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Depressive Symptoms Are Associated with Cognitive Function in the Elderly with Type 2 Diabetes

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Abstract.
Background: Type 2 diabetes (T2D) is a metabolic condition associated with poor clinical and cognitive outcomes including vascular disease, depressive symptoms, cognitive impairment, and dementia. In the general elderly population, depression has been consistently identified as a risk factor for cognitive impairment/decline. However, the association between depression and cognitive function in T2D has been understudied.
Objective: We investigated the association between depression and cognitive function in a large sample of cognitively normal elderly with T2D.
Methods: In this cross-sectional study, we examined 738 participants, aged 65–88 years old, enrolled in the Israel Diabetes and Cognitive Decline study. For each cognitive domain (Episodic Memory, Executive Function, Attention/Working Memory, Language/Semantic Categorization) and Overall Cognition, multiple linear regressions assessed its association with depression (score greater than 5 on the 15-item version of the Geriatric Depression Scale [GDS]), adjusting for age, sex, and education.
Results: Depression ($n=66$, 8.9%) was associated with worse performance on tasks of Executive Function ($p=0.004$), Language/Semantic Categorization ($p<0.001$), and Overall Cognition ($p<0.002$), but not Episodic Memory ($p=0.643$) or Attention/Working Memory ($p=0.488$). Secondary analyses using GDS as a continuous variable did not substantially change the results. Adjusting also for a history of antidepressant medication use slightly weakened the findings.
Conclusion: Significant associations of depression with several cognitive domains and Overall Cognition even in cognitively normal elderly with T2D, suggest that depression may have a role in impaired cognitive function in T2D, which may be attenuated by antidepressants.

Keywords: Cognitive domains, cognitive function, depressive symptoms, diabetes

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INTRODUCTION

In the general elderly population, the association between neuropsychiatric symptoms (and in particular depressive symptoms) and cognitive impairment/decline including dementia has been robustly found [1, 2]. This association has been reported in the elderly from different ethnic backgrounds [3] and has been supported by neuropathological findings [4, 5]. However, longitudinal studies have reported an association that affects only men [6] or those with higher educational attainment [7]. Other studies have found that other characteristics, such as age of onset of depression and prior cognitive impairment [8–10], can affect the association of depression with cognitive function.

In the general elderly population, the associations between depression and cognitive function differ by cognitive domain (for a review, see [11]), and have been reported for all domains [12]. Impairment in specific cognitive domains has also been reported, with substantial deficits observed in attention and information processing speed [13]. Differences may also be evident in populations with specific medical conditions, such as deficits in episodic memory in recurrent depression and deficits in attention and executive function in late-onset depression [14].

Indeed, elderly with type 2 diabetes (T2D) and depression are at higher risk of cognitive impairment/decline [15, 16]. However, the literature reporting on this association is scarce and inconsistent, and little is known about the cognitive domains that are compromised. In a cross-sectional study of elderly people with T2D, Brands and colleagues examined the association of depressive symptoms with five cognitive domains, but no association was found using either a cutoff score for depression, or the total number of symptoms, or using specific depression domain scores [17]. In contrast to this cross-sectional study, a longitudinal study found a significant association of depressive symptoms with cognitive decline in three cognitive tests representing psychomotor function, verbal memory, and executive function [18], which is largely consistent with those domains affected in the general elderly population with depression.

Thus, the present study investigated the cross-sectional association of depression with cognitive function in a well-characterized, cognitively normal (Clinical Dementia Rating [CDR] scale = 0 at the Israel Diabetes and Cognitive Decline [IDCD] study entry) elderly population with T2D. This study is aimed at extending findings from the depression literature in the general elderly population in two ways: (1) by examining the association of depression with cognitive function in elderly with T2D and (2) by identifying specific cognitive domains that are impaired.

