Impact of glycated hemoglobin A1C-lowering interventions on comorbid depressive symptoms in adults with type 1 or type 2 diabetes: A systematic review of intervention studies

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Key messages:

- Hyperglycemia represents a likely pathway linking diabetes and depression. RCTs on A1C reduction including depression assessment may help infer causality.
- Of 5 studies with relevant A1C reduction, 3 found parallel depression reduction. Of 4 studies associating A1C and depression changes, none found an association.
- There is insufficient data available to estimate the effect size of A1C reduction on depression. Future A1C intervention trials should consider including the assessment of depression.

Keywords: Diabetes mellitus, depressive symptoms, glycated hemoglobin A1C, intervention, randomized controlled trial, systematic review

Main text word count: 3,208

Abstract word count: 263

Number of tables: 2

Number of figures: 2

Supplementary materials: 2

Author disclosures:

The authors declare that they have no conflict of interest. No funding was received to assist with the preparation of this manuscript.

Abstract

Aims: Hyperglycemia constitutes a likely pathway linking diabetes and depressive symptoms; lowering glycemic levels may help reduce diabetes-comorbid depressive symptoms. Since randomized controlled trials can help understand causal impacts, we systematically reviewed the evidence regarding effects of A1C-lowering interventions on depressive symptoms.

Methods: PubMed, PsycINFO, CINAHL and EMBASE databases were searched for randomized controlled trials evaluating A1C-lowering interventions and including assessment of depressive symptoms published between 01/2000–09/2020. Study quality was evaluated using the Cochrane Risk of Bias tool. PROSPERO registration: CRD42020215541.

Results: We retrieved 1,642 studies of which twelve met our inclusion criteria. Nine studies had high and three unclear risk of bias. Baseline depressive symptom scores suggest elevated depressive symptoms in five studies. Baseline A1C was <8.0% (<64mmol/mol) in two, 8.0–9.0% (64–75mmol/mol) in eight and ≥10.0% (≥86mmol/mol) in two studies. Of five studies that found greater A1C reduction in the treatment group, three also found greater depressive symptom reduction in the treatment group. Of four studies analyzing whether change in A1C was associated with change in depressive symptoms, none found a significant association. The main limitation of these studies were the relatively low levels of depressive symptoms at baseline, limiting the ability to show lowering in depressive symptoms after A1C reduction.

Conclusions: We found insufficient available data to assess the effect size of A1C-lowering interventions on depressive symptoms. Our findings point to an important gap in the diabetes treatment literature. Future clinical trials testing interventions to improve glycemic outcomes might consider measuring depressive symptoms as an outcome to enable analysis of the impact of A1C reduction on depressive symptoms.

Abbreviations: A1C, glycated hemoglobin A_{1C}; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; PHQ, Patient Health Questionnaire; RCT, randomized controlled trial;

Introduction

Depression is a frequent complication of diabetes with major depression affecting approximately 10% to 12% of people with diabetes and another 7% to 19% reporting so-called subthreshold or minor depression [1–4]. Both clinical and subclinical depression have been associated with suboptimal diabetes outcomes including elevated glycated hemoglobin A1C (A1C) [5], reduced health [6], incident vascular complications of diabetes [7,8], and higher mortality rates [8-10]. Thus, comorbid depression in diabetes constitutes an important treatment target.

While it is accepted that depression is more common in people with diabetes than those without [1-3], the mechanisms linking diabetes and depressive symptoms are not fully understood. One likely pathway is through less optimal diabetes self-management with subsequent glycemic excursions or persistent hyperglycemia [11]. High blood glucose can directly affect the functioning and structure of brain cells resulting in altered mood states such as dysphoria [12,13]. It can also create somatic symptoms of depression such as tiredness, fatigue, loss of appetite as well as sleep and eating problems [14]. Finally, high glucose levels can create negative mood via thinking about suboptimal glycemic levels and related health risks (for example, self-blame and feelings of guilt and worry due to improvable treatment performance and outcome) [15]. It is therefore important to investigate potential causal effects of A1C reduction on depressive symptoms. This can help clarify the mechanisms linking diabetes and depression/depressive symptoms, and improve treatments.

Associations between A1C and depressive symptoms were variously identified in observational studies. An influential meta-analysis published two decades ago summarized the evidence until 2000 and found significant cross-sectional correlations between A1C and depressive symptoms in both major types of

diabetes [5]. Longitudinal observational studies that were conducted in the past twenty years have also supported associations: for example, higher A1C predicted persistently elevated or increasing depressive symptoms in diabetes [16] and increases in depressive symptoms were associated with increases in A1C in type 1 diabetes [17]. Furthermore, a large cohort study found that higher fasting plasma glucose, higher post-load glucose and higher A1C predicted incident depressive symptoms over four years in people with type 2 diabetes [18].

Yet, these observational studies cannot provide conclusive evidence to support that hyperglycemia can cause depressive symptoms and that lowering glycemic levels may reduce these symptoms. By contrast, intervention studies aiming to reduce A1C and also evaluating effects on depressive symptoms may help to identify potential causal relationship between A1C levels and depressive symptoms. We hypothesize that a greater A1C reduction in the treatment group would be associated with a concomitant greater reduction of depressive symptoms as compared to the control group. This pattern of parallel changes over time would demonstrate a causal link between hyperglycemia and depressive symptoms.

A recent meta-analysis of intervention studies found that psychological and pharmacological treatments for depression were effective in reducing depressive symptoms as well as A1C levels [9], suggesting that the reduction of depressive symptoms may have helped to improve glycemia. At present, however, there is no systematic review available that summarizes interventional data of treatments to improve A1C levels on concomitant effects on depressive symptoms (i.e., evaluating the effect of A1C-lowering on depressive symptoms).

Therefore, we conducted a systematic review of intervention studies evaluating treatment effects on A1C (primary outcome) and depressive symptoms (secondary outcome) to answer the following questions and to help elucidate a potential causal association between A1C levels and depressive symptoms:

1) Are interventions aiming to reduce A1C effective in reducing depressive symptoms?
2) Are reductions in A1C linked to reductions in depressive symptoms, irrespective of study arm allocation?

