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Reginaldo Tavares Franquez

INTERVENÇÕES PARA TRATAR TRANSTORNOS PSICOLÓGICOS EM PESSOAS COM DIABETES *MELLITUS*: UMA ABORDAGEM BASEADA EM ESTUDOS SECUNDÁRIOS

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Tese apresentada à Banca Examinadora do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Doutor em Ciências Farmacêuticas.

Orientadora: Profa. Dra. Cristiane de Cássia Bergamaschi Motta

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Aprovado em:

BANCA EXAMINADORA

Profa. Dra. Cristiane de Cássia Bergamaschi
Universidade de Sorocaba

Profa. Dra. Edilma Maria de Albuquerque Vasconcelos
Universidade de Sorocaba

Profa. Dra. Fabiane Raquel Motter
Hospital Sírio-Libanês

Profa. Dra. Jessica Cumpian Silva
Universidade de Sorocaba

Prof. Dr. Marcus Tolentino Silva
Universidade de Sorocaba

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“A educação é a arma mais poderosa que você pode usar para mudar o mundo.”

Nelson Mandela

RESUMO

Depressão e ansiedade podem ocorrer em pessoas com diabetes *mellitus* de todas as idades. Estas doenças são problemas comuns de saúde pública ocasionando impacto negativo significativo no funcionamento físico, psicológico, social e ocupacional dos indivíduos. Este estudo sumarizou e avaliou a efetividade e a segurança de intervenções para tratar transtornos psicológicos em pessoas com diabetes *mellitus,* descritos em dois estudos: 1) revisão de revisões sistemáticas que sumarizou as intervenções para tratar transtornos psicológicos nessa população; e 2) revisões sistemáticas de ensaios clínicos randomizados que avaliou a efetividade de intervenções de saúde eletrônica (e-Saúde). O artigo 1 “Intervenções para depressão e ansiedade em pessoas com diabetes *mellitus*” buscou informações nas bases de dados: *Cochrane Library*, *Medical Literature Analysis and Retrieval System Online* (MEDLINE), *Excerpta Medica dataBASE* (EMBASE), *Web of Science* e Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS), sem restrição de tempo e idioma, até julho de 2021. Os desfechos primários aferidos incluíram melhora na remissão da depressão, ansiedade e do sofrimento emocional relacionado ao diabetes e melhora na qualidade de vida. Os revisores, aos pares e de forma independente, selecionaram as revisões, extraíram seus dados e avaliaram sua qualidade metodológica. Foi realizada uma síntese narrativa dos achados. Incluíram-se 13 revisões sistemáticas (28.307 participantes) que apresentaram ao menos uma falha metodológica importante. Terapia Cognitiva Comportamental melhorou os desfechos de depressão, controle glicêmico (n= 5 revisões) e ansiedade (n= 1), em adultos e idosos; cuidados colaborativos (n= 2) e educação em saúde (n= 1) melhoraram depressão e valores glicêmicos, na população de adultos; e tratamento farmacológico (n= 3) melhorou desfechos de depressão. Em geral, as intervenções mostraram-se efetivas, entretanto, a qualidade da evidência foi baixa a moderada, para a maioria dos desfechos avaliados. O artigo 2 “Tecnologias de e-Saúde para o tratamento da depressão, ansiedade e sofrimento emocional em pessoas com diabetes *mellitus*” buscou informação nas bases de dados: *Cochrane Library*, MEDLINE, EMBASE, *Web of Science* e LILACS, até janeiro de 2023. Os desfechos primários incluíram melhora e/ou remissão da depressão, sintomas depressivos e/ou ansiedade, remissão do sofrimento emocional relacionado ao diabetes e melhoria da qualidade de vida. Os revisores, aos pares e de forma independente, selecionaram os

estudos e extraíram seus dados. Metanálises foram conduzidas e a qualidade da evidência foi avaliada pela abordagem *Grading of Recommendations Assessment, Development and Evaluation* (GRADE). Incluíram-se 10 ensaios clínicos randomizados (2.209 participantes) que em geral, apresentaram alta qualidade metodológica. A maior parte das tecnologias e-Saúde parecem ser promissoras para tratar os transtornos psicológicos. De acordo com as metanálises, observou-se melhora da depressão com as intervenções Autoajuda Guiada pela Internet ou Terapia Cognitiva Comportamental; da ansiedade com a intervenção Autoajuda Guiada ou Terapia Cognitiva Comportamental específica para diabetes; e do sofrimento emocional com as intervenções autoajuda guiada pela Internet, intervenção de TCC específica para diabetes, MyCompass ou resultados em saúde por meio do empoderamento do paciente. A qualidade da evidência variou de muito baixa a moderada. De acordo com as limitações da qualidade da evidência reportadas pelas revisões sistemáticas; e divergências observadas nos ensaios clínicos randomizados quanto as intervenções, população, tempo de acompanhamento e desfechos; tais achados precisam ser confirmados. Tais evidências auxiliarão pacientes e seus cuidadores e orientarão profissionais de saúde na escolha das intervenções para tratar transtornos psicológicos devido ao diabetes.

Palavras-chaves: ansiedade; depressão; diabetes *mellitus*; efetividade; intervenções farmacológicas. intervenções não farmacológicas; segurança; sofrimento emocional específico do diabetes.

ABSTRACT

Depression and anxiety can occur in people with diabetes mellitus of all ages. These diseases are common public health problems causing a significant negative impact on the physical, psychological, social and occupational functioning of individuals. This study summarized and evaluated the effectiveness and safety of interventions to treat psychological disorders in people with diabetes mellitus, described in two studies: 1) review of systematic reviews that summarized interventions to treat psychological disorders in this population; and 2) systematic reviews of randomized clinical trials that evaluated the effectiveness of electronic health (e-Health) interventions. Article 1 “Interventions for depression and anxiety in people with diabetes mellitus” searched for information in the following databases: Cochrane Library, Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Web of Science and Latin American Literature and the Caribbean in Health Sciences (LILACS), without restriction of time and language, until July 2021. The primary outcomes measured included improvement in the remission of depression, anxiety and emotional distress related to diabetes and improvement in quality of life. The reviewers, in pairs and independently, selected the reviews, extracted their data and assessed their methodological quality. A narrative synthesis of the findings was carried out. Thirteen systematic reviews (28,307 participants) that presented at least one important methodological flaw were included. Cognitive Behavioral Therapy improved depression, glycemic control (n=5 reviews) and anxiety (n=1) outcomes in adults and older adults; collaborative care (n= 2) and health education (n= 1) improved depression and glycemic values in the adult population; and pharmacological treatment (n=3) improved depression outcomes. In general, the interventions proved to be effective, however, the quality of evidence was low to moderate for most of the evaluated outcomes. Article 2 “E-Health Technologies for the treatment of depression, anxiety and emotional distress in people with diabetes mellitus” searched for information in the databases: Cochrane Library, MEDLINE, EMBASE, Web of Science and LILACS, until January 2023. Primary outcomes included improvement and/or remission of depression, depressive symptoms and/or anxiety, remission of diabetes-related emotional distress, and improvement in quality of life. The reviewers, in pairs and independently, selected the studies and extracted their data. Meta-analyses were conducted, and the quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We included 10 randomized clinical trials (2,209 participants) that, in general, had high methodological quality. Most eHealth technologies appear to be promising for treating psychological disorders. According to the meta-analyses, improvement in depression was observed with the Internet-Guided Self-Help or Cognitive Behavioral Therapy interventions; in anxiety with the Guided Self-Help intervention or specific Cognitive Behavioral Therapy for diabetes; and in emotional distress with the use of Internet-Guided Self-Help, Diabetes-Specific CBT, MyCompass, Internet-Guided Self-Help or Healthy Outcomes through Patient Empowerment. The quality of evidence ranged from very low to moderate. However, according to the limitations of the quality of

evidence reported by systematic reviews; and differences observed in randomized clinical trials regarding interventions, population, follow-up time and outcomes; such findings need to be confirmed. Such evidence will help patients and their caregivers and guide health professionals in choosing interventions to treat psychological disorders due to diabetes mellitus.

Keywords: anxiety; depression; diabetes mellitus; effectiveness; pharmacological interventions; non-pharmacological interventions; safety; emotional distress specific to diabetes.

LISTA DE QUADROS

LISTA DE FIGURAS

Artigo 1

Artigo 2

LISTA DE TABELAS

Artigo 1

Artigo 2

LISTA DE ABREVIATURAS E SIGLAS

AMSTAR-2	*Assessing the Methodological Quality of Systematic Reviews 2*
BDI	*Beck Depression Inventory*
BAT	*Behavior Activation Treatment*
CFF	Conselho Federal de Farmácia
CES-D	*Center for Epidemiologic Studies Depression Scale*
CBT	*Cognitive Behavioral Therapy*
coach-PCP	*Primary Care Provider coach*
DDS	*Diabetes Distress Scale*
ECR	Ensaio Clínico Randomizado
e-Health	*Electronic health*
e-Saúde	Saúde Eletrônica
EMBASE	*Excerpta Medica dataBASE*
GFAF	*Gardenia Fructus antidepressant formula*
GAD-7	*Generalized Anxiety Disorder Scale*
GRADE	*Grading of Recommendations Assessment, Development, and Evaluation*
HbA1c	Hemoglobina Glicada (*Haemoglobin A1c*)
HADS	*Hospital Anxiety and depression Scale*
HOPE	*Healthy outcomes through Patient Empowerment*
IMC	Índice de Massa Corporal
ISRD	Inibidores Específicos de Recaptação de Serotonina
ISRSN	Inibidores Seletivo de Recaptação de Serotonina e Noradrenalina
IDDM	*Insulin-Dependent Diabetes mellitus*
iCBT	*Internet-Based Cognitive Behavioral Therapy*
K-10	*Kessler 10 item psychological distress scale*
LILACS	Literatura Latino Americana e do Caribe em Ciências da Saúde
MEDLINE	*Medical Literature Analysis and Retrieval System Online*
MPI	*Minimal Psychological Intervention*
m-Health	*Mobile health*
NHMCR	*National Health and Medical Research Council*
NIDDM	*Non-insulin-dependent diabetes mellitus*
NR	*Not Reported*
OMS	Organização Mundial da Saúde
PAID	*Problem Areas in Diabetes*
PHQ-15	*Patient Health Questionnaire-15*
PHQ-9	*Patient Health Questionnaire-9*
PNS	Pesquisa Nacional De Saúde
PICOT	*Population, Intervention, Comparison, Outcome, Type of study*
PCP	*Primary Care Provider*
PI	*Psychological interventions*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*
RCT	*Randomized Clinical Trial*
RS	Revisão Sistemática
SD	*Standard Deviation*
SF-12 MCS	*Short Form 12 Item Mental Health Subscale*
SF-12 PCS	*Short Form 12 Item Physical Health subscale*

SSRI	*Specific Serotonin Reuptake Inhibitors*
SMD	*Standard Mean Difference*
SMS	*Short Messaging Service*
SR	*Systematic Review*
T1DM	*Type 1 diabetes mellitus*
T2DM	*Type 2 diabetes mellitus*
WHO CIDI-auto	*World Health Organization Composite International Diagnostic*

SUMÁRIO

1 APRESENTAÇÃO

Os transtornos psicológicos como depressão e ansiedade podem acometer pessoas com diabetes *mellitus* de todas as idades. Uma vez que diabetes e depressão são problemas comuns de saúde pública no mundo que crescem e ocasionam impacto negativo significativo no funcionamento físico, psicológico, social e ocupacional dos indivíduos; verificou-se a necessidade de avaliar e sumarizar a evidência científica a respeito das intervenções para tratamento de transtornos psicológicos que acometem pessoas com diabetes *mellitus* tipo 1 e 2.

Desta forma, esta tese avaliou a efetividade e a segurança de intervenções para tratar depressão, sintomas depressivos, ansiedade e/ou sofrimento emocional nessa população, por meio de estudos secundários.

O diabetes *mellitus* é um problema de saúde comum e crescente. Independentemente da idade, os transtornos psicológicos podem acometer pessoas com diabetes, mas os indivíduos com diabetes *mellitus* tipo 1 parecem ser mais susceptíveis quando comparados a aqueles com diabetes *mellitus* tipo 2. De acordo com a literatura, a presença de depressão e ansiedade nessa população impacta negativamente no controle glicêmico da doença e no comportamento de autocuidado.

A depressão é duas vezes mais comum em pessoas com diabetes *mellitus* tipo 1 ou tipo 2 comparado à população sem a doença. A presença destas doenças associadas resulta em inúmeras complicações de curto e longo prazo e aumento da mortalidade em comparação com as pessoas com apenas depressão ou diabetes. Além disso, pessoas com diabetes *mellitus* tem cerca de 1,5 vezes mais chances de apresentar sintomas de ansiedade comparado à população sem a doença. O sofrimento emocional relacionado ao diabetes ocorre por preocupações no controle da doença e das complicações que ela pode causar.

Entre as intervenções encontradas na literatura destacam-se como principais as psicológicas, farmacológicas, psicossociais e intervenções no estilo de vida, realizadas por meio presencial ou eletrônico (Saúde eletrônica ou e-Saúde).

Para maior esclarecimento e organização, este trabalho foi estruturado em: Referencial teórico, Objetivos, Resultados e Considerações finais.

Optou-se por escrever a tese em um dos formatos adotado pelo Programa de Pós-graduação em Ciências Farmacêuticas da Universidade de Sorocaba que consiste em descrever os seus produtos no item “Resultados”. Desta forma, este item

foi estruturado com duas produções científicas e uma produção técnica (APÊNDICE A).

O referencial teórico aborda os seguintes temas: i) transtornos psicológicos que acometem pessoas com diabetes *mellitus*; ii) considerações gerais nos cuidados de pessoas com diabetes *mellitus* e transtornos psicológicos; iii) intervenções para transtornos psicológicos em pessoas com diabetes *mellitus*; iv) tecnologias digitais; v) o uso de tecnologias digitais em pessoas com diabetes *mellitus* e transtornos psicológicos.

O tópico “Objetivos” faz referência aos objetivos “primários” e “secundários” traçados por essa revisão.

O tópico “Resultados” apresenta dois artigos científicos e um artigo de revisão publicado em revista técnica, descritos a seguir:

Artigo científico 1 *“Interventions for depression and anxiety among people with diabetes mellitus: review of systematic reviews”.*

Artigo científico 2 *“E-Health technologies for treatment of depression, anxiety and emotional distress in people with diabetes mellitus: systematic review”*.

Artigo de revisão “Depressão em pacientes com diabetes *mellitus*: contexto, diagnóstico e tratamento”, publicado no periódico “Boletim Farmacoterapêutica” do Conselho Federal de Farmácia.

As referências dos artigos seguem o formato adotado pelas revistas e as demais referências seguiram o formato Associação Brasileira de Normas Técnicas (ABNT). A sequência numérica das tabelas, figuras e referências, foi reiniciada em cada artigo.

Por fim, o item “Considerações finais” discorre sobre as principais conclusões dos achados dessa tese.

Faz-se importante contextualizar que a presente tese ocorreu em meio à pandemia do SARS-CoV-2. A restrição as atividades presenciais na universidade, influenciou a realização das atividades de pesquisa. Apesar das discussões terem ocorrido por meio de ferramentas virtuais, houve mudanças na rotina laboral e familiar que também interferiram nas atividades. Entretanto, mesmo com alterações de cronograma e atividades, a tese foi concluída dentro do prazo exigido.

2 REFERENCIAL TEÓRICO

2.1 Transtornos psicológicos que acometem pessoas com diabetes *mellitus*

A Federação Internacional de Diabetes (do inglês, *International Diabetes Federation*), em 2017, estimou que 8,8% da população mundial entre 20 e 79 anos de idade (424,9 milhões de pessoas) viviam com diabetes *mellitus*. Se as tendências atuais persistirem, o número de pessoas com a doença foi projetado para ser superior a 628,6 milhões, em 2045 (SOCIEDADE BRASILEIRA DE DIABETES, 2020).

Tanto a frequência de novos casos (incidência) como a de casos existentes (prevalência) são informações importantes para o conhecimento da carga que o diabetes representa para os sistemas de saúde. O Brasil está em quarto lugar entre os 10 países com o maior número de indivíduos com diabetes no mundo (SOCIEDADE BRASILEIRA DE DIABETES, 2020).

Dados da Pesquisa Nacional de Saúde (PNS) coletados em 2013 e 2015, demonstraram uma prevalência de 6,0% e 6,6%, respectivamente, em adultos brasileiros com diabetes *mellitus.* A prevalência foi maior no sexo feminino, naqueles com idade superior a 30 anos e em populações com baixa escolaridade, excesso de peso e obesidade (BRIGANTI *et al.*, 2019; MALTA *et al.*, 2019).

O diabetes *mellitus* tipo 1 está associado a uma maior prevalência de transtornos psicológicos comparado ao diabetes *mellitus* tipo 2 (KUNISS *et al.*, 2017; REWERS, 2016). Também, a depressão parece ser duas vezes mais comum em pessoas com diabetes *mellitus* tipo 1 ou tipo 2, comparado à população sem a doença (MOULTON; PICKUP; ISMAIL, 2015). Existe uma ligação biológica entre diabetes *mellitus* e depressão na qual acredita-se que alterações metabólicas e inflamatórias compensatórias à destruição autoimune de células beta sejam agravadas pela depressão (KONGKAEW *et al.*, 2014).

Revisão sistemática com meta-análise de estudos de coorte investigou a relação entre ter depressão como consequência do diabetes *mellitus*. Foram incluídos 16 estudos e observou-se que pessoas com diabetes apresentaram maior incidência cumulativa de depressão em comparação com pessoas sem a doença, demonstrou-se aumento de 1,3 vezes (risco relativo: 1,27; intervalo de confiança 95%: 1,2–1,4) no risco de ter depressão em adultos com diabetes *mellitus* (HASAN *et al*., 2014).

Revisão sistemática com meta-análise de ensaios clínicos investigou a associação entre diabetes *mellitus* tipo 1 e a frequência de sintomas de depressão e

ansiedade e o impacto destas condições no manejo do diabetes e no controle glicêmico. Foram incluídos 14 estudos (n=3,391) que observaram prevalência de 30,0% (intervalo de confiança 95%: 16,3 a 43,7%) de sintomas depressivos nesta população. Sintomas de ansiedade foram relatados em torno de 32% dos pacientes, o que aponta um impacto negativo no controle glicêmico (BUCHBERGER *et al*., 2016).

Vários fatores ambientais podem ativar as mesmas vias que levam ao diabetes *mellitus* e depressão. O estresse crônico ativo, o eixo hipotálamo-hipófise-adrenal e o sistema nervoso simpático são responsáveis pela elevação da síntese do cortisol, adrenalina e noradrenalina. A hipercortisolemia crônica e a ativação prolongada do sistema nervoso simpático promovem resistência à insulina e diabetes *mellitus* tipo 2, bem como a perturbação da neurogênese no hipocampo, região envolvida tanto na depressão quanto neste tipo de diabetes. Além disso, o estresse crônico gera produção elevada de citocinas inflamatórias que interagem com as células β pancreáticas, induzindo resistência à insulina, e o desenvolvimento do diabetes *mellitus* tipo 2 (BĂDESCU *et al*., 2016).

Distúrbios psicológicos ocorrem em pacientes com diabetes em todas as idades (PALLAYOVA; TAHERI, 2014). Depressão, ansiedade, sofrimento emocional relacionado ao diabetes e distúrbios de personalidade podem agravar o quadro clínico de pessoas que convivem com diabetes *mellitus*, sendo a depressão a comorbidade mais frequente (TRYGGESTAD; WILLI, 2015). Revisão sistemática identificou que adultos com diabetes *mellitus* tinham cerca de 1,5 vezes mais chances de apresentar sintomas de ansiedade (SMITH; DESCHÊNESS; SCHMITZA, 2018). Os sintomas de ansiedade comprometeram o manejo do diabetes e o controle glicêmico em adultos (JOHNSON *et al.*, 2013).

A depressão é um transtorno de humor que afeta negativamente a maneira como uma pessoa se sente, pensa e age. Pode ser associada a uma história familiar de depressão, trauma na primeira infância, estrutura cerebral, condições médicas, uso de drogas ou ambiente. Está associada a várias condições de saúde, como a diabetes, uma vez que pode elevar as atividades do sistema nervoso simpático e do eixo hipotálamo-hipófise-adrenal. O aumento das atividades do sistema nervoso simpático eleva as catecolaminas e, eventualmente, causam resistência à insulina. Por outro lado, as atividades elevadas do eixo adrenal levam a um aumento no cortisol

e, eventualmente, no nível de açúcar no sangue. Tanto a resistência à insulina quanto o aumento dos níveis de açúcar no sangue induzem o diabetes *mellitus* tipo 2 (ISMAIL; MATERWALA; KAABI, 2021).

Existe uma relação bidirecional entre depressão e diabetes *mellitus*. A depressão em pessoas com diabetes está associada a um risco aumentado de complicações macro e microvasculares. Por outro lado, complicações do diabetes aumentam o risco de transtorno depressivo, entretanto, o risco de desenvolver complicações do diabetes em pessoas deprimidas é maior comparado ao risco de desenvolver depressão em pessoas com complicações do diabetes (NOUWEN *et al*., 2019).

Os indivíduos que sofrem de ansiedade são caracterizados por preocupação desregulada, muitas vezes associada a sintomas somáticos induzidos pelo sofrimento (ATOSOY *et al.*, 2021). Há poucas pesquisas realizadas sobre a associação de diabetes com transtornos de ansiedade. Pessoas com diabetes e transtornos de ansiedade tem aumento da carga de sintomas do diabetes e suas complicações, piora dos níveis de glicose sanguínea, redução da qualidade de vida, aumento da depressão, aumento do índice de massa corporal (IMC) e maior incapacidade (SMITH *et al.*, 2013; ÖZDEMIR; ŞAHIN, 2019*).*

O sofrimento emocional relacionado ao diabetes está associado a vulnerabilidade psicossocial, como depressão, ansiedade, conflitos familiares relacionados a doença e autogerenciamento da doença (ITURRALDE *et al.*, 2019). O conceito de sofrimento emocional causado por diabetes engloba as preocupações dos pacientes sobre autocuidado, apoio, carga emocional e qualidade nos cuidados de saúde. Embora a depressão seja prevalente em pessoas com diabetes, descobriu-se que o sofrimento emocional é comum, com uma prevalência de 18 a 35% (FISHER *et al.*, 2009).

