

# Depressive Symptoms and Risk of Type 2 Diabetes in a National Sample of Middle-Aged and Older Adults

The English Longitudinal Study of Aging

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**OBJECTIVE** — To examine the association between baseline elevated depressive symptoms and incident type 2 diabetes in a national sample of people aged  $\geq 50$  years.

**RESEARCH DESIGN AND METHODS** — The sample consisted of 6,111 individuals free from self-reported doctor-diagnosed diabetes at baseline in 2002–2003. The eight-item Center for Epidemiological Studies–Depression (CES-D) scale was the measurement of depressive symptoms. Cox proportional hazards regression models were used to assess whether baseline elevated ( $\geq 4$ ) depressive symptoms were associated with a higher risk of type 2 diabetes over 45.8 months of follow-up.

**RESULTS** — The hazard ratio (HR) for diabetes was 1.62 (95% CI 1.15–2.29) in a model adjusted for age, sex, marital status, education, total net household wealth, cardiovascular and psychiatric and other noncardiovascular comorbidities, BMI, and health behaviors for participants with elevated CES-D symptoms compared with those without. Complementary analysis performed for a subsample ( $n = 5,090$ ) showed that additional adjustment of this model for use of antidepressants did not explain the association (HR 1.58, 95% CI 1.09–2.29).

**CONCLUSIONS** — Elevated depressive symptoms were associated with a higher risk of developing type 2 diabetes after accounting for sociodemographic, lifestyle, and clinical factors in a national sample of people aged  $\geq 50$  years.

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**D**epression is a known comorbid condition of diabetes. Individuals with diabetes have increased odds of being depressed and consistently higher prevalence rates of depression than their counterparts without diabetes (1). An accumulating body of research shows that type 2 diabetes is a risk factor for recurrent depression (2), but longitudinal studies also suggest that depression and elevated depressive symptoms are related to subsequent incidence of diabetes (3–10). Two recent meta-analyses of longitudinal studies suggest that depression is associated with a 40–60% increased

risk of developing type 2 diabetes (11,12). The etiology and pathogenic mechanism of this association is poorly understood. It has been suggested that unhealthy behaviors (i.e., physical inactivity and smoking), obesity, and use of psychotropic medication may be parts of the causal pathway linking depression to type 2 diabetes (3,11,13).

The majority of previous longitudinal studies on the association between depressive symptoms and incident diabetes have not accounted adequately for socioeconomic status (SES), and therefore their results might be biased because of resid-

ual confounding. They have also generally failed to account for baseline comorbidities such as cardiovascular, noncardiovascular, and psychiatric diseases, which might explain the association between depression and diabetes. Moreover, more research is needed on the use of antidepressants and other psychotropic medication as a depression-related risk factor for diabetes in older samples, since evidence on this issue is conflicting (6,8,9,14).

We used data from the English Longitudinal Study of Aging (ELSA), a national prospective cohort study of community-dwelling middle-aged and older men and women, to examine whether baseline elevated depressive symptoms measured by the Center for Epidemiological Studies–Depression (CES-D) scale were associated with a higher risk of developing type 2 diabetes. We adjusted for a wide range of potential confounders including education and wealth as markers of SES and baseline comorbidities including psychiatric diseases. We then explored whether health behaviors, BMI, and use of antidepressants or other psychotropic medication mediated the association between elevated baseline depressive symptoms and incident type 2 diabetes.

## RESEARCH DESIGN AND METHODS

The baseline ELSA interview (wave 1) in 2002–2003 included 11,523 community-dwelling individuals aged  $\geq 50$  years. The first follow-up interview was in 2004–2005 (wave 2) and the second was in 2006–2007 (wave 3). A physical examination took place in parallel with the first follow-up interview in 2004–2005 (nurse visit, wave 2). The ELSA sample was designed to be representative of the population of community-dwelling adults aged  $\geq 50$  years in England. It was drawn from households that had participated in the Health Survey for England (HSE) in 1998, 1999, and 2001, which is an annual cross-sectional health survey that uses nationally repre-

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sentative samples. All HSE households that contained at least one person aged  $\geq 50$  years who had consented to be re-contacted in the future were eligible for inclusion in the ELSA sample ( $n = 11,373$  households). The ELSA wave 1 sample consisted of 7,935 out of the 11,371 eligible HSE households (response rate 70%). HSE data predating ELSA baseline were therefore available for the ELSA participants (these data are known as ELSA wave 0).

