HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

Psychosom Med. 2014 September ; 76(7): 555–561. doi:10.1097/PSY.0000000000000082.

Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing (ELSA)

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Abstract

Objective—To examine whether the prospective association between depressive symptoms and glucose metabolism is bidirectional.

Methods—We used a national sample of 4,238 community-dwelling individuals aged ≥50 years from the English Longitudinal Study of Ageing. Participants were categorized into normoglycemic, impaired glucose metabolism (IGM), and undiagnosed and diagnosed diabetes using HbA1c and self-reported doctor diagnosis. Subthreshold and elevated depressive symptoms were defined by a score between 2 and 3 and ≥4, respectively, on the 8-item Center for Epidemiological Studies-Depression scale.

Results—In the age-adjusted model, categories of depressive symptoms were associated with incident undiagnosed (OR 1.54, 95% CI 0.86 to 2.73 and OR 1.91, 95% CI 1.03 to 3.57 for subthreshold and elevated depressive symptoms, respectively) and diagnosed diabetes (OR 1.53, 95% CI 0.80 to 2.93 and OR 3.03, 95% CI 1.66 to 5.54, respectively) over six years of follow-up. The latter association remained significant after adjustment for covariates. Depressive symptoms were not associated with future IGM. Diagnosed diabetes was associated with future elevated depressive symptoms in participants aged 52 to 64 years (OR 2.17, 95% CI 1.33 to 3.56), but not those aged 65 years and older (OR 0.96, 95% CI 0.59 to 1.57) over four years of follow-up. Adjustment for covariates partially explained this association. IGM and undiagnosed diabetes were not associated with subsequent elevated depressive symptoms.

Conclusions—These data suggest that there is a bidirectional association between depressive symptoms and diagnosed diabetes in people aged 52 to 64 years, but not people aged 65 years and older.

Keywords

depressive symptoms; type 2 diabetes; glucose metabolism; prospective study; older adults

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Evidence shows that the prevalence of depression is almost doubled in people with type 2 diabetes compared with people without diabetes (1, 2). However, the prevalence of depression in people with undiagnosed diabetes is similar to that of people without diabetes, but lower compared to that of people with diagnosed type 2 diabetes (3). Further, cross-sectional evidence indicates that depression might be weakly associated with insulin resistance (IR) measured using the homeostasis model assessment of insulin resistance (HOMA-IR or HOMA2-IR) (4), but not impaired glucose metabolism (IGM) defined as impaired glucose tolerance and impaired fasting glucose (3).

Longitudinal research suggests that the relationship between type 2 diabetes and depression is possibly bidirectional with elevated depressive symptoms increasing the risk of type 2 diabetes (5, 6) and type 2 diabetes and its complications increasing the risk of elevated depressive symptoms (6, 7).

Despite a large number of studies on the association between depression and diabetes, the evidence on the association between categories of depressive symptoms or depressive disorder and incident type 2 diabetes (8-13) is limited and inconsistent. Thus, it remains unclear whether subthreshold depressive symptoms are associated with increased risk of type 2 diabetes in the general population. Moreover, evidence on whether categories of depressive symptoms are associated with future IGM is scarce (10, 14) and the prospective association between categories of depressive symptoms and undiagnosed diabetes has yet to be studied.

Another issue that requires further exploration is the association between categories of glucose metabolism and subsequent elevated depressive symptoms. Two recent meta-analyses of prospective studies show that type 2 diabetes is rather weakly associated with subsequent elevated depressive symptoms (6, 7), but our knowledge of the prospective association between glucose metabolism categories and elevated depressive symptoms remains limited (15, 16).

We used a national sample of community-dwelling people aged 50 years and older to examine the prospective association between categories of depressive symptoms (no/one, subthreshold, or elevated depressive symptoms) and subsequent IGM and incident undiagnosed and diagnosed type 2 diabetes. Further, because the association between depressive symptoms and diabetes is likely bidirectional (6, 7), we examined the longitudinal association between categories of glucose metabolism and subsequent elevated depressive symptoms.

