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Depressive symptoms, psychiatric medication use, and risk of type 2 diabetes: results from the Health and Retirement Study

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ABSTRACT

Objective: This prospective study investigates the relationships between depressive symptoms, psychiatric medication use, and their interaction on risk of developing type 2 diabetes.
Method: Data come from the 1998–2010 waves of the Health and Retirement Study, a US nationally representative cohort of adults aged 51 years and older. Analysis is restricted to participants <65 years old who did not have diabetes in 1998 (N=8704). Depressive symptoms were assessed using the 8-item Center for Epidemiologic Studies–Depression Scale. Risk of diabetes over the 12-year follow-up period was assessed using Cox proportional hazard models with time-varying covariates.
Results: After adjusting for covariates, both depressive symptoms [hazard ratio (HR): 1.06, 95% confidence interval (CI): 1.02–1.09] and psychiatric medication use (HR: 1.57, 95% CI: 1.25–1.96) were associated with development of diabetes. The interaction between depressive symptoms and medication use was significant (beta=−0.240, P=.049), indicating that the association between elevated depressive symptoms and diabetes was higher among respondents not taking medications. The associations between depressive symptoms and medication use were also attenuated by increasing body mass index.
Conclusion: Findings highlight the complex relationship between depressive symptoms and psychiatric medications on diabetes risk and the need for a nuanced understanding of these factors.

1. Introduction

Psychiatric medications (e.g., antidepressants, anxiolytics, tranquilizers, and neuroleptics) are among the most commonly prescribed classes of medications in the United States. For example, nearly three in ten adults over the age of 50 years have used an antidepressant (e.g., selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), monoamine oxidase inhibitors, and other medications such as bupropion) in the past year [1]. The prevalence of psychiatric medication use increases with age [2,3], although the prevalence of psychiatric disorders such as depression and anxiety declines in later life [4,5]. While psychiatric medication use is common, only a minority of cases of depression or anxiety receive adequate medical care, including pharmacotherapy or psychotherapy [6].

Prospective, population-based studies have consistently indicated a bidirectional relationship between depression and type 2 diabetes [7–9]. Depression is thought to increase risk of type 2 diabetes through a combination of behavioral (e.g., smoking, poor diet, sedentary behavior, weight gain, sleep disturbances [8,10]) and biological (e.g., hypercortisolemia, inflammation, sympathetic nervous system activation [11–13]) mechanisms that impair insulin sensitivity and glucose metabolism. Many, but not all, studies of depression and risk of type 2 diabetes have accounted for the influence of antidepressant medication use using multivariable regression modeling and found that the association between depression and diabetes persisted after accounting for medication use.

As summarized in a recent systematic review by Barnard, Peveler, and Holt [14], several studies have reported statistically significant associations between antidepressant use and development of type 2 diabetes [15–20]. In one of the earliest analyses, Rubin et al. reported that, in the Diabetes Prevention Program, antidepressants but not depression syndrome as measured by the Patient Health Questionnaire were associated with transition to diabetes in two of the three arms of this trial [17,18]. Similarly, in one of the largest studies to date, Pan et al. reported a modest (on the order of 10–15% increased risk) but statistically significant association between antidepressant use and risk of type 2 diabetes [14]. More recently, Vimalananda and colleagues reported that antidepressant medication use was associated with risk of type 2 diabetes over a 12-year period that persisted after accounting for depressive symptoms as indicated by the Center for Epidemiologic Studies–Depression (CES-D) Scale [20]. Weight gain associated with some antidepressants may be a mediating mechanism linking depression and

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diabetes risk [16], and recent reviews indicate that some antidepressants impact glucose metabolism [13]. However, several randomized controlled studies have demonstrated that some classes of antidepressant medications are associated with weight loss and improved glycemic control among patients with both depression and diabetes [21–23]. Therefore, it remains unresolved as to whether antidepressant medication use, independent from depressive symptoms, is predictive of diabetes risk.

As summarized by Barnard and colleagues [13], the majority of prior studies of the relationship between psychiatric medication use and diabetes risk have been limited by infrequent, short follow-up periods that do not account for changes in medication use over time or that fail to account for depressive symptoms that themselves have been associated with onset of type 2 diabetes. Also, few studies have examined whether psychiatric medications moderate the association between depressive symptoms and diabetes risk. It is possible that, if depressive symptoms are well-controlled by medication, the subsequent risk of type 2 diabetes may be mitigated.