METHODS

Participants

The IDCD study design has been previously described in detail [19], for 897 participants with baseline data. Briefly, the IDCD recruited community-dwelling elderly with T2D (65+ years old) living in central Israel, from approximately 11,000 clients enrolled in the diabetes registry of the Maccabi Healthcare Services (MHS). The MHS diabetes registry was established in 1998 to facilitate diabetes management and to improve treatment. Any of the following criteria, primarily based on the American Diabetes Association, were assessed and sufficient for enrollment into the registry: 1) Hemoglobin A_{1c} Hemoglobin A_{1c} (HbA_{1c}) >55.7 mmol/mol; 2) Glucose >11.10 mmol/l on two exams more than three months apart; 3) purchase of diabetic medication twice within three months supported by a HbA1c >47.5 mmol/mol or Glucose >6.94 mmol/l within half a year; 4) diagnosis of type 2 T2D (ICD-9 code [http://www.icd9data.com/2007/Volume1]) by a general practitioner, internist, endocrinologist, ophthalmologist, or type 2 T2D advisor, supported by an HbA1c >47.5 mmol/mol or Glucose >6.94 mmol/l within half a year. These criteria have been validated by twenty physicians in MHS against their own practice record [20]. All blood assessments were performed during fasting. IDCD inclusion criteria were having T2D; normal cognition at entry; being free of any neurological (e.g., Parkinson's disease, stroke), psychiatric (e.g., schizophrenia), or other diseases (e.g., alcohol or drug abuse) that might affect cognition; and having an informant.

For the initial IDCD screening, the electronic medical records of potential participants were screened by the MHS team for diagnosis of dementia, and its subtypes, and for cholinesterase inhibitors. If any of these criteria were present in the potential participant's record, the potential participant was excluded from the study. Then, MHS personnel asked potential participants, on the phone, whether a doctor had ever told them that they have a memory problem, or

if they had ever been treated for a memory problem. Those who responded positively were excluded from the study.

Potential participants were assessed by an IDCD physician experienced in assessment and diagnosis of dementia, and were administered the CDR scale [21]. The CDR scale assesses the severity of cognitive and functional impairment in 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) through an interview with the participant and an informant. A score of 0 represents normal cognition (an inclusion criterion for the IDCD study), 0.5 represents questionable dementia, and scores of 1 through 3 reflect increasing severity of dementia [21, 22].

Those with a CDR > 0 (reflecting questionable or higher levels of dementia severity) were excluded from the IDCD study and referred back to their primary physician. Potential participants were also assessed by a neuropsychologist, who administered the broad neuropsychological battery. For descriptive purposes, global cognitive function was assessed with the Mini-Mental State Examination (MMSE) [23]. It assesses various areas of cognitive functions (orientation, concentration, memory, language, and visual construction) and is widely used as a cognitive screening instrument for dementia. Depression was assessed using the Geriatric Depression Scale (GDS).

IDCD eligibility was determined by a diagnostic consensus conference that included neurologists, psychiatrists, and neuropsychologists experienced with dementia, with at least two specialties present. It is important to note that the neuropsychological battery was not used in the process of screening for normal cognition since it was used to calculate the cognitive outcome measures.

This study employed prospective historical diabetes-related data from the MHS, and baseline cognitive and depression data collected by the IDCD study on 897 participants. The sample for this study consisted of the 738 IDCD participants with complete data on cognitive domains, demographic characteristics (age, sex, and education), T2D-related characteristics (HbA1c; number of follow-up years in the registry, a surrogate for duration of disease [24]; and whether medication for T2D was taken [no medication, hypoglycemic medication, and insulin or insulin + hypoglycemic medication]), and cardiovascular risk factors (body mass index, creatinine, total cholesterol, triglycerides, and diastolic and systolic blood pressure).

Study procedures and informed consent were approved by the Icahn School of Medicine at Mount Sinai, Sheba Medical Center, and MHS IRB committees. All participants signed an informed consent.

Predicted cognitive function/outcomes

For the IDCD study ($n = 897$), cognitive function at entry was assessed using 13 neuropsychological tests, grouped into cognitive domains according to the factor with the highest loading: (1) Episodic Memory: Word List Memory, Word List Recall, and Word List Recognition from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery [25, 26]; (2) Attention/Working Memory: Digit Span (forward and backward) from the Wechsler Memory Scale-Revised (WMS-R) [27]; (3) Language/Semantic Categorization: Similarities from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [28], Letter Fluency [29], and Animal Fluency [30]; and (4) Executive Function: Trail Making Test (A and B) [31], CERAD-Constructional Praxis, Shape Cancellation, and Digit Symbol from the WAIS-R [28]. Raw scores were converted to z scores using participants' means and SDs. A composite measure of global cognitive function (Overall Cognition) was created by averaging all the z scores. Scores for the four cognitive domains were calculated as averages of z scores.