Research Design and Methods

The data came from the English Longitudinal Study of Ageing (ELSA), a panel study of older people in England (see http://www.ifs.org.uk/ELSA). The ELSA sample was designed to represent the community-dwelling population aged 50 years and over in England and was selected from households that had earlier responded to the Health Survey for England. The ELSA baseline interview was in 2002-03. After the baseline interview follow-up interviews took place every other year. All interviews were face-to-face. Anthropometric data and blood samples were collected by nurses at participants' home during health examinations

that took place in parallel with the interviews in 2004-05 and 2008-09. ELSA has been approved by the National Research Ethics Service and informed consent has been obtained from the participants.

The sample comprised 11,391 men and women at baseline and 8,780 at the first follow-up interview in 2004-05 of whom 6,260 participated in the third follow-up interview in 2008-09. Blood samples were collected from 4,791 of these participants (4,497 with valid HbA1c values) in the first health examination, while blood samples from both health examinations were available for 3,752 participants (3,328 with valid HbA1c values). The sample in analysis 1 comprised 2,914 men and women after the exclusion of prevalent cases of self-reported diabetes or HbA1c≥6.5% at the first health examination (n=268) and participants with missing values in any of the variables used in the analysis (n=146). The follow-up time in this part of the analysis was six years (from 2002-03 to 2008-09).

The sample in analysis 2 comprised 4,238 men and women after excluding those with missing values in any of the variables used in the analysis (n=259) among participants who had a valid HbA1c value in the first health examination. This sample was larger than that of analysis 1 because of the use of different exclusion criteria i.e. cases of prevalent diabetes or HbA1c≥6.5% at the first health examination as well as those without diabetes data in the second health examination were not excluded from the analysis. The follow-up time in this part of the analysis was four years (from 2004-05 to 2008-09) because HbA1c had not been measured at baseline in 2002-03 and thus the baseline data could not be used.

Assessment of glucose metabolism and type 2 diabetes

Self-reported doctor-diagnosed diabetes and HbA1c were used to derive categories of glucose metabolism. HbA1c was categorized according to American Diabetes Association (ADA) criteria (17) in normoglycemia (HbA1c<5.7%), IGM (HbA1c from 5.7% to 6.4%), and diabetes (HbA1c≥6.5%). The glucose metabolism variable, which was the outcome in analysis 1 and the predictor in analysis 2, had the following categories: normoglycemia (no self-reported diabetes and HbA1c<5.7%), IGM (no self-reported diabetes and HbA1c from 5.7% to 6.4%), undiagnosed diabetes (no self-reported diabetes and HBA1c ≥6.5%), and diagnosed diabetes (self-reported diabetes).

The Health Survey for England 2004 technical report (http://bit.ly/YFUjar) can be used to obtain information about the measurement of HbA1c and other blood analytes in ELSA as both surveys used the same infrastructure and protocols to analyse the blood samples.

Measurement of depressive symptoms

Depressive symptoms were measured using the 8-item Centre for Epidemiologic Studies-Depression scale (CES-D) (18). CES-D is not a diagnostic instrument but is widely used to identify people at risk of depression (17, 18). The 8-item CES-D includes five depressed mood items and three somatic complaints items and its psychometric values are known and comparable to those of the full 20-item CES-D (18). A CES-D summary score was derived by summing responses to the eight dichotomous questions (possible range: 0-8). A dichotomous variable of elevated depressive symptoms, which was the outcome in analysis 2, was derived by dichotomizing the summary score around the cut point of 4 or higher,

which corresponds to the cut point of 16 or higher on the full 20-item CES-D (19). The sensitivity and specificity of this categorization has been reported to be excellent on the 8-, 9- and 10-item CES-D (i.e. in most cases >80%) and its positive predictive value acceptable (i.e. in most cases>40%) (20-22). To explore the potential impact of subthreshold depressive symptoms on subsequent glucose metabolism status we derived a 3-category variable of depressive symptoms with the following categories: “none or one depressive symptom” (CES-D score: 0-1); “subthreshold depressive symptoms” (CES-D score: 2-3); and “elevated depressive symptoms” (CES-D score: ≥4). This variable was the predictor in analysis 1.