Methods

Search strategy

This review follows the PRISMA guidelines for systematic reviews [20] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020215541). PubMed, PsycINFO (Ebsco), CINAHL (Ebsco) and EMBASE (OVID) were systematically searched for studies published from 01/01/2000 until 12/31/2020 based upon the following terms (including their variants): (I) glycemia/glycemic control, (II) depression/depressive symptoms, (III) cohort/longitudinal study (full search terms are given in Supplementary Table 1). Articles were required to be in English, Dutch, French, German or Spanish. RCTs published before 01/2000 were not included due to the meta-analysis by Lustman et al. [5] summarizing the evidence up until that date.

Selection criteria

Retrieved titles and abstracts were independently screened by two pairs of reviewers (MB + MS, RM + AG) with subsequent full-text screening by AS, MB, AG, JH and MS based on the following criteria: RCT

testing an intervention with the primary aim to reduce A1C; reporting an estimate of change in depressive symptoms; study sample size ≥ 50; adult sample (≥ 18 years); sample including people with type 1 and/or type 2 diabetes. Studies of interventions primarily aiming to reduce depressive symptoms (for example, cognitive behavioral therapy for mood problems, antidepressants) were excluded in order to focus on the unique effect of A1C reduction on depressive symptoms, and not the effects of a psychological or pharmacological intervention on depressive symptoms; as well as studies using interventions specifically targeted at improving both A1C and depressive symptoms simultaneously.

Data extraction

Data extraction was performed using a pilot-tested data sheet extracting the following characteristics: authors, publication year, country, sample size (baseline and follow-up), sample characteristics (i.e., age, sex distribution, diabetes duration, possible specific ethnicity), assessment methods for A1C and depressive symptoms, study duration, time and number of follow-up assessments, treatment group sizes, baseline descriptive scores and reported changes for the outcomes A1C and depressive symptoms (with confidence intervals, standard errors or *p*-values). For studies that presented A1C in NGSP units (%) only (*n*=11), IFCC units (mmol/mol) were calculated thereof.

Quality assessment

The quality of the included studies was assessed by JH, AS and MB using the Cochrane Risk of Bias tool for randomized trials [21] evaluating selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other types and sources of bias. Each item was rated as being of low, unclear or high risk of bias. The ratings were then

converted to Agency for Healthcare Research and Quality standards as described in the Cochrane Handbook [21].

Reviewers were not blinded to authorship or other information from the study, but the assessment was based on criteria defined a priori.

Results

Extracted studies

We retrieved 1,642 studies. Based on title and abstract reviewing, 173 full-text articles were assessed for eligibility. Twelve studies met the criteria for inclusion in the systematic review and were retained. Reasons for exclusion are given in Figure 1.

Please insert Figure 1 here

Quality assessment

According to the Cochrane Risk of Bias tool, a high risk of at least one form of bias was inferred for nine of the studies, while in three studies the risk was rated as unclear (full results in Supplementary Figure 1). The main reason for ratings of high risk of bias was incomplete outcome data with few studies addressing attrition (for example, no intention-to-treat analysis including dropped out participants) and possible selective reporting (three studies did not report all outcomes given in the protocol or registration, and six studies did not have a published protocol or registration). While all studies reported the use of random allocation, the amount of reported information varied notably (for example, the creation of a truly random sequence could not be inferred as concrete methods were not reported), and four studies were rated as having a high risk of bias due to probably invalid random allocation. None of the studies reported on having blinded participants and only three studies blinded key study personnel). However, the nature of the

198 interventions may have precluded blinding participants. Aside from that, in some studies, efforts were made
199 to control for contamination bias, either by conducting randomization at the community level in
200 geographically dispersed communities [30], or by performing initial assessments and routines in the control
201 group as well [22]. Multiple studies also used a different type of intervention, intervention with
202 augmentation component, or enhanced usual care as control condition, which could have limited bias due
203 to lack of blinding (Table 1).

204 Other risk of bias criteria such as allocation concealment were frequently not explicitly addressed,
205 suggesting that precautions around these sources of bias were not in place and therefore the risk of bias was
206 rated as high.

207

208 *Study characteristics, interventions and outcome measures*

209 Full study details are given in Table 1. Nine studies were carried out in North America (USA, Canada), two
210 in The Netherlands, one in Sweden. Nine studies focused on people with type 2 diabetes, two on type 1
211 diabetes, and one did not specify diabetes type. Five studies assessed ethnic minorities, that is, African
212 Americans and Latin Americans [28,30,35,36,39]. Seven studies were based on secondary analyses of
213 RCTs [23,26,28,30,32,36,39] for which additional information was retrieved from the primary publications
214 [24,27,29,31,33,37,40].

215

216 All retrieved studies evaluated behavioral interventions to improve A1C. Tested interventions comprised
217 diabetes self-management education and/or support [22, 25,32,35,36], self-management and/or glycemia
218 goal-setting [30,34,38], coaching by nurses, health workers or peers [28,30], peer support [Presley],
219 structured glucose self-monitoring [22,26], intensive glycemia management [23], and combinations thereof
220 [39] (Table 1). Two studies were based on principles of cognitive behavioral therapy [22,38] and one study

based on social cognitive theory [39]. Another study [36] used community-based participatory research principles throughout the process of developing, conducting and evaluating the intervention. Two studies [32,34] reported the use of motivational interviewing with one study specifying the aim to reduce ambivalence about changing health behaviors, alter risk perception and enhance self-efficacy [34, information from 33].

Interventions were administered by diabetes nurses [22, 38], psychologists [22,38], community health workers [25, 35,36], nurse case manager and/or community health workers [28], physicians [26,36], trained peer coaches [30], certified diabetes educators [32], or research assistants [34]. One study did not specify interventionist characteristics [23] and one study reported various teams of both professional and trained lay workers to having delivered the intervention [39]. Most treatments were provided in one-to-one settings, four were group-based, one included both single and group treatments.

Treatment duration and contact frequency varied from 1.5–24 months and weekly–quarterly, respectively. Interventions were compared to (enhanced) care as usual [23,26,28,30,34,39], waiting list [22], intervention without augmentation component [25,32,35], different intervention (blood glucose awareness training [38]) or sham intervention [36] (Table 1).

A1C levels were assessed using standard laboratory assessments (details in Table 1). Elevated baseline A1C (defined by values over 7.0% (53 mmol/mol), 7.5% (59 mmol/mol) or 8.0% (64 mmol/mol); Table 1) was an inclusion criterion in nine of the twelve studies. Mean baseline A1C ranged from 7.5–7.9% (59–63 mmol/mol) [30,34], 8.3–9.0% (67–75 mmol/mol) [22,23,26,28,32,36,38,39] and 10.0–10.2% (86–88 mmol/mol) [25,35] in two, eight and two studies, respectively.

