Title: Adults with type 2 diabetes benefit from self-management support intervention regardless of depressive symptoms

Authors:

Lindsay Mayberry, PhD, MS[1,2]
Lyndsay A. Nelson, PhD[1,2]
Jeffrey S. Gonzalez, PhD[3,4,5]

Affiliations:

[1] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[2] Vanderbilt Center for Diabetes Translation Research, Nashville, TN
[3] Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY
[4] Departments of Medicine (Endocrinology) and Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY
[5] New York Regional Center for Diabetes Translation Research, Bronx, NY

Corresponding Author:

Lindsay S. Mayberry, PhD, MS
2525 West End Ave. Suite 450
Nashville, TN 37203
Phone: (615) 875-5821
Fax: (615) 875-2201
Email: lindsay.mayberry@vumc.org

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Abstract

Aims: Elevated depressive symptoms are common among adults with type 2 diabetes (T2D). In a secondary analysis from an RCT of a diabetes self-management support intervention that did not target depressive symptoms, we sought to determine if depressive symptoms were reduced by the intervention or, alternatively, if intervention effects on hemoglobin A1c were lesser among persons with clinically elevated depressive symptoms (i.e., depressive symptoms an effect modifier).

Methods: We evaluated a text messaging intervention, REACH, in a diverse (half non-white, half underinsured) sample of N=506 adults with T2D. Participants completed the Patient Health Questionnaire-8 (PHQ) and A1c tests at baseline and 6 months. We conducted a factor analysis to identify somatic- and cognitive-affective symptoms on the PHQ. We tested our hypotheses with regression models, using interaction terms and subgroup analyses.

Results: REACH improved depressive symptoms among participants with *lower* baseline A1c (<8.5%; β=-.133, *p*=.007; cognitive β=-.107, *p*=.038; somatic β=-.131, *p*=.014) but not among participants with higher baseline A1c (≥8.5%; β=.040, *p*=.468). Baseline depressive symptoms did not modify the effect on A1c.

Conclusions: We found support for the hypothesis that depressive symptoms – both somatic- and cognitive-affective – may be an outcome, rather than an effect modifier, of effective diabetes self-management support interventions.

Keywords: depressive symptoms, type 2 diabetes, randomized controlled trial, glycemic control

1. Introduction

Persons with type 2 diabetes disproportionately experience elevated depressive symptoms and depression; estimates indicate around 10% have clinically elevated depressive symptoms and per a clinical interview, there is around 60% elevated risk of major depressive disorder relative to counterparts who do not have diabetes.[1, 2] Observational research indicates a bidirectional relationship[3-5] such that people with elevated depressive symptoms are more likely to develop type 2 diabetes and people with type 2 diabetes are more likely to develop elevated depressive symptoms. Comorbid diabetes and depression are linked to increased diabetes complications[6] and worse diabetes self-management[7-9] including less adherence to medications, less physical activity, less healthy eating, more smoking, more missed medical appointments, and worse glycemic control.[10]

Depressive symptoms consist of two types or sets of symptoms. Cognitive-affective symptoms include mental or psychological aspects such as feeling down, negative self-talk, and little interest or pleasure in doing things. Somatic-affective symptoms include physical aspects such as having low energy, difficulties sleeping, and poor appetite or overeating. Most studies focus only on overall depressive symptoms as indicated on self-report screening measures such as the Patient Health Questionnaire (PHQ)[11, 12] or the Center for Epidemiologic Studies Depression Scale (CES-D),[13] or as indicated by a clinical interview. Studies examining the cognitive-affective and somatic-affective symptom sets separately are rare[14] but may be needed to understand the associations between diabetes management and depressive symptoms. Somatic-affective symptoms are also symptoms of uncontrolled or highly variable glycemia.[15] A large population-based study found the association between diabetes and depression was primarily due to overlap in somatic-affective symptoms.[14] Moreover, due to the overlap in

somatic-affective symptoms of depression and progressed diabetes, some have recommended a higher cut point for the PHQ among persons with diabetes than in the general population.[16, 17] Observational research has shown repeatedly that depressive symptoms are associated with less self-care.[7, 8] However, there is mixed evidence as to whether reducing depressive symptoms might improve diabetes self-management,[9, 18-20] and there has been little examination of whether improvements in self-care affect depressive symptoms.