Participants with missing information on self-reported diabetes status or date of diagnosis of diabetes ( $n = 18$ ), or missing values in any of the employed covariates ( $n = 2,439$ ) along with participants who had no longitudinal data available ( $n = 2,078$ ) or were prevalent cases of diabetes at baseline ( $n = 877$ ), were excluded from analysis. The final sample for the main analysis consisted of 6,111 individuals (55.7% women). Individuals who dropped out of the study after having participated in its first wave were more likely to be older, male, of lower SES, more depressed, and have more chronic diseases than individuals who have not dropped out.

### Assessment of diabetes

The outcome measure was incident self-reported doctor-diagnosed type 2 diabetes, i.e., new cases of self-reported type 2 diabetes that were diagnosed after wave 1.

Because diabetes medication data were not available in wave 1, we investigated the degree of possible misclassification of diagnosed diabetes in our sample by using data on the use of diabetes medication from wave 0. This was collected by nurses who inspected and registered all medication taken by the participants. Medication information was available for the majority of the analytic sample ( $n = 5,092$  of the 6,113 who were initially selected for inclusion in the analytic sample). Among the 5,092 participants with medication data, there were only two individuals who had been misclassified as free of diabetes at baseline, while taking diabetes medication at wave 0, and who were thus excluded from analysis as prevalent cases of diabetes. This result suggests that there is minimal underreporting of diagnosed diabetes. The date of diagnosis of diabetes (month/year) used to calculate the follow-up time was also self-reported.

### Measurement of depressive symptoms

The eight-item CES-D scale was the measurement of depressive symptoms at baseline (15). CES-D measures self-reported depressive symptomatology and, although not a clinical diagnostic tool, it is widely used to identify people "at risk" of depression (16). The eight-item version we used had good internal consistency (Cronbach's  $\alpha$  around 0.8 in repeated measurements) and other psychometric values comparable to the full 20-item CES-D (15). We derived a CES-D summary score by summing responses to all eight dichotomous questions. We dichotomized the summary score using a cut point of four or higher ( $\geq 4$ ), which is equivalent to the conventional cut point of 16 or higher on the full 20-item CES-D (15).

### Measurement of covariates

Baseline sociodemographic, clinical, and lifestyle variables were used as covariates, since they are established risk factors for diabetes. Age was recorded as a continuous variable in years, with all participants aged over 90 years being assigned the value of 91. SES was assessed by educational attainment (university degree or equivalent, higher education but not university degree, A-level, O-level, secondary education, some foreign educational qualifications, or no educational qualifications) and by total net nonpension household wealth (household is defined as a couple with any dependent child) categorized using quintiles. Smoking (current smoker, exsmoker, never a smoker), frequency of alcohol consumption in the last 12 months (more than once a day, daily or almost daily, once or twice a week, once or twice a month, on special occasions only, not at all), and physical activity on a weekly basis (vigorous, moderate, mild, not at all) were also assessed. Information on marital status, existence of any longstanding illness or disability, and self-reported doctor-diagnosed cardiovascular (hypertension, angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm and stroke) and noncardiovascular morbidities including psychiatric diseases and cognitive impairments (chronic lung disease, asthma, arthritis, osteoporosis, cancer/malignant tumor excluding minor skin cancers, Parkinson's disease, emotional/nervous/psychiatric problems, Alzheimer's disease, and dementia or other serious memory impairment) was also

collected during the interviews. Because no anthropometric data were measured at baseline (wave 1), we used the average of BMI measurements from wave 0 and wave 2 as an estimate of BMI at wave 1. BMI was calculated from objective measurements of height and weight taken by nurses during a clinical examination. Details of the measurement protocol can be found at [http://www.ifs.org.uk/elsa/docs\\_w2/project\\_instructions\\_nurse.pdf](http://www.ifs.org.uk/elsa/docs_w2/project_instructions_nurse.pdf). Information about use of antidepressants and other psychotropic medications (i.e., antipsychotics and anxiolytics) was collected by nurses during wave 0.