Measurement of covariates

The following covariates were used as potential confounders: age, sex, marital status, socioeconomic position (i.e. categories of educational qualifications and quintiles of total net household wealth), and counts (0,1,2+) of self-reported doctor diagnosed cardiovascular (i.e. hypertension, angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, and stroke) and non-cardiovascular comorbidities (chronic lung disease, asthma, arthritis, osteoporosis, cancer/malignant tumour excluding minor skin cancers, Parkinson's disease, emotional/nervous/psychiatric problems, Alzheimer's disease, and dementia or other serious memory impairment). Smoking, frequency of alcohol consumption, physical activity, body mass index (BMI)(<25, ≥25 to <30, ≥30, and missing), fibrinogen, and high sensitivity C-reactive protein (CRP) were assessed as potential mediators of the examined associations (6, 23-27). In analysis 1, all covariates were measured at baseline in 2002-03 except for BMI and fibrinogen and CRP, which were measured in the first health examination in 2004-05. In analysis 2, all covariates were measured at the first follow-up interview in 2004-05.

Statistical analysis

Analysis 1: Depressive symptoms as a predictor of glucose metabolism—

Multinomial logistic regression was used to model the association between categories of depressive symptoms (none/one, subthreshold, or elevated depressive symptoms) at baseline in 2002-03 and categories of glucose metabolism (normoglycemia, IGM, and undiagnosed and diagnosed diabetes) in 2008-09. The analysis included only incident cases of diabetes (either self-reported or ascertained by HbA1c) i.e. new cases of diabetes that were diagnosed or identified after the first follow-up interview in 2004-05. Prevalent cases of diabetes that have been diagnosed or identified at the first follow-up interview or earlier were excluded from analysis. All incident cases were treated as cases of type 2 diabetes because they were 50 years and older at the time of diagnosis or identification. Despite using incident cases that were identified or diagnosed after the first follow-up interview in 2004-05 we used the baseline interview in 2002-03 as our baseline to allow time for depressive symptoms to exert their effect. Further, we have not excluded from our analysis participants with IGM in 2004-05 because this would have biased our results in relation to diabetes incidence. To examine whether depressive symptoms were associated with change in IGM, we conducted a supplementary analysis that did not include cases of IGM in 2004-05.

Initially we estimated an age-adjusted model, which was then gradually adjusted for sex and marital status, socioeconomic position, comorbidities, BMI, health behaviours (i.e. smoking,

frequency of alcohol consumption and physical activity), and inflammatory markers (i.e. fibrinogen and CRP). We used the pooled sample as there was no significant interaction by age or sex. We also performed non-response analysis to examine whether attrition and non-response to the health examination were related to the examined associations (see Table S1, Supplementary Digital Content 1).

Analysis 2: Glucose metabolism as a predictor of elevated depressive symptoms—Logistic regression models of the association between categories of glucose metabolism in 2004-05 and elevated depressive symptoms in 2008-09 were estimated. The modelling strategy was similar to that employed in analysis 1. In addition, all models were adjusted for elevated depressive symptoms in 2004-05 as the analysis aimed to examine the onset of elevated depressive symptoms in relation to glucose metabolism. Because the likelihood ratio test showed that the association between glucose metabolism categories and elevated depressive symptoms varied according to age (p value of interaction with age for diagnosed diabetes = 0.002) but not sex, we fitted two series of identical models for those aged 52 to 64 years and those aged 65 years and older. The cut point of 65 years was used because that was the mean age of our sample and the state pension age in the United Kingdom.

In supplementary analyses we assessed the potential effect of the duration of diabetes on our results by adjusting, in addition, for the duration of diabetes (in years) and excluding participants who were 40 years or younger when diagnosed with diabetes and thus possible cases of type 1 diabetes. Further, because diabetes is expected to be associated with the somatic complaints CES-D items irrespective of depressed mood, we examined whether diabetes was associated with the CES-D summary that did not include the somatic complaints items.