It remains unclear how to handle depressive symptoms when evaluating interventions designed to support diabetes self-management and improve glycemic control; interventions that effectively improve diabetes self-management may also lead to reduced depressive symptoms (i.e., depressive symptoms as an outcome) or interventions may be less effective for self-management outcomes among persons with elevated depressive symptoms (i.e., depressive symptoms as an effect modifier). There are several reasons to hypothesize self-management support interventions might reduce depressive symptoms among adults with type 2 diabetes. Improved diabetes self-management occasioned by effective self-management support interventions might alleviate depressive symptoms via physical and psychological benefits of improved physical activity and dietary choices. Somatic symptoms that might be related to or exacerbated by poor glycemic control or recurrent hyper- and hypo-glycemic events may be alleviated if adherence to medications improves. Cognitive-affective symptoms may also improve if the person feels efficacious in setting and reaching self-management goals.[21] On the other hand, persons with clinically elevated depressive symptoms may not benefit from a diabetes self-management support intervention that does not also address depressive symptoms. In this case, persons with both conditions would potentially be excluded from diabetes self-management support interventions that do not address depressive symptoms and enhanced focus

should be placed on designing interventions to address both conditions. Limited research has tested the hypothesis that depressive symptoms are an effect modifier of diabetes self-management support interventions, however a diagnosis of depression is a common exclusion criterion for such intervention studies.

1.1. Objective & Hypotheses

We conducted a secondary analysis from a randomized controlled trial (RCT)[22] evaluating a diabetes self-care support intervention that was successful in improving diabetes self-efficacy, self-care behaviors and glycemic control (hemoglobin A1c) to test two competing hypotheses about the role of depressive symptoms in diabetes self-care support interventions among adults with type 2 diabetes. Our overarching question was: are depressive symptoms a potential outcome or effect modifier of diabetes self-care support interventions that do not target depressive symptoms? Were depressive symptoms to be an outcome, we hypothesized reductions in depressive symptoms might be attributable to overlap between somatic-affective symptoms of depression and elevated A1c (e.g., fatigue). This would be supported if reductions in depressive symptoms were largely due to somatic-affective symptom reduction and/or more pronounced among those with higher A1c values. Were depressive symptoms to be an effect modifier, we hypothesized that persons with clinically elevated depressive symptoms might experience less benefit in A1c reductions than persons with fewer symptoms.

2. Methods

2.1. Study Context

REACH (Rapid Education/Encouragement and Communications for Health) is an individually tailored, automated, interactive text messaging intervention designed to improve type 2 diabetes management among racially diverse and predominantly disadvantaged adults.[23]

One-way text messages address each participant's barriers to diabetes medication adherence, provide information on each participant's prescribed diabetes medications, and support other self-care behaviors (i.e., dietary behavior, physical activity, self-monitoring of blood glucose). Two-way/interactive messages support monitoring medication adherence over time and give encouraging feedback on progress. Throughout the intervention experience, participants' barriers to adherence, prescribed medications, and daily schedule are updated/re-tailored. The intervention does not include content designed to address depressive symptoms.

We evaluated REACH in a parallel-groups, 15-month RCT wherein participants assigned to REACH received the text messaging intervention for 12 months[24] (Trial Registration Number NCT02481596). [1] We recruited English-speaking adults with type 2 diabetes who were prescribed daily diabetes medications from community health centers and Vanderbilt adult primary care clinics. Participants whose most recent A1c value was less than 6.8% were excluded, to increase the likelihood that enrolled persons could benefit from diabetes self-management support. Participants provided written informed consent to enroll. The study was powered to detect a 0.5% reduction in hemoglobin A1c with N=500, with goals of recruiting 50% with minoritized race/ethnicity and 50% with low socioeconomic status.[24] All participants received treatment as usual, free study A1c tests with a text message instructing how to obtain the result, print materials (e.g., quarterly newsletters), and access to a study helpline to ask questions about their diabetes medications. Study assessments occurred at baseline, 3-, 6-, 12- and 15-months post-baseline.

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[1] Participants randomly assigned to REACH were then randomly assigned to receive REACH only or REACH plus FAMS for the first 6 months of the study. FAMS added components to address family/friend involvement in adults' self-management via monthly phone coaching and the option to invite a support person to receive text messages. We conducted all analyses herein for REACH only versus control and REACH plus FAMS versus control. Results did not vary across intervention groups. For simplicity and to enhance power for subgroups effects, we focus this analysis on participants assigned to intervention (to receive *any* REACH) versus participants assigned to control. Details of each intervention and results have been published.