Poucos estudos abordam o sofrimento emocional na população com diabetes, embora afete quase um terço dos adultos com diabetes *mellitus* tipo 2. O sofrimento emocional é distinto da depressão, pois resulta da carga emocional que engloba preocupação, frustração, raiva e esgotamento do manejo do diabetes. Depressão ou sintomas depressivos exacerbam o sofrimento relacionado ao diabetes, já que ambas as condições impactam negativamente o controle glicêmico (ITURRALDE *et al.*, 2019; OWENS-GARY *et al.*, 2018).

O gerenciamento indesejável e inadequado da glicose sanguínea é um dos fatores que afetam o sofrimento emocional, de modo que pacientes com valores alterados relatam níveis mais altos de sofrimento emocional. O aumento da duração do diabetes tem sido apontado como outro fator importante no sofrimento emocional, que está intimamente ligado à presença de complicações diabéticas e controle glicêmico (PARSA; AGHAMOHAMMADI; ABAZARI, 2019). Pessoas com sofrimento emocional relacionado ao diabetes são 1,5 vezes mais propensos a ter descontrole glicêmico comparado a pacientes que não o têm (TOTESORA *et al.*, 2019).

O sofrimento emocional relacionado ao diabetes é um importante aspecto psicossocial do cuidado dessa população. Avaliar o sofrimento emocional e compreender quem passa por ele, ajuda profissionais de saúde a adaptar as intervenções para reduzi-lo, e permite que os pacientes se engajem melhor no autogerenciamento e alcancem seus objetivos de tratamento e controle do diabetes *mellitus* (WARDIAN *et al.*, 2018).

2.2 Considerações gerais nos cuidados de pessoas com diabetes *mellitus* e transtornos psicológicos

Pessoas com diabetes *mellitus* parecem ser mais propensas a transtornos psicológicos (AMERICAN DIABETES ASSOCIATION, 2019; MOULTON; PICKUP; ISMAIL, 2015). Este fato impacta além do controle glicêmico, uma vez que ambas as doenças ocasionam impacto negativo no funcionamento físico, psicológico, social, ocupacional e na qualidade de vida dos indivíduos, bem como nos encargos socioeconômicos (HOFMANN *et al.*, 2013).

O diagnóstico do diabetes e/ou a autogestão da doença contribuem para a presença de quadros de depressão e ansiedade, e piora da qualidade de vida (GUIDELINES FOR DIABETES CARE IN BERMUDA, 2009). A presença concomitante dessas doenças resulta em complicações de curto e longo prazo nesses indivíduos e no aumento da mortalidade, em comparação com as pessoas que apresentam apenas uma delas (HOFMANN *et al.*, 2013).

Acredita-se que a identificação da depressão em pessoas com diabetes *mellitus* esteja relacionada a outros transtornos psicológicos de angústia relacionada ao diabetes, como medos e preocupações com complicações e medicamentos ou sintomas físicos da doença como fadiga, alteração do apetite e dificuldade para dormir (DIETER; LAUERER, 2016).

Os profissionais envolvidos no cuidado desses pacientes devem considerar a triagem anual dos casos de diabetes *mellitus* e de transtornos psicológicos. Deve-se ter presente a avaliação para o diagnóstico da depressão, quando há complicações do diabetes ou mudanças significativas no estado clínico desses indivíduos (AMERICAN DIABETES ASSOCIATION, 2019).

Quando a depressão é diagnosticada em um paciente diabético, recomenda-se tratar a depressão como prioridade, pois a resposta aos medicamentos geralmente é observada entre 2 e 4 semanas para antidepressivos. Além disso, pacientes com melhor humor seguem com mais entusiasmo o tratamento do diabetes. Compreender as origens comuns do diabetes e da depressão e a conscientização de que ambas as doenças são comuns, contribuem na obtenção de melhores resultados em saúde (BĂDESCU *et al*., 2016).

Pessoas com diabetes *mellitus* e com sintomas de transtornos psicológicos devem ser encaminhadas a um profissional de saúde mental, se apresentarem as situações descritas no Quadro 1.

Quadro 1. Situações nas quais pessoas com diabetes *mellitus* necessitam de encaminhamento a um profissional de saúde mental

Sofrimento significativo relacionado ao controle do diabetes *mellitus*
Medo persistente de hipoglicemia
Resistência psicológica à insulina
Transtornos psicológicos (a exemplo da depressão, ansiedade e transtornos alimentares)

Fonte: The Royal Australian College of General Practitioners and Diabetes Australia, 2020, p.99.

É importante que os profissionais da saúde incluam perguntas sobre o bem-estar do paciente durante as consultas e/ou os atendimentos. O rastreamento da presença de depressão nos pacientes com diabetes pode ser feito por meio de duas perguntas:

1. No último mês, você, frequentemente, tem se sentido deprimido, triste ou sem esperança?

2. No último mês, você, frequentemente, tem sentido pouco interesse ou prazer pelas coisas em geral?

Se ambas as perguntas forem respondidas afirmativamente e se estas respostas permanecerem constantes por um período de pelo menos duas semanas,

um possível diagnóstico da depressão deve ser considerado e investigada a necessidade de tratamento (ABRAHAMIAN *et al.*, 2019). A triagem do status psicossocial de pacientes com diabetes *mellitus* contribui para verificar a presença de problemas psicológicos nos mesmos. O Quadro 2 demonstra os itens considerados na realização da triagem psicossocial e as principais preocupações relatadas pela pessoa com diabetes *mellitus*.

Na realização de uma avaliação que busque identificar pacientes com transtornos psicológicos, é importante que se use ferramentas padronizadas e validadas. As ferramentas descritas a seguir foram encontradas nas revisões sistemáticas e nos ensaios clínicos incluídos nos artigos desta tese.

Para a depressão, são descritas as ferramentas Questionário de Saúde do Paciente-9 (do inglês *Patient Health Questionnaire-9* – PHQ-9) (SANTOS *et al.*, 2013), Inventário de Depressão de Beck II (do inglês *Beck Depression Inventory II*) (GOMES-OLIVEIRA *et al.*, 2012), Escala de Avaliação de Depressão de Hamilton (do inglês *Hamilton Rating Scale for Depression* - HAM-D) (BARROSO *et al.*, 2018), Inventário de Depressão Maior (do inglês *Major Depression Inventory* – MDI) (PARCIAS *et al.*, 2011), Escala de Avaliação de Depressão para Crianças (do inglês *Children Depression Evaluation Scale* – CDRS) (PEREIRA; AMARAL, 2007) e Escala de Depressão Geriátrica (do inglês *Geriatric Depression Scale* – GDS) (PARADELA; LOURENÇO VERAS, 2005).

O Índice de Bem-Estar em Cinco Itens da Organização Mundial da Saúde (*World Health Organization Five Item Well Being Index* - OMS-5) e as Áreas de Problemas em Diabetes (*Problems Areas in Diabetes* - PAID) são ferramentas de triagem simples e confiáveis que se mostraram eficazes na detecção de depressão, e monitoramento do bem-estar dos pacientes. Tais ferramentas avaliam a depressão e também o sofrimento relacionado ao diabetes em pacientes com diabetes (DIETER; LAUERER, 2016).

Para identificar pacientes com ansiedade, algumas escalas utilizadas são a Escala Hospitalar de Ansiedade e Depressão (do inglês *Hospital Anxiety and Depression Scale* - HADS) (SOUSA; PEREIRA, 2008), Escala de Transtorno de Ansiedade Generalizada-7 (do inglês *Generalized Anxiety Disorder Scale-7* - GAD-7) (BALDWIN *et al.*, 2020), e Diagnóstico Internacional Composto da Organização Mundial da Saúde (do inglês *World Health Organization Composite International*

Diagnostic - WHO CIDI-auto), sendo esta última escala também usada para aferir ansiedade (VAN-BASTELAAR *et al.*, 2012).

Quadro 2. Triagem psicossocial e preocupações comuns reportadas pelos pacientes com diabetes *mellitus*

Triagem psicossocial	Preocupações comuns do paciente
▪ Atitudes sobre o diagnóstico de diabetes *mellitus*	▪ Preocupação com o futuro e com as possíveis complicações da doença
▪ Expectativas de gestão da doença e resultados	▪ Culpa e ansiedade por não estar no caminho certo com os objetivos do tratamento
▪ Humor ou afeto	▪ Não saber se o humor ou os sentimentos estão relacionados ao diabetes
▪ Qualidade de vida geral e diabetes	▪ Medo de viver com a doença ▪ Estar constantemente preocupado com alimentação (qualidade, quantidade e horário) ▪ Sentir-se privado de certos alimentos
▪ Recursos (sociais, emocionais e financeiros)	▪ Incapaz de lidar com o diagnóstico do diabetes
▪ Histórico psiquiátrico	▪ Sentir-se deprimido por viver com diabetes

Fonte: Guidelines For Diabetes Care In Bermuda, 2009, p.27.

A Escala de Ansiedade de Hamilton (do inglês *Hamilton Anxiety Scale* – HAS) tem demonstrado um grande efeito como ferramenta em intervenções psicológicas para avaliar os sintomas de ansiedade em pessoas com diabetes *mellitus* (XIE; DENG, 2017).

Para o sofrimento emocional relacionado ao diabetes, destaca-se algumas escalas como a Escala de Sofrimento Psicológico *Kessler* de 10 Itens (do inglês *Kessler 10 Item Psychological Distress Scale* - K-10) (NEWBY *et al.*, 2017), e Áreas Problemáticas no Diabetes (do inglês *Problem Areas in Diabetes* – PAID) (VAN-BASTELAAR *et al.*, 2012).

Os instrumentos são aplicados na visita inicial, em intervalos periódicos, e quando há uma mudança na doença, no tratamento ou nas circunstâncias de vida (YOUNG-HYMAN *et al.*, 2016). Como exemplo, o Inventário de Depressão de Beck II é comumente utilizado em adolescentes e adultos para avaliar os sintomas

depressivos e sua gravidade. O instrumento contém 21 itens que analisa os sintomas de depressão por autorrelato, de acordo com os critérios de diagnósticos listados no Manual de Diagnóstico e Estatística para Transtornos Mentais *(*do inglês *Diagnostic and Statistical Manual for Mental Disorders* - DSM*).* Pontuações mais altas indicam níveis mais altos de depressão. O instrumento é aplicado para fins de pesquisa e para a prática clínica e é um dos mais utilizados entre os profissionais da saúde (GARCÍA-BATISTA *et al.*, 2018).

2.3 Intervenções para transtornos psicológicos em pessoas com diabetes *mellitus*

Para o bom gerenciamento do diabetes e prevenção de complicações com risco de vida, a Associação Americana de Diabetes (do inglês *American Diabetes Association)* enfatiza o reconhecimento, tratamento e manejo da depressão e do sofrimento emocional relacionado ao diabetes em pessoas com diabetes *mellitus.* O reconhecimento precoce, triagem de rotina e uso de abordagens de tratamento baseadas em evidências para ambas as condições pode melhorar o controle glicêmico, pressão arterial e colesterol, bem como a saúde geral, e resulta em economia de custos médicos (OWENS-GARY *et al.*, 2018).

Entre as intervenções encontradas na literatura destacam-se como principais as psicológicas, farmacológicas, psicossociais e intervenções no estilo de vida, realizadas por meio presencial ou saúde eletrônica.

Recomenda-se que o tratamento da depressão no paciente com diabetes *mellitus* seja abrangente e multidisciplinar, e que inclua adequado suporte emocional e comportamental. As intervenções psicológicas são recomendadas quando o paciente apresenta sintomas leves de depressão. Cabe ao profissional da saúde avaliar a indicação do tratamento, bem como encaminhar o paciente para a psicoterapia (SOCIEDADE BRASILEIRA DE DIABETES, 2020). Feito o diagnóstico de depressão maior, intervenções farmacológicas devem ser combinadas com a psicoterapia (BAUMEISTER; HUTTER; BENGEL, 2014). Os antidepressivos devem ser usados para tratar a depressão aguda em pessoas com diabetes *mellitus* e como tratamento de manutenção para prevenir a sua recorrência nesses pacientes (MANCINI; HEGELE; LEITER, 2018).

Revisão sistemática que avaliou o efeito de intervenções farmacológicas e não farmacológicas para o tratamento da depressão em pacientes com diabetes *mellitus*

tipo 1 e tipo 2 mostrou que, em comparação com o tratamento usual, placebo ou lista de espera; as intervenções (uso de medicamentos, terapia de grupo, psicoterapia e cuidado colaborativo) mostraram um efeito significativo na melhora da depressão e no controle glicêmico desses pacientes (VAN-DER-FELTZ-CORNELIS *et al.*, 2021).

2.3.1 Intervenções psicológicas

Estudo que sintetizou informações de diretrizes de prática clínica e consensos sobre intervenções psicológicas para pacientes com diabetes *mellitus* tipo 2 mostrou que essas são indicadas como parte do tratamento da depressão e podem contribuir para mudanças significativas no índice de ansiedade, angústia e melhora na qualidade de vida (REESE; PETRAK; MITTAG, 2016).

Terapia cognitivo-comportamental (do inglês *Cognitive Behavioral Therapy* – CBT) é uma abordagem organizada e limitada no tempo com conteúdo como psicoeducação, ativação comportamental, reestruturação cognitiva e prevenção de recaídas. Pode reduzir os sintomas depressivos pela capacidade de identificar e avaliar pensamentos negativos. É uma intervenção efetiva para pacientes com doenças crônicas, que melhora as habilidades de autocuidado e favorece o reconhecimento da doença com o impacto que ela causa na vida do paciente (LI *et al.*, 2017; UCHENDU; BLAKE, 2017).

Revisões sistemáticas apontam que a Terapia Cognitivo Comportamental contribui para a remissão da depressão e melhora da qualidade de vida em pacientes com diabetes *mellitus* (BAUMEISTER; HUTTER; BENGEL, 2014; WINKLEY *et al.*, 2006, WINKLEY *et al.*, 2020; XIE; DENG, 2017). Ensaio clínico recente avaliou a efetividade dessa terapia em adultos com diabetes *mellitus* tipo 1, por meio do uso de mensagens *online* e em tempo real, para apoiar a autogestão e para melhorar o controle glicêmico nesses pacientes. Observou-se redução nos escores de depressão e nos valores de hemoglobina glicada (HbA1c) dos pacientes submetidos à intervenção, em até 12 meses após o tratamento (DOHERTY *et al.*, 2021).

A ansiedade, como sintoma ou transtorno, é comumente encontrada em adultos com transtornos depressivos. Para pessoas com diabetes, a Terapia Cognitiva Comportamental tem potencial para uso terapêutico juntamente com o tratamento padrão do diabetes *mellitus*, na melhora da ansiedade, depressão, glicemia e qualidade de vida (LI *et al.*, 2017).

Evidências indicam que intervenções baseadas na *web* são custo-efetivas, capazes de atingir um número maior de indivíduos, especialmente aqueles com um estilo de vida mais restritivo. Revisões recentes de intervenções baseadas na *web* em pessoas com diabetes *mellitus* tipo 2 sugeriram impactos positivos no controle da ansiedade (HADJICONSTANTINOU *et al.*, 2016).

Intervenções psicológicas para tratar sofrimento emocional relacionado ao diabetes focadas na emoção-cognição descritas na literatura incluem treinamento cognitivo comportamental para autogestão do diabetes, cognição focada na necessidade do paciente (contato *via* telefone), *coach* junto a um *software* de gerenciamento do diabetes, educação estruturada baseada em manuais sobre diabetes, programa de *coaching* de autogestão e intervenção focada na mudança de comportamento (realizada de maneira individual ou em grupo). Em geral, tais intervenções melhoram o controle glicêmico de pacientes com *diabetes mellitus* comparadas aos cuidados habituais. Entretanto, tais achados são inconclusivos e são necessários novos ensaios clínicos para confirmá-los (CHEW *et al.*, 2019).

A intervenção Redução do Estresse Baseado na Atenção Plena (do Inglês *Mindfulness-Based Stress Reduction* - MBSR*)* pode reduzir o sofrimento emocional relacionado ao diabetes e melhorar o gerenciamento da doença (WHITEBIRD *et al.*, 2018).

2.3.2 Intervenções farmacológicas

Revisões sistemáticas abordaram o tratamento farmacológico da depressão em pacientes com diabetes *mellitus.* Os estudos demonstraram melhora nos escores de gravidade e de remissão da depressão, bem como no controle glicêmico em adultos, com destaque para o uso dos Inibidores Seletivos da Recaptação de Serotonina (ISRS) (ABRAHAMIAN et al., 2019; BAUMEISTER; HUTTER; BENGEL, 2014).

Para que os antidepressivos comecem a produzir seus efeitos, é necessário o tempo de uso de pelo menos duas semanas, conhecido como período de latência. Para que ocorra redução expressiva dos sintomas, devem ser utilizados por pelo menos quatro semanas (BRASIL, 2012). O tratamento antidepressivo bem-sucedido deve continuar por nove a 12 meses, após a remissão dos sintomas, e, em casos em

que ocorra recorrências e recidivas frequentes, demanda terapia com duração indefinida (BMJ BEST PRACTICE, 2019).

O medicamento deve ser selecionado de acordo com o perfil do paciente e a existência de outras doenças (CIPRIANI *et al.*, 2018; DODD *et al.*, 2018). Comorbidades e possíveis interações medicamentosas devem ser consideradas, a fim de minimizar danos e maximizar a resposta terapêutica (BRASIL, 2012). Dentre as classes de antidepressivos, destaca-se o uso dos Inibidores Seletivos de Recaptação de Serotonina (ABRAHAMIAN et al., 2019; BAUMEISTER *et al.,* 2014). Na Relação Nacional de Medicamentos Essenciais (RENAME), consta a fluoxetina como antidepressivo pertencente a classe dos ISRS (BRASIL, 2022).

É importante destacar que o uso de antidepressivos também está associado a um maior risco de desenvolver diabetes *mellitus* tipo 2, especialmente quando utilizados em doses mais altas e por períodos prolongados (JESSE; CREEDY; ANDERSON, 2019). Desta forma, histórico de depressão, depressão atual e de uso de antidepressivos são fatores de risco para o desenvolvimento do diabetes, especialmente em indivíduos com obesidade e história familiar de diabetes *mellitus* tipo 2 (BARNARD; PEVELER; HOLT, 2013).

2.3.3 Intervenções psicossociais

As intervenções psicossociais fornecem informações e orientações para o diabetes, autogestão da doença e apoio psicológico. Entre elas, o cuidado colaborativo tem demonstrado efetividade em pessoas com diabetes *mellitus.* Este é um modelo de gestão coordenada, realizado na atenção primária à saúde, que envolve médicos, enfermeiros, profissionais de saúde mental, dentre outros que proporcionem o manejo ao paciente (HUANG *et al.*, 2013; PERRIN *et al.*, 2019).

Revisão sistemática observou que as intervenções psicossociais reduziram sintomas de sofrimento emocional específico do diabetes e os valores de HbA1c em adultos com diabetes *mellitus* tipo 2 comparado aos grupos controles (em geral, definidos como grupos de pacientes que receberam cuidados usuais) (DIRETRIZES CLÍNICAS EM SAÚDE MENTAL, 2018). O Quadro 3 descreve as intervenções psicossociais reportadas na literatura para depressão em pacientes com diabetes *mellitus*.

Quadro 3. Intervenções psicossociais utilizadas em pacientes com diabetes *mellitus*

Intervenções psicossociais que podem ser integradas aos planos de tratamento do diabetes *mellitus*:
▪ Cuidado colaborativo
▪ Intervenções motivacionais
▪ Estratégias de gerenciamento de estresse
▪ Treinamento de habilidades de enfrentamento
▪ Terapia familiar
▪ Gestão de caso

Fonte: Mancini et al., 2018. p.178-185[10].

2.3.4 Intervenções no estilo de vida

Revisão sistemática que avaliou intervenções no estilo de vida, como dieta e/ou atividade física, demonstrou diminuição dos escores de depressão e ansiedade em adultos com diabetes *mellitus* tipo 2 ou em risco de desenvolver a doença, apenas nos primeiros seis meses de intervenção. As intervenções por meio de sessões individuais ou em sessões em grupo foram associadas à melhora da depressão. Entretanto, a qualidade das evidências desses achados não foi avaliada pelo estudo, o que limita afirmar sobre a real efetividade dessa intervenção (CEZARETTO *et al.*, 2016).

2.4 Tecnologias digitais

A digitalização conecta cada vez mais o real com o mundo virtual, à medida que isso acontece, nosso entendimento sobre o significado do termo digitalização muda. Enquanto no final do século XX, a digitalização descrevia a conversão de informações de armazenamento analógico para digital, definições mais extensas são utilizadas hoje (EBERLE *et al.*, 2021). Uma definição centrada no ser humano descreve a digitalização como um processo no qual as pessoas e seus modos de vida e de trabalho são transferidos para um nível digital (HAMINE *et al.*, 2015).

A internet é uma fonte de comunicação rápida, eficiente e confiável. Sua ampla disponibilidade, a torna uma ferramenta de comunicação atraente entre pacientes e provedores. Ela tem sido útil em vários campos de saúde, desde videoconferência à suporte e educação ao paciente (HAMINE *et al.*, 2015).

A telemedicina, em particular, tem chamado a atenção de pacientes e cuidadores, a qual fornece *feedback* e aconselhamento em tempo hábil, o que torna o atendimento mais eficiente e responsivo às necessidades do paciente. Para pacientes que vivem em áreas rurais, cujo acesso ao cuidador é mais restrito, a telemedicina pode poupar-lhes tempo e custo de viagem (AZAR; GABBAY, 2009).

A Associação Americana de Telemedicina (do inglês *American Telemedicine Association*) define telemedicina como o uso de informações médicas trocadas de um local para outro, por meio de comunicações eletrônicas, para melhorar o estado de saúde clínica de um paciente (TORRE-DIEZ *et al.*, 2015).

A Organização Mundial da Saúde (OMS) (do Inglês *World Health Organization* - WHO) define saúde eletrônica (e-Saúde) (do inglês *eletronic Health – e-Health*) como a transferência de recursos de saúde e cuidados de saúde por meios eletrônicos. Como exemplo, esta ferramenta pode ser usada para possibilitar a realização de teleconsultas entre profissional da saúde e paciente. Saúde móvel, do inglês *mobile Health (m-Health*) é o uso de tecnologia sem fio para fornecer serviços de saúde e informações em dispositivos de comunicação móvel, como telefones celulares, *tablets* e *smartphones* (TORRE-DIEZ *et al.*, 2015).