### Statistical analysis

Baseline characteristics were examined by CES-D symptom categories. Diabetes incidence rates for each CES-D symptom category were calculated. The association between baseline CES-D symptom categories and incident diabetes was assessed by Cox proportional hazards regression models. Cox proportional hazards regression models were also used to confirm that BMI, health behaviors, and use of antidepressants were associated with diabetes and may therefore be mediators of the association between depressive symptoms and incident diabetes. Follow-up time was calculated as the time elapsed from the date of baseline interview to the first of either the date of diagnosis of diabetes or the date of the last ELSA interview in which the individual participated. Graphical plots (log-negative log survival plots) and statistical tests (Schoenfeld residuals test) were used to confirm the proportional hazards assumption. We assessed whether there were significant interactions between CES-D symptom categories and age and sex to investigate whether the association between depressive symptoms and incident diabetes varied by age or between men and women. As there were no significant interactions, we fitted a model adjusted for age and then additionally for sex, marital status, comorbidities, and SES. We then adjusted this basic model for BMI and health behaviors, first individually and then jointly, to estimate the effect of these factors on the examined association. We also assessed the percentage reduction in the depressive symptoms-related hazard ratio (HR) as BMI and health behaviors were added to the basic model. In addition, we assessed whether use of antidepressants or other psychotropic medication mediated the association of interest in a subsample of 5,090 individuals with

available medication data. First, we fitted a model adjusted for all confounders and mediators, and then we additionally adjusted this model for use of antidepressants or antidepressants and other psychotropic medication (i.e., antipsychotics and anxiolytics).

On the basis that the association between elevated depressive symptoms and diabetes might be causal, we calculated the fully adjusted population-attributable fraction (that is, the percentage of cases of diabetes that could have been prevented if all respondents were free of elevated depressive symptoms). For purposes of comparison, we also calculated the fully adjusted population-attributable fractions for covariates that were important known risk factors for diabetes, such as obesity and physical activity.

We assessed the possible impact of reverse causality (undiagnosed diabetes causing baseline depression) by repeating our multivariable analyses after the removal of all incident cases of diabetes that were diagnosed within the first 12 months after baseline ( $n = 6,086$ ). Sensitivity analyses were also performed to assess the impact of missing data by repeating analyses (except models including BMI and use of antidepressants and other psychotropic medication) in a larger sample ( $n = 8,228$ ), including all individuals who were excluded from the main analysis because of missing BMI values. All analyses were performed using STATA 9.2.

**RESULTS** — All differences in baseline characteristics between the CES-D symptom categories were significant except for age differences. Participants who reported elevated CES-D symptoms at baseline were more likely to be female, less educated, less wealthy, current smokers, and suffer from cardiovascular and other noncardiovascular chronic diseases than those who reported less than four or no CES-D symptoms. They were also less likely to be married, physically active, and consume alcohol frequently. Difference between the two categories in BMI was marginally significant (Table 1). BMI, health behaviors, and use of antidepressants were also related to incident diabetes (data not shown).

A total of 209 incident cases of type 2 diabetes were reported over an average of 45.8 months of follow-up. Participants with elevated CES-D symptoms had higher incidence of diabetes (16.7 per 1,000 person-years) than individuals

**Table 1—Baseline characteristics of 6,111 men and women without prevalent type 2 diabetes by baseline depressive symptoms: English Longitudinal Study of Aging, 2002–2003**