Depressive symptoms were assessed using common validated questionnaire measures able to detect changes over time (i.e., Center for Epidemiologic Studies Depression Scale (CES-D), Patient Health Questionnaire (PHQ)–8 or 9, Hospital Anxiety and Depression Scale (HADS)–depression subscale). Elevated depressive symptoms were not required for inclusion in any study; the baseline scores suggested low depressive symptoms in seven and moderately elevated depressive symptoms in five of the studies [28,32,35,38,39] based on established cut-off criteria (i.e., full 20-item CES-D ≥ 16, 10-item short-form CES-D ≥ 10, PHQ-9 and PHQ-8 ≥ 10, 7-item HADS depression subscale ≥ 8).

Please insert Table 1 here

Changes in A1C levels

Full results are given in Table 2. Changes in A1C and depressive symptoms by group are illustrated in Figure 2. Five studies found greater A1C reduction in the treatment group versus control group [22,26,36,38,39], four found equivalent reductions across the groups [25,28,34,35], one found an A1C reduction favoring the control group [32], one found no change in either group [30] and one did not report A1C over time [23] (yet, greater A1C reduction in the treatment group was shown in the primary study for the full cohort [24]). Generally, greater A1C change was seen in studies with higher baseline A1C.

Changes in A1C levels and concomitant changes in depressive symptoms

Five studies reporting greater A1C reductions in the treatment group. Of these, three found greater simultaneous reductions of depressive symptoms in the treatment group [22,26,39], one found similar depressive symptom reductions in both groups [38] and one found no depressive symptom changes in either

group [36]. In the last two studies, both groups had received an (sham)intervention. The first three studies used 'care as usual' or waiting list as control group.

Four studies found comparable A1C reductions across groups. Of these, one found significant depressive symptom reduction in the total sample but the changes per group were not reported [28], one found greater depressive symptom reduction in the control group [25], and two found no changes in either group [34,35]. Leyva et al [32] reported greater A1C reduction for the control group [32] but found no reduction in depressive symptoms. One study reported no A1C change over time [30] and found non-linear changes in depressive symptom which could not be interpreted conclusively.

Please insert Figure 2 here

Associations between changes in A1C and depressive symptoms

Four of the twelve studies [26,28,32,39] directly analyzed the association between changes in A1C and depressive symptoms. Three of these four studies had a study sample with elevated depressive symptoms at baseline [28,32,39], increasing the likelihood of finding a reduction in depressive symptoms. Two studies observed a significant depressive symptom reduction over time irrespective of treatment arm [26,28], while one found a reduction in the treatment group only [39], and one reported no change irrespective of treatment arm [32]. None of the studies found a significant association between changes in A1C and changes in depressive symptoms (Table 2).

Please insert Table 2 here

Discussion

Key results and implications

To the best of our knowledge, this systematic review is the first to evaluate the effect of A1C interventions on depressive symptom reductions in diabetes as assessed in RCTs. Our results might indicate that there is an effect of A1C reduction on depressive symptoms, but there is insufficient evidence available to establish any effect size. We observed a large heterogeneity of behavioral interventions, hindering the possibility for meta-analysis. In addition, direct analyses to assess whether changes in A1C levels were associated with reductions depressive symptoms were not significant, which is likely due to the small reductions achieved both in A1C and depressive symptom levels.

This review systematically compiles the available literature on the association of A1C reduction with reductions in depressive symptoms. Although the study is limited by the little evidence available, we found twelve studies meeting our inclusion criteria. All studies evaluated behavioral interventions for improving hyperglycemia, while we found no studies testing pharmacological interventions. Seven studies were secondary analyses of RCTs with primary results on A1c reduction reported separately. Furthermore, depressive symptom scores at baseline were low in seven of the studies, reducing the likelihood that improvement of depressive symptoms was possible due to floor effects. The quality assessment suggested limited methodological quality with nine studies classified as having a high risk of bias.

The limited availability of RCTs that investigate changes in depressive symptoms after A1C interventions constitutes a significant gap in the literature. Depression is a disruptive and common complication of diabetes, affecting 10% to 12% of diabetes patients [1-4]. Determination of changes in A1C and depressive symptoms by treatment group may help understand the causal relationships between hyperglycemia and depressive symptoms. Therefore, we advise upcoming RCTs to consider the addition of depressive symptom assessment. Such RCTs would optimally meet the following requirements: 1) include people with either type 1 or type 2 diabetes (as compared to both, due to the groups' significant differences in pathomechanisms and treatment); 2) select people with elevated glycaemia (i.e., A1C; or continuous

glucose monitoring-derived metrics such as mean sensor glucose, time in range or glucose management indicator from data over several weeks) – while additionally elevated depressive symptoms at baseline would be optimal, this cannot be expected for studies that do not focus primarily on depressive symptoms; 3) evaluate a behavioral and/or pharmacological treatment for improving glycaemia; 4) do not include intervention components specifically targeting depressive symptoms such as psychotherapeutic interventions (only care as usual to isolate the unique effect of the A1C improvement on depressive symptoms); 5) analyze the effects by group on both A1C (primary outcome) and depressive symptoms (secondary outcome); and 6) additionally analyze the relationship between these variables' changes using statistical test. Of the twelve studies included in this review, none met all of these criteria. In fact, seven studies were secondary analyses regarding depressive symptoms change, limiting possible inferences and increasing risks of bias.

The pathophysiologic mechanisms linking glycemia and depressive symptoms are incompletely understood. Depressive symptoms may result from (micro)vascular dysfunction [42], and recurrent hyperglycemia can increase the risk for microvascular dysfunction. Furthermore, innate immunity and chronic low-grade inflammation increase the risk for both type 2 diabetes and depressive symptoms, with inflammation also affecting endothelial function as well as A1C [43]. Depressive symptoms may also result from hyperglycemic levels affecting the functioning of brain cells, that is, hyperglycemia increases intraneuronal glucose levels which can induce oxidative stress and lead to neuronal damage; this may eventually result in depressive symptoms [44]. Finally, life stress might act as a mediator with chronic hyperglycemia affecting coping potential which increases stress levels and subsequently depressed mood [45]. Thus, there is a potential for positive effects of improved glycemic levels on depressive symptoms.

