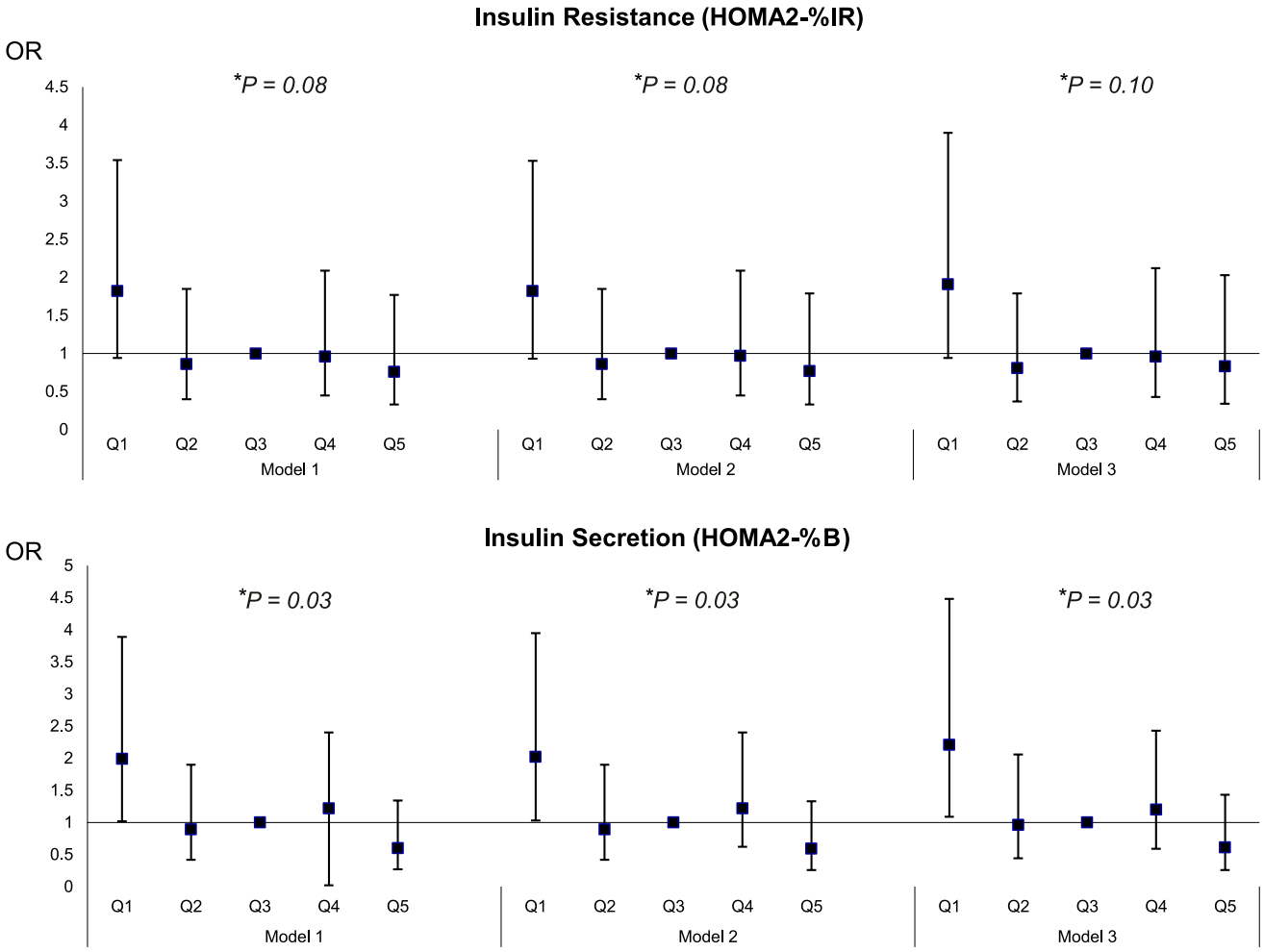

Figure 1—*Association between indices of insulin resistance and insulin secretion and new-onset DepS as measured by the CES-D over the 5-year follow-up in women. Median (range) ORs for HOMA2 insulin resistance quintiles are as follows: Q1 0.45 (0.34–0.52), Q2 0.62 (0.53–0.70), Q3 0.83 (0.71–0.95), Q4 1.12 (0.96–1.35), and Q5 1.87 (1.36–7.69). Median (range) percents for HOMA2 insulin secretion quintiles are as follows: Q1 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 is adjusted for age and ethnicity; model 2, model 1 plus adjustment for T2D prevalence at baseline; and model 3, model 2 plus adjustment for occupational grade, marital status, smoking, stroke, CHD, hypertension, low HDL cholesterol, use of lipid-lowering drugs, central obesity, and cognitive impairment. *All P values are for tests of heterogeneity in ORs of new-onset DepS.*

but not untreated patients with impaired fasting glucose had a higher incidence of DepS, suggesting that DepS may be a consequence of the treatment regimen (3). The lack of evidence supporting an association between fasting glucose level and DepS in the present study accords with these previous 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, the present analyses contribute to this area of research. Women with low levels of insulin secretion and insulin resistance appeared to have an increased risk of developing DepS. These women, compared with other women, had a slightly elevated fasting glucose level. 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 nondiabetic women who are very close to the onset of T2D and whose insulin secretion does not increase in response to increasing glucose levels.