	CES-D <4	CES-D ≥4	P
<i>n</i>	5,288	823	
Age (years)	63.6 ± 9.3	64.0 ± 9.8	0.24
Sex			<0.001
Male	2,453 (46.4)	256 (31.1)	
Female	2,835 (53.6)	567 (68.9)	
Marital status			<0.001
Nonmarried	1,506 (28.5)	388 (47.1)	
Married	3,782 (71.5)	435 (52.9)	
Education			<0.001
Degree or equivalent	706 (13.3)	59 (7.2)	
Higher education or equivalent	687 (13.0)	72 (8.7)	
General certificate of education: advanced level or equivalent	376 (7.1)	45 (5.5)	
General certificate of education: ordinary level or equivalent	977 (18.5)	126 (15.3)	
Certificate of secondary education	245 (4.6)	36 (4.4)	
Foreign or other type of qualifications	481 (9.1)	64 (7.8)	
No qualification	1,816 (34.4)	421 (51.1)	
Total net non-pension household wealth* [median (interquartile range)] (£)	160,010 (217,490)	81,962 (175,950)	<0.001
Any longstanding illness or disability			<0.001
No	2,735 (51.7)	233 (28.3)	
Yes	2,553 (48.3)	590 (71.7)	
Cardiovascular comorbidity†			<0.001
No cardiovascular disease	2,984 (56.4)	409 (49.7)	
At least one cardiovascular disease	2,304 (43.6)	414 (50.3)	
Other noncardiovascular comorbidity†			<0.001
No noncardiovascular disease	2,862 (54.1)	245 (29.8)	
At least one noncardiovascular disease	2,426 (45.9)	578 (70.2)	
Smoking status			<0.001
Never a smoker	2,024 (38.3)	245 (29.8)	
Exsmoker	2,447 (46.3)	353 (42.9)	
Current smoker	817 (15.4)	225 (27.3)	
Physical activity at least once a week			<0.001
Not at all	274 (5.2)	106 (12.9)	
Mild	562 (10.6)	178 (21.6)	
Moderate	2,658 (50.3)	380 (46.2)	
Vigorous	1,794 (33.9)	159 (19.3)	
Frequency of alcohol consumption			<0.001
Twice a day or more often	217 (4.1)	27 (3.3)	
Daily or almost daily	1,365 (25.8)	182 (22.1)	
Once or twice a week	1,800 (34.0)	205 (24.9)	
Once or twice a month	593 (11.2)	86 (10.6)	
Only on special occasions	898 (17.0)	200 (24.3)	
Not at all	415 (7.9)	123 (14.9)	
BMI (kg/m <sup>2</sup> )	27.5 ± 4.4	27.8 ± 5.0	0.045

Data are means ± SD or *n* (%) unless otherwise indicated. \*This is total household wealth (excluding pension savings) minus household debt. †Cardiovascular comorbidities included hypertension, angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, and stroke; noncardiovascular comorbidities included chronic lung disease, asthma, arthritis, osteoporosis, cancer/malignant tumor excluding minor skin cancers, Parkinson's disease, emotional/nervous/psychiatric problems, Alzheimer's disease, and dementia or other serious memory impairment.

**Table 2—Incidence and HRs (95% CI) of type 2 diabetes by baseline depressive symptoms in 6,111 men and women: English Longitudinal Study of Aging, 2002–2007**

	CES-D <4	CES-D ≥4
<i>n</i>	5,288	823
Incidence		
Incident cases ( <i>n</i> )	158	51
Follow-up (person-years)	20,262	3,051
Incidence rate of type 2 diabetes (per 1,000 person-years)	7.8	16.7
Cox regression models*		
Model 1: adjusted for age (linear term)	1.0 (reference category)	2.14 (1.56–2.94)
Model 2: model 1 + adjusted for age (quadratic term), sex, marital status, self-reported longstanding illness or disability, and cardiovascular and noncardiovascular comorbidities†	1.0 (reference category)	2.00 (1.44–2.79)
Model 3: model 2 + adjusted for educational attainment and total household wealth‡	1.0 (reference category)	1.74 (1.24–2.45)
Model 4: model 3 + adjusted for BMI	1.0 (reference category)	1.76 (1.25–2.46)
Model 5: model 3 + adjusted for health behaviors	1.0 (reference category)	1.58 (1.12–2.24)
Model 6: model 3 + adjusted for BMI and health behaviors	1.0 (reference category)	1.62 (1.15–2.29)

\*Results are presented in the form of HR (95% CI). †Cardiovascular comorbidities included hypertension, angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, and stroke. Noncardiovascular comorbidities included chronic lung disease, asthma, arthritis, osteoporosis, cancer/malignant tumor excluding minor skin cancers, Parkinson's disease, emotional/nervous/psychiatric problems, Alzheimer's disease, and dementia or other serious memory impairment. ‡This is total household wealth (excluding pension savings) minus household debt.

without (7.8 per 1,000 person-years) (Table 2).