Limitations and strengths

Due to heterogeneity of interventions and measurement methods, pooling of the data into a formal meta-analysis was not possible. The reviewed RCTs examined interventions which primarily aimed to lower A1C; thus, patients were usually selected by elevated A1C at baseline (in nine out of twelve studies); as a result, depressive symptoms, which frequently was a secondary outcome, were either low (in seven studies) or moderately elevated (in five studies) at baseline. In such studies, A1C levels may be lowered more substantially by the tested interventions, while depressive symptoms cannot be lowered to that same extent. This has limited the answering of our research questions. All reviewed studies assessed depression by use of self-report questionnaires rather than a clinical interview which is the diagnostic gold standard (46). However, the use of continuous measurements increases the statistical power for detecting effects and associations, therefore a severity score is preferred over a binary depression variable.

The strengths of this study are the comprehensive search including four databases, the analysis of intervention studies enabling evaluation of the temporality and causality of effects and the diversity of the included interventions providing a complete overview of the present evidence. While most research has focused on type 2 diabetes, we also included (and found at least two) studies concerning people with type 1 diabetes [22,38]. The systematic summary of available evidence is likely to stimulate innovative studies to fill the observed gap in scientific literature.

Conclusion and future perspectives

Based on the currently available intervention studies we found some evidence that interventions aimed at decreasing A1C levels also positively impact depressive symptoms. This might imply a potential direct effect of A1c reduction on the reduction of depressive symptoms. Our findings identified an important gap in the diabetes treatment literature. We therefore suggest the inclusion of depressive symptoms as a standard outcome measure in both RCTs that evaluate behavioral and pharmaceutical glucose-lowering

interventions. This would help provide a suitable evidence base to enable an analysis of the impact of glycemic improvement on depressive symptoms.

Acknowledgements

The authors would like to thank Rutendo Muzambi for her valuable support during the literature search.

Author contributions

AS: Conceptualization, Methodology, Formal analysis, Investigation, Writing –Original draft preparation, Visualization. **MB:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft preparation, Visualization. **AG:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing. **JWH:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing. **MTS:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing, Supervision. **MMI:** Writing – Review & Editing. **GN:** Writing – Review & Editing. **AN:** Writing – Review & Editing. **FP:** Writing – Review & Editing.

Author disclosures

The authors declare that they have no conflict of interest. No funding was received to assist with the preparation of this manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Characteristics of the reviewed studies.

Authors (year)	Country	Study sample	Study design, duration, time points	A1C measure-ment	Depression measurement	Treatment and control conditions	Group sizes at baseline (FU)
Amsberg et al., 2009 (22)	Sweden	Adults aged 18–65 years with T1DM and A1C >7.5% (59 mmol/mol) during past year, DM duration ≥2 years, BMI <30 kg/m^2 Ø age: 41.2 ±12.3 (range 19–65) years 51.4% women Ø DM duration: 21.6 ±10.8 (range 5–48) years Ø A1C at baseline: 8.5% (69 mmol/mol) ±0.8 [range 7.1–11.4% (54-101mmol/mol)] Ø depressive symptom score at baseline: 4.4 ±4.0	12-month RCT with two treatment arms 48 weeks 3 time points: baseline, 24 weeks, 48 weeks	Filter paper technique using an immunological assay by Roche (value in %)	HADS 7-item depression subscale (score range 0–21 = depressive symptom severity)	IG: Group treatment program consisting of 8 weekly 2-hour sessions led by a diabetes nurse and a psychologist, delivered in groups of 4–6 persons; sessions included an initial relaxation training, review of homework focused on self-care, introduction of a new theme and a related tool for behavior modification; participants wore a CGM device for 2 x 72 hours with data serving as biofeedback, supported by the diabetes nurse. CG: Waiting list group receiving routine diabetes care; participants attended initial assessments and routines regarding CGM but did not receive structured feedback on the glucose profiles.	IG: *n*=46 (36) CG: *n*=48 (38)
Anderson et al., 2011 (23); additional	USA and Canada	Adults with T2DM and A1C ≥7.5–11% (≥59–97 mmol/mol) with either a)	4-year RCT with two treatment arms	Standard laboratory	PHQ-9 (score range 0–27 = depressive	IG: Intensive glycemia management with a target A1C of 6.0% (42 mmol/mol).	IG: *n*=974 (208)

information taken from ACCORD Study Group, 2008 (24)		age 40–79 years with cardiovascular disease or b) age 55–79 years with significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CVD (HRQL substudy of the ACCORD trial) Ø age: 62.2 ±6.7 years 39.6% women Ø DM duration: 10 years Ø A1C at baseline: 8.3% (67 mmol/mol) ±1.1 Ø depressive symptom score at baseline: 5.4	4 time points: baseline, 12 months, 36 months, 48 months	assessment	symptom severity)	CG: Standard glycemic management with a target A1C between 7.0 and 7.9% (53 and 63 mmol/mol).	CG: *n*=982 (208)
Bluml et al., 2019 (25)	USA	Adults aged 21–85 years with T2DM and A1C >8.0% (64 mmol/mol), no diabetes self-management education in the past year Ø age: 54.4 ±10.6 years 58.7% women Ø DM duration: not	12-month RCT with two treatment arms 2 time points: baseline, 12 (range 6–18) months following baseline	Not reported	PHQ-2 (score range 0–6 = depressive symptom severity)	IG: DSME program augmented with telephonic support, provided by community health workers, every 2 weeks for 3 months, then 1 call per month until follow-up; focus lessons learned, and goals set during the DSME program. CG: DSME program only.	IG: *n*=221 (not reported) CG: *n*=225 (not reported)