The present findings are in accordance with the cross-sectional data from the British Women's Heart and Health Study (n = 4,286 women aged 60–79 years), in which prevalence of depression was inversely associated with insulin resistance (26). The present results also agree with a prospective study reporting that accumulation of factors related to high insulin sensitivity is associated with an increased risk of suicide in a Finnish population (33).

The reason why this association was found in only women remains unclear. To study whether this sex difference might reflect sex-specific characteristics of insulin metabolism, we performed additional analyses in which menopausal

Table 2—*Association between low insulin secretion and new onset DepS in nondiabetic women* (n = 687)

	Odds of developing DepS*	
	OR (95% CI)	*P* value
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 sociodemographic, 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 IL-6 (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

*OR for DepS in women with low insulin secretion levels (defined as having HOMA2-%B in the first quintile [HOMA2-%B ≤55.3%]) compared with those with higher insulin secretion levels (HOMA2-%B >55.3%). **OR 2.16 (95% CI 1.24–3.76) in the 684 women with data on inflammatory markers. †OR 2.89 (95% CI 1.46–5.70) in the 423 women with data on waking cortisol and 2.80 (1.42–5.51) in the 427 women with data on cortisol slope. ‡OR 2.48 (95% CI 1.31–4.67) in the 486 women with data on menopause status and 2.54 (1.24–5.19) in the 418 women with data on HRT.

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 the 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 in both men and women are needed to understand the underpinnings of these sex differences.

The present analysis took into account a wide range of clinical characteristics and health behaviors. Inflammatory markers, such as CRP and IL-6, and activation of the HPA axis have previously been linked with development of both 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 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 consider the possible physiologic pathway between inadequate insulin action and DepS through increased central serotonin production, as proposed by Golomb et al. (33). Briefly, because insulin action may suppress postprandial mobilization of nonesterified 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 Supplementary Fig. 2.

Limitations of the present findings include, first, the use of the CES-D scale to assess DepS because it is not a measure of clinically recognized psychiatric disorder. Although the CES-D 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-measured 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 the 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 second limitation relates to HOMA models as measures of insulin resistance and insulin secretion. Because HOMA2-%IR and HOMA2-%B use the same fasting values for estimation, we were unable to calculate the disposition index, which is a measure of insulin secretion that accounts for the underlying degree of insulin resistance (38). We therefore interpret the present findings cautiously. In the current study, the group of nondiabetic women with low HOMA2-%B values and increased risk of developing DepS tended to have low HOMA2-%IR and elevated fasting glucose values. This suggests that these women were in a prediabetic state, although at this stage, we do not have data to confirm this hypothesis.

A third 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 the findings. We cannot exclude the possibility that we observed the higher odds of DepS 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 DepS after taking into account a wide range of potential confounders and mediators, including sociodemographic 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 DepS was an artifact.

In conclusion, the 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 cardiometabolic disorders, cognitive impairment, inflammatory markers, cortisol secretion profiles, menopausal status, and HRT. This study supports the hypothesis of a direct impact of insulin secretion on new-onset depression risk in women. However, it does not exclude the possibility that DepS relate to T2D because, as in participants with longstanding T2D, insulin secretion is decreasing. Further

research is needed to establish the exact biological mechanisms linking insulin metabolism and depression risk and to clarify reasons for the observed gender differences.

Acknowledgments—The Whitehall II Study is supported by grants from the British Medical Research Council (G8802774); the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute (R01-HL-036310); the National Institute on Aging (R01-AG-013196 and R01-AG-034454); and the Agency for Health Care Policy and Research (HS06516). M.Ki. is supported by an Economic and Social Research Council professorial fellowship.

No potential conflicts of interest relevant to this article were reported.

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

T.N.A. carried out the statistical analyses, researched data, and wrote the manuscript. M.Ku., J.H., E.B., M.G.M., and J.E.F. researched data and reviewed and edited the manuscript. K.R., M.-L.A., and I.C. reviewed and edited the manuscript. A.G.T. and M.J.S. researched data, contributed to the discussion, and reviewed and edited the manuscript. M.Ki. researched data and cowrote the manuscript. T.N.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank all participating men and women in the Whitehall II Study; all participating Civil Service departments and their welfare, personnel, and establishment officers; the Occupational Health and Safety Agency; and the Council of Civil Service Unions. The Whitehall II Study team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants, and data entry staff who made the study possible.

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