Results

Analysis 1: Depressive symptoms as a predictor of glucose metabolism

Compared with participants with none or one depressive symptom, those with subthreshold or elevated depressive symptoms were more likely to be older, female, and smokers; and have cardiovascular and non-cardiovascular comorbidities and BMI>30kg/m^2 (see Table 1). They were also less likely to be married, highly educated, wealthy, physically active, and daily drinkers.

We identified 1,652 individuals with IGM, 69 cases of incident diagnosed diabetes, and 82 cases of incident undiagnosed diabetes. The prospective association between categories of depressive symptoms and glucose metabolism status is presented in Table 2. Depressive symptoms were not significantly related to future IGM in the main analysis as well as in the supplementary analysis where cases of IGM in 2004-05 were excluded (n=2,240; OR 1.05, 95% CI 0.84-1.33, and OR 1.08, 95% CI 0.83-1.42, for subthreshold and elevated depressive symptoms, respectively, in the age-adjusted model). The associations between depressive symptoms and both undiagnosed and diagnosed diabetes were graded in the age-adjusted model. Adjustment for covariates fully explained the association between depressive symptoms and undiagnosed diabetes, but only partially the association between depressive

symptoms and diagnosed diabetes. Supplementary analysis showed that those who were excluded from our study because of attrition (including deaths) or non-response to the first health examination (i.e. those who did not provide a blood sample) were more likely to be older, male, not married, and less wealthy and educated compared with those who were not. They were also more likely to have cardiovascular diseases and self-reported diabetes, be obese, and report elevated depressive symptoms.

Analysis 2: Glucose metabolism as a predictor of elevated depressive symptoms

Table 3 presents an analysis of the sample characteristics according to glucose metabolism categories. Compared with normoglycemic participants, those with diabetes were more likely to be older, male, and smokers; have cardiovascular and non-cardiovascular comorbidities and BMI>30km/m^2. Also, they were less likely to be married, highly educated, wealthy, physically active, and daily drinkers.

Table 4 presents the longitudinal association between glucose metabolism categories and subsequent elevated depressive symptoms stratified by age group. In the younger age group (52 to 64 years; n=2,223; n of cases of elevated depressive symptoms=247), participants with diagnosed diabetes had significantly increased risk of future elevated depressive symptoms compared with normoglycemic participants with adjustment for covariates partially explaining this association. The risk for participants with IGM and undiagnosed diabetes was not significantly different from that of the normoglycemic category. In the older age group (65 years and older; n=2,015; n of cases of elevated depressive symptoms=300), the risk of future elevated depressive symptoms was not associated with glucose metabolism.

In supplementary analyses, additional adjustment of the fully adjusted model for diabetes duration did not affect the results (OR 1.80, 95% CI 0.90-3.64, and OR 1.02, 95% CI 0.49-2.08, for participants with diagnosed diabetes compared with normoglycemic participants, in the younger and older age groups, respectively). The exclusion of possible cases of type 1 diabetes also did not affect these associations. Further, in the younger age group, diagnosed diabetes remained significantly associated with the CES-D summary score in the fully adjusted in the absence of somatic complaints items.

Discussion

In a national sample of older people, we found a dose-response association between categories of depressive symptoms and incident diabetes. We also found that diagnosed diabetes was associated with the risk of future elevated depressive symptoms in people aged 52 to 64 years, but not in people aged 65 years and older. IGM and undiagnosed diabetes were not associated with the onset of elevated depressive symptoms.

Depressive symptoms as a predictor of glucose metabolism

We found a positive graded association between categories of depressive symptoms and the risk of being diagnosed with diabetes, which remained significant in the fully adjusted model. Socioeconomic position, comorbidities, and health behaviours (i.e. smoking, alcohol consumption, and physical activity) partially explained this association. Most (8-10, 12) but

not all of previous longitudinal studies (12) reported a positive graded association between categories of depressive symptoms and diabetes, while one study found that less severe depression is as strongly related to diabetes as severe depression (8).

We also found a positive and graded but weaker association between categories of depressive symptoms and incident undiagnosed diabetes, which was fully attenuated after adjustment for socioeconomic position and comorbidities. To our knowledge no previous study has examined the association between categories of depressive symptoms and undiagnosed diabetes.