Os programas de *e-Health* têm vantagens como a fidelidade do processo de intervenção que está embutida neles, e o fato dos pacientes acessarem o tratamento quando quiserem e trabalharem em seu próprio ritmo, em privacidade. Os computadores podem ser preferíveis para alguns grupos como acesso restrito aos serviços de saúde (por exemplo, aqueles que vivem distantes de locais de atendimento à saúde) ou são relutantes em buscar atendimento presencial tradicional (por exemplo, os adolescentes) (FLEMING *et al.*, 2020).

Revisão sistemática que pesquisou informações sobre custo-utilidade e custo-efetividade da telemedicina, *e-Health* e *m-Health* identificou 35 trabalhos, dos quais 79% demonstram que a telemedicina reduziu os custos do atendimento. Estudos de custo-utilidade foram feitos apenas para sistemas de telemedicina. Observou-se poucos estudos de custo-utilidade e custo-efetividade que avaliaram os sistemas de *e-Health* e *m-Health*. Entre as principais limitações das avaliações econômicas do uso da telemedicina estão a falta de ensaios clínicos randomizados, estudos com tamanho de amostra pequenos e a ausência de dados de qualidade e medidas apropriadas (TORRE-DI´EZ *et al.*, 2015).

Estudos em telemedicina têm demonstrado sucesso na redução dos obstáculos geográficos e no recebimento de cuidados em modalidades tradicionais com a mesma ou maior efetividade. Entretanto, existem várias barreiras que precisam ser abordadas para que esta tecnologia se espalhe (KRUSE *et al.*, 2016).

Revisão sistemática que avaliou as barreiras para a adoção da telemedicina, encontrou 30 estudos, 33 barreiras e 100 ocorrências. Os problemas identificados foram equipe com deficiência técnica (11%), resistência à mudança (8%), custo (8%), reembolso (5%), idade do paciente (5%) e nível de educação do paciente (5%). As principais barreiras foram específicas da tecnologia e podem ser superadas por meio de treinamento, técnicas de gerenciamento de mudanças, além da interação pessoal entre paciente e provedor (KRUSE *et al.*, 2016).

Revisão de escopo procurou explorar barreiras e facilitadores para o uso da e-Saúde com o objetivo de informar o desenvolvimento futuro e a aceitação de intervenções de saúde digital e saúde mental. Dentre as barreiras destacam-se a falta de autoeficácia, conhecimento, apoio, funcionalidade e fornecimento de informações sobre os benefícios da e-Saúde. Os principais facilitadores foram o envolvimento ativo dos usuários alvo na concepção e entrega de programas neste formato, apoio para superar preocupações de privacidade e aumentar a autoeficácia no uso de tecnologia e integração de programas de e-saúde em serviços de saúde para acomodar multimorbidade com que pacientes normalmente apresentam (WILSON *et al*., 2021).

Revisão sistemática que pesquisou custo-utilidade e custo-efetividade de sistemas de telemedicina, saúde eletrônica (*e-Health*) e saúde móvel (*m-Health*) identificou 35 trabalhos relevantes. Alguns estudos de custo-efetividade demonstram que a telemedicina reduz os custos. Porém existem muitas limitações das avaliações econômicas de sistemas de telemedicina, principalmente a falta de ensaios clínicos randomizados, amostras pequenas e ausência de dados de qualidade e medidas adequadas (DE LA TORRE-DIÉZ *et al*., 2015).

2.5 Uso de tecnologias digitais em pessoas com diabetes *mellitus* e transtornos psicológicos

A adesão ao gerenciamento de doenças crônicas é fundamental para alcançar melhores resultados de saúde, qualidade de vida e cuidados de saúde com boa relação custo-benefício. À medida que a carga de doenças crônicas continua a crescer globalmente, também aumenta o impacto da baixa adesão. Com isso, *e-*

Health são cada vez mais utilizadas nos cuidados de saúde e na prática de saúde pública para a comunicação do paciente, monitoramento, educação e para facilitar a adesão ao gerenciamento dessas doenças (HAMINE *et al.*, 2015).

Os aplicativos (*apps*) para *smartphones* relacionados à saúde começaram a ganhar destaque em 2010, na qual estudos demonstraram a sua utilidade como complemento ao tratamento de doenças (HUANG *et al.*, 2018). Eles ajudam no gerenciamento do diabetes, como ajustes de medicações em resposta aos dados de monitoramento de glicose e até mesmo no estilo de vida dos usuários (FLEMING *et al.*, 2020).

E-Health tem potencial de reduzir o tempo de espera por consultas, eliminar a necessidade de encontros presenciais com o clínico e com isso, a carga de trabalho dos profissionais de saúde mental; ser mais econômico para as práticas; e encorajar táticas de autocuidado. Juntamente com os aplicativos, há evidências que mostram que receber informações de serviço de mensagens de texto curtas (*Short Message Service* - *SMS*) que envolvem psicoeducação, lembretes de medicamentos e *links* para páginas da *web* é vantajoso para o bem-estar físico e mental do paciente (RATHBONE *et al.*, 2017).

Revisão sistemática avaliou a eficácia e aceitabilidade de 15 aplicativos móveis para saúde mental em crianças e adolescentes. A aceitabilidade dos aplicativos era boa e o seu uso era moderado, entretanto, os autores concluíram que existem evidências de pesquisas insuficientes para apoiar o uso dos aplicativos para crianças, pré-adolescentes e adolescentes com problemas de saúde mental. Dado o número e o ritmo em que os aplicativos asão lançados, estudos de pesquisa metodologicamente robustos que avaliem sua segurança e efetividade são necessárias (GRIST; PORTER; STALLARD, 2017).

Revisão sistemática sobre o uso de *SMS* na atenção à saúde mental encontrou 36 estudos. As mensagens de texto foram usadas em uma ampla gama de situações de saúde mental como: abuso de substâncias (31%), esquizofrenia (22%) e transtornos afetivos (17%). Identificou-se quatro formas de seu uso: lembretes (14%), informações (17%), mensagens de apoio (42%) e procedimentos de automonitoramento (42%). No geral, os estudos relataram melhora na adesão ao tratamento e vigilância dos sintomas, e aumento da frequência às consultas e da satisfação com a gestão e os serviços de saúde. A compreensão do conteúdo da mensagem, estratégias preventivas e abordagens inovadoras derivadas do campo da

saúde mental são aplicáveis em outras especialidades médicas (BERROUIGUET *et al.*, 2016).

Revisão sistemática encontrou 89 estudos sobre intervenções digitais com foco na depressão, ansiedade e melhoria do bem-estar psicológico entre estudantes universitários. A maioria das intervenções (80%) foi realizada por meio de *site*, e a mais comum foi a terapia cognitiva-comportamental (31%). A maioria dos programas foi eficaz (47%) ou parcialmente eficaz (34%) na produção de mudanças benéficas nas principais variáveis de resultado psicológico. Apenas metade dos estudos apresentou resultados de usabilidade ou aceitabilidade. Intervenções digitais na saúde mental são eficazes para melhorar a depressão, ansiedade e bem-estar psicológico nesta população, mas novos estudos são necessários para determinar os elementos eficazes dessas intervenções (LATTIE *et al.*, 2019).

Pessoas com diabetes *mellitus* utilizam os aplicativos para telefones celulares para auxiliar no autogerenciamento da doença. Os inúmeros aplicativos disponíveis para auxiliar no controle do diabetes *mellitus* têm uma variedade de funções. Algumas funções, como calculadoras de dose de insulina, têm um potencial significativo na diminuição de danos. Diante disso, há necessidade de um processo de avaliação de aplicativos para dar confiança na qualidade e segurança do seu uso no gerenciamento do diabetes (BOYLE *et al.*, 2017).

Organizações internacionais, como os Fóruns Reguladores Internacionais de Dispositivos Médicos (do inglês *International Medical Device Regulators Forum)* e a OMS, fizeram avanços na classificação de diferentes tipos de tecnologia digital de saúde e sua integração no campo dos dispositivos médicos. À medida que o campo da saúde digital em diabetes continua a se desenvolver e se tornar mais integrado à vida cotidiana, é desejável garantir que ele seja baseado nas melhores evidências de segurança e efetividade (FLEMING *et al.*, 2020).

3 OBJETIVOS

3.1 Objetivo Primário

O objetivo do presente estudo foi sumarizar evidências sobre a efetividade e segurança de intervenções para tratar ansiedade e depressão em pessoas com diabetes *mellitus* tipo 1 e 2; e avaliar a efetividade e segurança de Saúde eletrônica (e-Saúde) por meio de uma revisão sistemática.

3.2 Objetivos Secundários

- Identificar intervenções para tratar depressão, sintomas depressivos e/ou de ansiedade em pessoas com diabetes *mellitus,* por meio de uma revisão de revisões sistemáticas com metanálises;
- Determinar a efetividade e segurança das intervenções reportadas pelas revisões;
- Descrever a qualidade da evidência reportada pelos estudos de revisão sistemática;
- Identificar as intervenções de e-Saúde disponíveis na literatura, por meio de revisão sistemática de ensaios clínicos randomizados;
- Avaliar a efetividade e segurança das intervenções e-Saúde;
- Identificar lacunas nas evidências atuais, avaliar suas implicações clínicas e fazer recomendações para pesquisas futuras.

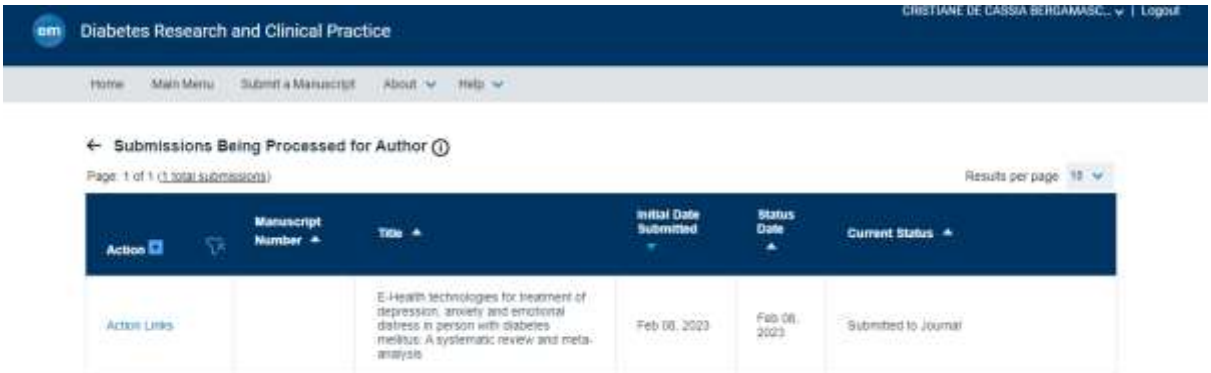
4 RESULTADOS

Esta tese é apresentada no formato de artigo científico, elaborado conforme as recomendações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (apêndice A).

Desta maneira, os resultados foram descritos em três artigos.

O artigo de número 1: “Interventions for depression and anxiety among people with diabetes mellitus: review of systematic reviews” foi aceito para publicação no periódico *Plos One*, em 31 de janeiro de 2023. O comprovante de submissão do artigo 1 está apresentado a seguir:

O artigo de número 2 “E-Health technologies for treatment of depression, anxiety and emotional distress in people with diabetes mellitus: systematic review and meta-analysis” foi submetido ao periódico *Diabetes Research and Clinical Practice* em 08 de fevereiro de 2023. O comprovante de submissão do artigo 2 está apresentado a seguir:



O artigo de número 3 é um produto técnico publicado no Boletim Farmacoterapêutico do Conselho Federal de Farmácia. Disponível em: https://www.revistas.cff.org.br/?journal=farmacoterapeutica&page=article&op=view&path%5B%5D=2860

Os artigos foram apresentados no formato adotado pelos periódicos.

4.1 Artigo 1

Title: Interventions for depression and anxiety among people with diabetes mellitus: review of systematic reviews

Running Title: Depression and anxiety in people with diabetes

Reginaldo Tavares Franquez[1], Isabela Muniz de Souza[1,] Cristiane de Cássia Bergamaschi[1]

[1]Pharmaceutical Sciences Graduate Course, University of Sorocaba, Sorocaba, São Paulo, Brazil

Universidade de Sorocaba, UNISO, Rodovia Raposo Tavares, Km 92.5, Sorocaba, SP 18023-000, Brazil
Tel: +55-15-21017104
cristiane.motta@prof.uniso.br

Author Contributions

R. F. developed the search, performed the systematic electronic searches, identified relevant articles for inclusion, extracted the data, performed the quality assessment of the studies, and drafted parts of the manuscript. I. M. identified relevant articles for inclusion, extracted the data, performed the quality assessment of the studies, and drafted parts of the manuscript. C. C. B. developed the search, performed the systematic electronic searches, and drafted the manuscript. All authors were involved in the development of the study concept. All authors have critically reviewed the manuscript and given permission for publication.

Abstract

This review of systematic reviews of randomized clinical trials summarized the available evidence regarding the effectiveness and safety of interventions to treat depression and/or anxiety in people with type 1 and type 2 diabetes. The sources of information searched were the Cochrane Library, MEDLINE, EMBASE, Web of Science and LILACS, until up to July 16, 2021. The interventions were compared with

placebo, active control or usual care. The measured primary outcomes were improvement in depression and anxiety remission, reduction of diabetes-specific emotional distress and improvement in quality of life. Two reviewers, independently, selected the reviews, extracted their data, and assessed their methodological quality using AMSTAR-2. A narrative synthesis of the findings was performed, according to the type of intervention and type of diabetes. Thirteen systematic reviews that included 28,307 participants were analyzed. The reviews had at least one critical methodological flaw. Cognitive Behavioral Therapy improved the mainly depression, glycemic values (n=5 reviews) and anxiety (n=1), in adults and elderly with diabetes. Collaborative care (n=2) and health education (n=1) improved depression and glycemic values, in adults with diabetes. Pharmacological treatment (n=2) improved depression outcomes only. The quality of the evidence was low to moderate, when reported. The interventions reported in literature and mainly the Cognitive Behavioral Therapy can be effective to treat people with diabetes and depression; however, such findings must be confirmed. This study can guide patients, their caregivers and health professionals in making decisions concerning the use of these interventions in the mental healthcare of people with diabetes.

Protocol Registration: PROSPERO (CRD42021224587).

Keywords: Anxiety, Depression, Effectiveness, Safety, Type 1 diabetes, Type 2 diabetes

Introduction

Diabetes mellitus is a disabling long-term health condition that is common and growing. Globally, it affects 8.3% of the population and is the leading cause of lost disability-adjusted life years (1,2). It was considered the ninth leading cause of death in 2019, with an estimated 1.5 million deaths caused by diabetes (3). It is estimated that 425 million individuals worldwide have diabetes, and it is expected that the number will increase to 629 million, in 2045 (4).

Psychological disorders can occur in people with diabetes of all ages (5). Type 1 diabetes seems to be associated with a higher prevalence of psychological disorders than type 2 diabetes (6).

Type 1 diabetes is the most common endocrine disorder in children and the self-management of this condition can be difficult mainly in children and adolescents

with psychological disorders. Adolescents are 2.3 times more likely to have psychological disorders than adults (7). Depression and anxiety in children and adolescents with type 1 diabetes also had a negative impact on the management of this condition and on self-care behavior's (8,9). Systematic review identified that adults with diabetes were approximately 1.5 times more likely to have anxiety symptoms (10). Another systematic review demonstrated that anxiety symptoms affected the management of type 1 diabetes and glycemic values in adults (11).

Depression is a common co-morbidity in people with diabetes. Both diseases are growing rapidly and have a negative impact on the physical, psychological, social, and occupational functioning of patients and their quality of life. The presence of these conditions results in numerous short-and long-term complications and an increase in mortality compared to people with depression or diabetes alone (12).

Depression is two times more likely in people with type 1 or type 2 diabetes than in people without the disease (13). Systematic reviews of 248 observational studies showed that 28% of adults with type 2 diabetes in the world (n=23,245,827) had depression. Almost one in four adults with type 2 diabetes had depression. Depression prevalence was lower in Europe (24%), Africa (27%), America (28%) and higher in Australia (29%) and Asia (32%) (14).

In addition to depression and anxiety, diabetes-specific distress has shown to be prevalent among people with diabetes (15). It is distinct from depression and refers to the fears, worries and frustrations that people experience while living with and managing diabetes (16,17).

The literature has shown that psychological disorders are present in the population with diabetes mellitus in different age groups and that there are a variety of interventions to treat these disorders in this population. However, the synthesis of these findings was not found in the literature that prompted the realization of this overview. By synthesizing the findings on effectiveness and safety of the interventions available to treat this subject, as well as highlighting the lack of information; this study can guide people with diabetes, their caregivers and health professionals in making decisions about the use of interventions in the mental healthcare of these patients.

Therefore, this study summarized the available evidence regarding the effectiveness and safety of interventions to treat psychological disorders, in people with type 1 and type 2 diabetes. More specifically, the review questions are as follows: What is the effectiveness and safety of interventions to treat depression and/or anxiety

in people with type 1 and type 2 diabetes? What is the quality of the evidence of these findings?

Methods

Protocol and register

This review of systematic reviews was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (18). The study protocol was registered in PROSPERO (CRD42021224587).

Eligibility criteria

Inclusion criteria

Inclusion criteria were described using the Population, Intervention, Comparison, Outcome, and Type of study (PICOT) framework.

Population: children, adolescents, adults and elderly with both type 1 or type 2 diabetes and depression, depressive symptoms, and/or anxiety. Distress was also considered if the study population had depression or anxiety.

Interventions: i) psychological interventions, psychodynamic psychotherapy, interpersonal psychotherapy, non-directive counseling or support, among others); ii) psychoeducational interventions (including information and guidance for diabetes and/or psychological self-management and support, such as collaborative care interventions, among others); iii) health education; iv) pharmacological interventions (in which patients received drugs that are used in the treatment of depression and/or anxiety); v) lifestyle interventions, among others.

Comparators: i) non-pharmacological interventions may include usual care or other interventions; ii) pharmacological interventions may include active control or placebo.

Outcomes: effectiveness and safety outcomes are described in “Measure outcomes”.

Type of study: systematic review of randomized clinical trials followed by meta-analysis. Systematic reviews with more than one study design were included, but the collected information was restricted for those outcomes reported by randomized clinical trials.

Exclusion criteria

Systematic review in which interventions consisted only of adherence to diabetes treatment (although interventions to improve the adherence to diabetes have effects on mood, they were not designed to treat depression or anxiety). Review that contained clinical trials included in other reviews with the most recent publication date.

Measure outcomes

Primary outcomes

The information was described by self-report, validated questionnaires, clinical diagnosis, or standardized interviews: depression improvement and/or remission (depression remission rate, reduction in depression severity score, and depression treatment response rate, among others); anxiety improvement and/or remission (reduced anxiety scores among others); reduction of diabetes-specific emotional distress; and quality of life improvement.

Secondary outcomes

The secondary outcomes were reduction in hemoglobin A1c (HbA1c) values, treatment costs, death from any cause, adverse drug reaction, adherence to treatment for diabetes, and complications arising from diabetes.

Search methods for primary studies

Electronic searches

The databases searched were as follows: Cochrane Library, MEDLINE (via PubMed), EMBASE, Web of Science, and LILACS (via Virtual Health Library). The search included studies without language restrictions or time limits. We used information sources to locate the studies from the beginning to the July 16, 2021.

Searching other resources

The lists of references of eligible studies, reviews, and systematic reviews were checked by the reviewers to identify other possible studies. The Grey Literature Report (https://www.greylit.org/library/search) and OpenGrey (http://www.opengrey.eu/) were searched for grey literature. If necessary, the main authors of the studies were contacted for additional information.

Search strategy

The search was conducted using the Medical Subject Headings (MeSH) terms for each disease: (diabetes mellitus) AND (depression OR depressive disorder OR anxiety) with the filter: systematic review (S1 Appendix).

Eligibility determination

Two reviewers (RF and IM), independently, assessed potentially relevant titles and abstracts and applied the eligibility criteria. The full texts of potentially eligible articles were obtained. These reviewers, independently, assessed the eligibility of each full text and resolved any disagreement by consensus. A third reviewer assisted with the final decision when necessary (CB). For duplicate publications, the article with the most complete data was used. The full article was requested from the author when necessary.

Data extraction

Calibration exercises were performed for data extraction by using a standardized form of Excel. Calibration occurred by extracting of at least two studies, followed by consensus among reviewers. Data extraction was performed by the same reviewers (RF and IM), independently, with discrepancies resolved by consensus between them. The third reviewer was contacted when necessary (CB). The study authors were contacted by email, if necessary.

The data collected from the eligible studies were as follows: author and year of publication, time considered when searching for relevant studies, number of randomized clinical trials included, type of intervention (non-pharmacological or pharmacological), results of the measured outcomes, and duration of follow-up. The participant data collected were as follows: number, type of diabetes, and type of psychiatric disorder.

Quality assessment of the studies

The Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) tool was used to appraise the methodological quality of the included systematic reviews (19). The tool evaluates the methodological aspects using 16 items and rating the confidence in the results of the review as high (no or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses), and critically low (more than one critical flaw with or without

non-critical weaknesses). Details about the tool are described in the footnote of S2 Table.

Data synthesis

The summary measures of the systematic reviews were described using odds ratio, relative risk and standard mean difference (SMD), followed by 95% confidence intervals (95% CI). We summarized the results using narrative synthesis according to the type of intervention and type of diabetes.

Heterogeneity was verified by the I^2 statistic which is classified as 0 to 25% (low heterogeneity), 50% (moderate heterogeneity), and 75% (high heterogeneity) (20).

For each outcome, the quality of evidence was collected from the systematic reviews according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. In this approach, randomized clinical trials begins with high-quality evidence, but can be assessed as low-quality evidence based on one or more of the following five categories of limitations: risk of bias, inconsistency, indirect evidence, inaccuracy, and publication bias (21).

Results

Literature search

A total of 1,086 reviews were identified for screening. Following the removal of duplicates, review of titles and abstracts and full text evaluation, 13 systematic reviews were included (S1 Figure). It was not necessary to contact the study authors in order to request the full text. The list of excluded articles is presented in S2 Appendix.