The HR for diabetes was 2.14 (95% CI 1.56–2.94) in the age-adjusted model for participants with elevated CES-D symptoms compared with individuals without (Table 2). Adjusting for other sociodemographic characteristics, comorbidities, and SES reduced the HR, but there remained an increased risk of diabetes in individuals with depressive symptoms. Additional adjustment for BMI did not affect the association, whereas additional adjustment for health behaviors reduced its strength, but did not completely explain it (22% reduction in the HR between the latter model and the reference model that was adjusted for sociodemographic characteristics, comorbidities, and SES) (Table 2). The association between depressive symptoms and incident diabetes remained significant, even after adjusting for all covariates (HR 1.62, 95% CI 1.15–2.29) (16% reduction in the HR between this model and the reference model) (Table 2). The percentage of cases of diabetes that could have been prevented if none of the respondents were exposed to elevated depressive symptoms was ~9% (95% CI 2–17%). The respec-

tive estimates for obesity (if all respondents had BMI <30 kg/m<sup>2</sup>) and physical activity (if all respondents performed vigorous/moderate-intensity physical activity more than once a week) were 30% (95% CI 20–39%) and 16% (4–27%), respectively.

The association between elevated depressive symptoms and incident diabetes remained significant, even when incident cases of diabetes that were diagnosed within the first 12 months after baseline were excluded from analysis (HR 1.49, 95% CI 1.02–2.16). Moreover, elevated depressive symptoms were significantly related to incident diabetes in a model adjusted for all covariates (1.63, 1.13–2.36) for the subsample of 5,090 individuals for whom information on use of medication was available. Adjustment of this model for use of antidepressants (1.58, 1.09–2.29) or antidepressants and other psychotropic medication (i.e., antipsychotics and anxiolytics) (1.60, 1.11–2.32) did not explain the examined association.

The sensitivity analysis performed in a larger sample that included in addition cases with missing BMI values showed that depression remained associated with diabetes in a model adjusted for all covari-

ates except for BMI and use of antidepressants or other psychotropic medication irrespective of missing data (HR 1.38, 95% CI 1.03–1.85), although the estimated association was weaker in this larger sample.

**CONCLUSIONS**— In a national sample of men and women aged ≥50 years, we found that elevated depressive (CES-D) symptoms at baseline were associated with a higher risk of developing type 2 diabetes. This association did not vary according to age and sex and was largely independent of known correlates of diabetes and depression and cardiovascular, psychiatric, and other comorbidities. Hypothesized mechanisms through which elevated depressive symptoms might affect incident diabetes involving health behaviors, BMI, and use of antidepressants explained little or nothing of the association. From a public health perspective, the burden of diabetes that could be attributed to elevated depressive symptoms was comparable, although less, to the burden of diabetes that can be attributed to the lack of physical activity.

In accordance with most previous studies and two recent meta-analyses (11,12), we found that elevated CES-D symptoms were associated with a higher risk of developing type 2 diabetes. Also, in agreement with previous studies (7), we found that baseline somatic comorbidities did not confound this association. In addition, we found that baseline psychiatric comorbidities and cognitive impairments similarly did not confound this association. To our knowledge, this article is the first to adjust simultaneously for such a wide array of baseline somatic and psychiatric comorbidities.

Most previous studies have adjusted their models for a single SES indicator (typically, this was education) (4,6–9). We accounted for SES in a more satisfactory way by adjusting not only for education but also for total net household wealth, which has been found to be related to diabetes more strongly than other indicators of SES in our sample (17). We still found, in accordance with all previous reports, that SES did not fully explain the association between elevated depressive symptoms and incident diabetes. We did demonstrate, however, that SES had the strongest individual confounding effect on the association between baseline depressive symptoms and incident diabetes.