Depressive symptoms were not associated with IGM. To date, only two longitudinal studies have examined this association in adult populations (10, 14) and results are equivocal. One study of US women found no association between elevated depressive symptoms and change in insulin resistance over time (14), but a Swedish study found significant associations between psychological distress and IGM in both men and women (10).

The existence of dose-response associations between categories of depressive symptoms and both undiagnosed and diagnosed diabetes suggests that depressive symptomatology influences the risk of developing diabetes in a systematic way. Although the exact mechanisms of this association remain unknown, there is evidence that hypothalamic-pituitary-adrenocortical axis dysregulation and inflammatory processes play a role in the pathogenesis and pathophysiology of depression (28, 29). In our data though inflammatory markers did not mediate the association after adjustment for socioeconomic, lifestyle, and clinical factors.

The difference in the strength of the associations between depressive symptoms and undiagnosed and diagnosed diabetes possibly indicates that depression not only increases the risk of developing diabetes but also the odds of obtaining a diagnosis of diabetes probably via social and behavioural pathways. One such pathway could pertain to the greater use of health services by depressed people (30), which is expected to increase their chances of obtaining a diagnosis of diabetes through opportunistic screening. Further, our finding that there is no medium-term longitudinal association between depressive symptoms and IGM ascertained using the ADA criteria should be treated with caution given the complexity and instability of IGM (31) and low sensitivity of the current HbA1c categorizations to detect IGM (32).

Glucose metabolism as a predictor of elevated depressive symptoms

We found that diagnosed diabetes was associated with increased risk of developing elevated depressive symptoms. Age though modified this association. Diagnosed diabetes was strongly associated with increased risk of subsequent elevated depressive symptoms in the younger age group (52 to 64 years), but not in the older age group (65 years and older). Socioeconomic position, comorbid chronic diseases, and health behaviours partially explained the association between diagnosed diabetes and subsequent elevated depressive symptoms. BMI was also relevant. Our supplementary analysis indicated that this age difference was not a function of diabetes duration. To our knowledge this is a new finding with potentially important implications for prevention programs and clinical practice. Two

recent cross-sectional studies provide initial evidence about the modifying effect of age on the association between diabetes and depression (33, 34). The first study found that younger age was associated with higher levels of depressive symptoms in diabetes patients (33). The second study found that the association between use of diabetes medication and use of antidepressants monotonically weakened according to age (34).

IGM and undiagnosed diabetes were not associated with elevations in depressive symptoms in our study. These findings fully concur with those of a recent meta-analysis of cross-sectional studies, which shows that there are no associations between either IGM or undiagnosed diabetes and prevalent depression (3). Longitudinal evidence also suggests that IGM and untreated diabetes are rather weakly associated with subsequent elevated depressive symptoms (16).

Supplementary analysis indicated that the strong association between diagnosed diabetes and elevated depressive symptoms in the younger age group association was not driven by the somatic complaints items and thus corroborates the conclusion that diagnosed diabetes is associated with future depressed mood and negative affect.

The age difference in the association between diagnosed diabetes and subsequent elevated depressive could be related to health- and age-related perceptions and stereotypes (35). Middle aged diabetes patients might have increased risk of elevated depressive symptoms because they might perceive diabetes as a disease of old age that should not have happened to them. This difference might also reflect age differences in the burden of diabetes (36). The majority of middle aged diabetes patients is likely still economically active and thus might have a greater difficulty to combine diabetes management with a busy daily program compared with older patients, whose majority has retired.

The findings from analysis 2 considered together point to the direction of a non-biological effect of diagnosed diabetes on future elevated depressive symptoms.

The use of a national sample makes our findings more generalizable to the population of community-dwelling people aged 50 years and over, while the use of a 6-year follow up allows adequate time for a medium-term examination of diabetes. The non-response analysis we performed indicated that both attrition and non-response to the health examination were associated with both depressive symptoms and diabetes. This probably makes our findings a conservative estimate of the positive association between depressive symptoms and diabetes. The use of self-reported doctor diagnosed diabetes leaves some room for disease misclassification, but the parallel use of HbA1c is expected to minimise this problem. Similarly, the ADA classification of HbA1c might have led to a misclassification of cases of IGM (32), which in turn might have biased our IGM-related results towards the null. Further, our findings regarding the association between undiagnosed diabetes and subsequent elevated depressive symptoms should be used with caution given the small number of cases of elevated depressive symptoms among people with undiagnosed diabetes.