Study characteristics

S1 Table describes the systematic reviews included according to the type of diabetes. The systematic reviews included accounted for 204 trials and 28,307 participants. Four studies included adults with type 2 diabetes and nine studies included adults with both type 1 and type 2 diabetes. No study specifically addressed the population of children and young people. All systematic reviews included adults with depression (n=13) and four of these studies also included people with anxiety. Only two reviews reported information on the duration of diabetes. The intervention

most reported was psychological (n=9). The studies were published mainly in China and United Kingdom, between the years 2012 and 2020.

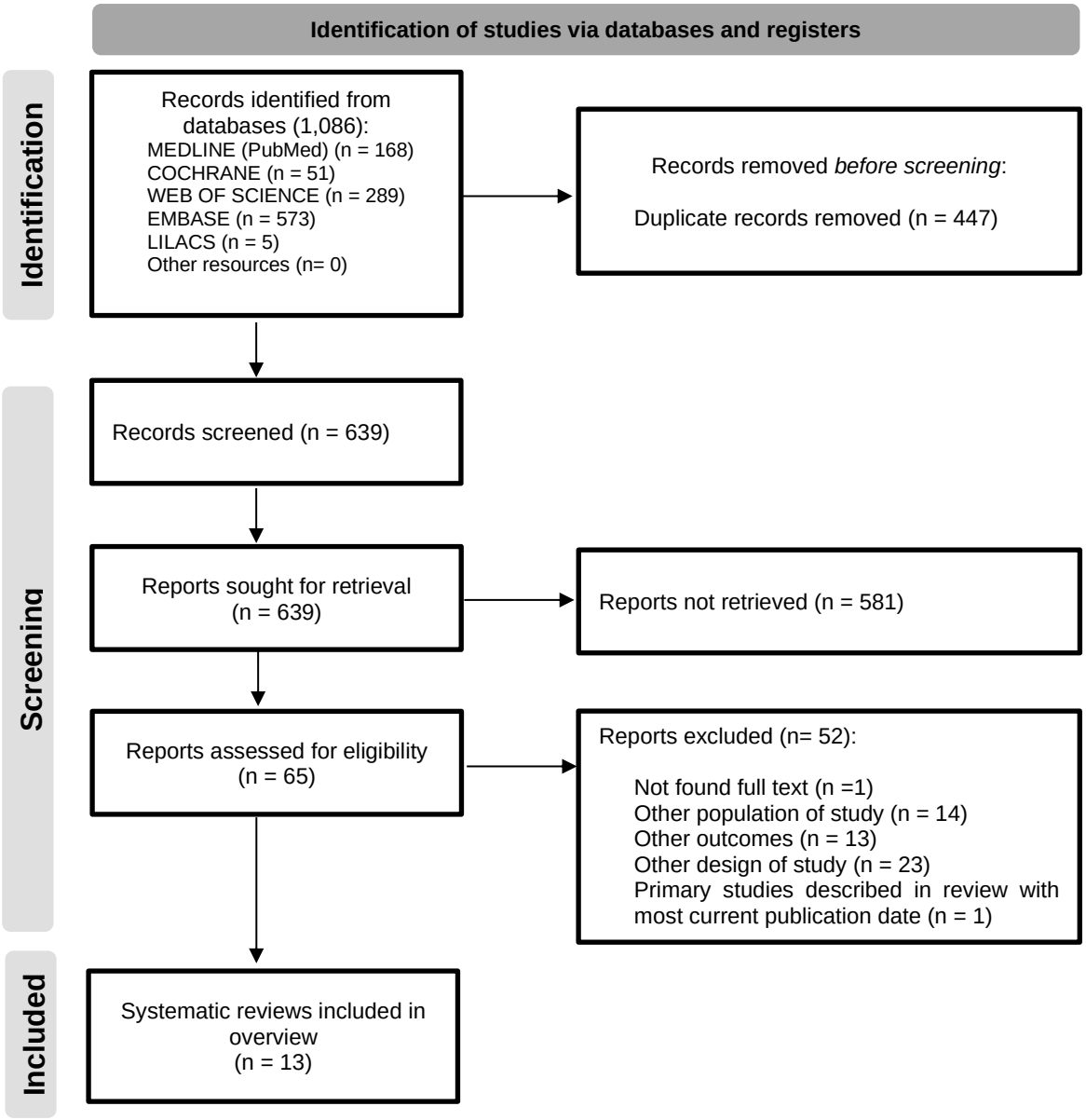
Methodological quality of systematic reviews

In general, the studies had methodological problems, mainly because the authors did not report statements that the methods were previously established; did not explain their selection of the study designs for inclusion; did not provide list of excluded studies and did not justify the exclusions. Information on the sources of funding was reported by one study only. They also did not conduct adequate investigations of publication bias and did not discuss its likely impact on the results of the review. The systematic reviews had at least one critical flaw and then were of low quality according to AMSTAR-2 (S2 Table).

Description of interventions and comparisons

The S1 Table describes the following interventions: psychological (n=9); psychoeducational (n=3); pharmacological (n=3) and health education (n=2). The outcomes reported by the studies were mainly about the effectiveness of the interventions: depression and anxiety improvement and/or remission, quality of life improvement, adherence to treatment for diabetes and reduction in HbA1c values. Only one study addressed the safety outcome with information on adverse drug reactions.

S1 Fig. Search flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

S1 Table. Characteristics of systematic reviews included (n=13)

Systematic review Country of study	N. of studies	N. of people	Age (years) (Range or mean ± SD)	*Psychological disorder	Intervention	Search period	Objectives of study
TYPE 2 DIABETES							
Berhe et al., 2020 (22) Ethiopia	7	1,983	Adults (18–87)	Depression and depressive symptoms	Psychological	Jan/2009 to Jun/2020	To analyze the literature for evidence of the effect of motivational interviewing intervention has on HbA1c and depression in adults with Type 2 diabetes
Xie et al., 2017 (23) China	31	2,616	Adults (NR)	Depression and anxiety	Psychological/ Psychosocial	Mar/2000 to Mar/2017	To explore the efficacy of psychosocial intervention in management of adults with Type 2 diabetes
Perrin et al., 2019 (24) United Kingdom	32	5,213	Adults (40–70)	Depression and distress	Psychoeducational	1946 to 2016	To determine interventions that successfully address depression and/or diabetes-specific emotional distress and HbA1c in adults with Type 2 diabetes
Hadjiconstantinou et al., 2016 (25) United Kingdom	9	3,612	Adults (24-67)	Depression, anxiety and distress	Web-based health education	1995 to 2016	To critically appraise and quantify the evidence on the effect of web-based interventions to improve well-being in people with Type 2 diabetes
TYPE 1 AND TYPE 2 DIABETES							
Baumeister et al., 2012 (26) Germany	19	1,592	Adults (45–71)	Depression	Psychological, pharmacological and health education	Up to Dec 2011	To determine the effects of this interventions for depression in adults with diabetes
**Li et al., 2017 (27) China	10	998	Any age (NR)	Depression and anxiety	Psychological	Up to May 2016	To examine the efficacy of CBT for people with diabetes and depression and to identify which aspects can be improved through intervention in these population
Ni et al., 2020 (28) China	7	741	≥ 16 years old (18-69)	Depression	Psychological	Up to Dec 2019	To determine the effectiveness of MBCT and MBSR on depression in people with diabetes
**Uchendu et al., 2016 (29) United Kingdom	09	1,445	Adults (37 ± 11)	Depression and anxiety	Psychological	1806 to 2014	To establish the effectiveness of CBT on glycemic values and comorbid diabetes-related distress, depression, anxiety and quality of life

							in the short, medium and longer term, among adults with diabetes
Vanderfeltz-Cornelis et al., 2020 (30) United Kingdom	32	3,543	Adults (NR)	Depression	Psychological, pharmacological, and psychoeducational	Up to Aug 2019	To provide an estimate of the effect of interventions on comorbid major depressive disorder or subthreshold depression in adults with diabetes
Wang et al., 2017 (31) China	5	834	Adults (NR)	Depression	Psychological	Up to Oct 2016	To evaluate the effect of CBT in improving the depression symptoms of adults with diabetes
Yang et al., 2020 (32) China	23	2,705	Adults (NR)	Depression	Psychological	2007 to Apr 2019	To provide an overview of the effectiveness of CBT for improving glycemic values, psychological, and physiological outcomes in adults with diabetes
Huang et al., 2013 (33) China	8	2,203	Any age (NR)	Depression	Psychoeducational	1806 to 2013	To examine whether collaborative care can improve depression and diabetes outcomes in people with both diseases
Li et al., 2020 (34) China	12	822	Any age (20-68)	Depression	Pharmacological	Up to May 2019	To evaluate the efficacy and safety of *Gardenia fructus* antidepressant formula for depression in people with diabetes

CBT (cognitive behavioural therapy). MBCT (mindfulness-based cognitive therapy). MBSR (mindfulness-based stress reduction). N (number). SD (Standard Deviation). NR (not reported)
*The tools/scales used by clinical trials to measure outcomes (depression, anxiety, among others) are available in **S3 Appendix.**
**Systematic reviews that reported duration of diabetes. These reviews included population that have at least 6 months of diagnosis of diabetes mellitus).

S2 Table. Methodological quality of the systematic reviews' assessment by AMSTAR-2 (n=13)

References	01	*02	03	*04	05	06	*07	08	*09	10	*11	12	*13	14	*15	16
Baumeister et al., 2012 (26)																
Berhe et al., 2020 (22)																
Hadjiconstantinou et al., 2016 (25)																
Huang et al., 2013 (33)																
Li et al., 2017 (27)																
Li et al., 2020 (34)																
Ni et al., 2020 (28)																
Perrin et al., 2019 (24)																
Uchendu et al., 2016 (29)																
Vanderfeltz-Cornelis et al., 2020 (30)																
Wang et al., 2017 (31)																
Yang et al., 2020 (32)																
Xie et al., 2017 (23)																

AMSTAR-2: Assessment of Multiple Systematic Reviews-2. *Issues considered by AMSTAR as critically important.

Yes	Partial Yes	No

1. *Did the research questions and inclusion criteria for the review include the components of PICO?*
**2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct it and did the report justify any significant deviations from the protocol?*
3. Did the review authors explain their selection of the study designs for inclusion in the review?
**4. Did the review authors use a comprehensive literature search strategy?*
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
**7. Did the review authors provide a list of excluded studies and justify the exclusions?*
8. Did the review authors describe the included studies in adequate detail?
*9. *Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*
10. Did the review authors report on the sources of funding for the studies included in the review?
**11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?*
12. If meta-analysis was performed, did the review authors assess the impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
**13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?*
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
**15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Psychological interventions (n= 9 reviews) (S3 Table)

Psychological interventions are those in which problems are understood in terms of emotions, cognitions and behaviors (35) as psychodynamic psychotherapy, interpersonal psychotherapy, supportive therapy, counseling therapy, CBT, psychoanalytically informed therapies, family systems therapy, among others. They can be performed individually, in groups or among families (23,26,35). CBT was the most studied intervention (five out of nine systematic reviews).

Population specified with type 2 diabetes (n= 2)

Motivational interviewing had no effect on reduction of depressive symptoms in adults with type 2 diabetes (3- and 24-months follow-up). This findings were based on clinical trials that had high heterogeneity and the quality of the evidence was not assessed (22).

One systematic review addressed intervention of social psychology, knows as psychosocial. This intervention reduced depressive and anxiety symptoms in adults with type 2 diabetes and improved glycemic values. However, the randomized clinical trials had high heterogeneity and the quality of the evidence was not assessed (23).

Population with type 1 and type 2 diabetes (n= 7)

CBT is an organized and time-limited approach with content such as psychoeducation, behavioral activation, cognitive restructuring, and relapse prevention. It can reduce depression by identifying and evaluating negative thoughts (27,29).

CBT, CBT via telephone, and CBT via internet (websites and/or virtual platforms as sources of information) showed beneficial effects on improvement of depression and glycemic values, in adults with type 1 and type 2 diabetes, compared to usual care or a waiting list; upon medium-term follow-up (up to 6 months) in case of the intervention using CBT and CBT via telephone; and during one-month follow-up in case of CBT via internet. Meta-analysis indicated high heterogeneity between the studies, and in general, the quality of the evidence was considered low, when reported (26).

S3 Table. Results of psychological interventions (n= 9 reviews)

References	Outcomes	N. of people	Meta-analysis results (95% CI)	Author's results	Publication bias and quality of evidence
PSYCHOLOGICAL INTERVENTIONS (n= 4 reviews)					
Berhe et al., 2020 (22)	**Reduction in depressive symptoms** (Motivational Interviewing vs control group) - session time of 30 minutes follow up was NR	68	WMD= -1.58 (-5.05 to -0.19) I^2=48%	Motivational Interviewing was not superior to control group	**PB=** absent (Egger's test) **GRADE=** NR
	Reduction in depressive symptoms (Motivational Interviewing vs control group) - session time of 60 minutes follow up was NR	1,031	WMD= -4.30 (-9.32 to -0.73) I^2=95%	Motivational Interviewing was not superior to control group	**PB=** absent (Egger's test) **GRADE=** NR
	Reduction in depressive symptoms (Motivational Interviewing vs control group) 3 months follow up	129	WMD= -4.45 (-10.58 to 1.69) I^2=96%	Motivational Interviewing was not superior to control group	**PB=** absent (Egger's test) **GRADE=** NR
	Reduction in depressive symptoms (Motivational Interviewing vs control group) 24 months follow up	970	WMD= -2.12 (-5.54 to 1.30) I^2=83%	Motivational Interviewing was not superior to control group	**PB=** absent (Egger's test) **GRADE=** NR
	Reduction in HbA1c values (Motivational Interviewing vs control) in adults follow up was NR	1,428	WMD= -0.27 (-0.46 to -0.09) I^2=38%	Motivational Interviewing was superior to control group	**PB=** absent (Egger's test) **GRADE=** NR
Ni et al., 2020 (28)	**Reduced depression scores** (MBSR or MBCT vs control group) follow up was NR	641	SMD= -0.84 (-1.16 to -0.51) I^2=72%	MBSR or MBCT was superior to control group	Publication bias= NR **GRADE=** NR
	Score of quality of life (mental health) (MBSR or MBCT vs control group) follow up was NR	443	MD= 7.06 (5.09 to 9.03) I^2=0%	MBSR or MBCT was superior to control group	Publication bias= NR **GRADE=** NR
	Score of quality of life (physical health) (MBSR or MBCT vs control group follow up was NR	443	MD= 3.14 (-0.38 to 6.67) I^2=73%	MBSR or MBCT was superior to control group	**PB=** NR **GRADE=** NR

	Reduction in HbA1c values (MBSR or MBCT vs control group) follow up was NR	578	MD= -0.28 (-0.47 to -0.09) I^2=0%	MBSR or MBCT was superior to control group	**PB=** NR **GRADE=** NR
Vanderfeltz-Cornelis et al., 2020 (30)	**Reduced depression scores** (Psychological Interventions vs control group) follow up was NR	NR	SMD= 0.56 (0.42 to 0.70) I^2=NR	Psychological Interventions was superior to control group	**PB=** Small effect (Begg funnel plot) **GRADE=** moderate to high
	Reduction in HbA1c values (Psychological Interventions vs control group) follow up was NR	NR	SMD= 0.61 (0.15 to 1.07) I^2=NR	Psychological Interventions was superior to control group	**PB=** Small effect (Begg funnel plot) **GRADE=** moderate to high
*Xie et al., 2017 (23)	**Reduced depression symptoms** (Psychosocial vs control group) until 16 months follow up	2,476	SMD= -1.50 (-1.83 to -1.18) I^2=92%	Psychological Interventions was superior to control group	**PB=** NR **GRADE=** NR
	Reduced anxiety symptoms (Psychosocial vs control group) until 16 months follow up	871	SMD= -1.18 (-1.50 to -0.85) I^2=79%	Psychological Interventions was superior to control group	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (Psychosocial vs control group) until 16 months follow up	1,765	SMD= -0.81 (-1.10 to -0.53) I^2=87%	Psychological Interventions was superior to control group	**PB=** NR **GRADE=** NR
COGNITIVE BEHAVIORAL THERAPY (n= 5 reviews)					
Baumeister et al., 2012 (26)	**Reduction in depression scores** (CBT vs usual care) until 6 months follow up	41	SMD= -1.10 (-1.75 to -0.45) I^2=66%	CBT was superior to usual care	**PB=** NR **GRADE=** NR
	Depression remission rate (CBT vs usual care) until 6 months follow up	41	OR= 4.67 (1.25 to 17.44) I^2=7%	CBT was superior to usual care	**PB=** NR **GRADE=** low
	Reduction in depression scores (CBT vs usual care) until 6 months follow up	42	MD= -1.40% (-2.60 to -0.20) I^2=78%	CBT showed a significant reduction compared to usual care	**PB=** NR **GRADE=** low
	Reduction in depression scores (Telephone-delivered CBT vs usual care) until 1 month of follow up	291	SMD= -0.42 (-0.66 to -0.18) I^2=86%	Telephone-delivered CBT was superior to usual care	**PB=** NR **GRADE=** NR

	Depression remission rate (Telephone-delivered CBT vs usual care) until 1 month of follow up	291	OR= 1.83 (1.12 to 3.00) I^2=57%	Telephone-delivered CBT was superior to usual care	**PB=** NR **GRADE=** moderate
	Reduction in depression scores (Web-based CBT vs waiting-list) until 6 months follow up	255	SMD= -0.29 (-0.41 to -0.17) I^2=66%	Web-based CBT was superior to control group	**PB=** NR **GRADE=** NR
	Depression remission rate (Web-based CBT vs waiting-list) until at 6 months follow up	255	OR= 2.20 (1.28 to 3.77) I^2=7%	Web-based CBT was superior to control group	**PB=** NR **GRADE=** low
	Reduction in HbA1c values (Web-based CBT vs waiting-list control group) until 6 months follow up	255	MD= 0.4% (0.1 to 0.7) I^2=78%	Web-based CBT was inferior to the waiting-list	**PB=** NR **GRADE=** low
Li et al., 2017 (27)	**Reduced depression scores** (CBT vs usual care) until 6 months follow up	381	SMD= −0.86 (−1.41 to − 0.31) I^2=81%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
	Reduced depression scores (CBT vs usual care) until 12 months follow up	719	SMD = −0.38 (−0.57 to −0.19) I^2=81%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
	Reduced anxiety scores (CBT vs usual care) until 6 months follow up	135	SMD = −0.04 (−0.76 to 0.67) I^2=77%	CBT did not show difference compared to control group	**PB=** NR **GRADE=** NR
	Reduced anxiety scores (CBT vs usual care) until 12 months follow up	115	SMD = −0.49 (−0.88 to −0.10) I^2=9%	CBT did not show difference compared to control group	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (CBT vs usual care) until 6 months follow up	303	SMD = −0.30 (−0.71 to 0.10) I^2=74%	CBT did not show difference compared to control group	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (CBT vs usual care) until 12 months follow up	705	SMD = −0.19 (−0.47 to 0.09) I^2=74%	CBT did not show difference compared to control group	**PB=** NR **GRADE=** NR

	Improvement in quality of life (CBT vs usual care) until 12 months follow up	653	SMD = 0.29 (0.08 to 0.51) I^2=38%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
Uchendu et al., 2016 (29)	**Reduced depression scores** (CBT vs control group) until 8 months follow up	487	SMD= -0.43 (-0.79 to -0.06) I^2=73%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
	Reduced depression scores (CBT vs control group) until 12 months follow up	662	SMD= -0.26 (-0.41 to -0.10) I^2=44%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
	Reduced anxiety scores (CBT vs control group) until 8 months follow up	194	SMD= -0.56 (-0.85 to -0.27) I^2=0%	CBT had improvement compared to control group	**PB=** NR **GRADE=** NR
	Reduced depression scores (CBT vs control group) until 12 months follow up	74	SMD= -0.33 (-0.79 to 0.13) $I^{2=}$NR	CBT did not have significant effect compared to control group	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (CBT vs usual care) until 8 months follow up	459	SMD= -0,36 (-0.55 to -0.18) I^2=44%	CBT had a significant effect compared to control group	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (CBT vs usual care) until t 12 months follow up	644	SMD= -0,11 (-0.26 to 0.05) I^2=0%	CBT did not have significant effect compared to control group	**PB=** NR **GRADE=** NR
Wang et al., 2017 (31)	**Reduced depression symptoms** (CBT vs usual care) post-intervention	466	SMD= –0.43 (-0.73 to -0.12) I^2=58%	CBT had a significant effect compared to control group	**PB=** absent (Egger's test and funnel plot) **GRADE=** NR
	Reduced depression symptoms (CBT vs usual care) until 12 months follow up	455	SMD= -0.38 (-0.54 to -0.23) I^2=25%	CBT had a significant effect compared to control group	**PB=** absent (Egger's test and funnel plot) **GRADE=** NR
Yang et al., 2020 (32)	**Reduced depression symptoms** (CBT vs control group) follow up was NR	NR	MD= -2.788 (-4.45 to -1.03) I^2=97%	CBT had a significant effect compared to control group	**PB=** minimal (Egger's test and funnel plot) **GRADE=** NR

Reduction in HbA1c values (CBT vs control group) follow up was NR	NR	MD= -0.275 (-0.44 to -0.12) I^2=87%	CBT had a significant effect compared to control group	**PB=** absent (Egger's test and funnel plot) **GRADE=** NR

95% CI (95% confidence interval). CBT (cognitive behavioural therapy). GRADE (grading of recommendations assessment, development and evaluation). HbA1c (haemoglobin A1c). I^2 (heterogeneity). MBCT (mindfulness-based cognitive therapy). MBSR (mindfulness-based stress reduction). MD (mean). NR (not reported). OR (odds ratio). PB (publication bias). RR (risk ratio). SMD (standardised mean differences). WMD (weighted mean differences).
*Psychological Interventions reported: interpersonal therapy, problem solving therapy, behavioural therapy and cognitive behavioural therap. Control groups: Not reported.

CBT showed positive effects on the response to treatment of depression in the long-term, in adults with type 1 and type 2 diabetes. There was no difference between the interventions in relation to response to anxiety, glycemic control, and the quality of life. In general, these findings were based on studies with high heterogeneity and presence of publication bias. The quality of evidence was not reported (27).

