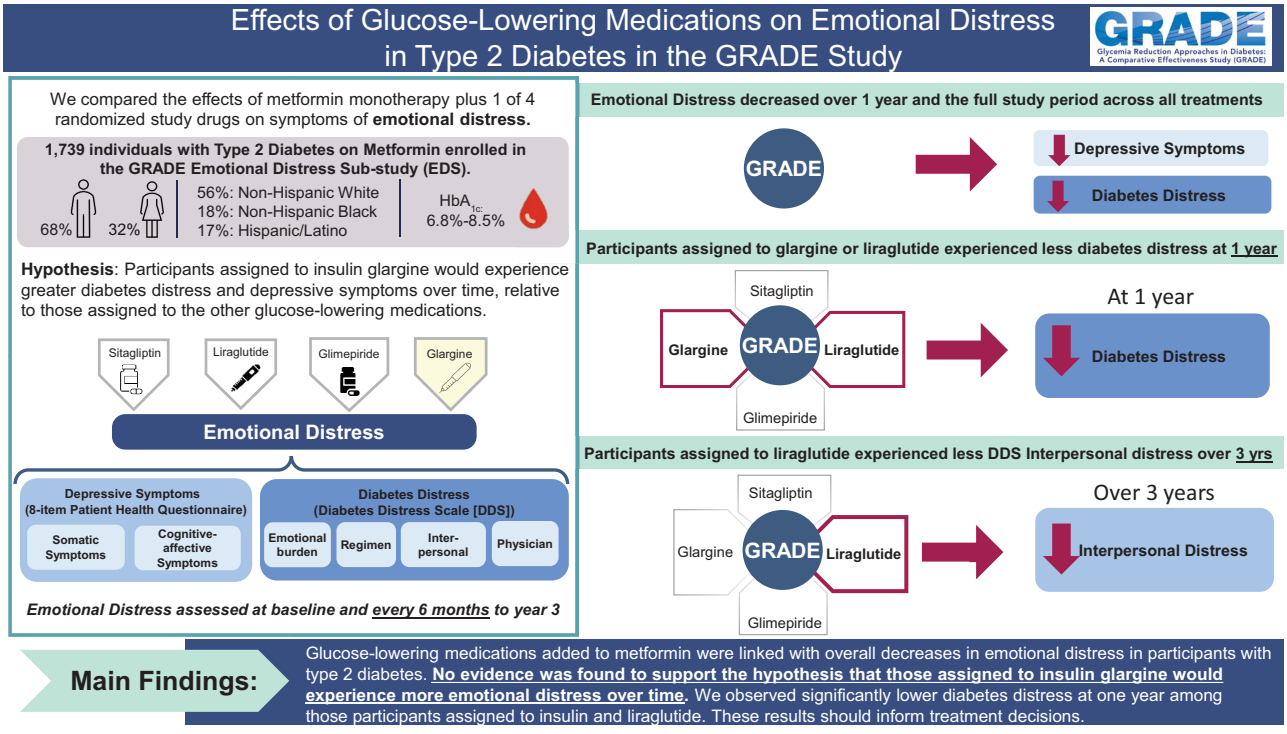
Diabetes Care
American Diabetes Association

# Differential Effects of Type 2 Diabetes Treatment Regimens on Diabetes Distress and Depressive Symptoms in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Jeffrey S. Gonzalez, Ionut Bebu, Heidi Krause-Steinrauf, Claire J. Hoogendoorn, Gladys Crespo-Ramos, Caroline Presley, Aanand D. Naik, Shihchen Kuo, Mary L. Johnson, Deborah Wexler, Jill P. Crandall, Anne E. Bantle, Valerie Arends, and Andrea L. Cherrington, for the GRADE Research Group

*Diabetes Care* 2024;47(4):610–619 | https://doi.org/10.2337/dc23-2459




## ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Prior research repeatedly showed a correlation between use of insulin therapy and increased emotional distress in type 2 diabetes.
- **What is the specific question(s) we wanted to answer?**
  Does the addition of basal insulin to metformin monotherapy cause increased emotional distress among adults with early type 2 diabetes?
- **What did we find?**
  No evidence supported the expected relationship. Instead, we found some evidence for less emotional distress with basal insulin and liraglutide.
- **What are the implications of our findings?**
  These findings are the first to test the causal association between insulin therapy and emotional distress in type 2 diabetes. Findings should inform providers and patients, both of whom are often hesitant to initiate insulin therapy because of anticipated burden.

# Differential Effects of Type 2 Diabetes Treatment Regimens on Diabetes Distress and Depressive Symptoms in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

*Jeffrey S. Gonzalez,[1,2,3,4] Ionut Bebu,[5] Heidi Krause-Steinrauf,[5] Claire J. Hoogendoorn,[1,2] Gladys Crespo-Ramos,[1,2] Caroline Presley,[6] Aanand D. Naik,[7] Shihchen Kuo,[8] Mary L. Johnson,[9] Deborah Wexler,[10] Jill P. Crandall,[2] Anne E. Bantle,[11] Valerie Arends,[12] and Andrea L. Cherrington,[13] for the GRADE Research Group**

*Diabetes Care 2024;47:610–619 | https://doi.org/10.2337/dc23-2459*

## OBJECTIVE

**We evaluated whether adding basal insulin to metformin in adults with early type 2 diabetes mellitus (T2DM) would increase emotional distress relative to other treatments.**

## RESEARCH DESIGN AND METHODS

**The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) of adults with T2DM of <10 years' duration, $HbA_{1c}$ 6.8–8.5%, and taking metformin monotherapy randomly assigned participants to add insulin glargine U-100, sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or the dipeptidyl peptidase 4 inhibitor sitagliptin. The Emotional Distress Substudy enrolled 1,739 GRADE participants (mean [SD] age 58.0 [10.2] years, 32% female, 56% non-Hispanic White, 18% non-Hispanic Black, 17% Hispanic) and assessed diabetes distress and depressive symptoms every 6 months. Analyses examined differences at 1 year and over the 3-year follow-up.**

## RESULTS

**Across treatments, diabetes distress (−0.24, $P < 0.0001$) and depressive symptoms (−0.67, $P < 0.0001$) decreased over 1 year. Diabetes distress was lower at 1 year for the glargine group than for the other groups combined (−0.10, $P = 0.002$). Diabetes distress was also lower for liraglutide than for glimepiride or sitagliptin (−0.10, $P = 0.008$). Over the 3-year follow-up, there were no significant group differences in total diabetes distress; interpersonal diabetes distress remained lower for those assigned to liraglutide. No significant differences were observed for depressive symptoms.**

## CONCLUSIONS

**Contrary to expectations, this randomized trial found no evidence for a deleterious effect of basal insulin on emotional distress. Glargine lowered diabetes distress modestly at 1 year rather than increasing it. Liraglutide also reduced diabetes distress at 1 year. Results can inform treatment decisions for adults with early T2DM.**