A total of N=506 participants were randomized in the RCT.[22] The sample was 54% female with average age 55.9 ± 9.6 years; 48% were non-Hispanic white, 39% non-Hispanic Black, 6% Hispanic, and 6% reported another or multiple race/ethnicities. Almost half were underinsured (23% uninsured, 25% public insurance only) and 61% had an annual household income less than $35,000. Nearly 12% of the sample was homeless. Participants reported having diabetes for 11.0 ± 7.9 years and the average baseline A1c was 8.6% ± 1.8%. On average, participants reported being prescribed 2.0 ± 0.8 hypoglycemic medications. Half (51%) were prescribed oral medication only, 16% were prescribed insulin only and 32% were prescribed both.

Randomization using optimal multivariate matching resulted in balance across conditions (i.e., standardized mean difference <.20) on sociodemographic and clinical characteristics (e.g., age, gender, race/ethnicity, socioeconomic indicators, diabetes duration, diabetes medication regimen) and baseline values of a priori outcomes of interest including hemoglobin A1c, diabetes self-care behaviors, and diabetes self-efficacy.[22] Among those assigned to REACH, response rates to interactive texts remained high throughout the 12-month intervention period. Over 90% of the study sample was retained throughout the trial. Further details on the development of the intervention,[23] the RCT protocol,[24] and effects on a priori outcomes[22] have been published.

To answer our research questions about the role of depressive symptoms, we focused this secondary analysis on RCT data collected at baseline and 6-months follow-up where a priori analyses indicated effects on diabetes management (i.e., self-care and A1c) were largest.[22] REACH effects on A1c were larger among participants with baseline A1c≥8.5%, therefore we included tests by baseline A1c in these secondary analyses. These tests accounted for the possibility that REACH affected depressive symptoms differently for persons with high or low

baseline A1c and, separately, that clinically elevated symptoms might modify REACH effects on A1c only among those with high or low baseline A1c.

2.2. Measures

Hemoglobin A1c was collected at participants' clinics using venipuncture or a point-of-care device or using an A1c kit provided by CoreMedica Laboratories. We used kits when participants did not have a clinic appointment aligning with a study assessment, when the clinic could not accommodate a study-related A1c blood draw, or per patient preference for convenience and to enhance retention. We also reviewed participants' electronic medical record for any A1c values occurring within the study assessment window.

Depressive symptoms were assessed with the validated Patient Health Questionaire-8 (PHQ)[11] which assesses the frequency of symptoms over the past 2 weeks according to diagnostic criteria. The 8-item version omits a question about suicidal thoughts and is often used in research where the interviewers are not qualified or able to provide adequate intervention (e.g., by telephone). Because this last item is the least frequently endorsed, the two versions have identical scoring thresholds.[11] Each symptom is assessed on scale from 0 = "not at all" to 3 = "nearly every day," yielding a continuous summed severity score from 0 to 24. PHQ scores ≥ 10 indicate clinically elevated symptoms.

2.3. Analyses

First, we conducted an exploratory factor analysis using baseline PHQ values to identify subscales assessing cognitive-affective and somatic-affective symptoms in our sample. Next, we used nonparametric tests of difference to compare baseline PHQ scores across study conditions, and across baseline A1c values to identify imbalances that might inform interpretation of results.

We tested our hypotheses with a series of regression models, including models testing overall effects, models with interaction terms using continuous measures (i.e., condition x baseline A1c or condition x baseline depressive symptoms), and models stratified to examine subgroup effects using categorical measures (i.e., high or low A1c, clinically elevated depressive symptoms or not) to illustrate the presence/absence of effect modification. Each regression model was adjusted for the baseline value of the outcome of interest to enhance precision and handle potential confounders without using multiple degrees of freedom. We initially ran the models with restricted cubic splines to allow for non-linear change in the outcome from baseline to follow-up. Splines did not affect the results, so we present results without them for simplicity and for more degrees of freedom in models examining subgroup effects.