CBT improved depression scores in adults and elderly with type 1 and type 2 diabetes (12 months of follow-up), while anxiety scores and HBA1c values decreased up to 8 months post-intervention. In general, the findings varied from low to high heterogeneity, and the quality of evidence was not reported (29).

CBT improved the depression scores of adults with type 1 and type 2 diabetes compared to control group, for up to 12 months of follow-up. The findings showed low to moderate heterogeneity, and the quality of the evidence was not reported. The authors warn of some limitations in the findings, such as sample size, intervention duration, different comparators, and a reduced number of evaluated outcomes (31).

Systematic review shown the effectiveness of CBT for improving glycemic values and reducing depression scores, in adults with type 1 and type 2 diabetes. In general, the findings were highly heterogeneous and the quality of the evidence was not reported (32). Mindfulness-based cognitive therapy (MBCT) and mindfulness-based stress reduction (MBSR) had significant effects compared to control group on reducing depression scores, reduction HbA1c values and quality of life improvement. This information is based on findings with high heterogeneity and the quality of evidence was not reported (28).

Systematic reviews provided an estimate of the effect of psychological interventions (not specified) on comorbid major depressive disorder or subthreshold depression in adults with diabetes. Reduction in the depression scores and in HbA1c values was observed. This information is based on findings with low heterogeneity, and moderate to high quality of evidence (30).

Psychoeducational interventions (n=3 reviews) (S4 Table)

Psychoeducational interventions provide information and guidance for diabetes care and/or psychological self-management (24). Among this type of intervention, collaborative care is a coordinated management model of primary health care that

involves doctors, nurses, mental health professionals, and other professionals who provide patient-oriented management based on guidelines at this level of care (24,33).

Population specified with type 2 diabetes (n=1)

One systematic review described the results of psychoeducational interventions grouped (did not show results by type of intervention). The interventions reduced diabetes-specific emotional distress and HbA1c values, in adults with type 2 diabetes, compared to controls (in general, defined as usual care). Most of the meta-analyses that explored the effect of specific interventions (subgroup analysis) verified no significant results supporting each intervention. However, a reduction in diabetes-specific emotional distress levels was observed for collaborative care compared to usual care. A reduction in HbA1c values for “digital platform” intervention was also compared to usual care. Such findings need to be confirmed since the quality of the evidence is low (24).

Collaborative care intervention (n=2 reviews) **(S4 Table)**

Population with type 1 and type 2 diabetes (n=2)

Systematic review showed positive effects of collaborative care on the rate of response to depression treatment in adults at 6, 12 and 24 months of follow-up. However, it did not seem to benefit in long-term depression remission (12 and 24 months). The intervention was also significantly associated with higher rates of adherence to antidepressant medication and oral hypoglycemic agents. Meta-analyses showed that improvement in depression outcomes were not accompanied by significant differences in HbA1c values between the groups, until 24 months of follow-up. The quality of evidence was not reported (33).

Other systematic review observed a moderate effect on depression score reduction and improvement of glycemic values with the use of collaborative care. The quality of evidence was moderate (30).

S4 Table. Results of psychoeducational interventions (n=3 reviews) and health education (n=2 reviews)

References	Outcomes	N. of people	Meta-analysis results (95% CI)	Author's results	Publication bias and quality of evidence
PSYCHOEDUCATIONAL INTERVENTIONS (n=3)					
*Huang et al., 2013 (33)	**Depression treatment response rate** (Collaborative care *vs* usual care) follow up was NR	1,096	RR= 1.96 (1.38 to 2.78) I^2= 59%	Increased treatment response rate in the Collaborative care group was significant	**PB**= NR **GRADE=** low
	Depression treatment response rate (Collaborative care *vs* usual care) until 6 months follow up	1,118	RR= 1.64 (1.28 to 2.10) I^2= 54%	Beneficial effect significant of Collaborative care group	Publication bias= NR **GRADE=** low
	Depression treatment response rate (Collaborative care vs usual care) until 12 months follow up	1,096	RR= 1.33 (1.05 to 1.68) I^2= 59%	Indicated a 33% relative increase in treatment response rate in Collaborative care group	**PB**= NR **GRADE=** low
	Depression remission rate (Collaborative care group *vs* usual care) until 6 months follow up	595	RR= 1.33 (1.01 to 1.75) I^2= 0%	Significant increase in the response with Collaborative care	**PB=** NR **GRADE=** low
	Depression remission rate (Collaborative care group *vs* usual care) until 12 months follow up	579	RR= 1.20 (0.93 to 1.55) I^2= 0%	Non-significant effect of depression remission rate	**PB=** NR **GRADE=** low
	Depression remission rate (Collaborative care *vs* usual care) until 24 months follow up	552	RR= 1.15 (0.87 to 1.52) I^2= 0%	Non-significant effect of Collaborative care	**PB=** NR **GRADE=** unclear
	Adherence to antidepressants (Collaborative care group *vs* usual care) follow up was NR	891	RR= 1.79 (1.19 to 2.69) I^2= 84%	Statistically significant positive effect to antidepressant medication	**PB=** NR **GRADE=** low

	Adherence to antidepressants and oral hypoglycaemic agents (Collaborative care group *vs* usual care) follow up was NR	238	RR= 2.18 (1.61 to 2.96) I^2= 0%	Significant positive effect on rates of adherence to medication	**PB=** NR **GRADE=** low
	Reduction in HbA1c values (Collaborative care group *vs* usual care) until 6 months follow up	1,101	MD= -0.06 (-0.24 to 0.12) I^2= 16%	Non-significant reduction in HbA1c values in favour of Collaborative care	**PB=** NR **GRADE=** low
	Reduction in HbA1c values (Collaborative care group *vs* usual care) until 12 months follow up	1,053	MD= -0.07 (-0.28 to 0.13) I^2= 36%	Non-significant reduction in HbA1c values in favour of Collaborative care	**PB=** NR **GRADE=** low
**Perrin et al., 2019 (24)	**Reduction of diabetes-specific emotional distress** (Psychoeducational group *vs* control group) follow up was NR	5,206	SMD= -0.13 (-0.25 to -0.01) I^2= 77%	Significant effect significant of psychoeducational interventions	**PB=** absent (Egger's test and funnel plot) **GRADE=** low
	Reduction in HbA1c values (Psychoeducational group *vs* control group) follow up was NR	5,206	SMD= -0.28 (-0.48 to -0.08) I^2= 71%	Significant effect significant of psychoeducational interventions	**PB=** absent (Egger's test and funnel plot) **GRADE=** low
Vanderfeltz-Cornelis et al., 2020 (30)	**Reduced depression scores** (Collaborative care vs control group) follow up was NR	NR	SMD= 0.43 (0.284 to 0.583) I^2= NR	Collaborative care had a moderate effect compared to control group	**PB=** small effect (Begg funnel plot) **GRADE=** moderate
	Reduction in HbA1c values (Collaborative care vs control group) follow up was NR	NR	SMD= 0.21 (0.05 to 0.36) I^2= NR	Collaborative care had a small effect compared to control group	**PB=** small effect (Begg funnel plot) **GRADE=** moderate
	HEALTH EDUCATION (n=2)				
Baumeister et al., 2012 (26)	**Depression remission rate** (Health education vs usual care) until 12 months follow up	59	OR= 3.33 (1.14 to 9.75) I^2= 57%	Health education was superior to usual care	**PB=** NR **GRADE=** moderate
	Reduction in HbA1c values (Health education vs usual care) until 12 months follow up	59	MD= -2.00 (-3.10 to -1.00) I^2= 83%	Health education was superior to usual care	**PB=** NR **GRADE=** low

Hadjiconstantinou et al., 2016 (25)	**Reduced depression scores** (Web-based interventions vs usual care) until 18 months follow up	1,321	SMD= -0.31 (-0.73 to 0.11) I^2= 89%	Effect was not significant compared to control	**PB=** absent (Egger's test and funnel plot) **GRADE=** NR
	Reduced distress scores (Web-based interventions vs usual care) until 18 months follow up	2,167	SMD= -0.11 (-0.38 to 0.16) I^2= 88%	Effect was not significant compared to control	**PB=** absent (Egger's test and funnel plot) **GRADE=** NR

95% CI (95% confidence interval). GRADE (grading of recommendations assessment, development and evaluation). HbA1c (haemoglobin A1c). I^2 (heterogeneity). MD (mean difference). NR (not reported). OR (odds ratio). PB (publication bias). RR (risk ratio). SMD (standardised mean difference).
*Interventions reported: multi-professional patient care; structured management plan; scheduled patient follow-up; enhanced inter-professional communication. Control groups reported: no additional intervention; usual care.
**Interventions reported: not reported. Control groups: not reported.

Health education (n=2 reviews) (S4 Table)

Population specified with type 2 diabetes (n=1)

Web-based health education (via telephone calls or SMS - short message service texts) provided information on education, peer support, and/or overall therapeutic components for adults with type 2 diabetes. The results did not differ in relation to depression and anxiety scores compared to control groups (usual care or sessions with a health professional or minimal computer support, among others). High heterogeneity was observed among studies and the quality of the evidence was not assessed (25).

Population with type 1 and type 2 diabetes (n=1)

Health education was superior to usual care in the depression remission and glycemic control. However, this information is based on findings with medium to high heterogeneity and moderate quality of evidence (26).

Pharmacological interventions (n=3 reviews) (S5 Table)

Population with type 1 and type 2 diabetes (n=3)

Specific serotonin reuptake inhibitors (SSRIs) showed improvement in short-term depression severity scores, short-term depression remission and glycemic control, in adults with type 1 and type 2 diabetes, compared to placebo. However, the evidence was of low quality, and the patients' follow-up period did not exceed six months. The authors reported that other outcomes, such as medium- and long-term depression and glycemic control outcomes, as well as healthcare costs, diabetes complications and mortality, were not evaluated in clinical trials. The review did not collect information on the adverse drug reaction (26).

Pharmacological treatment (mainly SSRIs) showed significant effects in terms of depression outcomes, but small in terms of glycemic values. Although interventions were effective for depression, they were not effective for glycemic control. However, the quality of evidence was not performed by review. The review did not collect information on the adverse drug reaction (30).

S5 Table. Results of pharmacological interventions (n= 3 reviews)

References	Outcomes	N. of people	Meta-analysis results (95% CI)	Author's results	Publication bias and quality of evidence
Baumeister et al., 2012 (26)	**Improvement depression severity scores** (Pharmacological interventions vs placebo) until 6 months follow up	306	SMD=-0.61 (-0.94 to -0.27) I^2= 47%	Beneficial effect of antidepressants	**PB=** NR **GRADE=** NR
	Improvement depression severity scores (SSRIs vs placebo) until 6 months follow up	241	SMD= -0.39 (-0.64 to -0.13) I^2= 0%	Beneficial effect of SSRIs	**PB=** NR **GRADE=** NR
	Depression remission rate (Pharmacological interventions vs placebo) until 6 months follow up	136	OR= 2.50 (1.21 to 5.15) I^2= 0%	Beneficial effect of antidepressants	**PB=** NR **GRADE=** low
	Depression remission rate (SSRIs vs placebo) - short-term	108	OR= 2.52 (1.11 to 5.75) I^2= 0%	Beneficial effect of SSRIs	**PB=** NR **GRADE=** NR
	Reduction in HbA1c values (Pharmacological interventions vs placebo) until 6 months follow up	238	MD= -0.4% (-0.60 to -0.10) I^2= 0%	Beneficial effect of antidepressants	**PB=** NR **GRADE=** low
Li et al., 2020 (34)	**Improvement depression severity scores** (*Gardenia Fructus* antidepressant formula vs no antidepressant) follow up was NR	71	RR= -2.53 (-4.80 to -0.27) I^2= 96%	*Gardenia Fructus* antidepressant formula had lower HAMD scores compared to control group	**PB=** NR **GRADE=** NR
	Improvement depression severity scores (*G. Fructus* antidepressant vs SSRIs) follow up was NR	225	RR= -0.62 (-1.07 to -0.18) I^2= 80%	*Gardenia Fructus* antidepressant formula had lower HAMD scores compared to SSRI group	**PB=** NR **GRADE=** NR
	Depression treatment response rate (*G. Fructus* antidepressant vs no antidepressant) follow up was NR	74	RR= 1.66 (0.97 to 2.83) I^2= 80%	*Gardenia Fructus* antidepressant formula did not significantly increase response rate compared to control group	**PB=** NR **GRADE=** NR

	Depression treatment response rate (*G. Fructus* antidepressant vs SSRIs) follow up was NR	79	RR= 1.12 (0.96 to 1.31) I^2= 0%	*G. Fructus* antidepressant formula did not significantly increase response rate compared to SSRI	**PB=** NR **GRADE=** NR
Vanderfeltz-Cornelis et al., 2020 (30)	**Reduced depression scores** (Pharmacological vs control group) follow up was NR	NR	ES= 0.57 (0.35 to 0.79) I^2= NR	Pharmacological had a significant effect compared to control group	**PB=** small effect (Begg funnel plot) **GRADE=** moderate to high
	Reduction in HbA1c values (Pharmacological vs control group) follow up was NR	NR	ES= 0.99 (0.13 to 1.80) I^2= NR	Pharmacological had a small effect compared to control group	**PB=** small effect (Begg funnel plot) **GRADE=** moderate to high

95% CI (95% confidence interval). I^2 (heterogeneity). GRADE (Grading of Recommendations Assessment, Development and Evaluation). HAMD (Hamilton Depression Scale). HbA1c (haemoglobin A1c). MD (Mean Difference). NR (Not Reported). OR (odds ratio). PB (publication bias). RR (risk ratio). SMD (standardised mean difference). SSRI (Specific Serotonin Reuptake Inhibitors).

Gardenia Fructus antidepressant formula significantly improved the depressive symptoms in people compared to no antidepressant treatment. However, the formula increased the incidence of headache/dizziness and diarrhea. *G. Fructus* antidepressant formula alone or in combination with SSRIs, reduced the depressive symptoms compared to SSRIs alone. Sensitivity analysis suggests that the findings could be inconclusive due to study heterogeneity (in terms of diagnostic criteria or methodological quality). The incidence of adverse events in the *G. Fructus* antidepressant formula group and the herbal medicine plus SSRI group was not statistically different from SSRI group (34).

Discussion

Summary of the main findings

This study included 13 systematic reviews, nine of which included people with both type 1 and type 2 diabetes and four included population with specific type 2 diabetes. No study reported only children and adolescents. The population described was mainly of adults with type 1 or type 2 diabetes and with depression.

In general, the interventions seem be effectiveness for most of the evaluated outcomes and mainly for depression, since only four reviews reported population with anxiety. The safety outcomes were restricted to report of adverse drug reactions, reported in only one review. It is important to emphasize that the reviews had methodological problems, which may limit confidence in the findings.

CBT is an organized and time-limited approach with content such as psychoeducation, behavioral activation, cognitive restructuring, and relapse prevention. It can reduce depression by identifying and evaluating negative thoughts. It can be useful for people with chronic illness by way of improving self-care skills and learning to adjust to the disease and its impact on their daily lives (27,29). This intervention showed promising results for most of the evaluated outcomes and mainly for depression, in adults with type 1 or type 2 diabetes. The anxiety outcome was reported in two studies, with divergent results between them (27,29). The divergences can be explained by differences in clinical trials included in reviews, since there was an overlap of around 30% of these studies included in both reviews. One systematic review observed improvement of the quality of life comparing CBT with usual care (26). In general, the findings were heterogeneous and there was lack of detail of reported evidence by three of five systematic reviews.

Other psychological interventions evaluated were psychosocial, mindfulness-based cognitive therapy, mindfulness-based stress reduction and motivational interviewing; except for the latter, the other interventions reduced depressive symptoms in adults.

Among psychoeducational interventions, two systematic reviews about collaborative care shown that the depression treatment response rate/depression scores, the HBA1c values and the adherence to treatment had improvements with this intervention. These findings were based on low to moderate quality of evidence (30,33). The use of a digital platform reduced HbA1c values compared to usual care (24).

Health education was superior to usual care in the depression remission and glycemic control, in adults with type 1 and type 2 diabetes (moderate quality of evidence) (26). Other review did not observe benefits of this web-based intervention to reduce depression or distress rate, in adults with type 2 diabetes (25).

Three systematic reviews addressed the use of drugs to treat depression in people with diabetes. The results shown that SSRIs seem to improve short-term depression severity scores, short-term depression remission and glycemic control compared with placebo (26). Other review show that the use of herbal medicine (*Gardenia Fructus*) alone and combined with SSRIs, improved the depressive symptoms compared to placebo and SSRI alone (34). The authors of reviews concluded that the results should be confirmed in people with type 1 and type 2 diabetes. It is important to highlight that some precautions must be considered in relation to the use of antidepressants, since that these drugs can interfere with the weight gain and the metabolic changes in the population with diabetes (36).

Strengths and limitations of the study

This review summarized the available evidence on interventions to treat depression and/or anxiety in people with type 1 and type 2 diabetes. Although the quality of the evidence reported was restricted to the information described by systematic reviews and can be affected by the methodological quality of these studies; the benefit of was to broadly demonstrate what the literature reports about the subject, as well as to highlight the lack of information. Furthermore, this study included a comprehensive literature search, all stages of selection and data extraction were performed, in both pairs and independently, and there was no language restriction with respect to the reviews included.

Of a total of 204 clinical trials identified within the systematic reviews, 37.8% of them were included in more than one review. There was no overlap of clinical trials about to the intervention's health education, collaborative care and some psychological interventions. Of the 66 clinical trials (included in the five systematic reviews) about CBT intervention, 31.0% of them had overlapped. Two reviews evaluating pharmacological interventions presented overlap in 50% of the articles included, however, one of them described in more detail the drugs and the evaluated outcomes.

It is important to emphasize that safety outcomes were restricted to report of adverse drug reactions and quality of life was assessed in only two systematic reviews. Costs, diabetes complications and mortality were not reported by clinical trials, although they are relevant outcomes to assessing the effectiveness and safety of interventions health care (24,26).

Most of the systematic reviews included adults with type 1 and type 2 diabetes and did not perform subgroup analyses for the type of psychological diseases (depression or anxiety), age or follow-up time. These findings could explain the heterogeneity observed in results, since psychological diseases can manifest themselves differently in people with type 1 and type 2 diabetes and the follow-up time also differed between the clinical trials.

Implications for clinical practice and research

CBT, collaborative care, health education (except web-based health education) and pharmacological interventions showed positive results, mainly for the treatment of depression and improve glycemic values of people with diabetes.

CBT showed to have promising results for most of the evaluated outcomes. This intervention showed to be more effective when the frequency of the meetings was at least four times a month (26). Collaborative care can also be an effective tool for professionals who want to improve medication adherence in these people (33). Health education can promote well-being in people with diabetes and emotional diabetes management (25). The pharmacological intervention was evaluated in few studies and this could have occurred, since trials on the treatment of depression are not limited to a specific population.

Although the interventions were effective in most of the evaluated outcomes, it is important to emphasize that the reviews had methodological problems, as well as there was heterogeneity in reported outcomes and absence of report of some

outcomes. The quality of the evidence was not cited in some reviews and, when evaluated, varied from low to moderate. It was observed that no systematic review about the population with anxiety assessed the quality of the evidence, limiting confidence in its findings. The population of children and adolescents has been little studied. Too no review addressed the effectiveness of combined interventions, which can be adopted to treat depression and/or anxiety in this population. In the face of these reports, additional clinical trials can confirm our findings and expand the scope of the research to include groups of people with specific age, types of diabetes and psychological disorders (depression, anxiety or diabetes-specific distress).

Conclusion

The interventions reported in literature can be effective to treat mainly adults with diabetes and depression and CBT showed promising results for treat this population for most of the evaluated outcomes. Considering the limitations observed in the reported of quality of evidence, future randomized clinical trials can confirm these findings, as well as consider the gaps identified in the literature. This study can guide patients, their caregivers and health professionals in making decisions concerning the use of these interventions in the mental healthcare of people with diabetes.

Supporting Information

S1 Table. Characteristics of systematic reviews included

S2 Table. Methodological quality of the systematic reviews' assessment by AMSTAR-2

S3 Table. Results of psychological interventions

S4 Table. Results of psychoeducational interventions and health education

S5 Table. Results of pharmacological interventions

S1 Fig. Search flow diagram

S1 Appendix. Search strategy

S2 Appendix. Characteristics of excluded studies

S3 Appendix. Supporting information file

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Declaration of competing interests

The authors report no conflicts of interest in this study.