[1]*Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY*
[2]*Division of Endocrinology and Fleischer Institute for Diabetes and Metabolism, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY*
[3]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, NY*
[4]*New York-Regional Center for Diabetes Translation Research, Albert Einstein College of Medicine, Bronx, New York, NY*
[5]*The Biostatistics Center, Department of Biostatistics and Bioinformatics, Milken Institute School of Public Health, The George Washington University, Rockville, MD*
[6]*Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL*
[7]*School of Public Health, University of Texas Health Science Center, Houston, TX*
[8]*Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI*
[9]*International Diabetes Center, Minneapolis, MN*
[10]*Diabetes Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA*
[11]*Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Minnesota, Minneapolis, MN*

THE GRADE STUDY

Among individuals with type 2 diabetes mellitus (T2DM), depressive symptoms and diabetes-related distress (together referred to here as emotional distress) are common and consistently associated with poor health outcomes (1–8). Because increases in each indicator of emotional distress are associated with T2DM treatment intensity, iatrogenic causes for emotional distress in diabetes seem plausible (9,10). For example, a meta-analysis of the literature concluded that individuals with T2DM who were prescribed insulin were at increased risk for depressive symptoms, should have their depressive symptoms routinely monitored, and should be offered psychological and educational interventions (11). However, available studies have not adequately disentangled confounding between intensive diabetes treatment and disease progression. Individuals living with T2DM who are treated with basal insulin are also more likely to experience worse glycemic control and increased prevalence of diabetes complications. Any correlational association between insulin therapy and emotional distress will be confounded by metabolic worsening, limiting the validity of conclusions that assume causal influence. Warning patients and providers about the increased risk of emotional distress associated with insulin therapy may further contribute to apprehension to begin insulin therapy because of anticipated burdens and decreases in quality of life, called "psychological insulin resistance" (12), which is prevalent among insulin-naive adults with T2DM as well as diabetes care providers and is associated with delays in appropriate initiation of basal insulin (13,14).

Cross-sectional studies have also found higher levels of depressive symptoms and diabetes distress among adults with T2DM taking oral glucose-lowering medications compared with those not prescribed glucose-lowering medications (15). However, other studies link metformin, alone or in combination with other glucose-lowering medications, to reductions in depressive symptoms among adults with T2DM (16). Other glucose-lowering medications have also been linked with improvements in emotional distress and investigations evaluating their utility as treatments for depression (17–19). Evaluation of changes in emotional distress over time in the context of T2DM treatment is needed to clarify the effects of T2DM treatment regimens, but these patient-reported outcomes are rarely included in large treatment trials. Current diabetes care guidelines emphasize depressive symptoms and diabetes distress as important outcomes that should be routinely assessed in practice (20). Because diabetes distress reflects the specific emotional burdens of living with diabetes and its treatment (8,21,22), it may be more sensitive than depressive symptoms to T2DM treatment effects (23–25), and a number of studies link insulin therapy to increased diabetes distress in T2DM (26). Examination of effects of T2DM treatment options in the context of a randomized controlled trial also addresses criticisms from advocates for patient-centered care who have criticized an overreliance on surrogate outcomes, such as glycated hemoglobin ($HbA_{1c}$) levels, and called for increased attention to outcomes important to people living with diabetes and their caregivers, including emotional distress (27). To date, providers and patients have limited information on the effects of T2DM treatments to inform their decision-making. Rigorous evaluations of the effect of T2DM treatment intensification on emotional distress are needed to inform providers and patients.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) presents a unique opportunity to overcome prior methodological limitations through a multicenter, unmasked randomized clinical trial comparing four commonly used glucose-lowering medications to maintain target $HbA_{1c}$ levels (24,28,29). The Emotional Distress Substudy (EDS) evaluated diabetes distress and depressive symptoms in a subset (34%) of GRADE participants (28). We expected increases in both measures over time across treatment groups based on expected increases in $HbA_{1c}$ and per-protocol treatment intensification. Informed by prior data, we hypothesized that participants assigned to insulin glargine U-100 would experience greater diabetes distress and (to a lesser degree) depressive symptoms over time relative to those assigned to the other glucose-lowering medications (28). Because GRADE primary and secondary glycemic outcome results were similar for insulin glargine and liraglutide (30), we also compared liraglutide to the remaining medications. Finally, we evaluated mediators of treatment effects on emotional distress and explored participant characteristics that predicted emotional distress over time.

## RESEARCH DESIGN AND METHODS

### Design

GRADE is a comparative effectiveness trial of 5,047 participants (age 21–88 years) with T2DM enrolled at 36 clinical centers and 9 subsites across the U.S. GRADE and EDS protocols are available in the Supplementary Material and prior publications (28,29). GRADE compared the effects of four common glucose-lowering medications added to metformin on glycemic control among diverse adults with T2DM for $<$10 years. The institutional review boards of each participating institution approved GRADE, and all participants provided informed consent.

### Participants

The EDS began more than halfway through recruitment for GRADE and engaged 26 of the 36 GRADE centers and 8 of the 9 subsites (28). Each site enrolled 4–138 participants between November 2015 and August 2017 and followed them through April 2021 (Fig. 1). Individuals

[12]Advanced Research and Diagnostic Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN
[13]Department of Medicine (General Internal and Preventive Medicine), University of Alabama at Birmingham, Birmingham, AL

Corresponding author: Jeffrey S. Gonzalez, grademail@bsc.gwu.edu

Received 22 December 2023 and accepted 19 January 2024

Clinical trial reg. no. NCT01794143, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.25075580.

*A complete list of members of the GRADE Research Group can be found in the supplementary material online.

This article is part of a special article collection available at https://diabetesjournals.org/collection/2066/Reports-from-the-GRADE-Study.

This article is featured in podcasts available at diabetesjournals.org/care/pages/diabetes_care_on_air.