Building on this research, the objective of this study was to examine the prospective relationship between depressive symptoms, psychiatric medication use, and their interaction on the risk of incident type 2 diabetes in a population-based cohort over a 12-year period. We modeled both depressive symptoms and medication use as time-varying exposures to account for changes over follow-up. Finally, building on emerging findings regarding the potential modifying role of weight gain in this relationship, we assessed whether the relationship between depressive symptoms and diabetes risk was moderated by body mass index (BMI).

2. Methods

2.1. Sample

Data come from the 1998–2010 waves of the Health and Retirement Study (HRS). The HRS is an open, longitudinal, nationally representative cohort study of adults over the age of 50 years and was designed to examine relationships between health and economic factors during work transitions in later life. Follow-up surveys have been administered every 2 years since 1992, and the sample is periodically refreshed with new cohorts to maintain representativeness and a steady-state sample size of approximately 20,000 individuals. Further details of the HRS and its survey design are described elsewhere [24]. The 1998 wave was used as baseline for this study because it was the first year that the HRS merged with the Study of Assets and Health Dynamics Among the Oldest Old, and during this wave, the sample was refreshed with a new cohort of respondents.

Of the 21,384 respondents interviewed in 1998, 16,721 did not report a diagnosis of diabetes in 1998 or any previous (1992–1996) wave. To reduce possible bias from a survivor effect, this sample was further restricted to those under the age of 65 years in 1998 (N=8810). The final analytic sample included 8704 respondents interviewed in 1998 who had complete data for diabetes status, depressive symptoms, psychiatric medication use, and all relevant covariates.

The HRS was approved by the institutional review board at the University of Michigan and all participants provided informed consent.

2.2. Diabetes status

Diabetes status was determined by self-report at each wave. Respondents were asked if they have ever been told by a doctor that they have diabetes or high blood sugar. For all follow-up waves, respondents were asked, "Since we last talked to you, that is since (last interview date), has a doctor told you that you have diabetes or high blood sugar?" If respondents had reported diabetes at a previous wave, they were asked to confirm this report at the present wave. Respondents were then asked the year that they were first told they had diabetes. Time since baseline to diagnosis of diabetes was calculated as the difference between 1998 and this reported year. If respondents were missing data on year of diagnosis, we instead used the year of the follow-up interview that the respondent first reported diabetes. Those who were lost to follow-up, died, or who never reported diabetes during the follow-up period were right-censored, with time to event defined as the year of last completed interview minus 1998.

2.3. Depressive symptoms

Depressive symptoms were assessed using the 8-item CES-D scale. The CES-D has been widely used in studies of late-life depressive symptoms and has good psychometric properties for use with older populations [25,26]. Participants were asked to report whether or not eight specific symptoms (e.g., *I felt depressed*; *I felt everything I did was an effort*; *My sleep was restless*) were experienced for much of the past week. The number of endorsed symptoms (positive symptoms were reverse-coded) was summed to create a total depressive symptom score (range: zero to eight). Valid data on at least six of the eight symptom items were required in order to create the summary CES-D score. Depressive symptoms were treated as a continuous variable for the main analysis. For a supplemental analysis examining clinically elevated levels of depressive symptoms, the CES-D score was dichotomized using cutpoints of <4 vs. ≥ 4 symptoms. These cutpoints have been established in earlier reports as indicative of clinically relevant depressive symptoms [25,27,28].

2.4. Psychiatric medication use

Psychiatric medication use was assessed by self-report at each biennial interview wave. Respondents were asked, "Do you now take tranquilizers, antidepressants, or pills for nerves?" coded as a dichotomous (yes/no) variable. In the later years of the study (2006–2010), an additional question was added to the HRS asking whether or not the respondent regularly took prescription drugs to help relieve anxiety or depression. For these years, an affirmative response to either question was coded as a "yes". Because of concerns regarding the quality of this measure of medication use, we first conducted a validation analysis using the HRS 2005 Prescription Drug Study (PDS).