2.3.1. Sample Size and Missing Data. A total of n=88 (17.4%) RCT participants were missing at least one A1c or PHQ value at baseline or 6-month follow-up – the values used in regression models – so we used multiple imputation using chained equations to impute m=50 datasets. We imputed PHQ data at the item level. The imputation model included all variables used in analyses, plus ancillary variables to enhance the validity of the imputations. Ancillary variables included A1c values and PHQ items from the 3-month follow-up assessment (91.5% complete) and participants' sociodemographic and clinical characteristics associated with depressive symptoms at baseline. The imputation model also accommodated planned interaction terms and subgroup analysis. Two percent (n=11) were missing a baseline A1c value and could not be classified as having a high or low baseline A1c for planned subgroup analyses (none were missing baseline PHQ), therefore subgroup analyses use imputed data for n=495 while overall models use imputed data for the full RCT sample of N=506.

3. Results

3.1. Factor analysis

We ran a principal components analysis using a maximum likelihood analysis with oblique rotation. Three Factors with Eigenvalues >1.0 were identified, but only one item (item 8) loaded on Factor 3. Therefore, we re-ran the analysis forcing a two Factor solution. The resulting pattern matrix is shown in **Table 1**. Five items loaded on Factor 1, which appeared to assess cognitive-affective depressive symptoms, and the remaining 3 items loaded on Factor 2, which appeared to assess somatic-affective depressive symptoms. None of the items loaded on more than one Factor. We expected item 8 to load with somatic-affective symptoms, but the loading for Factor 2 was 0.18 and further analysis indicated including this item in the somatic-affective subscale reduced the internal consistency reliability for both subscales. Cronbach's α for the full PHQ in our sample was 0.84, with α=0.80 for the cognitive-affective subscale and α=0.73 for the somatic-affective subscale. The Spearman correlation between these two subscales was 0.62 ($p<.001$).

Table 1. Patient Health Questionnaire 8 items with a 2-factor solution and oblique rotation from baseline data (N=506)

"Over the past 2 weeks, how often have you been bothered by any of the following problems?"	Factor 1	Factor 2
	Cognitive-Affective	Somatic-Affective
1. Little interest or pleasure in doing things	0.55	
2. Feeling down, depressed, or hopeless	0.86	
3. Trouble falling or staying asleep, or sleeping too much		0.62
4. Feeling tired or having little energy		0.80
5. Poor appetite or overeating		0.50

6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0.72	
7. Trouble concentrating on things, such as reading the newspaper or watching television	0.38	
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0.32	
Subscale Cronbach's α	0.80	0.73
Subscale mean ± standard deviation	2.58 ± 3.12	3.40 ± 2.58

Blank factor loadings were <0.30

3.2. Baseline Associations

At baseline, the average PHQ score was 6.0 ± 5.1, with 22% having elevated depressive symptoms using the ≥10 threshold. The sample reported more somatic-affective than cognitive-affective symptoms (3.4 ± 2.6 versus 2.6 ± 3.1, $p<.001$). Baseline PHQ scores were balanced across assigned study conditions ($p=0.54$). Forty-four percent of the sample had a baseline A1c ≥ 8.5%, and those with a high A1c reported more depressive symptoms than participants with a low baseline A1c. This was true of the PHQ total [6.7 ± 5.0 (25% with elevated depressive symptoms) versus 5.4 ± 5.1 (19% with elevated depressive symptoms), $p<.001$] and each of the symptom sets (cognitive-affective 2.9 ± 3.2 versus 2.3 ± 3.1, $p=.03$; somatic-affective 3.7 ± 2.6 versus 3.1 ± 2.6, $p=.005$).

3.3. Regression Models

For models with depressive symptoms as the outcome, we report standardized regression coefficients, β, which can be interpreted as the standard deviation change in depressive symptoms for REACH versus control (except for in the case of interaction terms). For models with A1c as the outcome, we report unstandardized coefficients, b, which can be interpreted as a real change in hemoglobin A1c (i.e., -0.20 represents an A1c reduction of 0.20%) for REACH versus control.

3.3.1. Are depressive symptoms an outcome of REACH? REACH did not improve depressive symptoms in the overall sample (**Table 2**), but significant interaction terms indicated the effect of REACH on PHQ scores varied by baseline A1c. REACH x baseline A1c interaction terms were significant regardless of symptoms set: PHQ total interaction term β=0.549 (*p*=.002), cognitive-affective β=0.449 (*p*=.013), and somatic-affective β=0.541 (*p*=.004). Subgroup effects in **Table 2** illustrate that REACH improved depressive symptoms – both cognitive-affective and somatic-affective symptoms – among participants with low baseline A1c but not among participants with high baseline A1c (**Table 2**).