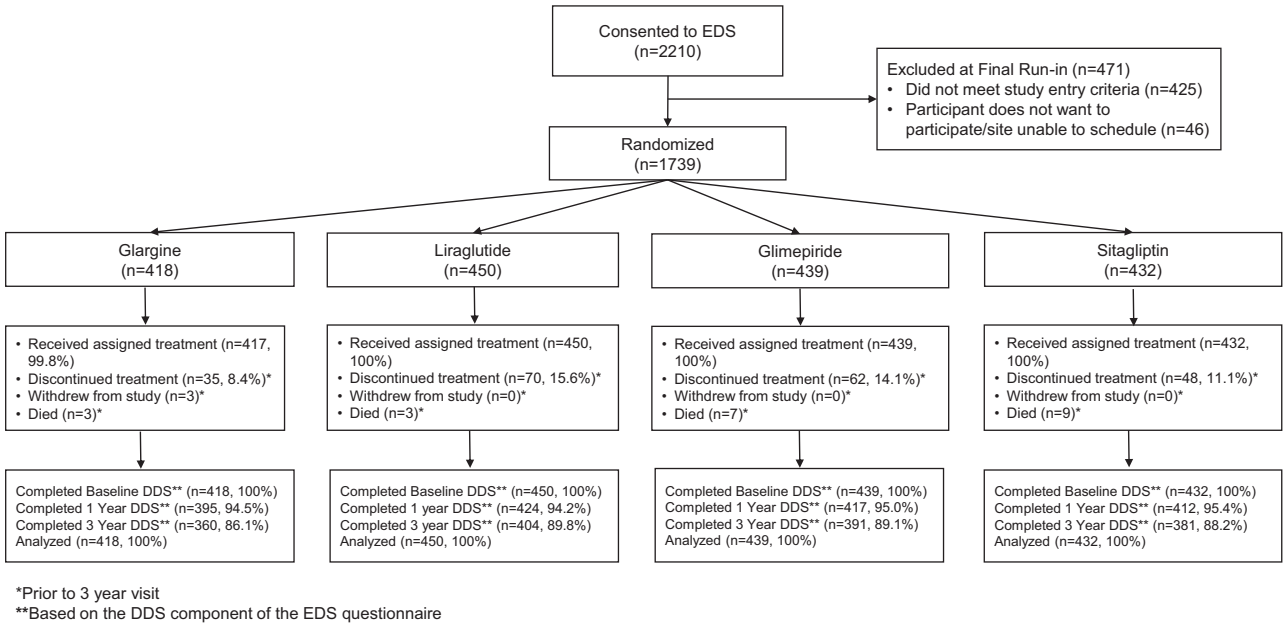



**Figure 1**—CONSORT (Consolidated Standards of Reporting Trials) diagram for EDS substudy to GRADE. Shown is the assignment of participants to the four treatment groups and completion of EDS.

aged ≥30 years (except American Indian and Alaska Native participants, who were eligible if ≥20 years) with T2DM diagnosis of <10 years' duration, $HbA_{1c}$ ≥6.8% (51 mmol/mol), treated with metformin alone, and willing to use injection therapy were included. After completing screening, eligible participants completed a 6- to 14-week run-in period, during which metformin was titrated to 1,000–2,000 mg/day.

## Procedures

Participants with $HbA_{1c}$ 6.8–8.5% (51–69 mmol/mol) at the final run-in visit were randomized to one of four treatment groups (1:1:1:1 ratio) via a centralized, site-stratified system. Participants and site staff were unmasked to treatment assignment. All four GRADE medications were approved by the U.S. Food and Drug Administration. They were basal insulin glargine U-100 (here termed glargine), sulfonylurea glimepiride, the glucagon-like peptide 1 receptor agonist liraglutide, and the dipeptidyl peptidase 4 inhibitor sitagliptin, used according to labeling.

Participants were evaluated quarterly for the primary GRADE metabolic outcome of $HbA_{1c}$ 7.0% (53.0 mmol/mol) or higher, confirmed at the next (usually quarterly) visit, and continued study medications until they reached the secondary GRADE metabolic outcome of a confirmed $HbA_{1c}$ level >7.5% (>58.5 mmol/mol) (29,30). At this point, glargine was added to the regimens of participants initially randomized to noninsulin medications; participants assigned to glargine who reached the secondary GRADE metabolic outcome added prandial rapid-acting insulin aspart. Those assigned to one of the three noninsulin medications who reached the tertiary GRADE metabolic outcome of $HbA_{1c}$ >7.5%, confirmed after addition of glargine, added rapid-acting insulin aspart; metformin was continued and the initially assigned noninsulin medication was discontinued. Insulin therapy was intensified in the original glargine treatment group for those meeting this tertiary outcome. Any additional glucose-lowering medications were prescribed by the participants' health care providers off-protocol. Approximately 2% (*N* = 32) of EDS participants added rescue insulin by 1 year, and 15% (*N* = 265) added rescue insulin by 3 years.

EDS participants received compensation for completion of assessments and were offered a copy of the American Diabetes Association (ADA) booklet *Diabetes and Your Emotional Health* (31) in English or Spanish. Participants screening positive for depression were offered treatment information, and, with permission, their health care providers were notified.

## Measures

The EDS followed participants for up to 3 years, assessing diabetes distress and depressive symptoms every 6 months over the follow-up period, with primary EDS outcomes evaluated at 1 year from baseline. Diabetes distress was assessed with the 17-item Diabetes Distress Scale (DDS), which includes the following subscales: *1*) emotional burden, i.e., emotions and overwhelming feelings related to living with diabetes, *2*) regimen distress, i.e., burden related to diabetes self-management, *3*) interpersonal distress, i.e., perceived lack of support and empathy from friends and family, and *4*) physician distress, i.e., perceived inadequacy of expertise, support, and clear direction from providers (22). Mean scores range from 1 to 6, and a score of ≥2 indicates clinically significant diabetes distress (32). The primary EDS diabetes distress outcome was a composite of the emotional burden and regimen distress subscales selected to capture item content that would be most sensitive to the effects of T2DM treatments. Secondary outcome analyses examined the four DDS subscales at 1 year and all diabetes distress measures over the full follow-up.

Depressive symptoms were measured with the eight-item Patient Health Questionnaire (PHQ-8), with scores ranging between 1 and 24, with higher scores indicating greater severity. The PHQ-8 screening cutoff score for clinical depression is ≥10 (33). The primary EDS depressive symptom outcome was the total

PHQ-8 score at 1 year. Somatic and cognitive-affective symptom scores were also examined separately at 1 year, and all depressive symptom measures over the full follow-up were evaluated as secondary outcomes.

Central laboratory–measured $HbA_{1c}$, BMI, and self-reported hypoglycemic events and other treatment side effects were collected quarterly over follow-up. Research staff recorded protocol-driven addition of insulin glargine and rapid-acting insulin to their randomized medication. Treatment satisfaction was measured by the Diabetes Treatment Satisfaction Questionnaire (34,35) every 6 months. These time-varying factors were prespecified potential mediators that could explain any observed treatment effects on the primary EDS outcomes (28).

### Statistical Analyses and Power

When comparing glargine group versus the other groups combined, a sample size of ~1,600 participants (~400 in the glargine group vs. ~1,200 in the other groups) provided 80% power to detect a small effect size (defined as the mean difference between groups divided by the pooled SD) of 0.18 and 90% power to detect an effect size of 0.20 using a two-sided test at $\alpha$ level 0.025 in an unadjusted linear model (28,36). Likewise, when comparing the liraglutide group with the glimepiride and sitagliptin groups combined, a sample size of ~1,200 participants (~400 in the liraglutide group vs. ~800 in the combined glimepiride and sitagliptin groups) provided 80% power to detect an effect size of 0.19 and 90% power to detect an effect size of 0.22. All these effect sizes are considered small. There is higher statistical power to detect the same effect sizes (or equivalently, the same power to detect smaller effect sizes) for analyses in longitudinal models using repeated values over the follow-up.