The PDS is an off-year supplement to the HRS that details exact prescriptions and usage for drugs currently being taken. The 2005 PDS was administered to a subsample of 2004 HRS respondents who were born in 1942 or earlier or who were covered by Medicare or Medicaid between 2002 and 2004. These medications were then categorized into classes using publicly available databases. The response rate to the 2005 PDS was 88.1% (N=4684) [29]. For those listing a drug on the PDS within the "psychiatric" classification, 62.7% listed an antidepressant (e.g., SSRI, TCA) and 44.4% listed an antianxiety drug (e.g., benzodiazepine, hypnotic, anxiolytic). Among those who reported psychiatric medication use in the 2004 HRS and completed the 2005 PDS, 72.9% reported taking a specific psychiatric medication (i.e., antidepressant, anxiolytic) in the PDS drug list. Among those who did not report taking a psychiatric medication in 2004, 85.8% did not list any psychiatric drugs on the PDS. The total concordance between the 2004 HRS psychiatric medication use variable and the 2005 PDS psychiatric medications variable was 84.5%. Considering the 1-year lag between these two surveys, this concordance was determined to be satisfactory to validate the self-report data. Because the PDS was not administered at each wave and its restricted sampling frame (i.e., respondents aged 65 years and older in 2007 or on Medicare/Medicaid), we could not use this data in our longitudinal analysis.

2.5. Covariates

Demographic covariates included age (in 1998), race/ethnicity (categorized as White, Black, Hispanic, and Other), gender, education (categorized as high school or less vs. at least some college), and

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socioeconomic status indexed as net worth (total assets minus total debt, categorized into quintiles). Tobacco and alcohol use and physical activity were assessed by self-report at baseline. Smoking status was categorized as current, former, and never smoker. Alcohol use was measured by a dichotomous variable indicating "heavy drinker" (defined as consuming an average of >2 drinks per day for men and >1 drink per day for women, consistent with US Department of Health and Human Services guidelines [30]). Physical activity was assessed by a dichotomous variable of whether or not the respondent engaged in vigorous exercise three or more times per week vs. less. Two health characteristics that impact diabetes risk and that were expected to have significant variability over the follow-up period, BMI and hypertension status, were treated as time-varying covariates. BMI (kg/m^2) was calculated from self-reported weight and height assessed at each wave. Physician diagnosis of hypertension (yes/no) was assessed by self-report at each wave.

2.6. Statistical analysis

Initially, differences in cumulative incidence of diabetes over the follow-up period and average time to event were assessed using chi-square tests and *F* tests. Next, Cox proportional hazard models were fit to estimate hazard ratios (HRs) of type 2 diabetes over the 12-year period. Depressive symptoms, psychiatric medication use, BMI, and hypertension status were treated as time-varying covariates. All other covariates were fixed at their baseline values because they did not violate the proportional hazard assumption or change substantially over time. In instances of time gaps between measurements for the time-varying covariates (i.e., missing data for a variable in one or more waves), values were imputed using the prior wave value; 12.7% of CES-D, 11.5% of psychiatric medication use, 12.2% of BMI, and 11.5% of high blood pressure values were imputed in this manner. The proportional hazard assumption was validated for baseline covariates by confirming that the interactions between the covariates and ln(time) were nonsignificant [31].

After fitting bivariate hazard models for each independent variable to estimate its crude relationship with diabetes risk, we fit a series of nested models adjusting for covariates. Model 1 included the two main effects (depressive symptoms and psychiatric medication use) plus their interaction (symptoms×medications). Model 2 included the covariates from Model 1 plus additional adjustment for demographic characteristics and socioeconomic status. Model 3 additionally adjusted for health behaviors (BMI, hypertension status, physical activity, alcohol use, and smoking status). We also examined whether the relationship between depressive symptoms, psychiatric medication use, and diabetes risk was moderated by BMI by fitting two- and three-way interactions between their main effects and BMI (i.e., symptoms×BMI, medications×BMI, and symptoms×medications×BMI). Further exploration of the interaction between depressive symptoms, psychiatric medication use, and BMI was conducted by calculating HRs for various combinations of these covariates at different levels. Finally, we conducted a supplemental analysis stratifying the sample by baseline CES-D (i.e., CES-D<4 vs. CES-D≥4) in order to examine whether these relationships varied by clinically elevated depressive symptomology. Relative model fit was evaluated with the Akaike Information Criterion (AIC) where smaller values indicate better fit. All analyses were performed using SAS version 9.4, and all *P* values represent two-tailed tests.