Depression predictor

Depression was the predictor variable, which was assessed by the 15-item version of the GDS [32]. The GDS is a widely used screening instrument for depressive symptoms in the elderly population, which follows a yes/no answer format. The cut-off score greater than 5, suggesting clinical depression, was used to define depression as a dichotomous status [33].

Statistical analyses

The association of depression with each cognitive outcome was examined using multiple regression analyses, with Episodic Memory, Attention/Working Memory, Language/Semantic Categorization, Executive Function, and Overall Cognition as the dependent variables. The primary analyses, Model 1, adjusted for the demographic characteristics of age, sex, and education. In secondary analyses, Model 2, we also adjusted for T2D-related characteristics

and cardiovascular risk factors, which are potential confounders that may be associated with cognitive function [34]. The association of depression with each cognitive outcome was also examined using the predictor as a continuous variable (GDS-15 total score).

We had information from the MHS that some participants ($n = 192$) received antidepressant medications at some time point since they entered the Diabetes Registry, suggesting they had depression. Thus, the main analyses were repeated adjusting also for antidepressants. In additional analyses, we applied multivariate analyses of covariance (MANCOVA) separately in those who had or had not taken any antidepressant to test the effects of depression status (non-depression versus depression) on cognitive functioning (the four cognitive domains and Overall Cognition), adjusting for demographics.

For each of the models of Tables 3 and 4, results for the five cognitive outcomes were considered "significant" if they met criteria of the Holm multiple comparisons procedure [35], an enhancement of the Bonferroni inequality, at the 0.05 level of significance.

For comparisons of two groups, the small (0.20), medium (0.50), and large (0.80) conventions for effect sizes of *t*-tests are widely used, while the effect sizes and conventions for the F-test are not. Therefore, *t*-test effect sizes are presented for F-tests comparing two groups. Effect size conventions for Pearson's chi-square are similarly not familiar. For a 2×2 table, the square root of Pearson's chi-square is the z-test for the difference between two proportions, analogous to the *t*-test for the difference between means. The corresponding effect size for the difference between proportions has the same small, medium, and large conventions as the *t*-test.

RESULTS

For the entire sample ($n = 738$), 66 (8.9%) were depressed and 672 (91.1%) were not depressed. Mean age was 71.9 ($SD = 4.7$). There were more men (60.3%) than women. The MMSE mean score was 28.1 ($SD = 1.7$), which is consistent with normal cognition. Table 1 presents the demographic, clinical, and cognitive characteristics of the sample

Table 1
Mean ± SD of demographic and clinical characteristics of the participants by their clinical status, non-depression versus depression

	Non-Depression	Depression	*p*	Effect Size
N	672	66	–	
Age	72.7 ± 4.6	73.1 ± 5.0	0.50[a]	0.09
Education	13.4 ± 3.5	11.6 ± 2.3	<0.001[a]	0.51
Male (%)	62.8	34.8	<0.001[b]	0.57
Female (%)	37.2	65.2		
# of follow up years in the registry	10.4 ± 1.5	10.4 ± 1.2	0.81[a]	0.03
Body mass index (kg/m^2)	28.3 ± 4.5	28.8 ± 4.8	0.43[a]	0.09
Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.3	0.07[a]	0.23
Total cholesterol (mg/dL)	180.3 ± 25.2	183.7 ± 23.8	0.29[a]	0.14
Triglycerides (mg/dL)	157.2 ± 65.0	167.3 ± 62.4	0.22[a]	0.16
Diastolic BP (mmHg)	76.7 ± 4.9	76.4 ± 4.4	0.62[a]	0.06
Systolic PB (mmHg)	134.8 ± 9.5	135.1 ± 8.8	0.87[a]	0.02
Hemoglobin A_{1c} (%), (mmol/mol)	6.8 (0.8), (51)	6.9 (0.8), (52)	0.24[a]	0.15
Type 2 diabetes medication (%)				
1- No medication ($n = 93$)	13.1	7.6	0.053[b]	0.09
2- Hypoglycemic medication ($n = 577$)	78.4	75.8		
3-[d] Insulin or insulin + hypoglycemic medication ($n = 68$)	8.5	16.7		
GDS-15	1.2 ± 1.3	7.5 ± 1.7	<0.001[a]	4.63
Antidepressant use ($n = 715$) (%)				0.45
Antidepressant use at any time point in the diabetes registry ($n = 192$)	25.1	45.9	<0.001[b]	
MMSE score ($n = 65$ for depression)	28.2 ± 1.6	27.2 ± 2.2	<0.001[a]	0.58
Attention/Working Memory (SEM)	0.051 (0.064)	–0.051 (0.208)	0.643[c]	0.06
Executive Function (SEM)	0.224 (0.120)	–0.956 (0.389)	0.004[c]	0.37
Language/Semantic Categorization (SEM)	0.250 (0.080)	–0.787 (0.260)	<0.001[c]	0.49
Episodic Memory (SEM)	0.139 (0.080)	–0.309 (0.261)	0.103[c]	0.21
Overall Cognition (SEM)	0.500 (0.187)	–1.480 (0.609)	0.002[c]	0.40