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S1 Appendix. Search strategy

MEDLINE (via PubMed) (n=136)

#1Diabetes Mellitus, Type 1 [MeSH] + Entry Terms	((((((((((((((((((((((((((((((((((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ("autoimmune"[All Fields] AND "diabetes"[All Fields])) OR "autoimmune diabetes"[All Fields]) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (("brittle"[All Fields] AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "brittle diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR "iddm"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ((("insulin"[All Fields] AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "insulin dependent diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR "insulin dependent diabetes mellitus 1"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ((("insulin"[All Fields] AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "insulin dependent diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR "insulin dependent diabetes mellitus 1"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (("juvenile"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields])) OR "juvenile onset diabetes"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ((("juvenile"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "juvenile onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (("juvenile"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields])) OR "juvenile onset diabetes"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ((("juvenile"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "juvenile onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (((ketosis"[All Fields] AND "prone"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "ketosis prone diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (((ketosis"[All Fields] AND "prone"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "ketosis prone diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR ((("sudden"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "sudden onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR (((sudden"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "sudden onset diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR "type 1 diabetes"[All Fields])) OR ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields]) OR "type i diabetes mellitus"[All Fields]))
#2Diabetes Mellitus, Type 2 [MeSH] + Entry Terms	((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("adult"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "adult onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("adult"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "adult onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR (((ketosis"[All Fields] AND "resistant"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "ketosis resistant diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR (((ketosis"[All Fields] AND "resistant"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "ketosis resistant diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR (("maturity"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields])) OR "maturity onset diabetes"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("maturity"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "maturity onset diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("maturity"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) OR "maturity onset diabetes"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("maturity"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "maturity onset diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR "mody"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR "niddm"[All Fields]) OR "niddms"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((((("non"[All Fields] AND "insulin"[All Fields]) AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "non insulin dependent diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("noninsulin"[All Fields] AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "noninsulin dependent diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("noninsulin"[All Fields] AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "noninsulin dependent diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((((("non"[All Fields] AND "insulin"[All Fields]) AND "dependent"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "non insulin dependent diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("slow"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields]))) OR (("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR ((("slow"[All Fields] AND "onset"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])))) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR (("stable"[All Fields] AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "stable diabetes mellitus"[All Fields])) OR (("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) OR "type 2 diabetes"[All Fields])) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields])) OR ((("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All

	Fields]) OR ((("type"[All Fields] AND "ii"[All Fields]) AND "diabetes"[All Fields]) AND "mellitus"[All Fields])) OR "type ii diabetes mellitus"[All Fields]))
#3Depression [MeSH] + Entry Terms	((((((((((((((((((((((((((((((((((("depressed"[All Fields] OR "depression"[MeSH Terms]) OR "depression"[All Fields]) OR "depressions"[All Fields]) OR "depression s"[All Fields]) OR "depressive disorder"[MeSH Terms]) OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR "depressivity"[All Fields]) OR "depressive"[All Fields]) OR "depressively"[All Fields]) OR "depressiveness"[All Fields]) OR "depressives"[All Fields]) ((((((((((("depressed"[All Fields] OR "depression"[MeSH Terms]) OR "depression"[All Fields]) OR "depressions"[All Fields]) OR "depression s"[All Fields]) OR "depressive disorder"[MeSH Terms]) OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR "depressivity"[All Fields]) OR "depressive"[All Fields]) OR "depressively"[All Fields]) OR "depressiveness"[All Fields]) OR "depressives"[All Fields])) OR (((("depression"[MeSH Terms] OR "depression"[All Fields]) OR ("depressive"[All Fields] AND "symptom"[All Fields])) OR "depressive symptom"[All Fields])) OR ((("depression"[MeSH Terms] OR "depression"[All Fields]) OR ("depressive"[All Fields] AND "symptoms"[All Fields])) OR "depressive symptoms"[All Fields])) OR ((("depression"[MeSH Terms] OR "depression"[All Fields]) OR ("emotional"[All Fields] AND "depression"[All Fields])) OR "emotional depression"[All Fields])) OR ((("depression"[MeSH Terms] OR "depression"[All Fields]) OR ("emotional"[All Fields] AND "depressions"[All Fields]))))
#4Depressive Disorder [MeSH] + Entry Terms	(("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("depressive"[All Fields] AND "disorders"[All Fields])) OR "depressive disorders"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("depressive"[All Fields] AND "neuroses"[All Fields])) OR "depressive neuroses"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("depressive"[All Fields] AND "neurosis"[All Fields])) OR "depressive neurosis"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("depressive"[All Fields] AND "syndrome"[All Fields])) OR "depressive syndrome"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("depressive"[All Fields] AND "syndromes"[All Fields])) OR "depressive syndromes"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("endogenous"[All Fields] AND "depression"[All Fields])) OR "endogenous depression"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("endogenous"[All Fields] AND "depressions"[All Fields])) OR "endogenous depressions"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR "melancholia"[All Fields]) OR "melancholias"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR "melancholia"[All Fields]) OR "melancholias"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("neurotic"[All Fields] AND "depression"[All Fields])) OR "neurotic depression"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("neurotic"[All Fields] AND "depressions"[All Fields])) OR "neurotic depressions"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("unipolar"[All Fields] AND "depression"[All Fields])) OR "unipolar depression"[All Fields])) OR ((((("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields])) OR "depressive disorder"[All Fields]) OR ("unipolar"[All Fields] AND "depressions"[All Fields])) OR "unipolar depressions"[All Fields]))
#5Anxiety [MeSH] + Entry Terms	((("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR "anxieties"[All Fields]) OR "anxiety s"[All Fields])) OR ((("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR "hypervigilance"[All Fields]) OR "hypervigilant"[All Fields])) OR (("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR "nervousness"[All Fields])) OR ((("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR ("social"[All Fields] AND "anxieties"[All Fields])) OR "social anxieties"[All Fields])) OR ((("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR ("social"[All Fields] AND "anxieties"[All Fields])) OR "social anxieties"[All Fields])) OR ((("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) OR ("social"[All Fields] AND "anxiety"[All Fields])) OR "social anxiety"[All Fields]))
#6Anxiety Disorders [MeSH] + Entry Terms	((((("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields])) OR "anxiety disorders"[All Fields]) OR ("anxiety"[All Fields] AND "disorder"[All Fields])) OR "anxiety disorder"[All Fields])) OR (("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields])) OR "anxiety disorders"[All Fields])) OR ((((("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields])) OR "anxiety disorders"[All Fields]) OR (("neurotic"[All Fields] AND "anxiety"[All Fields]) AND "states"[All Fields])) OR "neurotic anxiety states"[All Fields])) OR ((((("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields])) OR "anxiety disorders"[All Fields]) OR (("neurotic"[All Fields] AND "anxiety"[All Fields]) AND "states"[All Fields])) OR "neurotic anxiety states"[All Fields]))
#7	**#1 OR #2 AND #3 OR #4 OR #5 OR #6**
#8	**Systematic Review [Publication type]**
#9	**#7 AND #8**

LILACS (via Virtual Health Library) (n=5)

#1	*((tw:((diabetes mellitus) OR (hyperglycemia) OR (glucose intolerance) OR (type 1 diabetes mellitus) OR (autoimmune diabetes) OR (brittle diabetes mellitus) OR (brittle diabetes mellitu) OR (insulin dependent diabetes mellitus) OR (insulin-dependent diabetes mellitus) OR (insulin-dependent diabetes mellitus 1) OR (juvenile onset diabetes mellitus) OR (juvenile-onset diabetes mellitus) OR (ketosis prone diabetes mellitus) OR (ketosis-prone diabetes mellitus) OR (sudden onset diabetes mellitus) OR (sudden-onset diabetes mellitus) OR (type i diabetes mellitus) OR (autoimmune diabetes) OR (juvenile-onset diabetes) OR (type 1 diabetes) OR (iddm) OR (insulin dependent diabetes mellitus 1) OR (insulin-dependent diabetes mellitus) OR (insulin-dependent diabetes mellitus 1) OR (juvenile onset diabetes) OR (juvenile-onset diabetes) OR (juvenile-onset diabetes mellitus) OR (ketosis-prone*

	diabetes mellitus) OR (sudden-onset diabetes mellitus) OR (type 1 diabetes) OR (type 1 diabetes mellitus) OR (adult-onset diabetes mellitus) OR (adult onset diabetes mellitus) OR (ketosis resistant diabetes mellitus) OR (ketosis-resistant diabetes mellitus) OR (maturity onset diabetes mellitus) OR (maturity-onset diabetes mellitus) OR (maturity onset diabetes) OR (maturity-onset diabetes) OR (non insulin dependent diabetes mellitus) OR (non-insulin-dependent diabetes mellitus) OR (noninsulin dependent diabetes mellitus) OR (noninsulin-dependent diabetes mellitus) OR (slow onset diabetes mellitus) OR (slow-onset diabetes mellitus) OR (stable diabetes mellitus) OR (type ii diabetes mellitus) OR (mody) OR (niddm) OR (slow-onset diabetes mellitus) OR (stable diabetes mellitus) OR (type 2 diabetes) OR (type 2 diabetes mellitus)))
#2	*(tw:((depression) OR (depressions) OR (depressive symptom) OR (depressive symptoms) OR (emotional depression) OR (emotional depressions) OR (depressive disorder) OR (depressive disorders) OR (depressive neuroses) OR (depressive neurosis) OR (depressive syndrome) OR (depressive syndromes) OR (endogenous depression) OR (endogenous depressions) OR (melancholia) OR (melancholias) OR (neurotic depression) OR (neurotic depressions) OR (unipolar depression) OR (unipolar depressions) OR (anxiety) OR (hypervigilance) OR (nervousness) OR (social anxieties) OR (social anxiety) OR (anxiety disorders) OR (anxiety disorder) OR (anxiety neuroses) OR (neurotic anxiety state) OR (neurotic anxiety states)))*
#3	*(tw:(systematic review)))*
#4	*(db:("LILACS") AND type_of_study:("systematic_reviews"))*
#5	*#1 AND #2 AND #3 AND #4*

Cochrane Library (n=43)

#1	(Diabetes Complications) OR (Diabetes Mellitus, Type 1) OR (Diabetes Mellitus, Type 2)
#2	(Depression) OR (Depressive Disorder) OR (Anxiety) OR (anxiety disorders)
#3	#1 AND #2 in Cochrane Reviews with Child Health, Common Mental Disorders, Metabolic and Endocrine Disorders, Complementary Medicine, Public Health in Cochrane Groups

Web of Science (n=231)

#1	TS=((Autoimmune Diabetes) OR (Brittle Diabetes Mellitus) OR (IDDM) OR (Insulin Dependent Diabetes Mellitus) OR (Insulin Dependent Diabetes Mellitus 1) OR (Insulin-Dependent Diabetes Mellitus) OR (Insulin-Dependent Diabetes Mellitus 1) OR (Juvenile Onset Diabetes) OR (Juvenile Onset Diabetes Mellitus) OR (Juvenile-Onset Diabetes) OR (Juvenile-Onset Diabetes Mellitus) OR (Ketosis Prone Diabetes Mellitus) OR (Ketosis-Prone Diabetes Mellitus) OR (Sudden Onset Diabetes Mellitus) OR (Sudden-Onset Diabetes Mellitus) OR (Type 1 Diabetes) OR (Type 1 Diabetes Mellitus) OR (Type I Diabetes Mellitus) OR (Adult Onset Diabetes Mellitus) OR (Adult-Onset Diabetes Mellitus) OR (Ketosis Resistant Diabetes Mellitus) OR (Ketosis-Resistant Diabetes Mellitus) OR (Maturity Onset Diabetes) OR (Maturity Onset Diabetes Mellitus) OR (Maturity-Onset Diabetes) OR (Maturity-Onset Diabetes Mellitus) OR (MODY) OR (NIDDM) OR (Non Insulin Dependent Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Slow Onset Diabetes Mellitus) OR (Slow-Onset Diabetes Mellitus) OR (Stable Diabetes Mellitus) OR (Type 2 Diabetes) OR (Type 2 Diabetes Mellitus) OR (Type II Diabetes Mellitus))
#2	TS=((Depression) OR (Depressions) OR (Depressive Symptom) OR (Depressive Symptoms) OR (Emotional Depression) OR (Emotional Depressions) OR (Depressive Disorder) OR (Depressive Disorders) OR (Depressive Neuroses) OR (Depressive Neurosis) OR (Depressive Syndrome) OR (Depressive Syndromes) OR (Endogenous Depression) OR (Endogenous Depressions) OR (Melancholia) OR (Melancholias) OR (Neurotic Depression) OR (Neurotic Depressions) OR (Unipolar Depression) OR (Unipolar Depressions) OR (Anxiety) OR (Hypervigilance) OR (Nervousness) OR (Social Anxieties) OR (Social Anxieties) OR (Social Anxiety) 0R (Anxiety Disorder) OR (Anxiety Disorders) OR (Neurotic Anxiety State) OR (Neurotic Anxiety States))
#3	TS=(systematic review)
#4	#3 AND #2 AND #1

EMBASE (n=413)

#1	'non insulin dependent diabetes mellitus'/exp AND [embase]/lim
#2	'insulin dependent diabetes mellitus'/exp AND [embase]/lim
#3	'depression'/exp AND [embase]/lim
#4	'major depression'/exp AND [embase]/lim
#5	'depressive disorder'/exp AND [embase]/lim
#6	'endogenous depression'/exp AND [embase]/lim
#7	'melancholia'/exp AND [embase]/lim
#8	'anxiety disorder'/exp AND [embase]/lim
#9	'anxiety'/exp AND [embase]/lim
#10	'nervousness'/exp AND [embase]/lim
#11	#1 OR #2
#12	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#13	#11 AND #12 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

S2 Appendix. Characteristics of excluded studies (n= 52)

Study	Reason for exclusion
AZAMI G, SOH KL, SAZLINA SG, SALMIAH MS, AAZAMI S. Behavioral interventions to improve self-management in Iranian adults with type 2 diabetes: a systematic review and meta-analysis. J Diabetes Metab Disord 2018;17:365–80.	Other population
BEATTY, L.; LAMBERT, S. A systematic review of internet-based self-help therapeutic interventions to improve distress and disease-control among adults with chronic health conditions. Clinical Psychology Review, v. 33, n. 4, p. 609–622, 2013.	Other design of study
BRIERLEY, S. et al. psychological interventions for young people with Type 1 diabetes: A metaanalysis. Diabetic Medicine, v. 30, p. 177-178. 2013	Not found full text
CELIK, A.; FORDE, R.; STURT, J. The impact of online self-management interventions on midlife adults with type 2 diabetes: A systematic review. British Journal of Nursing, v. 29, n. 5, p. 266–272, 2020.	Other outcomes
CEZARETTO, A. Interdisciplinariedade na resposta a intervenções em hábitos de vida para redução de risco cardiometabólico e a influência da depressão. p. 141, 2015.	Other design of study
CEZARETTO A, FERREIRA SRG, SHARMA S, SADEGHIRAD B, KOLAHDOOZ F. Impact of lifestyle interventions on depressive symptoms in individuals at-risk of, or with, type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2016;26:649–62.	Other outcomes
CHAPMAN A, LIU S, MERKOURIS S, ENTICOTT JC, YANG H, BROWNING CJ, et al. Psychological interventions for the management of glycemic and psychological outcomes of type 2 diabetes mellitus in China: A systematic review and meta-analyses of randomized controlled trials. Front Public Heal 2015;3:1–22.	Other population
CHEW, B. H. et al. Psychological interventions for diabetes-related distress in adults with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews, v. 2015, n. 1, 2015.	Other population
ELLIOTT, S. Cognitive behavioural therapy and glycaemic control in diabetes mellitus. Practical Diabetes, v. 29, n. 2, p. 67–71, 2012.	Other design of study
GUTIERREZ, A. P. et al. Effectiveness of Diabetes Self-Management Education Programs for US Latinos at Improving Emotional Distress: A Systematic Review. Diabetes Educator, v. 45, n. 1, p. 13–33, 2019.	Other design of study
HARKNESS, E. et al. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: A systematic review and meta-analysis. Diabetes Care, v. 33, n. 4, p. 926–930, 2010.	Other design of study
HONGASANDRA, N. R. et al. Effectiveness of yoga for patients with diabetes mellitus. Current Science, v. 113, n. 7, p. 1337–1353, 2017.	Other population
HUFFMAN, J. C. et al. Positive psychological interventions for patients with type 2 diabetes: Rationale, theoretical model, and intervention development. Journal of Diabetes Research, v. 2015, 2015.	Other design of study
ISMAIL, K.; WINKLEY, K.; RABE-HESKETH, S. Ismail2004_Lancet 363_1589-97.pdf. Lancet, v. 363, p. 1589–97, 2004.	Other outcomes
JENKINS, D. J. Psychological, physiological, and drug interventions for type 2 diabetes. The Lancet, v. 363, n. 9421, p. 1569–1570, maio 2004.	Other design of study
JEREMIAH, O. J. et al. Evaluation of the effect of insulin sensitivity-enhancing lifestyle- A nd dietary-related adjuncts on antidepressant treatment response: Protocol for a systematic review and meta-analysis. Systematic Reviews, v. 8, n. 1, p. 1–11, 2019.	Other design of study
JESSE, C. D.; CREEDY, D. K.; ANDERSON, D. J. Effectiveness of psychological interventions for women with type 2 diabetes who are overweight or obese: A systematic review protocol. JBI Database of Systematic Reviews and Implementation Reports, v. 17, n. 3, p. 281–289, 2019.	Other design of study
JEWELL, R. R.; GOREY, K. M. Psychosocial interventions for emergent adults with type 1 diabetes: Near-empty systematic review and exploratory meta-analysis. Diabetes Spectrum, v. 32, n. 3, p. 249–256, 2019.	Other outcomes
KOK, J. L. A.; WILLIAMS, A.; ZHAO, L. Psychosocial interventions for people with diabetes and co-morbid depression. A systematic review. International Journal of Nursing Studies, v. 52, n. 10, p. 1625–1639, 2015.	Other design of study
KONG LN, HU P, ZHAO QH, YAO HY, CHEN SZ. Effect of peer support intervention on diabetes distress in people with type 2 diabetes: A systematic review and meta-analysis. Int J Nurs Pract. v. 26, n. 5, e12830, 2020.	Other population
LEE, S. W. H. et al. Interventions for people with type 2 diabetes mellitus fasting during Ramadan. Cochrane Database of Systematic Reviews, v. 2018, n. 11, 2018.	Other design of study
LEE HJ, LEE M, HA JH, LEE Y, YUN J. Effects of healthcare interventions on psychosocial factors of patients with multimorbidity: A systematic review and meta-analysis. Arch Gerontol Geriatr. v. 25, n. 91, 104241, 2020 .	Other population
LOPRESTI, A. L. Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. Australian and New Zealand Journal of Psychiatry, v. 51, n. 6, p. 565–582, 2017.	Other design of study
LIU F, GUAN Y, LI X, XIE Y, HE J, ZHOU ZG, et al. Different Effects of Structured Education on Glycemic Control and Psychological Outcomes in Adolescent and Adult Patients with Type 1 Diabetes: A Systematic Review and Meta-Analysis. Int J Endocrinol 2020;2020.	Other population
MARKOWITZ, S. M. et al. A review of treating depression in diabetes: Emerging findings. Psychosomatics, v. 52, n. 1, p. 1, 2011.	Other design of study
MARTINEZ, K. et al. Psychological factors associated with diabetes self-management among adolescents with Type 1 diabetes: A systematic review. Journal of Health Psychology, v. 23, n. 13, p. 1749–1765, 2018.	Other design of study
MATHIESEN, A. S. et al. Psychosocial interventions for reducing diabetes distress in vulnerable people with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, v. 12, p. 19–33, 2019.	Other outcomes
MCBAIN, H. et al. Self-management interventions for type 2 diabetes in adult people with severe mental illness. Cochrane Database of Systematic Reviews, v. 2014, n. 11, 2014.	Other population
MCCOY, M. A.; THEEKE, L. A. A systematic review of the relationships among psychosocial factors and coping in adults with type 2 diabetes mellitus. International Journal of Nursing Sciences, v. 6, n. 4, p. 468–477, 2019.	Other design of study
MUSSELMAN, D. L. et al. Relationship of depression to diabetes types 1 and 2: Epidemiology, biology, and treatment. Biological Psychiatry, v. 54, n. 3, p. 317–329, 2003.	Other design of study

NASKAR, S.; VICTOR, R.; NATH, K. Depression in diabetes mellitus—A comprehensive systematic review of literature from an Indian perspective. Asian Journal of Psychiatry, v. 27, p. 85–100, 2017.	Other outcomes
NOORDALI, F.; CUMMING, J.; THOMPSON, J. L. Effectiveness of mindfulness-based interventions on physiological and psychological complications in adults with diabetes: A systematic review. Journal of Health Psychology, v. 22, n. 8, p. 965–983, 2017.	Other design of study
O'HARA, M. C. et al. A systematic review of interventions to improve outcomes for young adults with Type 1 diabetes. Diabetic Medicine, v. 34, n. 6, p. 753–769, 2017.	Other outcomes
PADILLA, V. L. et al. Neurocognitive impairment in patients with comorbid diabetes mellitus and depression. Personalized Medicine in Psychiatry, v. 1–2, p. 2–10, 2017.	Other design of study
POUWER F, SCHRAM MT, IVERSEN MM, NOUWEN A, HOLT RIG. How 25 years of psychosocial research has contributed to a better understanding of the links between depression and diabetes. Diabet Med. v. 37, n. 3, p. 383-392, 2020.	Other design of study
RAYNER, L. et al. Antidepressants for depression in physically ill people. Cochrane Database of Systematic Reviews, n. 4, 2008.	Other population
REY VELASCO, E. et al. Pre-empting the challenges faced in adolescence: A systematic literature review of effects of psychosocial interventions for preteens with type 1 diabetes. Endocrinology, Diabetes and Metabolism, v. 3, n. 2, 2020.	Other outcomes
SCHMIDT, C. B. et al. Systematic review and meta-analysis of psychological interventions in people with diabetes and elevated diabetes-distress. Diabetic Medicine, v. 35, n. 9, p. 1157–1172, 2018.	Other population
STEED, L.; COOKE, D.; NEWMAN, S. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. Patient Education and Counseling, v. 51, n. 1, p. 5–15, 2003.	Other design of study
SUMLIN, L. L. et al. Depression and Adherence to Lifestyle Changes in Type 2 Diabetes: A Systematic Review. The Diabetes Educator, v. 40, n. 6, p. 731–744, 2014.	Other outcomes
THABREW, H. et al. E-Health interventions for anxiety and depression in children and adolescents with long-term physical conditions. Cochrane Database of Systematic Reviews, v. 2018, n. 8, 2018.	Other population
TOUMPANAKIS, A.; TURNBULL, T.; ALBA-BARBA, I. Effectiveness of plant-based diets in promoting well-being in the management of type 2 diabetes: A systematic review. BMJ Open Diabetes Research and Care, v. 6, n. 1, 2018.	Other design of study
UDEDI, M. et al. The effect of depression management on diabetes and hypertension outcomes in low- and middle-income countries: A systematic review protocol 11 Medical and Health Sciences 1117 Public Health and Health Services 11 Medical and Health Sciences 1103 Clinical . Systematic Reviews, v. 7, n. 1, p. 1–5, 2018.	Other design of study
VAN DER FELTZ-CORNELIS, C. M. et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: A systematic review and meta-analysis. General Hospital Psychiatry, v. 32, n. 4, p. 380–395, 2010.	Primary studies described in review with most current publication date
VAN DER HEIJDEN, M. M. P. et al. Effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in type 2 diabetes mellitus: A systematic review. Diabetologia, v. 56, n. 6, p. 1210–1225, 2013.	Other design of study
VAN LAAKE-GEELEN, C. C. M. et al. The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: A systematic review. Scandinavian Journal of Pain, v. 19, n. 3, p. 433–439, 2019.	Other population
WANG, F. et al. The effects of qigong on anxiety, depression, and psychological well-being: A systematic review and meta-analysis. Evidence-based Complementary and Alternative Medicine, v. 2013, 2013.	Other outcomes
WANG, M. Y. et al. A systematic review of the efficacy of non-pharmacological treatments for depression on glycaemic control in type 2 diabetics. Journal of Clinical Nursing, v. 17, n. 19, p. 2524–2530, 2008.	Other design of study
WINKLEY K, LANDAU S, EISLER I, ISMAIL K. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: Systematic review and meta-analysis of randomised controlled trials. Br Med J 2006;333:65–8.	Other population
WINKLEY K, UPSHER R, STAHL D, POLLARD D, BRENNAN A, HELLER S, et al. Systematic review and meta-analysis of randomized controlled trials of psychological interventions to improve glycaemic control in children and adults with type 1 diabetes. Diabet Med 2020;37:735–46.	Other population
YU, X.; CHAU, J. P. C.; HUO, L. The effectiveness of traditional Chinese medicine-based lifestyle interventions on biomedical, psychosocial, and behavioral outcomes in individuals with type 2 diabetes: A systematic review with meta-analysis. International Journal of Nursing Studies, v. 80, n. July 2017, p. 165–180, 2018.	Other population
ZHOU, Z. et al. Effects of tai Chi on physiology, balance and quality of life in patients with type 2 diabetes: A systematic review and meta-analysis. Journal of Rehabilitation Medicine, v. 51, n. 6, p. 405–417, 2019.	Other outcomes

4.2 Artigo 2

Title: E-Health technologies for treatment of depression, anxiety and emotional distress in people with diabetes mellitus: systematic review and meta-analysis

Running Title: E-Health for treatment of depression, anxiety and distress in people with diabetes

Authors: Reginaldo Tavares Franquez[1], Mariana Del Grossi Moura[1], Delaine Cristina Ferreira McClung[1], Silvio Barberato-Filho[1], Luciane Cruz Lopes, Marcus Tolentino Silva[1], Fernando de Sá Del-Fiol[1], Cristiane de Cássia Bergamaschi[1]*

[1]Pharmaceutical Sciences Graduate Course, University of Sorocaba, Sorocaba, São Paulo, Brazil

***Corresponding Author:** Cristiane de Cássia Bergamaschi, Universidade de Sorocaba, UNISO, Rodovia Raposo Tavares, Km 92.5, Sorocaba, SP 18023-000, Brazil. Tel: +55-15-21017104
E-mail adresses: cristiane.motta@prof.uniso.br

Conflict of interest statement: The authors report no conflicts of interest in this study.