Table 2. Effects of REACH on change in depressive symptoms from baseline to 6-months; overall and stratified by baseline A1c

	Full Sample N=506		Baseline HbA1c < 8.5% n=278		Baseline HbA1c ≥ 8.5% n=217	
	β	*p*	β	*p*	β	*p*
Total depressive symptoms	-.066	.070	**-.133**	**.007**	.040	.468

Cognitive-affective symptoms	-.053	.163	**-.107**	**.038**	.031	.593
Somatic-affective symptoms	-.064	.104	**-.131**	**.014**	.041	.497

3.3.2. Are depressive symptoms an effect modifier of REACH? We did not find any evidence that the effect of REACH on 6-month A1c was modified by baseline depressive symptoms. In other words, there was no significant REACH x depressive symptoms interaction term in the full sample (b=-.027, p=.378, n=495) or among those with high baseline A1c (b=-.031, p=.556, n=216) or low baseline A1c (b=-.004, p=.906, n=278). To further understand the effects of REACH among patients with clinically elevated depressive symptoms, we examined effects among participants with clinically elevated and not clinically elevated baseline PHQ scores (**Table 3**). We are less powered to detect statistical significance in models restricted to participants with clinically elevated baseline depressive symptoms, but report subgroup effects for illustrative purposes. Effect sizes in **Table 3** illustrate that participants with low baseline A1c values did not experience A1c reductions, regardless of baseline depressive symptoms, whereas participants with high baseline A1c values experienced similarly sized A1c reductions regardless of baseline depressive symptoms.

Table 3: REACH effects on 6-month HbA1c - Subgroups by Baseline HbA1c and PHQ

	Baseline A1c < 8.5%	Baseline A1c ≥ 8.5%
Not clinically elevated baseline PHQ	b = -.002 p = .990 n = 224	b = -.635 p = .047 n = 163

Clinically elevated baseline PHQ	b = .117 p = .777 n = 54	b= -.764 p = .175 n = 53

4. Discussion

We examined the role of depressive symptoms – outcome or effect modifier – in a secondary analysis from an RCT evaluating an effective diabetes self-management support intervention in a diverse sample of adults with type 2 diabetes. We found nuanced support for depressive symptoms as an outcome, and no support for depressive symptoms as an effect modifier. The intervention reduced both cognitive-affective and somatic-affective depressive symptoms but only among participants with a baseline A1c value less than 8.5%. In the context of our primary RCT finding,[22] where A1c effects were present at 6 months for participants with baseline A1c ≥ 8.5% but not for participants with baseline A1c < 8.5%, our results have some surprising implications for the interplay between glycemic control and depressive symptoms. First, our findings contradict our hypotheses that reductions in depressive symptoms occasioned by REACH would be due to somatic-affective symptom reduction associated with improved glycemic control and more pronounced among participants with high A1c at baseline. Although extant evidence suggests the progression of diabetes may contribute to depressive symptoms over time,[3, 25] our findings indicate no somatic-affective symptom reduction among the subgroup of patients who experienced A1c reductions over this 6-month period. Perhaps this is because 6 months is relatively short and experimental examination is warranted to test the effects of long-term, sustained A1c reductions on both somatic- and cognitive-affective depressive symptoms. Second, because the group with lower baseline A1c did not experience a REACH effect on A1c

but did experience benefits in both types of depressive symptoms, benefits on depressive symptoms appear to be independent of benefits on A1c.

The next reasonable question becomes what *does* account for the REACH effect on depressive symptoms, if not improved glycemic control? REACH did improve participants' medication adherence, dietary behavior, and self-efficacy regardless of baseline A1c.[22] Thus, it is reasonable to suggest that self-management changes benefited these participants' energy and affect even though their diabetes was already relatively well-controlled without much room for A1c improvement. To hypothesize what might be driving reductions in depressive symptoms occasioned by diabetes self-management support interventions (if not A1c improvements), we looked for RCTs evaluating the effects of type 2 diabetes self-management support interventions on depressive symptoms, excluding any intervention that also addressed depressive symptoms. We identified seven such RCTs[26-32] of which three[28, 29, 31] found evidence of an effect on depressive symptoms. Consistent with our findings from the REACH RCT, two[28, 31] of these three studies also reported improvements in self-efficacy and self-care behaviors alongside the reduction in depressive symptoms. In contrast, of the four studies that found no effect on depressive symptoms, three either did not look for or did not find evidence of effects on self-care behaviors or self-efficacy (the exception being Chamany et al.[32] who reported improved dietary behaviors and physical activity). Our findings in context of the extant literature suggest improvements in self-efficacy and self-care may be present when depressive symptoms are also reduced, suggesting potential mechanisms for depressive symptom reduction. However, this would not explain our finding that participants with higher baseline A1c did not experience depressive symptom reductions while also experiencing improved medication adherence, dietary behavior, and self-efficacy. In addition, baseline imbalance (i.e., regression to the mean in PHQ