BP, blood pressure; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; SEM, Standard Error of the Mean. [a]*p*-value by Student's *t*-test, [b]Pearson's chi-square for percentages, 2 categories. [c]Analysis of covariance controlling for age, sex, and education. [d]Since 63 participants received both hypoglycemic and insulin medication and 5 received only insulin, they were combined. Pearson's chi-square for percentages, effect size, 10 small, 30 medium, 0.50 large.

Table 2
Correlations among five cognitive outcomes and cognitive tests

Cognitive Outcomes	n	Episodic Memory	Executive Function	Language/ Semantic Categorization	Attention/ Working Memory	Overall Cognition
			Correlations			
Attention/ Working Memory	738	0.234	0.466	0.487	—	0.657
Executive Function	738	0.259	—	0.558	0.466	0.844
Language/Semantic Categorization	738	0.344	0.558	—	0.487	0.804
Episodic Memory	738	—	0.259	0.344	0.234	0.588
Overall Cognition	738	0.588	0.844	0.804	0.687	—
			Cognitive Tests			
Attention/Working Memory						
Digit Span Forward	738	0.156	0.350	0.417	0.877	0.576
Digit Span Backward	738	0.253	0.467	0.437	0.879	0.643
Executive Function						
Trails A	737	0.202	0.801	0.435	0.331	0.661
Trails B	712	0.252	0.811	0.481	0.484	0.739
Praxis	734	0.132	0.608	0.359	0.257	0.506
Digit Symbol	737	0.264	0.811	0.544	0.435	0.744
Shape Cancellation	700	0.99	0.648	0.230	0.202	0.461
Language/ Semantic Categorization						
Letter Fluency	731	0.259	0.446	0.855	0.441	0.668
Animal Fluency	738	0.293	0.409	0.794	0.331	0.616
Similarities	737	0.274	0.486	0.754	0.398	0.650
Episodic Memory						
Word List Memory	738	0.815	0.815	0.284	0.414	0.305
Word List Recall	738	0.815	0.200	0.235	0.109	0.440
Word List Recognition	738	0.635	0.101	0.127	0.113	0.307

**$p < 0.001$.

by depression status (i.e., non-depression versus depression groups). The depression group had, on average, fewer years of education ($p < 0.001$), lower MMSE scores ($p < 0.01$), by definition had higher depression scores, and were more likely to have taken antidepressants ($p < 0.001$) than the non-depression group. The depression group had a majority of women, while the non-depression group had a majority of men ($p < 0.001$). With the exception of Attention/Working Memory ($p = 0.643$), the depression group performed more poorly on all cognitive domains ($p \leq 0.019$) and Overall Cognition ($p = 0.002$) than the non-depression group.

For the 738 participants in this study, Table 2 shows the intercorrelations among the four cognitive domains and Overall Cognition, and their correlations with the 13 neuropsychological tests.

Table 3 presents multiple regression results: the primary analyses adjusting for demographics (Model 1), and the secondary analyses adjusting for T2D-related characteristics and cardiovascular risk factors (Model 2). Model 1 analyses showed significant associations of depression with poorer cognitive performance in the Executive Function domain (partial r = –0.106, $t = –2.893$, $p = 0.004$), Language/Semantic Categorization domain (partial r = –0.139, $t = –3.79$, $p < 0.001$), and Overall Cognition (partial r = –0.114, $t = –3.096$, $p = 0.002$). Although strongly significant, these associations (individually) explained ≤0.019 of the variability in cognitive performance. These results remained largely unchanged using Model 2.