Of 1,739 participants assessed at baseline, 1,648 (95%) provided EDS primary outcome data (see Supplementary Table 1). Analyses for each outcome included all available participants with nonmissing data for that variable. Baseline characteristics of the EDS cohort were presented using percentages for categorical variables (e.g., sex) and means with SD for continuous variables (e.g., $HbA_{1c}$). Linear models assessed the difference in the primary diabetes distress outcome (average of the DDS emotional burden and regimen distress subscales) at 1 year between the glargine group and the other three treatment groups combined, using a two-sided test at $P < 0.025$. Models were adjusted for baseline diabetes distress, age, and duration of T2DM. If significant, longitudinal models (with the same adjustments) using generalized estimating equations accounting for the within-participant correlation over time assessed the difference in diabetes distress over the entire follow-up (up to 3 years), again at $P < 0.025$. Similar analyses assessed differences in the primary depressive symptom outcome (PHQ-8 total score) between the glargine group and the other three treatment groups combined at 1 year from baseline, and, if significant, over the entire follow-up (both at $P < 0.025$). Similar analyses were then conducted for secondary outcomes. No adjustments were made for multiplicity for these secondary analyses; $P < 0.01$ was considered significant. Additional analyses compared participants initially assigned to liraglutide with participants assigned to the sitagliptin and glimepiride groups, combined. The liraglutide group was also compared to those assigned to glargine. Holm-adjusted pairwise comparisons were also conducted.

We then assessed whether treatment satisfaction, hypoglycemia and other treatment side effects, addition of glargine and rapid-acting insulin, and change in $HbA_{1c}$ and BMI over time mediated the observed treatment group differences by adding these variables to the models examining primary outcomes at 1 year (37). Separately for glargine versus the other three treatment groups combined, longitudinal models with generalized estimating equations assessed the associations of diabetes distress and depressive symptoms over time with age, sex, socioeconomic status, and race/ethnicity in models adjusted for corresponding baseline scores. The GRADE Coordinating Center at the George Washington University Biostatistics Center conducted the data analyses. All analyses were prespecified.

### Data and Resource Availability

This article is based on follow-up data and outcome assessments from the 1,739 participants enrolled into the EDS. The GRADE and EDS database will be available in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository in 2024.

## RESULTS

The baseline characteristics were well distributed across treatment groups for this diverse, majority male, and recently diagnosed sample (Table 1). The prevalence of clinically significant diabetes distress and depression were 25% and 9%, respectively. The primary diabetes distress and depressive symptom measures were moderately correlated ($r$ = 0.46) across the entire follow-up period; diabetes distress ($r$ = 0.22) and depressive symptoms ($r$ = 0.08) were also correlated with increased $HbA_{1c}$ over time.

### Primary Outcomes

Counter to expectations, across all treatment groups, diabetes distress (−0.24, 95% CI [−0.28, −0.21], $P < 0.0001$) and depressive symptoms (−0.67, 95% CI [−0.82, −0.51], $P < 0.0001$) decreased significantly at 1 year compared with baseline (Supplementary Table 2). Opposite to what was hypothesized, the primary diabetes distress outcome was significantly lower at 1 year among participants assigned to glargine compared with the other three treatments combined (difference = −0.101, 95% CI [−0.164, −0.037], $P$ = 0.002) (Table 2 and Fig. 2*A*). There were no significant differences for depressive symptoms (Table 2 and Fig. 2*B*).

### Secondary Outcomes

Among DDS subscales at 1 year, only regimen-related distress was significantly lower for glargine compared with other groups combined, mirroring differences observed for the primary diabetes distress outcome (Table 2). Interpersonal distress was also significantly lower for participants assigned to liraglutide compared with glimepiride and sitagliptin combined (difference = −0.165, 95% CI [−0.247, −0.083], $P < 0.001$) (Table 2).

Over the 3-year follow-up, diabetes distress (−0.213, 95% CI [−0.244, −1.182], $P < 0.001$) and depressive symptoms (−0.577, 95% CI [−0.714, −0.440], $P < 0.001$) decreased across all treatment groups. There were no significant differences in diabetes distress or depressive symptoms over the full follow-up among participants assigned to glargine compared with the other treatments (Supplementary Table 3).

**Table 1—Baseline characteristics overall (*n* = 1,739 participants) and by treatment group**

| | Overall (*n* = 1,739) | Glargine (*n* = 418) | Glimepiride (*n* = 439) | Liraglutide (*n* = 450) | Sitagliptin (*n* = 432) |
|---|---|---|---|---|---|
| Age (years) | 57.97 (10.21) | 57.4 (10.07) | 57.64 (10.35) | 58.54 (10.35) | 58.28 (10.06) |
| T2DM duration (years) | 4.21 (2.81) | 4.11 (2.78) | 4.35 (2.91) | 4.16 (2.8) | 4.23 (2.76) |
| Sex, *N* (%) | | | | | |
| Male | 1,175 (68) | 288 (69) | 278 (63) | 317 (70) | 292 (68) |
| Female | 564 (32) | 130 (31) | 161 (37) | 133 (30) | 140 (32) |
| Race/ethnicity, *N* (%) | | | | | |
| Non-Hispanic White | 967 (56) | 238 (57) | 225 (51) | 259 (58) | 245 (57) |
| Hispanic | 292 (17) | 68 (16) | 84 (19) | 65 (14) | 75 (17) |
| Non-Hispanic Black | 316 (18) | 79 (19) | 89 (20) | 82 (18) | 66 (15) |
| Non-Hispanic other | 164 (9) | 33 (8) | 41 (9) | 44 (10) | 46 (11) |
| Smoking, *N* (%) | | | | | |
| Never | 900 (52) | 224 (54) | 228 (52) | 237 (53) | 211 (49) |
| Past | 617 (35) | 143 (34) | 142 (32) | 161 (36) | 171 (40) |
| Current | 222 (13) | 51 (12) | 69 (16) | 52 (12) | 50 (12) |
| BMI (kg/m$^2$) | 34.1 (6.48) | 34.39 (6.27) | 33.98 (6.66) | 34.3 (6.32) | 33.71 (6.66) |
| Hypertension, *N* (%) | 1,486 (85) | 353 (84) | 376 (86) | 387 (86) | 370 (86) |
| Hyperlipidemia, *N* (%) | 1,672 (96) | 402 (96) | 425 (97) | 429 (95) | 416 (96) |
| Education, *N* (%) | | | | | |
| High school/GED or less | 517 (30) | 117 (28) | 140 (32) | 137 (30) | 123 (28) |
| Some college | 511 (29) | 134 (32) | 126 (29) | 132 (29) | 119 (28) |
| College/graduate school | 711 (41) | 167 (40) | 173 (39) | 181 (40) | 190 (44) |
| Income (USD), *N* (%) | | | | | |
| <10k | 93 (5) | 24 (6) | 20 (5) | 24 (5) | 25 (6) |
| 10–20k | 163 (9) | 47 (11) | 35 (8) | 48 (11) | 33 (8) |
| 20–50k | 477 (27) | 103 (25) | 114 (26) | 131 (29) | 129 (30) |
| >50k | 766 (44) | 192 (46) | 196 (45) | 185 (41) | 193 (45) |
| Missing | 240 (14) | 52 (12) | 74 (17) | 62 (14) | 52 (12) |
| Living arrangement, *N* (%) | | | | | |
| Living alone | 295 (17) | 78 (19) | 65 (15) | 74 (16) | 78 (18) |
| With another adult | 1,376 (79) | 324 (78) | 351 (80) | 363 (81) | 338 (78) |
| With children only | 68 (4) | 16 (4) | 23 (5) | 13 (3) | 16 (4) |
| Employment, *N* (%) | | | | | |
| Employed | 974 (56) | 232 (56) | 249 (57) | 243 (54) | 250 (58) |
| Retired | 459 (26) | 110 (26) | 111 (25) | 123 (27) | 115 (27) |
| Other | 306 (18) | 76 (18) | 79 (18) | 84 (19) | 67 (16) |
| Prescribed medications for depression or anxiety, *N* (%) | 319 (18) | 83 (20) | 80 (18) | 75 (17) | 81 (19) |
| PHQ-8 total | 3.45 (3.96) | 3.62 (3.96) | 3.32 (4.02) | 3.61 (4.15) | 3.24 (3.69) |
| PHQ-8 positive screen, *N* (%) | 151 (9) | 42 (10) | 34 (8) | 47 (10) | 28 (6) |
| Diabetes distress: emotional burden and regimen distress | 1.86 (0.85) | 1.82 (0.72) | 1.86 (0.95) | 1.87 (0.85) | 1.87 (0.87) |
| Diabetes Distress Scale positive screen, *N* (%) | 431 (25) | 101 (24) | 101 (23) | 116 (26) | 113 (26) |
| $HbA_{1c}$ (%) | 7.51 (0.48) | 7.53 (0.48) | 7.49 (0.47) | 7.5 (0.48) | 7.53 (0.49) |