		reported Ø A1C at baseline: 10.2% (88 mmol/mol) ±1.7 Ø depressive symptom score at baseline: 1.6 ±1.8					
Fisher et al., 2011 (26); additional information taken from Polonsky et al., 2011 (27)	USA	Adults aged ≥25 years with T2DM and A1C ≥7.5–12.0% (≥59–108 mmol/mol) not using insulin, DM duration >1 year Ø age: 55.8 ±10.7 years 46.8% women Ø DM duration: 7.6 ±6.1 years Ø A1C at baseline: 8.9% (74 mmol/mol) ±1.2 Ø depressive symptom score at baseline: 6.22 ±5.73	12-month cluster RCT with two treatment arms 5 time points: baseline, 3 months, 6 months, 9 months, 12 months	Bio-Rad Variant II and Variant II Turbo hemoglobin testing systems	PHQ-8 (score range 0–24 = depressive symptom severity)	IG: Collaborative program instructing how to gather, interpret, and utilize structured SMBG data to make treatment changes together with treating physicians; participants recorded a 3-day, 7-point SMBG profile before each visit (months 1, 3, 6, 9, 12) along with energy levels and meal sizes; they learned how to identify and address problematic glucose patterns. CG: Enhanced usual care with quarterly diabetes-focused physician visits; free SMBG meters and strips; no additional SMBG training or analysis system.	IG: *n*=256 (188) CG: *n*=227 (216)
Gary et al., 2005 (28); additional information taken from	USA	African American adults aged 35–75 years with T2DM living in East Baltimore	3-year follow-up of the original 2-year RCT 2 time points: baseline, 36 months	High-pressure liquid chromatography	CES-D (score range 0–60 = depressive symptom severity)	Participants were randomized to 4 parallel arms receiving primary care interventions to improve metabolic control: 1) usual care (UC) only=control condition; 2) usual care + nurse case manager (NCM); 3) usual care + community health worker (CHW); 4) usual care + nurse case manager–community health worker team (NCM+CHW); interventions were provided face to face or via telephone	*n*=186 (110) *From Gary et al., 2003:*

Gary et al., 2003 (29)		Ø age: 58.8 ±8.8 years[1] 76.5% women[a] Ø DM duration: 9.2 ±8.0 years[1] Ø A1C at baseline: 8.6% (71 mmol/mol) ±2.0[1] Ø depressive symptom score at baseline: 15.9				and included counseling regarding diabetes self-care practices (diet, exercise, foot care, vision care, SMBG, medication adherence, smoking cessation) and physician reminders regarding preventive health care services; interventions began after randomization and went until the end of the 2-year study.	UC: *n*=34; NCM: *n*=38; CHW: *n*=41; NCM+CHW: *n*=36; at baseline.
Khodneva et al., 2016 (30); additional information taken from Safford et al., 2015 (31)	USA	Adults with diabetes (type not specified), 87.4% African American individuals Ø age: 60.2 ±12.1 years 75.3% women Ø DM duration: 13.3 ±11.9 years Ø A1C at baseline: 7.9% (63 mmol/mol) ±2.0 Ø depressive symptom score at baseline: 6.4 ±5.6	1-year cluster RCT with extended follow-up at 12–21 months after baseline 2 time points: baseline, 12–15 months, up to 177 days after 1-year follow-up	Bayer DCA2000 A_{1c} Hemoglobin Blood Analyzer (using capillary finger stick blood)	PHQ-8 (score range 0–24 = depressive symptom severity)	IG: Peer support intervention provided by trained peer coach; initial 45–60 min phone or in-person meeting, then weekly phone meetings over 2 months, then monthly phone meetings over 8 months; themes were: setting individual self-management goals, coaching on goal achievement, planning for encounter with diabetes care provider. CG: Usual care: 1-hour group diabetes education at enrolment; received personalized diabetes card including A1C and weight data and a 5 min counseling session explaining the results and basic diabetes self-management activities.	IG: *n*=198 (168) CG: *n*=226 (187)
Leyva et al., 2011 (32); additional information taken from	USA	Adults aged 30–80 years with T2DM and A1C ≥7.5% (≥59 mmol/mol) recruited at a large hospital medical center in	Longitudinal secondary analysis using data of a 6-month RCT with four treatment arms	HPLC ion capture method (Tosh Medics Inc., San Francisco, CA) in central laboratory	CES-D (score range 0–60 = depressive symptom severity)	Participants were randomized to receive either diabetes education with motivational interviewing (MI), with or without use of a patient self-management assessment report generated by a web tool, or standard DSME, with or without the summary report from the web tool, i.e., the	*n*=234 (191), thereof 148 with sufficient A1C data for analysis

Welch et al., 2011 (33)		Springfield, MA, thereof 12.0% Latin American people Ø age: 55.4 ±10.1 years 59.2% women Ø DM duration: 8.2 ±6.9 years Ø A1C at baseline: 8.8% (73 mmol/mol) ±1.2 Ø depressive symptom score at baseline: 16.4 ±11.4	2 time points: baseline, 6 months			four groups were: MI alone, MI with report, DSME alone, DSME with report; interventions went over 6 months.	
Malanda et al., 2016 (34)	Netherlands	Adults aged 45–75 years with T2DM and A1C >7.0% (>53 mmol/mol), DM duration ≥1 year, no regular self-monitoring of glucose levels Ø age: 61.6 ±7.8 years 33.7% women Ø DM duration: 6.7 years Ø A1C at baseline: 7.5% (59 mmol/mol) ±0.7 Ø depressive symptom	12-month RCT with three treatment arms 3 time points: baseline, 4 months, 12 months	Not reported	PHQ-9 (score range 0–27 = depressive symptom severity)	IG1: Self-monitoring of blood glucose (SMBG); participants were asked to perform 3 pre- and 3 postprandial SMBG checks a day on two separate days each week* IG2: Self-monitoring of urine glucose (SMUG); participants were asked to perform urine tests after dinner on two separate days each week* *Participants in IG1/2 were allowed to adjust their self-monitoring frequency from 8 weeks after baseline. CG: Usual care, that is, no regular self-monitoring of	IG1: *n*=60 (53) IG2: *n*=59 (43) CG: *n*=62 (55)

		score at baseline: 3.6 ±4.4				glucose.	
Presley et al., 2020 (35)	USA	African American adults aged ≥19 years with T2DM and A1C ≥7.5% (≥59 mmol/mol) from Jefferson County, Alabama Ø age: 54.9 ±8.3 years 71.1% women Ø DM duration: 8.7 ±7.6 years Ø A1C at baseline: 10.0% (86 mmol/mol) ±1.7 Ø depressive symptom score at baseline: 10.0 ±6.1	6-month RCT with two treatment arms 2 time points: baseline, 6 months	Point-of-care testing using Bayer Now+ testing kits	CES-D 10-item short form (score range 0–30 = depressive symptom severity)	IG: Community-based diabetes self-management education plus 6 months of mHealth-enhanced peer support consisting of 12 weekly phone calls and then 3 monthly phone calls from community health workers who used a novel web application to communicate with participants' healthcare teams. CG: Community-based diabetes self-management education only.	IG: *n*=70 (62) CG: *n*=50 (35)
Rosland et al., 2015 (36); additional information taken from Spencer et al., 2011 (37)	USA	African American (48.1%) or Latin American (51.9%) adults with T2DM living in eastside or southwest Detroit Ø age: 53.2 ±11.6 years 71.3% women Ø DM duration: 8.8 ±8.1	6-month RCT with two treatment arms 2 time points: baseline, 6 months	A1C analysis in a central laboratory	PHQ-9 (score range 0–27 = depressive symptom severity)	IG: 6-month DSME and support intervention including community health worker-delivered group diabetes management classes, home visits to help set and follow up on diabetes management goals, and accompaniment to physician appointments to model activated participation. CG: Participants were contacted once per month to update contact information.	IG: *n*=89 (56) CG: *n*=94 (52)