We repeated the Model 1 analyses by examining depression as a continuous variable (GDS-15 total score) and adjusting for demographics. Results remained significant, with a slight increase in effect size, for the same three cognitive outcomes, Executive Function, Language/Semantic Categorization, and Overall Cognition (partial $r \leq –0.175$, $t \leq –4.818$, $p < 0.001$), and one additional domain, Episodic Memory, became significant (partial r = –0.093, $t = –2.538$, $p = 0.011$). These results remained largely unchanged using Model 2. Of note, since GDS-15 total score was not normally distributed, when the

Table 3
Associations of depression, as assessed by the dichotomized GDS-15, with performance on cognitive domains and overall cognition

	Partial r[a]	β (95% CI)	*p*	Partial r[b]	β (95% CI)	*p*
Attention/Working Memory	–0.017	–0.102 (–0.531, 0.328)	0.643	–0.016	–0.094 (–0.525, 0.336)	0.668
Executive Function	–0.106	–1.180 (–1.981, –0.379)	**0.004**[c]	–0.103	–1.123 (–1.918, –0.329)	**0.006**[c]
Language/Semantic Categorization	–0.139	–1.037 (–1.573, 0.500)	**<0.001**[c]	–0.138	–1.025 (–1.562, –0.487)	**<0.001**[c]
Episodic Memory	–0.060	–0.448 (–0.987, 0.090)	0.103	–0.058	–0.431 (–0.973, 0.111)	**0.119**
Overall Cognition	–0.114	–1.980 (–3.235, –0.724)	**0.002**[c]	–0.112	–1.954 (–3.216, –0.692)	**0.002**[c]

T2D, type 2 diabetes; HbA1c, hemoglobin A1c; BMI, body mass index; BP, blood pressure; β, Average difference in cognitive performance (dependent variable) of participants with depression compared to those without depression. [a]Adjusting for demographics (age, sex, and education). [b]Adjusting for demographics, T2D-related characteristics (HbA1c, number of follow up years in the registry, and type 2 diabetes medication), and cardiovascular risk factors (BMI, creatinine, total cholesterol, triglycerides, and diastolic and systolic BP). [c]Significant at 0.05 level by Holm multiple comparisons procedure.

Table 4
Means and standard error of the mean (*SEM*) of Z scores of cognitive performance by antidepressant use and depression status

Cognitive domain	Non-Antidepressant					Antidepressant				
	Non-depression	Depression	*F* (*df* = 1, 518)	*p*	Effect Size	Non-depression	Depression	*F* (*df* = 1, 187)	*p*	*Effect Size*
n	490	33				164	28			
Attention/Working Memory	0.145 (0.075)	0.014 (0.296)	0.184	0.668	0.08	–0.170 (0.127)	0.099 (0.312)	0.632	0.428	0.16
Executive Function	0.496 (0.139)	–0.686 (0.544)	4.415	**0.036**	0.38	–0.429 (0.245)	–0.880 (0.600)	0.478	0.490	0.14
Language/Semantic Categorization	0.382 (0.092)	–0.630 (0.361)	7.335	**0.007**[a]	0.49	–0.006 (0.169)	–0.604 (0.412)	1.785	0.183	0.27
Episodic Memory	0.193 (0.089)	0.324 (0.348)	0.134	0.715	0.07	0.058 (0.176)	–0.339 (0.430)	0.724	0.396	0.17
Overall Cognition	0.840 (0.212)	–0.795 0.830)	3.627	0.057	0.34	–0.184 (0.395)	–0.865 (0.967)	0.422	0.517	0.13

Note: Adjusting for age, sex, and education. Effect size is for *t*-test comparing two groups. [a]Significant at 0.05 level by Holm multiple comparisons procedure.

Model 1 analyses were repeated using logarithmic transformation (which reduced kurtosis to –0.8 from its original value of 3.6), findings remained largely consistent, but Episodic Memory was no longer significant ($p = 0.062$).

In the subsample of 715 participants with antidepressant use information, the results for the association of depression with poorer Executive Function ($p = 0.026$) and Overall Cognition ($p = 0.040$) lost significance by the Holm criterion, but the Language/Semantic Categorization domain ($p = 0.002$) remained significant. The MANCOVA in this subsample showed that among the 26.9% ($n = 192$) who had taken any antidepressant, cognitive functioning was similar in the depressed and non-depressed groups (Table 4). The latter result remained non-significant when cognitive outcomes were compared by antidepressant classes (i.e., Selective-Serotonin Reuptake Inhibitors [SSRIs], Serotonin-Norepinephrine Reuptake Inhibitors [SNRIs], and tricyclics). However, due to the small sample size, the antidepressant class result should be interpreted with caution since the largest comparison consisted of those who were taking SSRIs ($n = 36$) versus those who were not ($n = 30$). In contrast, among those who had not taken antidepressants, test performance was significantly worse in the depressed subgroup in the Language/Semantic Categorization ($p = 0.007$) domain, as compared to the non-depressed group (Table 4).