Data are shown as mean (SD) for continuous variables and percent for discrete variables. GED, graduate equivalency degree; PHQ-8, eight-item Patient Health Questionnaire (depressive symptoms).

### Additional Analyses

At 1 year, participants assigned to liraglutide had significantly lower diabetes distress compared with those assigned to either glimepiride or sitagliptin (difference = −0.097, 95% CI [−0.169, −0.026], $P = 0.008$). There was no significant difference in the primary diabetes distress measure between participants assigned to liraglutide and those assigned to glargine (Table 2 and Fig. 2*A*). Depressive symptoms showed no significant differences

**Table 2—Differences in diabetes distress and depressive symptoms at 1 year from baseline**

| | Glargine vs. other three groups combined | | | | Liraglutide vs. glargine group | | | | Liraglutide vs. glimepiride and sitagliptin groups combined | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Difference* | LL | UL | *P* value | Difference* | LL | UL | *P* value | Difference* | LL | UL | *P* value |
| Diabetes distress | | | | | | | | | | | | |
| Primary diabetes distress | −0.101 | −0.164 | −0.037 | **0.002** | 0.042 | −0.037 | 0.119 | 0.289 | −0.097 | −0.169 | −0.026 | **0.008** |
| Emotional distress subscale | −0.065 | −0.130 | −0.000 | 0.049 | 0.023 | −0.057 | 0.103 | 0.572 | −0.073 | −0.148 | 0.003 | 0.058 |
| Regimen-related distress subscale | −0.135 | −0.213 | −0.058 | **0.001** | 0.061 | −0.033 | 0.155 | 0.206 | −0.122 | −0.208 | −0.036 | **0.006** |
| Physician-related distress subscale | −0.061 | −0.129 | 0.006 | 0.075 | 0.027 | −0.053 | 0.106 | 0.511 | −0.056 | −0.130 | 0.017 | 0.133 |
| Interpersonal distress subscale | −0.067 | −0.143 | 0.010 | 0.088 | −0.035 | −0.123 | 0.053 | 0.438 | −0.165 | −0.247 | −0.083 | **<0.001** |
| Depressive symptoms | | | | | | | | | | | | |
| Primary depressive symptoms | −0.165 | −0.487 | 0.158 | 0.316 | 0.307 | −0.095 | 0.709 | 0.135 | 0.189 | −0.135 | 0.513 | 0.252 |
| Somatic symptoms score | −0.025 | −0.070 | 0.020 | 0.275 | 0.056 | −0.001 | 0.112 | 0.053 | 0.043 | −0.004 | 0.089 | 0.072 |
| Cognitive-affective symptoms score | −0.013 | −0.059 | 0.033 | 0.574 | 0.010 | −0.046 | 0.065 | 0.737 | −0.008 | −0.052 | 0.036 | 0.724 |

LL, lower limit; UL, upper limit. Significant *P* values are in boldface. *Difference in means at 1 year.

(Table 2 and Fig. 2*B*). Neither diabetes distress nor depressive symptoms significantly differed between liraglutide versus glimepiride and sitagliptin over the entire follow-up. However, among DDS subscales, interpersonal distress remained significantly lower for participants assigned to liraglutide versus glimepiride and sitagliptin combined (difference = −0.101, 95% CI [−0.167, −0.036], $P = 0.003$) (Supplementary Table 3). Pairwise comparisons among all treatment groups showed significant differences between glimepiride and glargine, sitagliptin and glargine, and glimepiride and liraglutide at 1 year without significant differences over the entire follow-up (Supplementary Table 4).

Mediation analyses for the primary diabetes distress outcome at 1 year between the glargine group and the other three groups combined was not mediated by treatment satisfaction, hypoglycemia, other treatment side effects, additions of rapid-acting insulin, BMI, or $HbA_{1c}$. Limited evidence for mediation by change in BMI was found for the primary diabetes distress outcome at 1 year between the liraglutide group and the glimepiride and sitagliptin groups combined. Adjustment for potential mediators did not materially change the results for depressive symptoms (Supplementary Tables 5 and 6).

Age was negatively associated with diabetes distress both in the glargine group ($P = 0.001$) and in the other three groups combined ($P < 0.001$) (Supplementary Table 7). Compared with non-Hispanic White individuals, Hispanic participants had higher diabetes distress in the glargine group, while all other non-White race/ethnicity subgroups had higher diabetes distress in the liraglutide, glimepiride, and sitagliptin groups combined compared with non-Hispanic White individuals. The only statistically significant association for depressive symptoms was a negative association with age among participants in the liraglutide, glimepiride, and sitagliptin groups combined ($P = 0.002$) (Supplementary Table 7).