		years Ø A1C at baseline: 8.7% (72 mmol/mol) ±2.2 Ø depressive symptom score at baseline: 5.0 ±5.0					
Van der Ven et al., 2005 (38)	Netherlands	Adult out-patients with T1DM and A1C ≥8.0% (≥64 mmol/mol) on two consecutive occasions prior to the study, DM duration >1 year, multiple daily insulin-injections or CSII Ø age: 37.8 ±10.6 (range 20–60) years 59.1% women Ø DM duration: 18.0 ±10.4 (range 1–50) years Ø A1C at baseline: 8.9% (74 mmol/mol) ±1.2 [range 6.7–12.9% (50–118 mmol/mol] Ø depressive symptom score at baseline: 16.0 ±11.0 (range 0–48)	3-month RCT with two treatment arms 2 time points: baseline, 3 months	A1C was assayed at central laboratory (HPLC, BioRad, Veenendaal, NL)	CES-D (score range 0–60 = depressive symptom severity)	IG: Six weekly 2-h CBT group sessions with main components cognitive restructuring and individual goal-setting; sessions followed the format of review of homework, introduction of session theme, exercise and group discussion; themes were: individual goal-setting, role of cognition and emotions in diabetes self-care, stress, worrying about complications, diabetes and interpersonal relationships, diabetes management as teamwork. CG: Six weekly 2-h sessions blood glucose awareness training aimed at preventing/correcting extreme glucose fluctuations.	IG: *n*=45 (32) CG: *n*=43 (36)

Wang et al., 2014 (39); additional information taken from Rosal et al., 2011 (40)	USA	Latin American adults aged ≥18 years with T2DM and A1C ≥7.5% (≥59 mmol/mol) Ø age: 16.3% 18–44 years, 29.8% 45–54 years, 32.9% 55–64 years, 21.0% ≥65 years 76.6% women Ø DM duration: not reported Ø A1C at baseline: 8.98% (75 mmol/mol) ±1.9 Ø depressive symptom score at baseline: 21.6 ±12.4	12-month RCT with two treatment arms 3 time points: baseline, 4 months, 12 months	A1C was estimated from fasting blood samples analyzed in the same laboratory	CES-D (score range 0–60 = depressive symptom severity)	IG: 12-month culturally and literacy-tailored group-based intervention in Spanish, 12 weekly sessions, followed by eight monthly sessions targeting diabetes knowledge, attitudes/self-efficacy, self-management behaviors, glucose values logs, attitudinal change and desired behaviors, use of bingo games, making traditional food healthier. CG: Participants in the usual care condition received no intervention.	IG: *n*=124 (109) CG: *n*=128 (107)

513 CBT, cognitive behavioral therapy; CES-D, Center for Epidemiologic Studies Depression; CG, control group; CGM, continuous glucose monitoring;
514 CVD, cardiovascular disease; DM, diabetes mellitus; DSME, Diabetes self-management education; HADS, Hospital Anxiety and Depression; A1C,
515 glycated hemoglobin A1c; HPLC, high-performance liquid chromatography; IG, intervention group; PHQ, Patient Health Questionnaire; RCT,
516 randomized controlled trial; SMBG, self-monitoring of blood glucose; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

517 [a] Based on n=149 participants as reported in Gary et al. (2003).

518 **Table 2. Principal findings of the reviewed studies.**

Authors (year)	A1C change (baseline to FU) in %-points (mmol/mol)	Depressive symptom change (baseline to FU)	Association between changes	Results summarized
Amsberg et al., 2009 (22)	24-week FU: IG: –1.0 [from 8.5 (69) ±0.9 to 7.5 (59)] CG: –0.06 [from 8.5 (69) ±0.8 to 8.4 (68)] Adjusted follow-up between-group difference: –0.94 (95% CI –1.36 to –0.51), $p<0.001$ 48-week FU: IG: –0.78 [from 8.5 (69) ±0.9 to 7.7 (61)] CG: –0.29 [from 8.5 (69) ±0.8 to 8.21 (66)] Adjusted follow-up between-group difference: –0.49 (95% CI –0.87 to –0.11), $p=0.012$	24-week FU: IG: –0.74 (from 4.5 ±3.7 to 3.76) CG: +0.28 (from 4.3 ±4.2 to 4.58) Adjusted between follow-up group difference: –0.81 (95% CI –2.25 to 0.62), $p=0.262$ 48-week FU: IG: –0.99 (from 4.5 ±3.7 to 3.51) CG: +0.79 (from 4.3 ±4.2 to 5.09) Adjusted between follow-up group difference: –1.59 (95% CI –2.98 to –0.18), $p=0.027$	Not assessed	Greater A1C reduction in the IG accompanied by slightly greater depressive symptom reduction in the IG at 48-week FU; relation between A1C and depressive symptom changes undetermined.

Anderson et al., 2011 (23); additional information taken from ACCORD Study Group, 2008 (24)	Not reported for the substudy sample. *From ACCORD Study Group:* In the overall ACCORD sample, median A1C changes were: At 1-year FU (*n*=9,542): IG: –1.7 [from 8.1 (65) to 6.7 (50) (IQR 6.2–7.2 (44–55))] CG: –0.6 [from 8.1 (65) to 7.5 (59) (IQR 7.0–8.2 (53–66))] Stable median levels of 6.4 (46) [IQR 6.1–7.0 (43–53)] in the IG and 7.5 (59) [IQR 7.0–8.1 (53–65)] in the CG were maintained throughout the follow-up period including the 4-year FU (*n*=3,450).	IG: –0.9 (95% CI –1.5 to 0.3) from 5.6 (baseline) CG: –1.0 (95% CI –1.7 to 0.4) from 5.2 (baseline) Adjusted between-group difference: *p*=0.441	Not assessed	Small non-significant depressive symptom reductions in both groups; depressive symptom changes similar across groups irrespective of standard versus intensive glycemia management; relation between A1C and depressive symptom changes undetermined.
Bluml et al., 2019 (25)	IG: –1.7 [from 10.4 (90) ±1.7 to 8.7 (72) ±1.9] CG: –1.4 [from 10.1 (87) ±1.7 to 8.7 (72) ±1.8] Between-group difference of change (group x time	IG: 0.0 (from 1.4 ±1.9 to 1.4 ±1.9) CG: –0.6 (from 1.9 ±1.9 to 1.3 ±1.7) Between-group difference of changes (group x time	Not assessed	Significantly greater depressive symptom reduction in the CG (i.e., CG improved only), while both groups improved in A1C similarly (i.e., no significant difference between groups); relation between A1C and depressive symptom changes undetermined.