2.7. Sensitivity analysis of diabetes status

Up to 25% of cases of type 2 diabetes are undiagnosed [32], and thus, we conducted a sensitivity analyses to determine whether this measurement error materially impacted our results. In 2006, blood spots were collected from a random sample of 50% of the HRS cohort as part of the "Enhanced Face-to-Face Interviews"; blood spots were collected from the remaining 50% of the cohort in 2008 [33]. We used these blood spots to (1) evaluate the validity of self-reported diabetes status as compared to elevated blood glucose as indicated by hemoglobin A1c (HbA1c)≥6.5% from the blood spots, using the latter as the "gold standard" [34], and (2) assess whether the measurement error in self-report diabetes status was nondifferential relative to both depression status and psychiatric medication use at those waves. If misclassification of diabetes status is not associated with either depressive symptoms or psychiatric medication use, the measures of association between the exposures and risk of diabetes will be biased toward, rather than away, from the null [35].

3. Results

3.1. Main results

At baseline, 57.4% of respondents reported at least one depressive symptom and 6.7% were currently using a psychiatric medication. Respondents who reported taking a psychiatric medication had higher mean CES-D scores (3.36 for those taking a medication vs. 1.34 for those not) and higher prevalence of clinically elevated depressive symptoms (45.3% vs 12.5%, respectively). The average follow-up time was 9.76 years (SD=3.44). The cumulative incidence of diabetes during the follow-up period was 18.5%. As shown by Table 1, respondents who developed diabetes were more likely to have elevated depressive symptoms ($P<.0001$), be using a psychiatric medication ($P=.0034$), be male ($P=.0210$), be obese ($P<.0001$), or have hypertension ($P<.0001$) at baseline. They were less likely to be White ($P<.0001$), highly educated ($P<.0001$), wealthy ($P<.0001$), engage in vigorously active ($P<.0001$), or be a heavy drinker ($P<.0001$). Also shown in Table 1, those with more depressive symptoms ($P<.0001$) and those using psychiatric medication ($P=.0241$) had significantly shorter average time to diabetes or censorship.

Results of Cox proportional hazard models are shown in Table 2. Both depressive symptoms and psychiatric medication use were significantly associated with elevated risk of developing diabetes. The interaction between CES-D and psychiatric medication use was significant (beta=−0.240, $P=0.049$) and including this term improved relative model fit as indicated by the AIC. Fig. 1 illustrates the unadjusted baseline relationship between CES-D, psychiatric medication use, and their interaction on risk of diabetes over the follow-up period. The two-way interactions between CES-D and BMI (beta=−0.004, $P=0.045$), psychiatric medication use, and BMI (beta=−0.041, $P=0.001$) and the three-way interactions between CES-D, psychiatric medication use, and BMI (beta=0.006, $P=0.121$) also improved goodness of fit and were included in the final model.

As shown by Tables 2 and 3, in the fully adjusted model, the relative hazard (HR) of incident diabetes increased by 6% for every 1 unit increase in CES-D [95% confidence interval (CI): 1.02–1.09] for respondents not taking psychiatric medications. However, for respondents who were taking a psychiatric medication, CES-D was not related to diabetes risk (HR: 0.98, 95% CI: 0.93–1.03). Psychiatric medication use was associated with 57% greater risk of diabetes (95% CI: 1.25–1.96) for respondents who did not endorse any depressive symptoms (CES-D=0). However, psychiatric medication use was not significantly associated with diabetes risk for respondents who endorsed four or more depressive symptoms (Table 3).

Table 3 displays the HRs for incident diabetes according to combined categories of CES-D, psychiatric medication use, and BMI derived from the fully adjusted model. The influence of both increasing depressive symptoms and psychiatric medication use on diabetes risk declined with increasing BMI. For example, a 1-unit increase in CES-D was associated with elevated risk of diabetes for respondents who are normal weight (e.g., HR: 1.09 if BMI=20 kg/m^2) or overweight (e.g., HR: 1.05 if BMI=30 kg/m^2). However, CES-D was not significantly associated with diabetes risk for respondents who were obese (e.g., HR: 1.03 if BMI=35 kg/m^2). Similarly, psychiatric medication use was associated

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Table 1
Baseline characteristics and cumulative incidence of diabetes over the 12-year follow-up period: the HRS.