## CONCLUSIONS

In this diverse population with T2DM on metformin monotherapy and randomly assigned to an additional glucose-lowering medication, we observed an overall improvement in diabetes distress and depressive symptoms over the first year of

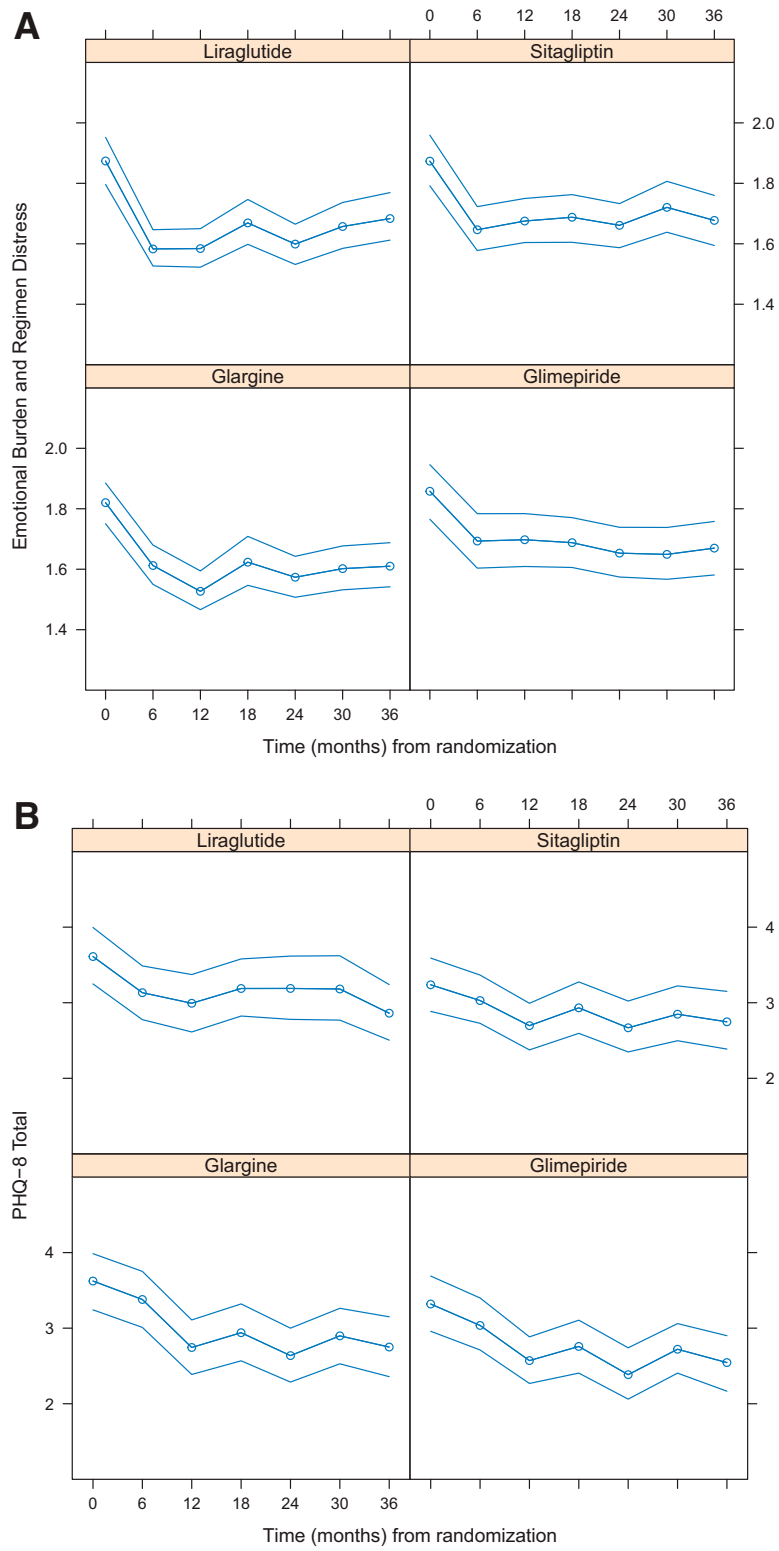



**Figure 2**—Longitudinal diabetes distress and depressive symptoms profiles (mean and 95% confidence limits) by GRADE treatment group. PHQ-8, eight-item Patient Health Questionnaire. *A*: Longitudinal diabetes distress profiles. *B*: Longitudinal depressive symptoms profiles.

treatment. Counter to our expectations, levels of diabetes distress and depressive symptoms throughout the 3-year follow-up remained below baseline, despite treatment intensification with a second glucose-lowering medication and experiencing deteriorating glycemic control and per-protocol treatment intensification. Statistically significant differences in diabetes distress at 1 year were observed among the treatment groups. However, the direction of these differences ran counter to our hypothesis: participants assigned to glargine had significantly lower diabetes distress at 1 year compared with the other three treatment groups combined. Those assigned to liraglutide, the other injectable medication, also experienced lower diabetes distress relative to those assigned to sitagliptin or glimepiride but did not differ from those assigned to glargine at 1 year. Examination of diabetes distress subscales showed that these differences were primarily driven by lower distress related to managing the treatment regimen for glargine and liraglutide compared with other treatments; post hoc analyses showed interpersonal distress was also significantly lower for liraglutide compared with glimepiride or sitagliptin at 1 year. At 1 year, very few (2%) EDS participants had experienced treatment intensification with rescue insulin per GRADE's protocol. Thus, these significant differences, which run in the opposite direction of our expectations, are mostly reflective of treatment regimens that reflect the randomly assigned medications. These differences largely dissipated over time, and more EDS participants (15%) experienced the addition of rescue insulin by the end of the follow-up. The liraglutide group continued to experience significantly lower interpersonal distress related to their diabetes over the full 3-year follow-up. Treatment differences were not observed for overall depressive symptoms or somatic and cognitive-affective symptoms separately, when evaluated at 1 year or over the full follow-up. Thus, as we expected, diabetes distress was more sensitive to treatment differences than depressive symptoms. As the assessment of diabetes distress is framed within the context of dealing with "problems" related to diabetes, this is consistent with conceptual discussions of distinctions between diabetes distress and depressive symptoms in diabetes (23,25). Statistically significant treatment group differences were limited to aspects of emotional distress related to diabetes self-management and diabetes-related support received from friends and family. Our results highlight the distinctions between diabetes distress and depressive symptoms, which shared only 21% of their variance in the current study, and the benefits of assessing diabetes distress

to identify treatment-related stressors that may contribute to emotional distress (e.g., "Feeling that I am often failing with my diabetes routine") and can and should be addressed as part of diabetes care (22).

The GRADE study, with randomly assigned T2DM treatments, represents a unique opportunity to experimentally test the effects of intensive treatment to glycemic targets on emotional distress among adults with T2DM. Results challenge the prevailing dogma that insulin causes emotional distress in T2DM, which has been based on correlational evidence vulnerable to confounding between treatment intensification and metabolic worsening (11). Our experimental findings provide strong evidence to address well-documented clinical inertia (38,39) and so-called psychological insulin resistance in the treatment of T2DM (12–14). Results of our well-powered analyses suggest it is very unlikely that insulin glargine per se contributes to increased diabetes distress or depressive symptoms over time.

Results do not support depression treatment effects specific to a particular glucose-lowering medication, as suggested by a handful of small treatment trials and population-based studies (16–19). Although the observed effects for diabetes distress are in line with our expectation for greater sensitivity of this measure relative to depressive symptoms (28), differences in diabetes distress were modest, relatively short-lived, and of unclear clinical significance. Furthermore, these effects were not explained by most potential mediators. However, evidence for effect attenuation by adjustment for change in BMI for liraglutide compared with glimepiride and sitagliptin suggests that weight loss is implicated in explaining this difference.