DISCUSSION

This study investigated the association of depression with performance on four different cognitive domains and on Overall Cognition in participants with T2D. Depression was associated with poorer cognitive performance on Executive Function and

Language/Semantic Categorization, and with poorer Overall Cognition, but not on Episodic Memory or Attention/Working Memory, after adjusting for demographics (age, sex, and education). With the exception of Episodic Memory, which was not significant, these results are largely consistent with those on the association between depression and cognition in the general elderly population. The Episodic Memory result suggests that impaired memory may be less frequently observed in the depressed diabetic population as compared to the depressed general elderly population. T2D is associated with vascular risks and diseases, which in turn are associated with impairment in information processing speed. Most of the tasks in the Language/Semantic Categorization and the Executive Function domains were timed, for which good performance relied heavily on how fast participants processed the information on which they were being tested.

Depression explained $\leq$1.9% of the variability in each cognitive domain and in Overall Cognition. These results remained largely unchanged after further adjusting for T2D-associated characteristics and cardiovascular risk factors. Although, this might be a result of the relatively small prevalence (8.9%, as assessed by the GDS) of depression in this sample, the associations were less significant when antidepressant use (which yielded a higher rate: 26.9%, $n = 715$) was used as the predictor of cognition. It is noteworthy that the 8.9% prevalence is similar to that reported in non-T2D population-based studies [36], but smaller than that reported in T2D studies [37]. This discrepancy can be at least partially explained by the inclusion of a population-based sample as compared to a clinical sample, the eligibility criteria of the study, which required normal cognition, and the depression screening method. It is also possible that the potential effects of T2D on cognitive function masked the association of depression with cognitive function. This latter possibility is not the case in studies of depression in the general elderly population since these older adults may or may not have T2D.

The lack of report of the effect sizes of the association make comparisons of these results with those of other studies challenging. One cross-sectional study with a small sample ($n = 52$ white non-diabetic older adults) reported larger effect sizes (correlations ranging from 0.311 to 0.497) for the associations between depressive symptoms (as measured by the total score or two individual items from the Hamilton Depression Rating Scale) [38] and cognitive status, after controlling for demographics [3].

However, our results are in line with studies that included a T2D population and found either no association or small effects. For example, Brands and colleagues failed to find an association of cognitive performance with the cut-off score, the total score, or subdomain scores from the Beck Depression Inventory [17]. The longitudinal study by Sullivan and colleagues with a sample size of over 2,700 participants reported a link between depression and cognitive decline, with results remaining significant after adjusting for important confounders such as demographics, lipid treatment, and cardiovascular disease, and when the depression instrument was used as a continuous variable [18]. Although, Sullivan et al. addressed a different question from ours on the role of depression in cognition, their reported effect sizes were also small. The discrepancy in research findings across different studies may reflect, at least partially, differences in research design/methodology (e.g., longitudinal versus cross-sectional design, sample size and characteristics of participants, instruments used to assess depression and cognitive performance, and operational definition of depression: cutoff score, total depression score, or clinical diagnosis based on established diagnostic criteria). Results for the dichotomized GDS-15 and total score were largely similar. The IDCD sample is by eligibility criteria cognitively normal at baseline. Although within normal cognition the sample showed substantial variability in cognitive performance, it is possible that exclusion of cognitively impaired individuals explains the small association of depression with cognition in this sample. Consistent with this argument, elderly who were hospitalized for major depression and had symptoms of dementia that subsided after treatment for depression had a 4.7-times higher risk of developing frank dementia after a period of 3 years compared to hospitalized patients whose depression was not accompanied by dementia symptoms [9].