	interaction): p=0.207	interaction): p=0.031		
Fisher et al., 2011 (26); additional information taken from Polonsky et al., 2011 (27)	*From Polonsky et al.:* IG: –1.2 [from 8.9 (74) ±1.2 to 7.7 (61)] CG: –0.9 [from 8.9 (74) ±1.2 to 8.0 (64)] Between-group difference of change: –0.3, p=0.04	IG: –1.66 (from 6.54 ±0.38 to 4.54 ±0.33), p<0.0001 CG: –1.14 (from 5.85 ±0.36 to 5.05 ±0.35), p=0.0011 Between-group difference of changes: p=0.28 <u>For subgroup with baseline PHQ-8 ≥10:</u> IG: –5.77 (from 14.53 ±0.45 to 8.76 ±0.80) CG: –3.07 (from 14.26 ±0.51 to 11.19 ±0.90) Between-group difference of changes: p<0.04	Adding A1C change as a control variable to the analysis of depressive symptom change by group indicated no differences in findings, i.e., significant between group differences were maintained for depressive symptoms.	Greater A1C reduction in the IG; significant depressive symptom reduction in both groups; greater reduction in people with higher baseline depressive symptoms, in this subsample a greater depressive symptom reduction in the treatment group; effect on depressive symptoms independent of A1C reduction.
Gary et al., 2005 (28); additional information taken from Gary et al., 2003 (29)	*From Gary et al., 2003:* 1) UC: 0.0=reference [from 8.5 (69) ±2.0] 2) NCM: –0.31 ±0.49	–3.3 (from 15.9 to 12.6), p<0.05, for total sample (between-group differences in depressive symptom change not reported)	Association between changes in depressive symptoms and A1C: p=0.910	A1C and depressive symptoms improved across groups without significant differences between groups; significant depressive symptom reduction for total sample; change in depressive symptoms score was not associated with change in A1C.

	compared to UC [from 8.8 (73) ±2.2], within group change from baseline: n.s. (p>0.05) 3) CHW: –0.30 ±0.48 compared to UC [from 8.4 (68) ±2.0], within group change from baseline: n.s. (p>0.05) 4) NCM+CHW: –0.80 ±0.52 compared to UC [from 8.6 (71) ±1.9], within group change from baseline: p<0.05 Adjusted between group differences of changes: n.s. (all p>0.05)			
Khodneva et al., 2016 (30); additional information taken from Safford et al., 2015 (31)	*From Safford et al.:* IG: –0.004 ±1.5 (from 8.0 (64) ±2.1), n.s. CG: –0.070 ±1.3 (from 7.9 (63) ±1.9), n.s. Adjusted follow-up between-group difference: p=0.68	Changes in depressive symptom scores differed between groups over time (p=0.03) in a non-linear way, i.e., at 12 to 15 months of follow-up, control participants showed greater depressive symptom reduction, after 15 months, intervention participants showed greater reduction.	Not assessed	Ambiguous changes in depressive symptoms between groups and no significant changes in A1C; relation between A1C and depressive symptom changes undetermined.
Leyva et al., 2011 (32); additional information taken from	For Latin American people (n=14): –0.63 ±1.44 [from 9.1 (76)], n.s.	For Latin American people (n=14): –6.9 ±9.7 (from 22.7), p<0.05	No sign. association between change in depressive symptoms and change in A1C	Significant overall A1C reduction; significant depressive symptom reduction in Latin American group only; no significant association between change in A1C

Welch et al., 2011 (33)	For non-Latin American people (n=134): –0.59 ±1.44 [from 8.8 (73)], p<0.01 *From Welch et al.:* Total sample change: –0.58 ±1.33 (p<0.01) Multiple regression: Groups receiving MI had a significantly lower mean change in A1C than those not receiving MI (β=0.41, SE=0.19, p=0.037)	For non-Latin American people (n=134): –1.2 ±8.7 (from 15.5), n.s. Between-group difference of changes: p=0.04	in either group (non-Latin Americans: β=0.024, SE=0.015, p=0.12; Latin Americans: β=0.028, SE=0.051, p=0.59)	and change in depressive symptoms.
Malanda et al., 2016 (34)	IG1: –0.1 ±0.9 (from 7.5 (59) ±0.6 to 7.4 (57) ±0.9) IG2: –0.4 ±1.2 (from 7.7 (61) ±1.0 to 7.3 (56) ±0.8) CG: –0.2 ±0.6 (from 7.4 (57) ±0.6 to 7.2 (55) ±0.7) Adjusted between-group differences of changes: IG1 vs CG: –0.0 (95% CI –0.2 to 0.1), n.s.	IG1: –0.4 ±2.8 (from 4.5 ±4.4 to 4.1 ±4.6) IG2: +0.5 ±2.0 (from 2.6 ±3.4 to 3.1 ±3.7) CG: –0.5 ±3.2 (from 3.6 ±5.1 to 3.1 ±4.7) Adjusted between-group differences of changes: IG1 vs CG: –0.2 (95% CI –0.7 to 0.4), n.s.	Not assessed	Small overall A1C reduction; at the same time no relevant changes in depressive symptoms; relation between A1C and depressive symptom changes undetermined.