Our data also provide important information on racial/ethnic disparities in emotional distress over time. Hispanic individuals, non-Hispanic Black individuals, and people from other non-White ethnic backgrounds were more likely to experience increased diabetes distress if assigned to liraglutide, glimepiride, or sitagliptin compared with non-Hispanic White individuals, and Hispanic individuals were also significantly more likely to experience increased diabetes distress when assigned to glargine. A meta-analysis did not find significant differences between ethnic minorities and White participants in prevalence of diabetes distress in T2DM, but treatment regimen was not considered (6). Further research is required to better understand these differences. Consistent with prior evidence (8,10,40), older adults were less likely to experience diabetes distress or depressive symptoms, regardless of treatment group. Ethnic disparities and age differences in the relative benefits in emotional distress for these treatments can inform future efforts targeting patients at elevated risk for experiencing emotional distress associated with T2DM treatment.

While this study is unique in providing an opportunity to causally evaluate T2DM treatment effects on emotional distress in a large, diverse, well-characterized, and randomized cohort, there are limitations inherent to our design. First, the generalizability of our findings is limited to those with T2DM of $<$10 years' duration. Importantly, treatment was provided at no cost to participants, which may have reduced emotional distress associated with dealing with insurance and financial burdens of T2DM treatment in the U.S. The level of care and support received in GRADE may not be representative of typical practice settings where individuals with early T2DM typically receive their care. This may have limited exposure to stressors that typically cooccur with prescription of insulin therapy (e.g., increased costs) and provided resources to mitigate against the experience of emotional distress (e.g., education and support for implementation of self-injection and hypoglycemia risk management). Furthermore, those with strong negative views of insulin or other injectables would have been less likely to participate and could have had a different experience with the treatments evaluated in GRADE. The observed decreases in emotional distress across treatment groups over time may at least partially reflect the effect of this supportive environment, a placebo effect, or spontaneous improvement, a limitation of all clinical trials lacking a placebo arm. Despite these limitations on generalizability, the scientific rigor of our design provides a strong experimental test for whether taking basal insulin per se leads to an increase in emotional distress among adults with early T2DM. Results strongly contradict that hypothesis and suggest that, in care contexts that are similar to that achieved by the GRADE clinical sites, glargine insulin and liraglutide may actually lead to somewhat lower levels of distress related to diabetes compared with alternatives.

Our study cannot speak to the role of mental health disorders in these relationships. Levels of depressive symptoms and diabetes distress were lower in our sample than in other studies of clinical populations that were more heterogeneous with respect to diabetes progression and treatment (6,8,10). Thus, these findings may not generalize to populations with high levels of diabetes distress or depressive symptoms. Further, our results cannot speak to the role of depressive disorders in explaining our findings, as diagnoses were not possible based on the data collected. Furthermore, the clinical significance of the observed decrease in emotional distress over time is difficult to ascertain. Although prior research has suggested even moderate elevations in diabetes distress (i.e., DDS score $\geq$2) are clinically meaningful (32), we are not aware of established thresholds for minimal clinically meaningful change for the DDS used in the current study. Finally, the study was designed to strongly control the type I error for the primary outcomes. While the secondary analyses were conducted at a more stringent level (0.01 instead of 0.05), these secondary analyses are exploratory, and their results should be interpreted with care.

In adults with T2DM, intensive diabetes management added to metformin was associated with an overall trajectory of decreasing emotional distress over time. Counter to our expectations, we found no evidence for an effect of assignment to basal insulin glargine on increased emotional distress among GRADE participants. Rather, those assigned to glargine and liraglutide experienced statistically significant reductions in diabetes distress to a modestly greater degree at 1 year than those assigned to glimepiride and sitagliptin; those assigned to liraglutide continued to experience less interpersonal distress related to their diabetes over the full follow-up compared with those assigned to glimepiride or sitagliptin. Previously published results of the primary metabolic outcome analyses for GRADE showed that glargine and liraglutide were modestly more effective in reaching and maintaining glycemic targets with lower hypoglycemia risk than glimepiride. The current results from the GRADE EDS provide guidance to providers and patients when considering emotional well-being as a patient-important outcome of adding a second glucose-lowering

medication to metformin in adults with relatively early T2DM.

**Acknowledgments.** The GRADE Study Research Group is deeply grateful to our participants whose loyal dedication made GRADE possible.