Psychological distress like depression can be an emotional reaction to a chronic medical condition such as T2D and may have different biological etiologies. In the elderly, depression that is associated with cerebrovascular disease has been referred to as "vascular depression." [39]. This concept has also been supported by the presence of microbleeds in late-onset depression as compared to early onset depression [40]. The small effect size of the association between depression and cognition in T2D is surprising in view of the strong link between vascular disease and T2D (for a review, see [41]). Indeed,

our results showed that participants with depression were not more likely to present with vascular risks (body mass index, total cholesterol, triglycerides, and diastolic and systolic blood pressure) than those without. This is consistent with Brands and colleagues' findings showing that depression was neither linked to hypertension, nor to micro- or macrovascular events, nor to white matter abnormalities [17]. Overall, these findings suggest that mechanisms underlying depression in T2D might originate from neurobiological substrates other than cerebrovascular risks/diseases [42–45], or be linked to cerebrovascular disease [46] such as brain atrophy, interleukins, and cortisol levels. In the general elderly population with major depressive disorder, Smagula and colleagues reported significant findings from pilot data on the associations among immunological markers, brain structure, and executive function [47]. Similarly, Charlton and colleagues reported an association between pro-inflammatory cytokines and memory function in late-life depression [48].

Within the depression group, relatively more participants took some diabetes medication and received more intensive treatment including insulin, which may suggest that depressed elderly with diabetes are at heightened risk of worse disease or poor diabetes management (due to difficulty following a diet or medication adherence), and of poorer cognitive performance before receiving intensive T2D treatment.

Because depression is strongly associated with psychomotor retardation [49], we reorganized the neuropsychological tests into composites of timed and untimed tests (data not shown). Partial correlations with depression showed that the depression group tended to perform worse on both types of tests (partial r controlling for demographics: timed, $r = -0.073$, $p = 0.06$; untimed, $r = -0.100$, $p = 0.007$), but the effects were small.

An area of research that remains largely unresolved in the general and T2D populations, is the effect of antidepressant medication on cognition. In the general elderly population, at least two classes of antidepressants, the SNRIs (specifically duloxetine) and the atypical antidepressants (specifically vortioxetine), have been reported to improve cognitive function, in particular memory and executive function [50, 51]. However, another class of antidepressant, the SSRIs (specifically citalopram), has been reported to decrease overall cognitive function in patients with AD [52]. Similarly, another study found MMSE scores declined after treatment with SSRIs for depression or Obsessive-Compulsive Disorder [53]. In this study, we examined associations of antidepressant classes with cognitive functioning in participants who had taken antidepressants at any time point since entering the MHS diabetes registry ($n = 192$). Our results showed that there were no significant differences in cognitive functioning between depressed and non-depressed participants who were on antidepressants of any class, or in those who were on a specific antidepressant class. However, the latter has to be interpreted with caution due to the small sample size of the subgroups.

This study had several limitations including the cross-sectional design, so causation cannot be inferred. The study lacked a non-T2D control group that would permit examining whether the associations found and their strengths are generalizable to non-T2D elderly. Similarly, this study excluded cognitively impaired T2D participants (such as those with mild cognitive impairment), thus preventing examination of the association in those who are at heightened risk of dementia. The use of follow up years in the diabetes registry as a surrogate for duration of T2D was a truncated estimate for all those who already had T2D when entering the registry, so the reported values are underestimates. Neuroimaging data that were not available could have helped explore the biological basis of depression and of diminished cognition in this sample (e.g., white matter hyperintensities and silent brain infarcts). To the extent that cerebrovascular disease may be a biological mechanism linking the association between depression and poorer cognition in T2D, excluding participants with stroke (an eligibility criterion of the IDCD study) could have diminished the magnitude of the associations. This study did not include as predictors age of depression onset or duration since then. Recent longitudinal studies finding age or duration modulation of dementia risk associated with depression suggest that depression may be an early sign of dementia, a condition that shares a common cause, or even dementia that was misdiagnosed [10, 54–56].

Strengths of this study included a large sample size, a well-characterized diagnosis of T2D, well-defined and numerous measurements of T2D characteristics, and a comprehensive neuropsychological battery. This battery permitted the evaluation of Overall Cognition and specific cognitive domains. Availability of antidepressant treatment information through the MHS registry permitted exploration of its contribution to the relationship of depression with cognition.

In summary, these results showed a significant but small association between depression and cognitive function; depression and impaired cognition may have common but also other distinct underlying neurobiological mechanisms. Investigation of these mechanisms may be an important goal for future research that includes T2D and non-T2D elderly.

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