We hypothesized that obesity and unhealthy behaviors would be potential mechanisms linking depression to diabetes. Depression can lead to obesity, which is a major risk factor for diabetes through stimulating increased activity of the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system (11). Moreover, depression is related to unhealthy behaviors such as physical inactivity and smoking (18), which are also risk factors for diabetes (19,20). However, we found that neither BMI, despite being a powerful correlate of incident diabetes, nor health behaviors substantially mediated the association between CES-D and diabetes. These findings are in agreement with most but not all (6) previous studies, which have shown that neither BMI nor health behaviors fully explained the observed association (3–5,7–10). We also found that use of antidepressants and other psychotropic medication could not explain the observed association. This is consistent with the findings of most (6,8,9) but not all (14) previous studies and with our finding that obesity did not mediate the association between depression and diabetes, since use of antidepressants was expected to affect diabetes largely through change in weight (21). Our findings in relation to use of antidepressants should be treated with some caution, since data on use of antidepressants and other psychotropic medication predate the ELSA baseline data.

Future research on the mechanism of the association between elevated depressive symptoms and incident diabetes should concentrate on factors other than obesity, unhealthy behaviors, and use of antidepressants. It is possible that there are common causes underlying the relationship, such as factors from early life that are risk factors for both depression and diabetes. Low birth weight has been found to be related to diabetes (22) and possibly with depressive symptoms (23). Further, low birth weight has been found to modify the association of diabetes or cardiovascular disease with depression in a sample of older adults (24). Alternatively, there may be biological pathways where depression leads to biological changes, which then result in diabetes (11,13,21). Biological pathways related to glucose homeostasis such as hypothalamic-pituitary-adrenocortical axis dysregulation and sympathetic nervous system stimulation warrant further exploration (21). Inflammation is another candidate pathway, but was found not to explain the

association between depression and diabetes in recent studies (8,10).

The use of a large national sample of community-dwelling men and women aged  $\geq 50$  years is a major advantage of our study. The detailed assessment of SES and background psychiatric, cognitive, and physical health problems means that appropriate adjustment was made for a wide range of potential confounding variables. Accounting for both wealth and education diminished the chances of residual confounding because of inadequate adjustment for SES and therefore strengthened previous evidence that SES did not fully explain the association between depressive symptoms and incident diabetes. CES-D measures depressive symptoms experienced in the past week and, therefore, does not account for history of depression. By accounting for baseline psychiatric comorbidities, we showed that elevated baseline depressive symptoms were related to a higher risk of diabetes irrespective of background depressive disorder or other psychiatric disease.

A limitation of our study is the use of self-reported diabetes as the outcome measure. However, comparing baseline self-reported diabetes with objective information about the use of diabetes medication from wave 0 indicated minimal misclassification of cases of diagnosed diabetes. The possibility of undiagnosed diabetes influencing our findings remains. A recent cross-sectional study using data from wave 2 indicated that 18.5% ( $n = 36$ ) of all cases of diabetes in the ELSA sample were undiagnosed (25). Reverse causality is thus a potential issue, since there is the possibility that some depressive symptomatology at baseline may be a result of undetected prevalent cases of diabetes. However, elevated CES-D symptoms remained related to risk of developing diabetes, even after having excluded from analysis all incident cases of diabetes that were diagnosed within the first 12 months after the baseline. Further, there is evidence showing that untreated diabetes is not associated with the incidence of depressive symptoms (10).

Missing data and attrition are unavoidable in large cohorts based on a national general population sample such as ELSA. In supplementary analyses, we showed that our findings remained similar in a larger sample that included individuals with missing BMI information. We would expect attrition to have made our results more conservative, since individuals who

dropped out from ELSA were less educated, and there is evidence (3,9) that the depression-related risk of developing type 2 diabetes is higher among individuals who are less educated irrespective of age, sex, race, health behaviors, BMI, and family history of diabetes.

Our research suggests that elevated depressive symptoms were associated with a higher risk of developing type 2 diabetes in middle-aged and older adults. SES and baseline comorbidities including psychiatric diseases did not fully explain this association. There was little evidence that obesity, unhealthy behaviors, or use of antidepressants substantially mediated this association. Future research should explore the etiology and mechanism of this association. Action to prevent and treat depression might contribute to the fight against diabetes.

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