Because of the use of CES-D, which is a screening instrument and not a diagnostic interview, and our inability to account for life-time history of depression, it is unknown whether our findings are fully applicable to clinical depression patients. Further, our

inability to account for the use of antidepressants might have biased our findings towards the null. Finally, the observational nature of our work did not allow for any causal inferences, while it is possible that some of the observed associations are confounded by factors unaccounted for in our study.

In conclusion, our findings indicate that there is a bidirectional association between depressive symptoms and diagnosed diabetes in people younger than 65 years, but not people aged 65 years and older. They also suggest that elevated depressive symptoms are associated with incident diabetes in people aged 50 years or older and that this association is likely dose-response. Further, they indicate that the association between diagnosed diabetes and the onset of elevated depressive symptoms is age dependent since only younger than 65 years people had increased risk of developing elevated depressive symptoms. Assessing the glucose metabolism status of people aged 50 years and older with depressive symptoms and focusing on people younger than 65 years with diabetes as a population at risk of depression might be proven useful in clinical practice and prevention programs. Future research should replicate our work and explore the biological plausibility of the association between depressive symptoms and diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was not supported by any third party. The English Longitudinal Study of Ageing (ELSA) is supported by the National Institute on Ageing (Grants 2RO1AG7644-01A1 and 2RO1AG017644) and a consortium of the United Kingdom government departments coordinated by the Office for National Statistics. The developers and funders of ELSA and the Archive do not bear any responsibility for the analyses or interpretations presented here.

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Abbreviations

BMI	Body Mass Index
CES-D	Center for Epidemiological Studies – Depression scale
ELSA	English Longitudinal Study of Ageing
IGM	Impaired Glucose Metabolism

Table 1

Baseline characteristics by depressive symptom category in 2,914 women and men without diabetes, English Longitudinal Study of Ageing, 2002-03

	CES-D score: 0-1 (n=2,093)	CES-D score:2-3 (n=484)	CES-D score:≥4 (n=337)	*P* value[a]
Age, years, mean (SD)	61.9 (8.4)	63.0 (9.0)	62.3 (9.3)	.025
Female, n (%)	1,099 (52.5)	318 (65.7)	237 (70.3)	<.001
Married, n (%)	1,579 (75.4)	308 (63.6)	188 (55.8)	<.001
University degree or equivalent, n (%)	340 (16.2)	62 (12.8)	31 (9.2)	<.001
Wealthiest quintile (≥£292,700), n (%)	631 (30.1)	120 (24.8)	41 (12.2)	<.001
No cardiovascular comorbidities, n (%)	1,317 (62.9)	261 (53.9)	188 (55.8)	<.001
No non-cardiovascular comorbidities, n (%)	1,233 (58.9)	198 (40.9)	105 (31.2)	<.001
Never a smoker, n (%)	852 (40.7)	182 (37.6)	110 (32.6)	.004
Daily or almost daily consumption of alcohol, n (%)	685 (32.7)	131 (27.1)	85 (25.2)	<.001
Vigorous physical activity at least once a week, n (%)	824 (39.4)	152 (31.4)	81(24.0)	<.001
BMI>30 (weight in kg)/(height in meters)^2, n (%)[b]	474 (23.2)	119 (25.9)	105 (32.9)	.036
Fibrinogen, g/l, median (IQR)	3.0 (0.8)	3.2 (0.8)	3.2 (0.9)	.39
C-reactive protein, mg/l, median (IQR)	1.7 (2.2)	2.2 (3.3)	2.3 (3.7)	.087

Abbreviations: BMI, Body Mass Index; CES-D, Center for Epidemiological Studies – Depression scale; IQR, interquartile range; SD, standard deviation

[a] *P* values were generated using chi-square, Kruskal-Wallis, and analysis of variance tests for categorical, ordinal, and continuous covariates, respectively.

