Supplementary Appendix

Does emotional distress predict worse glycemic control over time? Results from the GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness) Study

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Table of Contents

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Supplementary Table 1. Baseline characteristics table with percent for categorical variables and mean (standard deviation) for quantitative variables, overall and by ever reaching secondary outcome or not.

	Overall	Ever Confirmed Secondary Outcome (HbA1c > 7.5%)		p-value
		No (n=1001)	Yes (n=738)	
Age (years)	57.97 (10.21)	60.01 (9.59)	55.20 (10.37)	**<0.0001**
T2D Duration (years)	4.21 (2.81)	4.45 (2.87)	3.88 (2.69)	**0.0001**
Sex (%)				
Male	68	69	66	
Female	32	31	34	0.1101
Race/Ethnicity				
Non-Hispanic White	56	59	51	
Hispanic	17	13	21	
Non-Hispanic Black	18	19	17	
Non-Hispanic Other	9	9	10	**<0.0001**
Smoking Status (%)				
Never	52	48	57	
Past	35	38	32	
Current	13	14	12	**0.0001**
BMI (kg/m^2)	34.09 (6.47)	33.97 (6.35)	34.26 (6.64)	0.2932
Education (%)				
High school/GED or Less	30	28	32	
Some college	29	31	28	
College/Graduate School	41	41	41	0.0522
Income (%)				
<10k	6	6	7	
10-20k	11	10	12	
20-50k	32	30	34	
50k+	51	54	47	0.0112
Living Status (%)				
Living Alone	17	17	17	
With another adult	79	79	79	
With children only	4	3	5	0.3428
Employment (%)				
Employed	56	52	61	
Retired	26	32	19	
Other	18	16	20	**<0.0001**
Any Diabetes-Related Complications (%)				
FALSE	59	57	61	
TRUE	41	43	39	0.3003
Any Macrovascular Disease (%)				
FALSE	93	92	93	
TRUE	7	8	7	0.2579
Medication Adherence	89.88 (11.05)	90.75 (10.61)	88.71 (11.52)	**0.0001**
HbA1c (%)	7.51 (0.48)	7.40 (0.44)	7.65 (0.49)	**<0.0001**
HbA1c (mmol/mol)	59 (5)	57 (5)	60 (5)	**<0.0001**

hs-CRP** (mg/L)	4.17 (4.60) 2.61(1.22,5.26)	3.98 (4.50) 2.44(1.17,4.9)	4.41 (4.73) 2.76(1.42,5.57)	**0.0017**
PHQ-8 Total	3.44 (3.96)	3.31 (3.92)	3.62 (4.00)	0.0201
DDS Average	1.67 (0.74)	1.63 (0.69)	1.72 (0.80)	**0.0045**

Employment: Employed=Currently employed full or part-time, full-time homemaker, or Seasonally employed; Retired= Currently retired; Other=Currently not employed, Student, Never worked or disabled, or Other; Any Diabetes-Related Complication: prior amputation, retinopathy, nephropathy (presence of either ACR≥30 mg/g or eGFR<60 ml/min/m^2), or neuropathy (presence of either Diabetic peripheral neuropathy using a composite cut-off including both the MNSI questionnaire score and the clinical examination; or Cardiovascular autonomic neuropathy defined using two HRV indices: standard deviation of normally conducted R-R intervals <8.2 ms, and root mean square of successive differences between normal-to-normal R-R intervals <8 ms); Any Macrovascular Disease: prior MI or stroke.

*p-values from unadjusted Cox proportional hazards models.

**hs-CRP has a distribution skewed to the right (Supplementary Figure 1), and both mean (SD) and median (1st and 3rd quartiles) are reported.

Supplementary Table 2. Number of events, average time to even, and rates for the two outcomes, first overall and then separately by PHQ-8 Total score </≥10, and by DDS Average score </≥2.

	Participants	Primary Outcome (Confirmed HbA1c ≥ 7%)			Secondary Outcome (Confirmed HbA1c > 7.5%)		
	n	Events	Follow-up (years)	Rate[*]	Events	Follow-up (years)	Rate[*]
Overall	1739	1157	2.1	31.0	738	3.0	14.2
PHQ-8<10	1584 (91%)	1054	2.2	30.9	667	3.0	14.0
≥10	151 (9%)	101	2.1	32.2	70	2.8	16.7
DDS<2	1291 (75%)	839	2.2	29.5	533	3.0	13.6
≥2	431 (25%)	305	2.0	36.3	199	2.8	16.2

*Rate=number of events per 100 individuals at risk for one year.

Supplementary Table 3. Association of depression symptoms and diabetes distress with subsequent risk of primary and secondary outcome adjusted for potential mediators.

	Primary Metabolic Outcome[*]		Secondary Metabolic Outcome[**]	
	Hazard Ratio (95% Confidence Interval)	p-value	Hazard Ratio (95% Confidence Interval)	p-value
A. Adjusted for Medication Adherence				
Separate models				
PHQ-8 Total Score	1.01 (1.00-1.03)	0.120	1.02 (1.00-1.04)	0.021
DDS Average Score	1.03 (0.95-1.11)	0.500	1.03 (0.94-1.14)	0.500
Joint Model				
PHQ-8 Total Score	1.01 (0.99-1.03)	0.180	1.02 (1.00-1.04)	0.029
DDS Average Score	1.00 (0.92-1.09)	0.907	0.99 (0.89-1.10)	0.862
B. Adjusted for hs-CRP				
Separate models				
PHQ-8 Total Score	1.01 (1.00-1.03)	0.080	1.02 (1.00-1.04)	0.019
DDS Average Score	1.04 (0.96-1.12)	0.372	1.04 (0.95-1.15)	0.369
Joint Model				
PHQ-8 Total Score	1.01 (1.00-1.03)	0.155	1.02 (1.00-1.04)	0.034
DDS Average Score	1.01 (0.93-1.10)	0.798	1.00 (0.90-1.11)	0.976
C. Adjusted for both Medication Adherence and hs-CRP				
Separate models				
PHQ-8 Total Score	1.01 (1.00-1.03)	0.123	1.02 (1.00-1.04)	0.027
DDS Average Score	1.04 (0.95-1.11)	0.522	1.03 (0.94-1.14)	0.483
Joint Model				
PHQ-8 Total Score	1.01 (0.99-1.03)	0.18	1.02 (1.00-1.04)	0.039
DDS Average Score	1.00 (0.92-1.09)	0.937	0.99 (0.90-1.10)	0.912

[*]HbA1c $\geq$7% subsequently confirmed. [**] HbA1c >7.5% subsequently confirmed. Models adjusted for: sex, race/ethnicity, randomized treatment group, and baseline values of age, duration of T2DM, BMI, and HbA1c.

Supplementary Table 4. P-values for tests of homogeneity of the effects of the baseline PHQ-8 Total score and DDS Average score on the risk of primary and secondary outcome failure.

	Primary Outcome (Confirmed HbA1c ≥ 7%)	Secondary Outcome (Confirmed HbA1c > 7.5%)
PHQ-8 Total Score	0.0205	0.1373
DDS Average Score	0.6115	0.9804

Models adjusted for: sex, race/ethnicity, randomized treatment group, and baseline values of age, duration of T2DM, BMI, and HbA1c.

Supplementary Figure 1. Distribution (density) of the hs-CRP (mg/L) values.