	Overall (*N*, %)	Did not develop diabetes (*N*, %)	Developed diabetes (*N*, %)	chi^2 test *P* value	Time to diabetes or censorship (mean, SD)	*F* test *P* value
Total sample (*N*)	8810	7178 (81.5)	1632 (18.5)	–	9.8 (3.4)	–
CES-D				<.0001		<.0001
0	3506 (42.6)	2978 (44.4)	528 (34.6)		10.1 (3.2)	
1–3	3497 (42.5)	2790 (41.6)	707 (46.4)		9.7 (3.5)	
4+	1225 (14.9)	936 (14.0)	289 (19.0)		9.3 (3.7)	
Psychiatric medication use				0.0034		0.0241
No	8109 (93.3)	6635 (93.7)	1474 (91.7)		9.8 (3.4)	
Yes	581 (6.7)	447 (6.3)	134 (8.3)		9.4 (3.6)	
Age (years)				0.3438		<.0001
<55	2722 (30.9)	2230 (31.1)	492 (30.1)		9.7 (3.5)	
55–59	3139 (35.6)	2532 (35.3)	607 (37.2)		9.6 (3.6)	
60–64	2949 (33.5)	2416 (33.7)	533 (32.7)		10.0 (3.3)	
Race				<.0001		<.0001
White	6689 (75.9)	5600 (78.0)	1089 (66.7)		9.3 (3.7)	
Black	1198 (13.6)	895 (12.5)	303 (18.6)		9.3 (3.7)	
Hispanic	732 (8.3)	539 (7.5)	193 (11.8)		9.4 (3.5)	
Other	191 (2.2)	144 (2.0)	47 (2.9)		9.9 (3.4)	
Gender				0.0210		<.0001
Male	3572 (40.5)	2869 (40.0)	703 (43.1)		10.0 (3.3)	
Female	5238 (59.5)	4309 (60.0)	929 (56.9)		9.5 (3.6)	
Education				<.0001		<.0001
HS or less	5018 (57.0)	3969 (55.4)	1049 (64.3)		9.5 (3.5)	
At least some college	3780 (43.0)	3198 (44.6)	582 (35.7)		10.0 (3.3)	
Net worth				<.0001		<.0001
<$30,000	1775 (20.1)	1363 (19.0)	412 (25.2)		9.9 (3.4)	
$30,001–99,999	1967 (22.3)	1512 (21.1)	455 (27.9)		10.0 (3.3)	
$100,000–199,999	1592 (18.1)	1303 (18.2)	289 (17.7)		9.5 (3.6)	
$200,000–399,999	1638 (18.6)	1382 (19.3)	256 (15.7)		10.3 (3.1)	
$400,000+	1838 (20.9)	1618 (22.5)	220 (13.5)		9.2 (3.7)	
BMI				<.0001		<.0001
<30	6436 (74.1)	5585 (78.8)	851 (53.2)		10.0 (3.3)	
30+	2251 (25.9)	1502 (21.2)	749 (46.8)		9.0 (3.8)	
High blood pressure				<.0001		<.0001
No	5562 (64.0)	4772 (67.3)	790 (49.3)		10.1 (3.2)	
Yes	3130 (36.0)	2316 (32.7)	814 (50.7)		9.2 (3.7)	
Vigorous activity				<.0001		<.0001
No	4374 (49.7)	3449 (48.1)	925 (56.7)		9.5 (3.6)	
Yes	4432 (50.3)	3726 (51.9)	706 (43.3)		10.0 (3.3)	
Smoking status				0.8788		<.0001
Never	3444 (39.4)	2799 (39.3)	645 (39.8)		9.4 (3.5)	
Former	3260 (37.3)	2665 (37.4)	595 (36.7)		9.8 (3.5)	
Current	2046 (23.4)	1666 (23.4)	380 (23.5)		10.0 (3.3)	
Heavy drinker				<.0001		0.4741
No	8194 (93.4)	6634 (92.8)	1560 (95.7)		9.8 (3.4)	
Yes	583 (6.6)	513 (7.2)	70 (4.3)		9.9 (3.4)	

with elevated risk of diabetes for respondents who were normal weight (e.g., HR: 1.84 if BMI=20 kg/m^2) or overweight (e.g., HR: 1.33 if BMI=30 kg/m^2), but not for respondents who were obese (HR: 1.13 if BMI=35 kg/m^2).

Finally, Table 4 shows the results of the supplemental analysis stratifying the sample by clinically elevated depressive symptoms at baseline. Among respondents with low levels of depressive symptoms at baseline, the interaction between psychiatric medication use and CES-D was marginally significant (beta=−0.347, *P*=0.050) and indicated that medication use was associated with diabetes risk only for those with consistently low levels of depressive symptomology over the follow-up period. Psychiatric medication use was not related to diabetes risk among respondents who had low levels of depressive symptomology at baseline but who developed clinically elevated depressive symptomology (i.e., CES-D ≥4) over the follow-up period. Consistent with this finding, psychiatric medication use was not related to diabetes risk among respondents with clinically elevated depressive symptoms at baseline.