[b] Estimates are based on 2,821 participants with non-missing data.

Table 2

Odds ratios (95% CI) of IGM and incident undiagnosed and diagnosed diabetes by depressive symptom category in 2,914 women and men without diabetes, English Longitudinal Study of Ageing, 2002-09

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Predictor	**OR (95% CI)**	**OR (95% CI)**	**OR (95%CI)**	**OR (95% CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
				IGM (vs. normoglycemia)			
CES-D score:0-1	Reference	Reference	Reference	Reference	Reference	Reference	Reference
CES-D score:2-3	1.11 (0.90-1.37)	1.09 (0.89-1.35)	1.08 (0.87-1.33)	1.05 (0.84-1.30)	1.05 (0.84-1.30)	1.00 (0.80-1.25)	1.01 (0.81-1.26)
CES-D score:≥4	1.12 (0.87-1.43)	1.10 (0.86-1.42)	1.05 (0.82-1.36)	1.02 (0.78-1.33)	1.01 (0.77-1.31)	0.95 (0.73-1.25)	0.94 (0.72-1.23)
P value for trend	.26	.33	.55	.78	.86	.77	.73
				Undiagnosed diabetes (vs. normoglycemia)			
CES-D score:0-1	Reference	Reference	Reference	Reference	Reference	Reference	Reference
CES-D score:2-3	1.54 (0.86-2.73)	1.50 (0.84-2.68)	1.32 (0.73-2.38)	1.15 (0.63-2.09)	1.13 (0.62-2.05)	1.01 (0.54-1.88)	0.99 (0.53-1.84)
CES-D score:≥4	1.91 (1.03-3.57)	1.83 (0.97-3.46)	1.49 (0.77-2.87)	1.27 (0.64-2.52)	1.22 (0.61-2.43)	1.16 (0.57-2.37)	1.14 (0.55-2.33)
P value for trend	.023	.037	.18	.46	.54	.72	.77
				Diagnosed diabetes (vs. normoglycemia)			
CES-D score:0-1	Reference	Reference	Reference	Reference	Reference	Reference	Reference
CES-D score:2-3	1.53 (0.80-2.93)	1.71 (0.89-2.29)	1.53 (0.79-2.98)	1.47 (0.75-2.87)	1.50 (0.76-2.94)	1.37 (0.69-2.73)	1.36 (0.68-2.71)
CES-D score:≥4	3.03 (1.66-5.54)	3.56 (1.91-6.62)	2.94 (1.55-5.58)	2.98 (1.53-5.78)	3.09 (1.57-6.09)	2.82 (1.41-5.62)	2.81 (1.40-5.62)
P value for trend	<.001	<.001	.001	.002	.001	.004	.005

Abbreviations: CES-D, Center for Epidemiological Studies – Depression scale; CI, Confidence Intervals; IGM, Impaired Glucose Metabolism; OR, Odds Ratio

Model 1 is adjusted for age

Model 2 is adjusted for age, sex, and marital status

Model 3 is adjusted for Model 2 and education and household wealth

Model 4 is adjusted for Model 3 and cardiovascular and non-cardiovascular comorbidities

Model 5 is adjusted for Model 4 and BMI categories

Model 6 is adjusted for Model 5 and health behaviors (i.e. smoking, physical activity, and frequency of alcohol consumption)

Model 7 is adjusted for Model 6 and inflammatory markers (i.e. fibrinogen and high sensitivity C-reactive protein)

Table 3

Baseline characteristics by glucose metabolism category in 4,238 women and men, English Longitudinal Study of Ageing, 2004-05