Abstract

This systematic review of randomized clinical trials (RCT) summarized the available evidence regarding the effectiveness of e-Health technologies for the treatment of depression, anxiety, and emotional distress in people with diabetes mellitus. The databases searched were the Cochrane CENTRAL, MEDLINE, EMBASE, Web of Science, and LILACS; up to January 2023. The primary outcomes were improvement and/or remission of depression, depressive symptoms and/or anxiety, remission of diabetes-related emotional distress, and improvement in quality of life. Reviewers, in pairs and independently, selected the studies and extracted their data. Meta-analyses were conducted, and the quality of evidence was assessed following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Ten RCT and 2,209 participants were analyzed. In general, the studies had high methodological quality. The interventions were web-based programs (n=5) and

telehealth (n=5). It was observed improvement of depression with the use of Internet-Guided Self-Help or Telephone-Delivered Cognitive Behavioral Therapy (CBT); improvement of anxiety with Internet-Guided Self-Help or Diabetes-specific CBT interventions; and improvement of emotional distress with the use of Internet-Guided Self-Help, Diabetes-Specific CBT, MyCompass, Internet-Guided Self-Help and Healthy Outcomes through Patient Empowerment. The follow-up ranged from 3 to 12 months and the quality of evidence ranged from very low to moderate. Due to divergences in interventions, populations, follow-up time and outcome measures; these findings must be confirmed in future clinical trials.

Keywords: Anxiety. Depression. Diabetes Distress. E-Health. Type 1 diabetes mellitus. Type 2 diabetes mellitus.

Introduction

Diabetes mellitus is a chronic disease with a high global prevalence, affecting 8.3% of the world's population, and is the leading cause of disability-adjusted life years lost [1,2]. Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes among adults, accounting for approximately 90% of cases [3]. If not treated properly, this disease can cause serious complications, affecting the quality of life and increasing the risk of death. In addition, when patients have concomitant depression, their adherence to diabetes treatment may be reduced [3,4].

The occurrence of depression is 2 to 3 times greater in people with diabetes mellitus, with most cases being undiagnosed [1]. The relationship between depression and diabetes mellitus complications appears bidirectional, where diabetes mellitus is associated with an increased risk of developing macrovascular and/or microvascular complications, subsequently increasing the risk of depression [5].

Electronic health (e-Health) is the transfer of health resources and health care through electronic means, such as text-based programs to multimedia and interactive programs, virtual reality, and biofeedback programs [6,7].

Telehealth or telemedicine involves the use of medical information exchanged from one site to another via electronic communication to improve a patient's clinical health status [6]. The use of telehealth is increasing when it is used for communication, education, and monitoring of the patient, and to facilitate adherence to the management of chronic diseases [8]. Mobile health (m-Health) is the use of wireless

technology to provide health services and information in mobile communication devices such as tablets, monitoring devices, and smartphones [6].

Given the growing number of patients with diabetes mellitus worldwide and their likelihood to develop psychological disorders, as technology improves and health interventions become available on computers and cell phones, it can be useful for treating depression and anxiety in this population [9].

The digital transformation in health is recent and the evidence on the effectiveness of e-Health, specifically in the population with diabetes mellitus and psychological disorders, seems to be limited.

Systematic reviews that evaluated the effectiveness of e-Health interventions for the treatment of diabetes mellitus [10,11] had non-restricted population to psychological disorders. Systematic review that evaluated the use of web-based interventions to improve the well-being of patients with depression, emotional distress, and concomitant T2DM [12] had its findings restricted to the year 2015. Two systematic reviews assessed the evidence on the effectiveness of e-Health interventions in patients with chronic diseases [9,13]; however, the population was not restricted to patients with diabetes or included clinical trials in which the population did not have psychological disorders. In addition, new clinical trials that contain information relevant to this topic were not included in previous reviews.

Then, this systematic review evaluated the effectiveness and safety of e-Health technologies in the treatment of depression, depressive symptoms, anxiety, and emotional distress in people with Type 1 and Type diabetes mellitus. This study answered the following question: Which e-Health technologies are effective and safety to treat these psychological disorders in people with diabetes mellitus?

Methods

Protocol and register

This review systematic was reported according to the Cochrane Handbook for Systematic Reviews of Interventions [14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [15]. The protocol of this study was registered in PROSPERO (CRD42022314773).

Eligibility criteria

These criteria were described using the Population, Intervention, Comparison, Outcome, and Type of study (PICOT) framework.

Inclusion criteria

Population: children, adolescents, adults and elderly with both type 1 diabetes mellitus (T1DM) or T2DM and the psychological disorders (depression, depressive symptoms, anxiety and/or diabetes-related emotional distress). Such disorders could be reported by clinical diagnosis, validated mental health measures, self-report or standardized interviews.

Interventions: any intervention carried out through static or interactive websites, automated emails, website-based applications, automated phone calls, text messages, among others; that aimed to improve depression, depressive symptoms, anxiety and diabetes-related emotional distress.

Comparators: usual care or other e-Health intervention reported by the studies.

Outcomes: effectiveness and safety.

Type of study: Randomized Controlled Trial (RCT) were included because they are the best study design for evaluating the effect of health interventions.

Exclusion criteria

Type of study: studies that evaluated only the outcome “adherence to diabetes treatment” and/or that did not report outcomes on mental health were excluded. Conference papers too met exclusion criteria.

Measure outcomes

Primary outcomes

Improvement and/or clinical remission of depression, depressive symptoms and/or anxiety (remission rate, reduction in severity score and/or treatment response rate); remission of diabetes-related emotional distress; and improvement on quality of life of patients.

Secondary outcomes

Control of diabetes mellitus (decrease in values of HbA1c or glycemia and/or complications of disease), *s*atisfaction with the intervention or acceptability, increase in diabetes-related self-care activities, diabetes treatment adherence rate and psychotropic medication adherence rate.

Selection of Studies

Electronic searches

The databases searched were as follows: Cochrane Central Register of Controlled Trial (CENTRAL); MEDLINE (via PubMed); EMBASE; Web of Science; LILACS (via Virtual Health Library); and databases specified for clinical trials: ISRCTN Register (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). The included studies had no language restrictions or time limits. We used information sources from the beginning data of databases to January 2023.

Search strategy

The search was conducted using the Medical Subject Headings (MeSH) terms with filter for RCT. The strategies were adapted for each database and they are available in Appendix 1.

The terms used were: ((Diabetes Complications) OR (Diabetes Mellitus Type 1) OR (Diabetes Mellitus Type 2)) AND ((Depression) OR (Depressive Disorder) OR (Anxiety) OR (Anxiety Disorders)) AND ((Digital Technology) OR (Telemedicine) OR (Telehealth*) OR (mobile telehealth) OR (Telecommunication*) OR (Internet Intervention) OR (ehealth) OR (e-Health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Mobile Device) OR (Mobile) OR (Mobile App) OR (Mobile Phone) OR (App*) OR (Application*) OR (Web-based) OR (Web-based intervention) OR (Online-based) OR (Interactive) OR (Online) OR (On-line) OR (Website*) OR (Electronic Health*)).

Eligibility determination

Pairs of reviewers (RF and MP, RF and DM, MT and FF), independently, assessed relevant titles and abstracts and applied the eligibility criteria. The full texts of potentially eligible articles were obtained. These reviewers, independently, assessed the eligibility of each full text and resolved any disagreement by consensus. A third reviewer assisted with the final decision, when necessary (CB or SBF). For duplicate publications, the article with the most complete data was used.

Data extraction

Calibration exercises were performed for data extraction by using a standardized form according to the eligibility criteria. Data extraction was performed

independently, by the same reviewers, and the discrepancies resolved by consensus between them. The third reviewer was contacted, when necessary (CB or LCL). The study authors were contacted by email, when necessary.

The data collected from the eligible studies were as follows: author and year of publication, study location, funding of study, population, number of participants, mean age of participants, type of diabetes mellitus, type of psychiatric disorder, intervention, comparator, measured outcomes and duration of follow-up.

Assessment of risk of bias of included studies

The version of the Cochrane Handbook for Systematic Reviews of Interventions was used to assess risk of bias [14].

Two reviewers (RF and MP), independently, assigned the risk of bias for each clinical trials, according to the following criteria:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants and care providers for each main outcome: was knowledge of the allocated treatment adequately prevented during the trial?
4. Blinding of outcome assessors for each main outcome: was knowledge of the allocated treatment adequately prevented during the trial?
5. Incomplete outcome data for each main outcome: did more than 10% of participants with draw and were incomplete outcome data adequately addressed?
6. Selective outcome reporting: was there any suggestion of selective outcome reporting?
7. Other sources of bias: was the trial apparently free of other problems that could put it at high risk of bias?

The reviewers assigned response options of 'definitely yes,' 'probably yes,' 'probably no,' and 'definitely no' for each of the domains, with 'definitely yes' and 'probably yes' ultimately being assigned a low risk of bias and 'definitely no' and 'probably no,' a high risk of bias. The reviewer’s resolved disagreements via consensus and a third reviewer (CB) were contacted, if necessary.

Data synthesis and measures of effect

Meta-analyses were conducted for the outcomes of interest; however, we grouped the results of different interventions, since it was not possible to measure

them for by each intervention due to excessive heterogeneity between interventions and comparators. Meta-analyses were conducted by using the STATA software (v. 14.2 Stata Corp, College Station, United States). The significance level adopted was off 5%. Random effects meta-analyses were employed, which are conservative in that they consider within-studies and between-studies differences when calculating the error term used in the analysis.

We used standardized mean differences (SMD) to analyze continuous outcomes, followed by 95% confidence interval (95% CI) e predictive interval. Prediction interval is centered at the summary estimate, and its width accounts for the uncertainty of the summary estimate, the estimate of study standard deviation in the true treatment effects and the uncertainty in study standard deviation estimate [16]. Heterogeneity was verified by the I^2 statistic, classified as 0 to 25% (low heterogeneity), 50% (moderate heterogeneity), and 75% (high heterogeneity) [17].

Other findings were described in tables and narrative synthesis. In cases in that some data would be missing or unclear, we contacted the study authors to obtain relevant data.

Quality of evidence

We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to appraise the confidence in estimates [18]. RCT start at high confidence and can be rated down based on risk of bias, indirectness, imprecision, inconsistency and publication bias; they can then be graded at levels of moderate, low and very low confidence [19].

Results

Literature search

The search strategy identified 5,025 studies. After removing duplicates, 4,298 articles were included for title and abstract screening, 81 of which were selected for full-text analysis, and 10 RCT met the inclusion criteria (Figure 1). A list of excluded articles is presented in Appendix 2.

Characteristics of studies

The present study gathered findings from 2,209 participants, on average 55.9% of whom were women. RCT were developed mainly in the USA. All studies included

an adult population and the age ranged on average from 46.7 to 64.3 years. The T2DM population predominated (n=5; 55.6%) and 5 other studies were of participants with T1DM and T2DM. A great number of participants had depressive disorders or depressive symptoms (n=7; 66.7%). Most studies received funding, mainly from government and health research services (Table 1).

Risk of bias of the included studies (Figure 2)

Randomization and allocation

All included RCT reported sufficient data on the random sequence generation method. The allocation concealment method was considered to have a low risk of bias in 8 studies [20–27], and only 2 studies [28,29] did not provide details about how the patients were allocated to groups.

Blinding

One study did not mention how blinding was performed, and it was unclear whether patients, staff, and outcome assessors were blinded [28]. The other RCT ensured the generation of a random sequence of participants.

Incomplete outcome data

In another RCT, it was not possible to judge whether there was incomplete reporting of outcomes [29]. The other studies reported a loss of follow-up for the participants as the reason for exclusion.

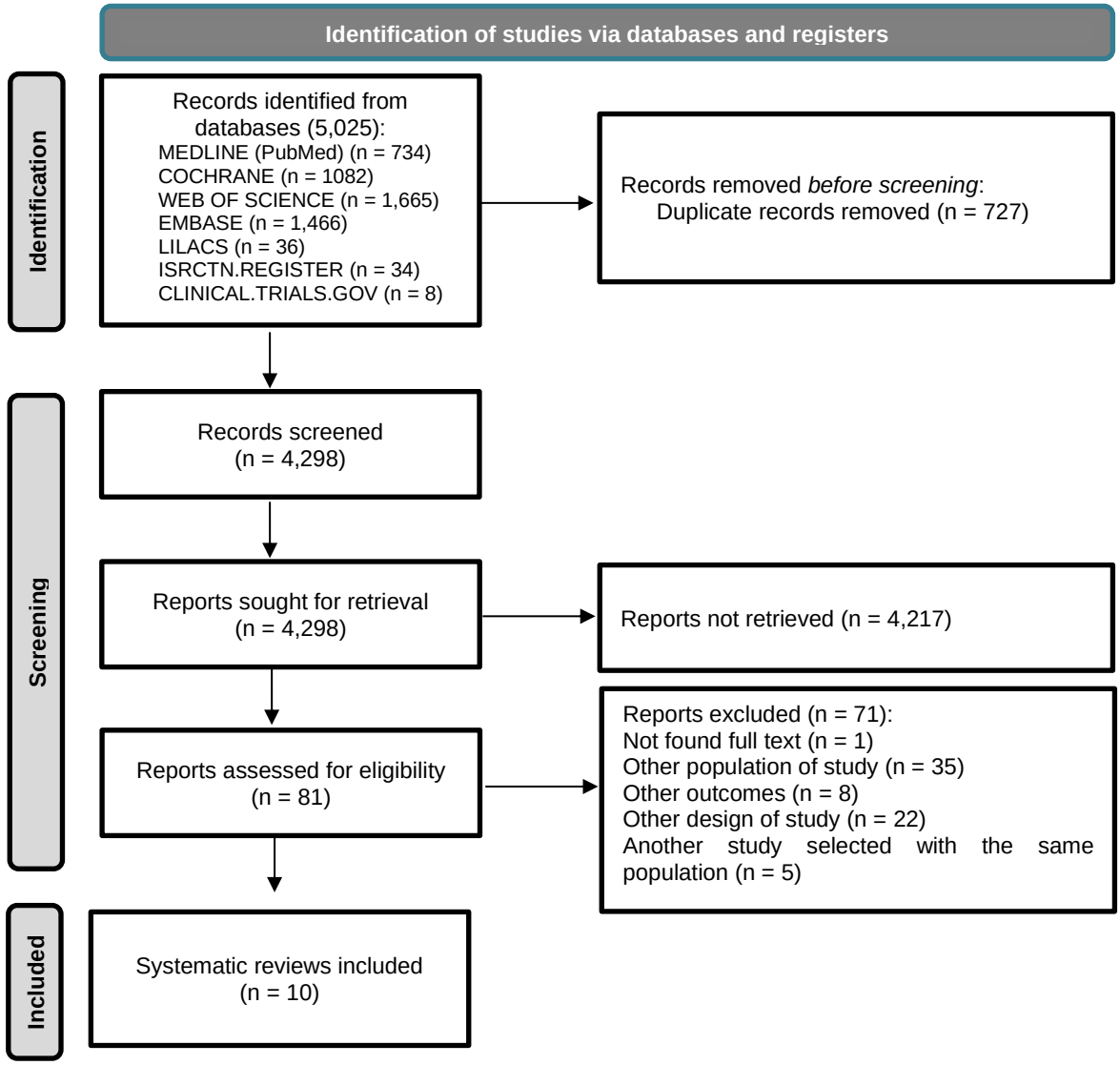
Selective reporting of outcomes

We did not observe this bias in most studies, because the clinical trial registry was made available. One study mentioned having a protocol [28], but we did not have access to it, but we considered that it included all outcomes of interest.

Other biases

All studies mentioned their funding, in which they declared nonprofit and/or potential conflicts of interest.

Figure 1. Search flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 2. Review authors' judgements about each risk of bias item for each included study

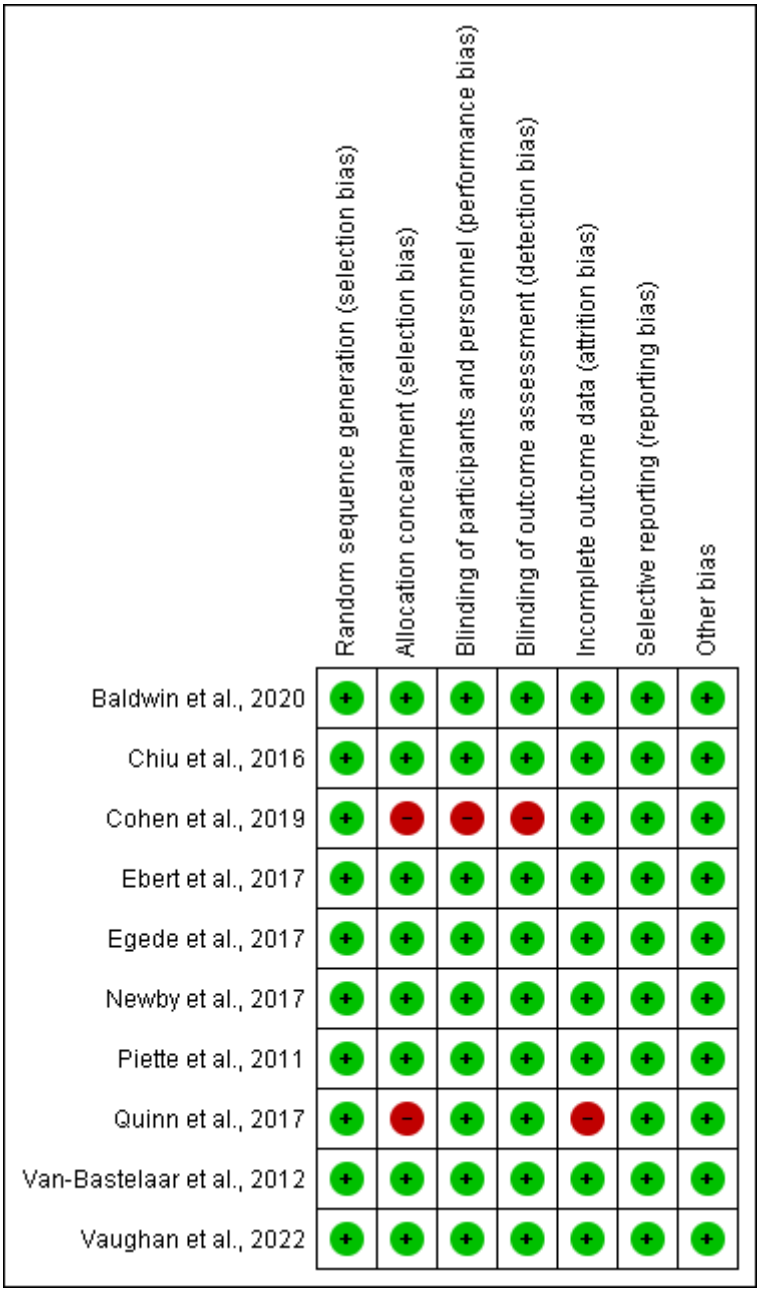


Table 1. Characteristics of randomized controlled trials and participants (n=10 studies and 2,209 participants)

Authors and publication year	Study Location	Population (years)	Women (%)	Sample (n)	Mean age in years (SD)	Type of diabetes	Psychological disorders	Funding Clinical trial registration protocol
Baldwin et al., 2020 [20]	Australia	Adults	64.3	723	57.7 (10.6)	T2DM	Mild-to-moderate depressive symptoms	Australian Government Department of Health and National Health and Medical Research Council **Protocol:** ACTRN12615000931572
Chiu et al., 2016 [21]	Taiwan	Adults (≥50)	48.3	182	64.6 (8.9)	T2DM	Minor depressive symptoms and diabetes-related emotional distress	National Science Council in Taiwan **Protocol:** NCT02473081
Cohen et al., 2019 [28]	USA	Adults	7.4	27	61.8 (10.8)	T1DM and T2DM	Depression	Federal Services Junior Investigator Research Grant Program (American Health-System Pharmacy) **Protocol:** not reported
Ebert et al., 2017 [22]	Germany	Adults	44.5	260	50.8 (11.8)	T1DM and T2DM	High depressive symptoms	The BARMER GEK and the European Union **Protocol:** DRKS00004748
Egede et al., 2017 [23]	USA	Older adults (≥58)	88	90	63.1 (4.2)	T2DM	Major depression disorder	Veterans Affairs Health Services Research and Development program **Protocol:** NCT00324701
Newby et al., 2017 [24]	Australia	Adults	71.1	90	46.7 (12.6)	T1DM and T2DM	Major depressive disorder	No specific grant from any funding agency in the public, commercial, or not-for-profit sectors **Protocol:** ACTRN12613001198718
Piette et al., 2011 [25]	USA	Adults (≥21)	51.5	291	56.0 (10.1)	T2DM	Depressive symptoms	National Institutes of Health **Protocol:** NCT01106885
Quinn et al., 2017 [29]	USA	Adults	49.1	114	52.6 (8.2)	T2DM	Depression and diabetes-related emotional distress	Maryland Industrial Partnerships program and James Clark School of Engineering's Maryland Technology Enterprise Institute **Protocol:** NCT01107015
Van-Bastelaar et al., 2012 [26]	Netherlands	Adults	60.7	255	50.0 (12.0)	T1DM and T2DM	Major depressive disorder, anxiety and diabetes related emotional distress	Dutch Diabetes Research Foundation **Protocol:** ISRCTN24874457

Vaughan et al., 2012 [27]	USA	Adults	10.2	225	50.0	T1DM and T2DM	Depression	Veterans' Health Administration Health Services Research and Development Office and the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases **Protocol:** NCT01572389

N (number of participants). SD (Standard Deviation). T1DM (Type 1 Diabetes Mellitus). T2DM (Type 2 Diabetes Mellitus).