	IG2 vs CG: –0.1 (95% CI –0.2 to 0.3), n.s.	IG2 vs CG: –0.8 (95% CI –1.9 to 0.3), n.s.		
	IG1 vs. IG2: –0.2 (95% CI –0.5 to 0.1), n.s.	IG1 vs. IG2: +0.6 (95% CI –0.4 to 1.7), n.s.		
Presley et al., 2020 (35)	IG: –0.5 [from 10.1 (87) ±1.7 to 9.6 (81) ±1.9]	IG: +0.3 (from 10.2 ±6.2 to 10.5 ±6.3), n.s.	Not assessed	A1C improved in both groups similarly, while depressive symptoms did not change (or tended to increase); relation between A1C and depressive symptom changes undetermined.
	CG: –0.7 [from 9.8 (84) ±1.7 to 9.1 (76) ±1.9]	CG: +1.1 (from 9.7 ±5.8 to 10.8 ±6.8)		
	Sign. of time effect (across groups): p=0.004	Sign. of time effect (across groups): p=0.21		
	Between-group difference of changes (group x time interaction): p=0.75	Between-group difference of changes (group x time interaction): p=0.48		
Rosland et al., 2015 (36); additional information taken from Spencer et al., 2011 (37)	IG: –1.0 ±1.9 [from 8.7 (72) ±2.3 to 7.7 (61) ±1.7], p<0.01	IG: –0.4 ±5.3 (from 5.2 ±6.0 to 4.6 ±4.5), p=0.58	Not assessed	Significant A1C reduction in the IG, while no change in the CG; no significant changes of depressive symptoms in either group; relation between A1C and depressive symptom changes undetermined.
	CG: 0.0 ±1.5 [from 8.6 (71) ±2.1 to 8.6 (71) ±2.4], p=0.85	CG: +0.7 ±4.8 (from 4.8 ±3.8 to 5.2 ±4.9), p=0.29		
	Between-group difference of changes: p<0.01 (*from Spencer et al.*)			

Van der Ven et al., 2005 (38)	IG: –0.2 [from 8.9 (74) ±1.14 to 8.7 (72) ±1.24], n.s. CG: +0.3 [from 8.9 (74) ±0.92 to 9.2 (77) ±1.10), n.s. Sign. of change for total sample: p=0.36 Between-group difference of changes (linear regression): B=−0.45 (95% CI −0.86 to −0.04), p=0.03	IG: –3.4 (from 16.9 ±12.77 to 13.5 ±12.62)[a] CG: –2.3 (from 15.5 ±10.05 to 13.2 ±7.38)[a] Sign. of change for total sample: p<0.001 Between-group difference of changes (linear regression): B=−0.54 (95% CI −3.95 to 2.88), p=0.76	Not assessed	Significantly different A1C changes between groups with IG tentatively better and CG tentatively worse at follow-up (cave! effect sizes very small); at the same time both groups showed small improvements in depressive symptoms; relation between A1C and depressive symptom changes undetermined.
Wang et al., 2014 (39); additional information taken from Rosal et al., 2011 (40)	*From Rosal et al.:* <u>4-month FU:</u> IG: –0.88 (95% CI –1.15 to –0.60) from 9.1 (76) ±2.0 CG: –0.35 (95% CI –0.62 to 0.07) from 8.9 (74) ±1.8 Between-group difference of changes: –0.53 (–0.92 to –0.14), p>0.008 <u>12-month FU:</u>	<u>4-month FU:</u> IG: –3.3 (from 20.8 ±12.2 to 17.5 ±13.0) CG: –0.5 (from 22.3 ±15.5 to 21.8 ±12.4) Between-group difference of changes (group x time effect): β=−2.63, p=0.04 Group means differed at 4 months with p=0.011	Linear mixed regression (IG only): No sign. association between changes in A1C and depressive symptoms (p>0.05)	A1C improved in both groups with significantly greater improvement in the IG at 4-month FU; significant depressive symptom reduction only in the IG; no evidence of an association between changes in A1C and depressive symptoms.

IG: –0.46 (95% CI –0.77 to –0.13) from 9.11 (76) ±2.0 CG: –0.20 (95% CI –0.53 to 0.13) from 8.9 (74) ±1.8 Between-group difference of changes: –0.25 (95% CI –0.72 to 0.22), p>0.293	12-month FU: IG: –2.3 (from 20.8 ±12.2 to 18.5 ±13.0) CG: +0.3 (from 22.3 ±15.5 to 22.6 ±13.4) Between-group difference of changes (group x time effect): β=−2.05, p=0.13 Group means differed at 4 months with p=0.021	

519 CG, control group; CI, confidence interval; CVD, cardiovascular disease; FU, follow-up; A1C, glycated hemoglobin A1c; IG, intervention group;
520 n.s., not significant.

521 [a] p not reported.

522

Figure legends

Figure 1. PRISMA flow chart showing study selection

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Notes: Included were: Randomized controlled trials; evaluating an intervention to improve A1C; including adult participants (≥18 years) with type 1 or type 2 diabetes; providing data on depression change; reported in English, Dutch, French, German or Spanish. Excluded were: Studies with a sample size <50; using combined child-adult samples; regarding individuals with impaired glucose tolerance, borderline diabetes, or gestational diabetes; with specific interventions for reducing depressive symptoms

Figure 2. Changes in A1C and depressive symptoms by group in the reviewed studies

This figure gives an overview of all studies included in the systematic review, showing changes in A1C and depression side by side. Note that the first studies, with high A1C levels at baseline, show some change in depression scores, while later studies, with lower A1C levels do less so.

CES-D, Center for Epidemiologic Studies Depression; CG, control group; CI, confidence interval; FU, follow-up; HADS, Hospital Anxiety and Depression; A1C, glycated hemoglobin A_{1c}; IG, intervention group; PHQ, Patient Health Questionnaire

Notes: A1C values are given in % only for ease of presentation. (22) used HADS-7. (25) used PHQ-2. (26,30) used PHQ-8. (23,34,36) used PHQ-9. (35) used CES-D-10. (28,32,38,39) used CES-D. CES-D score range 0–60; CES-D-10 score range 0–30; HADS depression score range 0–21; PHQ-2 score range 0–6; PHQ-8 score range 0–24; PHQ-9 score range 0–27. For secondary studies, additional information was taken from primary RCT reports: For (23) from (24); for (26) from (27); for (28) from (29); for (30) from (31); for (32) from (33); for (36) from (37); for (39) from (40)

546 *Additional explanations:* For (23): changes in A1C were not reported (however, results for the full ACCORD
547 sample suggest greater A1C reduction in the IG at 4-year FU (24)). For (28): between-group differences in
548 depressive symptom changes were not reported. For (30): changes in depressive symptoms differed between
549 groups in a non-linear way, i.e., at 12-to-15-month FU, the CG showed a greater reduction, while at 15+ month
550 FU the IG showed a greater reduction