3.2. Sensitivity analysis of diabetes status

Combining the 2006 and 2008 blood spot collections and using HbA1c≥6.5% as the gold standard, the sensitivity of self-report diabetes was 76.4% and the specificity was 86.5%. Limiting the sample to those who reported they did not have diabetes, the proportion of respondents with undiagnosed diabetes was 5.4% among those with CES-D≥4 and 4.2% among those with CES-D<4 (chi^2=3.0, *P*=0.081). The proportion of respondents with undiagnosed diabetes was 3.4% among those taking a psychiatric medication and 4.5% among those who were not (chi^2=3.3, *P*=0.697). Together, these results indicate that the self-report assessment of diabetes status in this sample has acceptable sensitivity/specificity and that the measurement error inherent in this assessment is nondifferential relative to psychiatric medication use and depressive symptoms.

4. Discussion

The three main findings of this study are: First, both depressive symptoms and psychiatric medication use are related to diabetes risk in midlife and late life, and the association between depressive symptoms and diabetes risk is moderated by psychiatric medication use. Specifically, our data are consistent with a threshold effect whereby the relative increase in diabetes risk only occurs at the lower end of depressive symptomology, and once a threshold of "clinically significant" elevated symptomology is met (indicated by either CES-D≥4 or use of medications), there is no additional risk of diabetes associated with

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Table 2
Predictors of incident diabetes over the 12-year follow-up period: the HRS (N=8704).

Effect	Unadjusted crude HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CES-D	1.09 (1.07–1.12)	1.10 (1.07–1.13)	1.07 (1.04–1.10)	1.06 (1.02–1.09)
Psychiatric medication use	1.43 (1.25–1.64)	1.52 (1.23–1.86)	1.62 (1.32–1.99)	1.57 (1.25–1.96)
Age	1.01 (1.00–1.02)		1.01 (1.00–1.02)	1.01 (1.00–1.02)
Race (reference: White)				
Black	1.63 (1.43–1.85)		1.37 (1.19–1.58)	1.11 (0.96–1.28)
Hispanic	1.67 (1.43–1.96)		1.35 (1.15–1.60)	1.43 (1.21–1.69)
Other	1.62 (1.21–2.16)		1.55 (1.15–2.09)	1.51 (1.12–2.04)
Female gender	0.85 (0.77–0.94)		0.79 (0.71–0.88)	0.74 (0.66–0.82)
At least some college education	0.71 (0.64–0.78)		0.86 (0.77–0.96)	0.89 (0.80–1.00)
Net worth (reference: <$30,000)				
$30,001–99,999	0.96 (0.84–1.10)		1.09 (0.94–1.25)	1.10 (0.95–1.26)
$100,000–199,999	0.73 (0.63–0.85)		0.89 (0.76–1.04)	0.99 (0.84–1.16)
$200,000–399,999	0.62 (0.53–0.73)		0.78 (0.66–0.93)	0.91 (0.77–1.08)
$400,000+	0.47 (0.40–0.55)		0.62 (0.52–0.75)	0.79 (0.66–0.96)
BMI (kg/m^2)	1.09 (1.09–1.10)			1.09 (1.08–1.10)
Hypertension	2.27 (2.05–2.52)			1.76 (1.58–1.97)
Vigorous activity	0.71 (0.64–0.78)			0.85 (0.77–0.95)
Smoking status (reference: never)				
Former	1.00 (0.89–1.11)			0.95 (0.84–1.06)
Current	1.07 (0.94–1.22)			1.18 (1.03–1.36)
Heavy drinker	0.63 (0.50–0.80)			0.78 (0.61–1.00)
AIC	–	27,341	27,208	26,243

Because of the interactions between these variables, the HR for CES-D, psychiatric medication use, and BMI are shown at set levels of these covariates. For Models 1 and 2, the HR for CES-D score is for psychiatric medication use=0, and HR for psychiatric medication use is for CES-D=0. For Model 3, the HR for CES-D is for psychiatric medication use=0 and mean BMI, the HR for psychiatric medication use is for CES-D=0 and mean BMI, and the HR for BMI is for psychiatric medication use=0 and mean CES-D.

more severe symptomology. Second, the association between both depressive symptoms and psychiatric medication use is attenuated by increasing BMI. Third, the results of our sensitivity analysis are consistent with the hypothesis that misclassification of diabetes status was not differentially associated with these two exposures (indicating our findings are conservative) and that the association between psychiatric medication use and risk of diabetes is not solely an artifact of clinical ascertainment bias.