	Normoglycemia (n=2,913)	IGM (n=958)	Undiagnosed diabetes (n=69)	Diagnosed diabetes (n=298)	*P* value[a]
Age, years, mean (SD)	64.4 (8.7)	66.8 (9.3)	65.7 (8.1)	66.7 (8.5)	.032
Female, n (%)	1,646 (56.5)	540 (56.4)	30 (43.5)	141 (47.3)	.004
Married, n (%)	2,030 (69.7)	615 (64.2)	42 (60.9)	204 (68.5)	.008
University degree or equivalent, n (%)	450 (15.5)	104 (10.9)	4 (5.8)	35 (11.7)	<.001
Wealthiest quintile (≥£360,020), n (%)	731 (25.1)	197 (20.6)	9 (13.0)	43 (14.4)	<.001
No cardiovascular comorbidities, n (%)	1,593 (54.7)	442 (46.1)	33 (47.8)	66 (22.2)	<.001
No non-cardiovascular comorbidities, n (%)	1,345 (46.2)	377 (39.4)	22 (31.9)	129 (43.3)	.001
Never a smoker, n (%)	1,173 (40.3)	341 (35.6)	19 (27.5)	98 (32.9)	<.001
Daily or almost daily consumption of alcohol, n (%)	739 (25.4)	172 (18.0)	10 (14.5)	47 (17.2)	<.001
Vigorous physical activity at least once a week, n (%)	1,006 (34.5)	273 (28.5)	15 (21.7)	60 (20.1)	<.001
BMI>30 (weight in kg)/(height in meters)^2, n (%)[b]	644 (22.8)	326 (35.8)	31 (48.4)	132 (46.2)	<001

Abbreviations: BMI, Body Mass Index; IGM, Impaired Glucose Metabolism; SD, standard deviation

[a] *P* values were generated using chi-square, Kruskal-Wallis, and analysis of variance tests for categorical, ordinal, and continuous covariates, respectively.

[b] Estimates are based on 4,088 participants with non-missing data.

Table 4

Odds ratios (95% CI) of elevated depressive symptoms by glucose metabolism category in 4,238 women and men, English Longitudinal Study of Ageing, 2004-09

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Predictor	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95%CI)**
			Younger age group:52 to 64 years			
Normoglycemia	Reference	Reference	Reference	Reference	Reference	Reference
IGM	1.22 (0.86-1.73)	1.23 (0.86-1.75)	1.19 (0.83-1.70)	1.15 (0.80-1.66)	1.14 (0.79-1.64)	1.03 (0.70-1.49)
Undiagnosed diabetes	1.27 (0.45-3.60)	1.38 (0.47-4.04)	1.31 (0.44-3.85)	1.23 (0.41-3.69)	1.18 (0.39-3.53)	1.01 (0.33-3.11)
Diagnosed diabetes	2.17 (1.33-3.56)	2.40 (1.45-3.98)	2.12 (1.26-3.56)	2.06 (1.20-3.53)	1.96 (1.14-3.39)	1.83 (1.06-3.18)
			Older age group:65 years and older			
Normoglycemia	Reference	Reference	Reference	Reference	Reference	Reference
IGM	1.22 (0.90-1.65)	1.24 (0.92-1.68)	1.20 (0.88-1.63)	1.15 (0.84-1.57)	1.15 (0.84-1.58)	1.15 (0.83-1.58)
Undiagnosed diabetes	1.17 (0.43-3.14)	1.18 (0.43-3.25)	1.05 (0.37-2.93)	0.90 (0.32-2.58)	0.90 (0.31-2.57)	0.74 (0.26-2.14)
Diagnosed diabetes	0.96 (0.59-1.57)	1.04 (0.63-1.71)	0.96 (0.58-1.59)	0.89 (0.53-1.47)	0.88 (0.53-1.47)	0.81 (0.48-1.37)

Abbreviations: CI, Confidence Intervals; IGM, Impaired Glucose Metabolism; OR, Odds Ratio

Model 1 is adjusted for age and elevated depressive symptoms in 2004-05

Model 2 is adjusted for Model 1 and sex and marital status

Model 3 is adjusted for Model 2 and education and household wealth

Model 4 is adjusted for Model 3 and cardiovascular and non-cardiovascular comorbidities

Model 5 is adjusted for Model 4 and BMI categories

Model 6 is adjusted for Model 5 and health behaviors (i.e. smoking, physical activity, and frequency of alcohol consumption).