scores) does not account for this unexpected finding, as PHQ scores were slightly higher among participants with high baseline A1c and this group did not experience a reduction in depressive symptoms. Our analysis was the first to examine differential intervention effects on depressive symptoms for participants with low versus high A1c. Therefore, we recommend others investigating intervention effects on depressive symptoms seek to replicate this unexpected finding.

Even when interventions address both diabetes self-management and depressive symptoms, effects on depressive symptoms among adults with type 2 diabetes are small. A 2020 systematic review and metanalysis[33] identified n=14 studies of psychological interventions in type 2 diabetes, combining interventions that did and did not explicitly address depressive symptoms, and found average effects on depressive symptoms of -.28 [95% CI -.63 to .06]. The magnitude of the standardized effect of REACH on depressive symptoms was -.133 among participants with lower A1c, within the range identified in the metanalysis. In our sample, this effect equated to approximately a .70 lower score on the PHQ total and .35 lower score on each of the subscales. In sum, diabetes self-management support interventions are not likely to make substantive improvements in depressive symptoms. An experimental study evaluating a diabetes self-management support intervention delivered with and without an intervention targeting depression among patients with clinically elevated depressive symptoms would determine the additive value of this additional content – although it may be difficult to power given small effect sizes. In this context, a repeated measures design assessing changes in self-efficacy, self-care behaviors, A1c, and depressive symptoms could also help to unpack the interplay between these variables.

A clear finding from this analysis was that persons with comorbid diabetes and clinically elevated depressive symptoms received a benefit in glycemic control consistent with that of their counterparts without elevated depressive symptoms. Our finding aligns with other studies which have tested depressive symptoms as an effect modifier of diabetes self-management interventions. Rosland et al.[34] found no A1c effect modification by depressive symptoms in their community health worker-led intervention. Likewise, in Moskowitz et al.'s[35] peer health coaching intervention, depressive symptoms did not moderate effects on A1c. Consistent with the REACH RCT, participants in both studies were predominantly racial/ethnic minorities with lower income. This suggests diverse persons with elevated depressive symptoms may benefit from interventions that address only diabetes self-management. Of course, they may benefit more from interventions that address both conditions,[7, 36, 37] but collectively these findings indicate participants with elevated depressive symptoms can benefit from diabetes self-management support interventions and should not be excluded.

Our examination of the role of depressive symptoms was a secondary analysis from an RCT designed to evaluate the effects of mobile phone-delivered diabetes self-management support on glycemic control and self-care behaviors. Accordingly, the large RCT sample provided sufficient power for tests of effect modification. However, because we did not intentionally recruit persons with clinically elevated depressive symptoms, we were underpowered to estimate subgroup effects among participants with clinically elevated depressive symptoms. Also, REACH was a mobile phone-delivered intervention and findings may not generalize to diabetes self-care interventions delivered via other modalities. On the other hand, results are consistent with other in-person interventions in the literature. The sample was a socioeconomically and racially diverse sample of adults with type 2 diabetes, enhancing

generalizability, but participants were recruited from a specific region in Tennessee. Finally, given prior research suggesting differential relationships between cognitive-affective and somatic-affective depressive symptoms and diabetes outcomes, it is a strength of our study to have examined symptom sets separately in the context of an RCT. We encourage other studies to pursue similar examinations given several findings were contrary to our hypotheses and warrant further investigation. We also recommend persons with elevated depressive symptoms not be excluded from interventions providing diabetes self-management support to improve self-care and glycemic control.

Author Contributions

L.S.M. and L.A.N oversaw all aspects of the REACH RCT. L.S.M. and J.S.G. conceptualized the research questions. L.S.M. planned and conducted analyses and wrote the manuscript. L.A.N. and J.S.G. edited the manuscript and all authors approved the submitted version.

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