Our interpretation of the moderating impact of psychiatric medication use on the association between depressive symptoms and diabetes risk is that this result indicates a threshold (or ceiling) effect: that is, a relative increase in diabetes risk only occurs at the low end of depressive symptomology. This is consistent with the findings of Campayo and colleagues (2010) who reported that depression severity was not related to diabetes risk once diagnostic criteria were met [36] and those of Pan et al. who reported that low levels of depressive symptomology were predictive of diabetes risk [9]. The corollary to this pertains to the association between psychiatric medications and diabetes risk: respondents taking medications had consistently higher depressive symptoms throughout the follow-up period, and thus, a ceiling/threshold effect of depressive symptoms would explain why relative increases

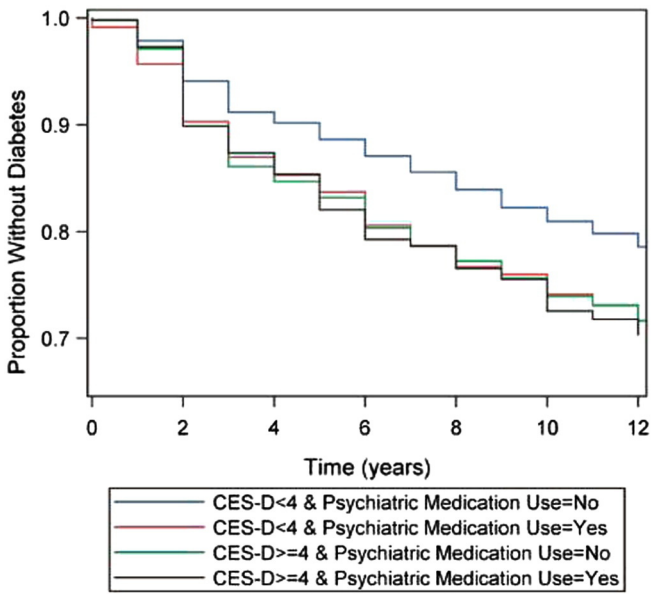

Fig. 1. Kaplan–Meier plot of time to diabetes onset predicted by baseline CES-D and psychiatric medication use in the HRS (N=8704); 1998-2010.

Table 3
Relative hazard of diabetes according to combined categories of CES-D, psychiatric medication use, and BMI: HRS 1998–2010.

Effect	HR (95% CI)
CES-D (1 unit increase) at psychiatric medication use=0 and	
BMI=20	1.09 (1.03–1.15)
BMI=25	1.07 (1.03–1.11)
BMI=28.20 (mean)	1.06 (1.02–1.09)
BMI=30	1.05 (1.02–1.08)
BMI=35	1.03 (1.00–1.06)
BMI=40	1.01 (0.96–1.05)
CES-D (1 unit increase) at psychiatric medication use=1 and	
BMI=20	0.96 (0.88–1.05)
BMI=25	0.97 (0.91–1.04)
BMI=28.20 (mean)	0.98 (0.93–1.03)
BMI=30	0.98 (0.93–1.03)
BMI=35	0.99 (0.94–1.05)
BMI=40	1.00 (0.93–1.07)
Psychiatric medication use at mean BMI=28.20 and	
CES-D=0	1.57 (1.25–1.96)
CES-D=1	1.45 (1.21–1.75)
CES-D=2	1.34 (1.14–1.58)
CES-D=3	1.24 (1.06–1.47)
CES-D=4	1.15 (0.96–1.39)
CES-D=5	1.07 (0.85–1.34)
CES-D=6	0.99 (0.75–1.30)
CES-D=7	0.92 (0.66–1.27)
CES-D=8	0.85 (0.58–1.24)
Psychiatric medication use at mean CES-D=1.37 and	
BMI=20	1.84 (1.41–2.41)
BMI=25	1.57 (1.28–1.92)
BMI=30	1.33 (1.13–1.57)
BMI=35	1.13 (0.94–1.35)
BMI=40	0.96 (0.76–1.21)

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Table 4
Relative hazard of diabetes according to combined categories of CES-D, psychiatric medication use, and BMI stratified by baseline depressive symptoms.