**Funding.** The GRADE Study was supported by a grant from the NIDDK of the National Institutes of Health under award no. U01DK098246. The planning of GRADE was supported by a U34 planning grant from the NIDDK (U34-DK-088043). The American Diabetes Association supported the initial planning meeting for the U34 proposal. The National Heart, Lung, and Blood Institute and the Centers for Disease Control and Prevention also provided funding support. The Department of Veterans Affairs provided resources and facilities. Additional support was provided by grants P30 DK017047, P30 DK020541, P30 DK020572, P30 DK072476, P30 DK079626, P30 DK092926, U54 GM104940, UL1 TR000170, UL1 TR000439, UL1 TR000445, UL1 TR001102, UL1 TR001108, UL1 TR001409, 2UL1TR001425, UL1 TR001449, UL1 TR002243, UL1 TR002345, UL1 TR002378, UL1 TR002489, UL1 TR002529, UL1 TR002535, UL1 TR002537, UL1 TR002541, and UL1 TR002548. Educational materials have been provided by the National Diabetes Education Program. Material support in the form of donated medications and supplies has been provided by Becton, Dickinson and Company, Bristol-Myers Squibb, Merck & Co., Novo Nordisk, Roche Diagnostics, and Sanofi. The GRADE EDS was supported by a grant from the NIDDK of the National Institutes of Health under award number R01 DK104845. Additional support was provided by grant number P30 DK111022.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Duality of Interest.** J.S.G. reports consulting fees from Virta Health, payment or honoraria for a virtual presentation in São Paulo, Brazil, in 2020, from the Worldwide Initiative for Diabetes Education, support for travel from the ADA Professional Conference Planning Committee, participation in a data monitoring committee for Vanderbilt University investigator Lindsay Mayberry, and receipt of Abbott Freestyle Libre devices outside the submitted work. C.J.H. reports grants from the National Institute on Aging, NIDDK, and JDRF outside the submitted work. G.C.-R. reports grants from JDRF and support for travel from the Let's Empower and Prepare (LEAP) program (funded by ADA) outside the submitted work. C.P. reports grants from the National Center for Complementary and Integrative Health and ADA outside the submitted work. A.D.N. reports grants from the Center for Innovations in Quality, Effectiveness, and Safety outside the submitted work. M.L.J. reports grants for HealthPartners Institute from Sanofi, Lilly, and Novo Nordisk outside the submitted work. D.W. reports serving on data monitoring committees for Novo Nordisk, including the Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) and Semaglutide Cardiovascular Outcomes (SOUL) trials, outside the submitted work. A.E.B. reports grants from the National Institutes of Health and support for travel from the ADA. A.E.B. serves on two data safety and monitoring boards for the University of Minnesota outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** All authors affirmed that authorship is merited based on the International Committee of Medical Journal Editors (ICMJE) authorship criteria. J.S.G., I.B., H.K.-S., C.P., S.K., V.A., and A.L.C. contributed to the conception and design of the research. M.L.J., D.W., J.P.C., A.E.B., and V.A. contributed to the acquisition of data. I.B. contributed to statistical analysis of data. J.S.G., I.B., H.K.-S., C.J.H., G.C.-R., C.P., A.D.N., S.K., D.W., and J.P.C. contributed to the interpretation of data and results. J.S.G. and H.K.-S. contributed to the acquisition of funding. J.S.G., H.K.-S., M.L.J., and V.A. contributed to the supervision and management of research. J.S.G., I.B., and C.J.H. contributed to the drafting of the manuscript. I.B., H.K.-S., C.J.H., G.C.-R., C.P., A.D.N., S.K., M.L.J., D.W., J.P.C., A.E.B., V.A., and A.L.C. contributed to the critical review of the manuscript. J.S.G. and I.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. Beran M, Muzambi R, Geraets A, et al.; European Depression in Diabetes (EDID) Research Consortium. The bidirectional longitudinal association between depressive symptoms and $HbA_{1c}$: a systematic review and meta-analysis. Diabet Med 2022;39:e14671
2. Fisher L, Mullan JT, Arean P, Glasgow RE, Hessler D, Masharani U. Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. Diabetes Care 2010;33:23–28
3. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008;31:2398–2403
4. Hayashino Y, Okamura S, Tsujii S, Ishii H; Diabetes Distress and Care Registry at Tenri Study Group. Association between diabetes distress and all-cause mortality in Japanese individuals with type 2 diabetes: a prospective cohort study (Diabetes Distress and Care Registry in Tenri [DDCRT 18]). Diabetologia 2018;61:1978–1984
5. Nouwen A, Adriaanse MC, van Dam K, et al.; European Depression in Diabetes (EDID) Research Consortium. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med 2019;36:1562–1572
6. Perrin NE, Davies MJ, Robertson N, Snoek FJ, Khunti K. The prevalence of diabetes-specific emotional distress in people with type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2017;34:1508–1520
7. Schmitt A, Bendig E, Baumeister H, Hermanns N, Kulzer B. Associations of depression and diabetes distress with self-management behavior and glycemic control. Health Psychol 2021;40:113–124
8. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. Lancet Diabetes Endocrinol 2015;3:450–460
9. Liu Y, Chen L, Zhou H, et al. Does awareness of diabetic status increase risk of depressive or anxious symptoms? Findings from the China Multi-Ethnic Cohort (CMEC) study. J Affect Disord 2023;320:218–229
10. Nouwen A, Nefs G, Caramlau I, et al.; European Depression in Diabetes Research Consortium. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care 2011;34:752–762
11. Bai X, Liu Z, Li Z, Yan D. The association between insulin therapy and depression in patients with type 2 diabetes mellitus: a meta-analysis. BMJ Open 2018;8:e020062
12. Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes Care 2005;28:2543–2545
13. Hosomura N, Malmasi S, Timerman D, et al. Decline of insulin therapy and delays in insulin initiation in people with uncontrolled diabetes mellitus. Diabet Med 2017;34:1599–1602
14. Wallia A, Molitch ME. Insulin therapy for type 2 diabetes mellitus. JAMA 2014;311:2315–2325
15. Berge LI, Riise T, Tell GS, et al. Depression in persons with diabetes by age and antidiabetic treatment: a cross-sectional analysis with data from the Hordaland Health Study. PLoS One 2015;10:e0127161
16. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression—a population-based cohort and nested case-control study. Psychoneuroendocrinology 2022;140:105715
17. Kessing LV, Rytgaard HC, Ekstrøm CT, Knop FK, Berk M, Gerds TA. Antidiabetes agents and incident depression: a nationwide population-based study. Diabetes Care 2020;43:3050–3060
18. Moulton CD, Hopkins CWP, Ismail K, Stahl D. Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials. Psychoneuroendocrinology 2018;94:91–103
19. Moulton CD, Rokakis AS, Pickup JC, Young AH, Stahl D, Ismail K. Sitagliptin for depressive symptoms in type 2 diabetes: a feasibility randomized controlled trial. Psychosom Med 2021;83:913–923
20. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
21. Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. Diabetes Care 1995;18:754–760
22. Polonsky WH, Fisher L, Earles J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care 2005;28:626–631
23. Fisher L, Gonzalez JS, Polonsky WH. The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision. Diabet Med 2014;31:764–772
24. Fisher L, Skaff MM, Mullan JT, et al. Clinical depression versus distress among patients with

type 2 diabetes: not just a question of semantics. Diabetes Care 2007;30:542–548
25. Gonzalez JS, Fisher L, Polonsky WH. Depression in diabetes: have we been missing something important? Diabetes Care 2011;34:236–239
26. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. Diabet Med 2007;24:48–54
27. Rodriguez-Gutierrez R, McCoy RG. Measuring what matters in diabetes. JAMA 2019;321:1865–1866
28. Cherrington AL, Krause-Steinrauf H, Bebu I, et al.; GRADE Research Group. Study of emotional distress in a comparative effectiveness trial of diabetes treatments: rationale and design. Contemp Clin Trials 2021;107:106366
29. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254–2261
30. Nathan DM, Lachin JM, Balasubramanyam A, et al.; GRADE Study Research Group. Glycemia reduction in type 2 diabetes—glycemic outcomes. N Engl J Med 2022;387:1063–1074
31. American Diabetes Association. *Diabetes & Your Emotional Health*. Alexandria, VA, American Diabetes Association, 2015
32. Fisher L, Hessler DM, Polonsky WH, Mullan J. When is diabetes distress clinically meaningful? Establishing cut points for the Diabetes Distress Scale. Diabetes Care 2012;35:259–264
33. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114:163–173
34. Bradley C. Diabetes Treatment Satisfaction Questionnaire (DTSQ). Health Psychology Research Ltd. Available from www.healthpsychologyresearch.com
35. Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care 1999;22:530–532
36. Lachin JM. *Biostatistical Methods: The Assessment of Relative Risks*. 2nd ed. Hoboken, NJ, Wiley, 2011
37. MacKinnon D. *Introduction to Statistical Mediation Analysis*. New York, NY, Routledge, 2012
38. Hirsch IB, Gaudiani LM. Using insulin to treat poorly controlled type 2 diabetes in 2020. JAMA 2020;323:2419–2420
39. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–3417
40. Hessler DM, Fisher L, Mullan JT, Glasgow RE, Masharani U. Patient age: a neglected factor when considering disease management in adults with type 2 diabetes. Patient Educ Couns 2011;85:154–159