Effect	Baseline CES-D<4 HR (95% CI)	Baseline CES-D≥4 HR (95% CI)
Total *N*	6936	1214
CES-D (1 unit increase) at mean BMI=28.20 and		
Psychiatric medication use=No	1.05 (1.00–1.09)	1.03 (0.97–1.10)
Psychiatric medication use=Yes	0.95 (0.88–1.03)	1.06 (0.95–1.19)
Psychiatric medication use at mean BMI=28.20 and		
CES-D=0	1.80 (1.41–2.30)	0.72 (0.37–1.38)
CES-D=1	1.64 (1.35–2.00)	0.74 (0.43–1.28)
CES-D=2	1.49 (1.24–1.80)	0.76 (0.48–1.20)
CES-D=3	1.36 (1.09–1.70)	0.79 (0.54–1.15)
CES-D=4	1.24 (0.93–1.64)	0.81 (0.58–1.13)
CES-D=5	1.13 (0.79–1.61)	0.84 (0.61–1.16)
CES-D=6	1.03 (0.66–1.59)	0.87 (0.60–1.24)
CES-D=7	0.93 (0.55–1.57)	0.89 (0.58–1.38)
CES-D=8	0.85 (0.46–1.56)	0.92 (0.55–1.56)

in CES-D was not related to diabetes risk among this group. The supplemental analysis that stratified the sample by clinically elevated depressive symptoms at baseline is consistent with this explanation because it shows that neither increasing depressive symptoms nor psychiatric medication use was related to diabetes risk for those with elevated depressive symptoms at baseline. In short, our interpretation is that, once a threshold level of "clinically significant" depressive symptomology has been met (indicated either by CES-D≥4 or clinical detection of depressive symptoms as proxied by use of psychiatric medications), a *relative* increase in depressive symptoms does not predict increased diabetes risk.

Two of our findings contrast with recent reports. First, in this study, the association between psychiatric medication use and risk of diabetes was only observed among those with less severe depressive symptomology. Although this finding needs to be replicated in samples with more detailed data regarding specific medications, these findings contrast with a recent analysis of the Black Women's Health Study (BWHS) that indicated that the association between antidepressant medication use and diabetes risk was strongest among those with elevated depressive symptoms, suggesting a synergistic effect [20]. Second, our findings indicate that the association between both depressive symptoms and psychiatric medication use is attenuated by increasing BMI. It is possible that BMI mediates the association between these exposures and diabetes risk or that the relatively modest effects of depression and medication use are simply overwhelmed by the influence of such a potent diabetes risk factor like obesity. However, we note that the analysis of the BWHS found that both depressive symptoms and antidepressant use were associated with diabetes risk even among obese respondents [20]. While differences in sample composition may contribute to these contrasting findings, together these studies indicate that future research should explicitly investigate potential interrelationships between psychiatric medications, depressive symptoms, and BMI on diabetes risk.

Results should be interpreted in light of study limitations. First, all variables were derived by self-report and thus may be subject to reporting bias. This was of particular concern for the self-report of psychiatric medication use and diabetes status. However, our validation analysis using the 2005 PDS showed high concordance between the self-reported questionnaire and specific psychotropic drugs from the PDS. Additionally, our sensitivity analysis showed that misclassification of diabetes status in the 2006 and 2008 waves, indicated by HbA1c≥6.5%, was not significantly associated with either depressive symptoms or psychiatric medication use, and thus, associations would be biased toward the null [35]. The CES-D is also not a diagnostic instrument, and thus, we may not have been able to capture all clinically relevant components of depressive symptomology. Finally, while over 95% of diabetes in the adult population are type 2, without additional biological data, we cannot confirm that no cases were type 1.

The study also has several strengths. This is among the first studies of diabetes risk to explicitly focus on the interaction between depressive symptoms and psychiatric medications using a nationally representative cohort. The long follow-up period and relatively frequent (every 2 years) assessments allowed us to model depressive symptoms and psychiatric medication use as time-varying covariates to account for change in status over time. Finally, we were able to account for important confounders, such as physical activity, smoking status, and alcohol use, and explicitly investigated effect modification by BMI.

5. Conclusions

Our findings add to the growing body of research on how depressive symptoms, psychiatric medication use, and diabetes risk interrelate in midlife and late-life. In particular, our results highlight the complex relationship between depressive symptoms and psychiatric medications on diabetes risk and the need for a nuanced understanding of these factors. Examining the potential interactions between these variables can inform the development of targeted intervention strategies, as well as open the door to examining novel hypotheses regarding the mechanisms linking depressive symptoms and diabetes risk for older adults.

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