Description of interventions and main findings

Clinical trials included the following e-Health interventions: web-based programs (n= 5) and telehealth interventions (n= 5). The description of the interventions and the main findings of each study are presented in Tables 2 and 3, respectively.

Web-based program **(n= 5) (Table 2)**

Description of myCompass

The myCompass program was evaluated in people with T2DM and mild to moderate depressive symptoms and compared to “Healthy Lifestyles” Attention Control Intervention. This comparator replicated the delivery mode and core functionality of myCompass, but without content therapeutic. myCompass lasted up to 8 weeks and contained 12 interactive mental health modules, which allowed users to monitor three of 20 cognitive-behavioral variables. Program users received automated emails about their use, as well as SMS reminders, home activities, mental health care tips, motivational statements, and self-monitoring data reports; at weeks 1, 3, 5, and 7 [20].

Main findings

At the 12 months follow-up, both programs improved depression, diabetes-related emotional distress (Diabetes Distress Scale—DDS) and HBA1c values in relation to baseline measures (Table 3). With respect to program acceptability, approximately 55% of myCompass participants and 11% of Healthy Lifestyles participants reported that the program was convenient and easy to use [20].

Description of Internet-based Cognitive Behavioral Therapy (iCBT) program

The effectiveness of the iCBT program was evaluated in people with T1DM or T2DM and major depressive disorder and compared with usual care. The iCBT consisted of 6 online classes (with 5 days intervals between them) involving components such as psychoeducation, behavioral activation, cognitive restructuring, problem solving, graded exposure, relapse prevention, and assertiveness skills. The program lasted 10 weeks and at the end of each class, the participants had to complete the “homework” and had access to extra resources, frequently asked questions, and recovery stories from former participants. The program was supported

by psychologists or psychiatrists with qualifications at the master's or doctoral levels. Professionals monitored participants' depressive symptoms and psychological stress and contacted them via email and telephone to provide clinical support [24].

Main findings

iCBT was superior to usual care in improving diabetes-specific emotional distress at the 3 months follow-up (Table 3). Satisfaction with using the program and the confidence in recommending the program to a friend with similar problems was assessed only in the intervention group. Most participants reported feeling somewhat to very satisfied with the program (n=27; 85%) and feeling somewhat to very confident about recommending the program to a friend (n=28; 88%) (24).

Description of Mobile Diabetes Health (coach Primary Care Provider)

The impact of mobile diabetes health intervention on emotional well-being was compared to usual care, in adults with T2DM and distress and/or depression. Participants in the intervention group had access to the Coach Primary Care Provider software (coach-PCP). Physicians had access to patient data and provided reports with patient treatment recommendations every 3 months. Patients reported data on blood glucose levels, amounts of carbohydrates consumed, medications used for diabetes, and comments about diabetes self-care. They received automated messages about self-management of the disease, medication use guidelines, and reminders to use educational materials [29].

Main findings

At the 12 months follow-up, an improvement in DDS was observed in relation to baseline measures; however, no difference was observed between the intervention and usual care [29].

Description of Diabetergestemd (DbG.nl)

This study evaluated whether the online diabetes-specific CBT program (DbG.nl) for patients with T1DM or T2DM and diabetes-specific major depressive disorder, anxiety or emotional distress was more effective than waiting list (control group). The intervention consisted of 8 classes, held weekly, composed of psychoeducation, and focused on skills such as relaxation, cognitive restructuring, positive reinforcement, and social skills. The course contained written and spoken information and homework (with email feedback), under the supervision of a

psychologist. Upon completion of the study, the patients filled feedback forms and were interviewed via telephone. Patients in the waiting-list group received a password that allowed them to log into the web-based intervention, if they still had depressive symptoms [26].

Main findings

The diabetes-specific CBT program (DbG.nl) was effective in reducing anxiety at the 3 months follow-up (Table 3). Given its web-based administration, this treatment has the potential to reach large patient populations and is cost effective [26].

Description of Internet-Guided Self-Help Intervention

The effects of Internet-Guided Self-Help intervention (Get.On Diabetes and Depressive Disorders) was compared with usual care (plus online psychoeducation), in people with T1DM or T2DM and depression. This program contains 6 online sessions based on 2 main components of treatment: behavioral activation and problem solving. Two optional sessions addressed weight and sleep issues, and the seventh booster session (4 weeks after the completion of the last session) aimed to support participants in transferring skills to the routine of daily living. Each session lasted approximately 45 to 60 minutes, and within 48 hours of completing the session, participants received written feedback from trained psychologists [22].

Main findings

Internet-Guided Self-Help intervention improved depression (2 months follow-up), anxiety (2- and 6-months follow-up) and diabetes-specific emotional distress (2- and 6-months follow-up) (Table 3). The intervention group was not superior to control group in terms of glycemic control, diabetes self-management, and diabetes acceptance [22].

Telehealth interventions (n= 5) (Table 2)

Description of Telephone-delivered in Minimal Psychological Intervention (MPI)

Minimal Psychological Intervention was compared to usual care on improving psychological well-being and glycemic control, in patients with T2DM. Participants in the intervention group received in addition to usual care, 3 to 4 telephone calls (lasting 30 to 60 minutes) from nursing and psychology professionals, certified as diabetes educators. During the consultations, issues related to food, sleep, exercise and glycemic control, as well as general and specific health conditions of diabetes, were

addressed. Patients also talked about their feelings and lifestyle changes after their diabetes diagnosis. In this way, the educators understood about their daily routines, concerns and behaviors and, based on this information, discussed with the patients possible solutions to the problems raised [21].

Main findings

The intervention reduced diabetes-specific emotional distress (at 1 month follow-up). In patients with baseline HbA1c less than 8%, was observed improvement in blood glucose values (up to 3 months). In patients with baseline HbA1c equal/greater than 8%, no difference was observed in these measures (at 3 and 8 months follow-up) [21]. It was not possible to perform meta-analyses for this study due to lack of information.

Description of Health Buddy® Program

Clinical trial evaluated whether a disease management telehealth program performed by pharmacists is superior to the same intervention offered by nurses, in improving adherence to medication treatment in people with T1DM or T2DM and depression. Health Buddy® collects and sends information about a patient's health conditions, such as vital signs, symptoms and behaviors. The program provides alerts to remind patients to take their medication and check their feet, for example. Patients had their blood glucose and blood pressure measured using medical devices. After each session, there were educational questions for the patient to answer before submitting their results. Nurses or pharmacists received alerts from the Program about test results, food intake, self-care behavior, management of health-related symptoms, and patients' depressive symptoms. These professionals could contact over the phone to discuss your health care [28].

Main findings

In 6 months after the intervention, no difference was observed in depression scores, HBA1c values and on improvement in adherence to medication treatment for cardiovascular diseases, depression and overall medications when the program was offered by pharmacist or nurse (Table 3) [28].

Description of Telemedicine-delivered Behavior Activation Treatment (BAT)

Multicenter clinical trial evaluated the impact of BAT in elderly people with T2DM and depression compared to the same intervention offered in medical centers

or outpatient clinics. Therapists were masters-level counselors with at least five years' clinical experience, were trained prior to the study, and overseen through weekly supervise meetings. Therapists conducted online and face-to-face sessions and to ensure that treatments were the same between groups, sessions were randomly audited [23].

Main findings

BAT was superior to face-to-face treatment in achieving lower HBA1c values in adults with T2DM and depression, in 6 months period [23]. This study only evaluated this outcome and it was not possible to perform meta-analyses for this study due to lack of information.

Description of Telephone-Delivered Cognitive Behavioral Therapy (CBT)

This study evaluated the impact of CBT compared to usual care, in the management of patients with T2DM and depressive symptoms. The program was conducted by trained nurses and included an initial phase of 12 weekly sessions and another 9 monthly booster sessions. At first, Telephone-Delivered CBT focused exclusively on patients' depressive symptoms, and after 5 sessions, they introduced the pedometer-based walking program. Weekly, nurses held group sessions in which they discussed the most problematic situations with patients and proposed strategies to resolve them. The sessions were recorded and reviewed by a supervisor in order to adjust the conduct. Nurses received contributions from professionals from the primary care teams, trained to work in some stages of the intervention. These professionals were alerted if the patient reported suicidal ideation, discontinuation of antidepressant medication on their own, persistent elevation of depressive symptoms, or the need for prescription. The usual care patients did not receive the weekly group sessions, but some educational materials (such as the self-help book based on CBT and too used in the intervention group) [25].

Main findings

Three months after the interventions, Telephone-Delivered CBT (combined with a pedometer-based walking program) decreased depressive symptoms, but had no difference in improving of quality of life, HBA1c values and medication adherence compared to control group (Table 3) [25].

Description of the Healthy Outcomes through Patient Empowerment (HOPE)

This study evaluated whether HOPE reduced levels of diabetes-related emotional distress compared to Enhanced Usual Care (EUC) with education, in patients with depression and uncontrolled T1DM and T2DM. Participants of the intervention group received a collaborative, goal-setting ‘‘active’’ intervention for the first 6 months that occurred biweekly for telephone-based sessions 1–3 and monthly for sessions 4–6. Then they received three, bimonthly maintenance sessions of 15 min during months 7–12. HOPE’s sessions were led by trained health care professional (nurses, social workers, psychologists, clinical pharmacists) that received ongoing support by a behavioral health expert (about topics: building rapport, goal setting, engaging in positive lifestyle activities, healthy eating, relaxation, managing negative thoughts, and medication management). EUC group participants received educational materials on depression and anxiety.

Main findings

Remission of diabetes-related emotional distress was observed in the intervention group compared to control group for the subscales of PAID (emotional) at the 12-months (Table 3). The results demonstrate that the PAID questionnaire subscales provide insight into the treatment of diabetes related depression. However, while emotional and social burdens may decrease by HOPE intervention, treatment burdens were not adequately targeted.

Meta-analysis for measure outcomes

The meta-analysis was grouped according to the instrument used to evaluated the outcomes (Appendix 3). The quality of the evidence is described in Table 3 and Appendix 4.

Improvement and/or clinical remission of depression: it was observed improvement of this outcome for the Internet-Guided Self-Help intervention compared to usual care plus web psychoeducation (2- and 6-months follow-up, low quality of evidence) and for Telephone-Delivered CBT compared to usual care (6 months follow-up, moderate quality of evidence) (20, 22, 24, 25, 26, 27).

Improvement and/or clinical remission of anxiety: Internet-Guided Self-Help intervention compared to usual care (plus web psychoeducation) was superior on improvement and/or clinical remission of anxiety (after 2 and 6 months) of intervention,

as well as diabetes-specific CBT (DbG.nl) was better to this outcome compared to waiting-list (3 months follow-up). These results had moderate quality of evidence (20, 22, 24, 26).

Remission of diabetes-related emotional distress: Internet-Guided Self-Help intervention and Diabetes-Specific CBT compared to usual care (plus web psychoeducation) and waiting-list; respectively; improved this outcome after 2 months of the intervention. Likewise, iCBT improved this outcome compared to usual care (3 months follow-up). myCompass, Internet-Guided Self-Help and Healthy Outcomes through Patient Empowerment compared to Healthy Lifestyles, Usual care plus web psychoeducation and Enhanced Usual Care; respectively, had improvement of this outcome after 6 months of the intervention. These results had moderate quality of evidence [20, 22, 24, 26,27,29].

Improvement in quality of life: No change was observed in the iCBT compared to usual care (3 months follow-up, moderate quality of evidence) and Telephone-Delivered CBT compared to usual care (12 months follow-up, low quality of evidence) (24, 25).

Glycemic control: No change was observed in the value of HbA1c for the interventions (iCBT, myCompass, Pharmacist-Led Telehealth, Internet-Guided Self-Help intervention, Telephone-Delivered CBT) compared, respectively, to controls (usual care, Healthy Lifestyles, Nurse-Led Telehealth, usual care plus web psychoeducation, Healthy Lifestyles, usual care) at 3-, 6- and 12-months follow-up. These results had very low or low quality of evidence [20, 22, 24, 25, 28].

Medication adherence: No change in adherence to drugs for diabetes, of drugs for depression and all drug combined for the Pharmacist-Led Telehealth and Telephone-Delivered CBT interventions compared, respectively, to controls (Nurse-Led Telehealth, usual care), at 6- and 12-months follow-up. These results had very low or low quality of evidence [25, 28].

Table 2. Description of interventions evaluated by randomized controlled trials included (n=10 studies, 2,209 participants)

Authors and publication date	Purposes of study	Type of Intervention (n)	Type of Comparator (n)	Conclusions
WEB-BASED PROGRAM				
Baldwin et al., 2020 [20]	To evaluate the efficacy of an electronic mental health program (myCompass) for improving social and occupational functioning in people with T2DM and mild-to-moderate depressive symptoms	myCompass (n= 368)	Healthy Lifestyles (n= 355)	No difference was observed between the groups in relation to improvement of depression, anxiety and distress, follow-up 12 months after the intervention
Ebert et al., 2017 [22]	To examine the effects of an Internet-Based Guided Self-Help intervention for comorbid depressive symptoms in people with diabetes	Internet-Guided Self-Help (n= 130)	Usual care plus web psychoeducation (n= 130)	The use of Internet-Guided Self-Help intervention for depression in people with diabetes can have sustained effects on depressive symptoms, anxiety and well-being and emotional distress associated with diabetes
Newby et al., 2017 [24]	To examine the efficacy of a generic 6 lesson iCBT delivered over 10 weeks for people with diabetes mellitus and major depressive disorder	iCBT (n= 42)	Usual care (n=45)	ICBT improved diabetes-specific emotional distress and can be an efficacious, accessible treatment option for people with T1DM or T2DM. Future studies should explore whether this program can improve acceptability, adherence and evaluate the long-term outcomes
Quinn et al., 2017 [29]	To determine the impact of Mobile Diabetes Intervention on emotional well-being measured by diabetes distress and depression among adults with T2DM	Coach Primary Care Provider (n= 58)	Usual care (n= 56)	We found no definitive overall or sex-specific effect of the intervention on diabetes distress or depression on follow-up 12 months after the intervention. However, this study makes important contribution to the understanding of mobile health interventions and the impact on emotional health
Van-Bastelaar et al., 2012 [26]	To test the effectiveness of Diabetes-Specific CBT (DbG.nl) in patients with diabetes mellitus and major depressive disorder, anxiety disorder or elevated diabetes-specific emotional distress	Diabetes-Specific CBT (DbG.nl) (n= 125)	Waiting-list (n= 130)	Web-based CBT can be effective in patients with T1DM or T2DM with anxiety disorder but showed no benefit for depression and distress. Given its web-based administration, this treatment has the potential to reach large patient populations and to be cost effective
TELEHEALTH				

Table 2 *(Continued)*

Vaughau et al., 2012 [27]	To evaluate whether a collaborative, goal-setting, and behavioral telehealth intervention reduced diabetes distress levels in patients with T1DM and T2DM	Healthy Outcomes through Patient Empowerment (HOPE) (n=136)	Enhanced Usual Care (EUC) (n=89)	Reductions in diabetes-related emotional distress were observed in the intervention group compared to control group for the PAID subscale (emotional) at the 12-months. PAID questionnaire subscales provide insight into the treatment of diabetes related depression. While emotional and social burdens may decrease by HOPE intervention, treatment burdens were not adequately targeted
Chiu et al., 2016 [21]	To evaluate the impact of Minimal Psychological Intervention on improving psychological well-being and glycemic control in patients with T2DM	Minimal Psychological Intervention (n= 85)	Usual care from their family physicians (n= 89)	Telephone-Delivered Minimal Psychological Intervention might be a feasible and effective method for decreasing diabetes-specific distress and improving glycemic control in people with poor glycemic control
Cohen et al., 2019 [28]	To determine whether a Pharmacist-Led Telehealth disease management program was superior to usual care of nurse-led telehealth in people with diabetes and depression	Telehealth Health Buddy (Pharmacist-Led) (n= 13)	Telehealth Health Buddy (Nurse-Led) (n= 14)	Over a 6 months period, no difference was observed between the groups for improvement on depression scores; medication adherence for cardiovascular antidepressants and overall medications; and HbA1c values
Egede et al., 2017 [23]	To evaluate the impact of telemedicine-delivered Behavior Activation Treatment (BAT) on glycaemic control in older adults with diabetes and depression	Telemedicine BAT (n= 43)	Presential BAT (n= 47)	Telemedicine-delivered activation treatment was superior to use of same treatment in face-to-face format, in achieving lower HbA1c values in people with T2DM (single outcome evaluated by the study)
Piette et al., 2011 [25]	To evaluate the impact of Telephone-Delivered CBT combined with a pedometer-based walking program in management of depressive symptoms, physical activity and diabetes-related outcomes	Telephone-Delivered CBT (n= 145)	Usual care (n= 145)	Telephone-Delivered CBT combined with a pedometer-based walking program significantly decreased depressive symptoms, but not improved in quality of life, adherence and glycemic control compared to usual care

BAT (Behavioral Activation Treatment). CBT (Cognitive Behavioral Therapy). EUC (Enhanced Usual Care). HOPE (Healthy outcomes through Patient Empowerment). ICBT (Internet-Based Cognitive Behavioral Therapy). MD (mean). NHMRC (National Health and Medical Research Council). PAID (Problem Areas in Diabetes) PCP (Primary Care Provider). SD (Standard Deviation). T1DM (Type 1 Diabetes Mellitus). T2DM (Type 2 Diabetes Mellitus).

Table 3 - Meta-analysis of the outcomes of the randomized controlled trials included

Tools	Follow-up months	Intervention/Comparator	Number of RCT (Population)	SMD (95% CI) Heterogeneity (%)	Quality of evidence (GRADE)
Improvement and/or clinical remission of depression					
PHQ-9	3	myCompass/Healthy Lifestyles iCBT/Usual care	2 (263/286)	-0.32 (-1.18 to 0.53) 91.3%	Very low
	6	myCompass/Healthy Lifestyles Pharmacist-Led Telehealth/Nurse-Led Telehealth	2 (229/235)	0.18 (-0.40 to 0.75) 58.7%	Low
	12	My Compass/Healthy Lifestyles	1 (148/156)	0.11 (-0.12 to 0.33) NA	Low
PHQ-15	3	iCBT/Usual care	1 (31/45)	-0.21 (-0.67 to 0.24) NA	Low
CES-D	1	Diabetes-Specific CBT (DbG.nl)/Waiting-list	1 (20/24)	.96 to 0.23) NA	Moderate
	2	Internet-Guided Self-Help/Usual care plus web psychoeducation	1 (128/127)	-0.89 (-1.15 to -0.63) NA	Low
	3	Diabetes-Specific CBT (DbG.nl)/Waiting-list	1 (21/24)	-0.30 (-0.89 to 0.29) NA	Low
	6	Pharmacist-Led Telehealth/Nurse-Led Telehealth Internet-Guided Self-Help/Usual care plus web psychoeducation	2 (89/117)	-0.25 (-1.32 to 0.83) 85.6%	Very low
BDI	12	Telephone-Delivered CBT/Usual care	1 (145/146)	-0.42 (-0.65 to -0.19) NA	Moderate
Improvement and/or clinical remission of anxiety					
GAD-7	3	myCompass/Healthy Lifestyles iCBT/Usual care	2 (263/286)	-0.28 (-1.10 to 0.54) 90.5%	Very low
	6	myCompass/Healthy Lifestyles	1 (216/221)	0.0 (-0.19 to 0.19) NA	Low
	12	myCompass/Healthy Lifestyles	1 (148/156)	0.0 (-0.22 to 0.22) NA	Low
HADS	2	Internet-Guided Self-Help/Usual care plus web psychoeducation	1 (99/114)	-0.84 (-1.12 to -0.56) NA	Moderate
	6	Internet-Guided Self-Help/Usual care plus web psychoeducation	1 (79/103)	-0.72 (-1.02 to -0.42) NA	Moderate
WHO CIDI-auto	1	Diabetes-Specific CBT (DbG.nl)/Waiting-list	1 (22/25)	-0.29 (-0.86 to 0.29) NA	Low
	3	Diabetes-Specific CBT (DbG.nl)/Waiting-list	1	-0.60 (-1.18 to -0.02)	Moderate

Table 3 *(Continued)*

			(23/25)		
Remission of diabetes-related emotional distress					
PAID/DDS	1 and 2	Diabetes-Specific CBT (DbG.nl)/Waiting-list Internet-Guided Self-Help/Usual care plus web psychoeducation	2 (120/138)	-0.52 (-0.77 to -0.27) 0%	Moderate
	3	iCBT/Usual care Diabetes-Specific CBT (DbG.nl)/Waiting-list myCompass/Healthy Lifestyles	3 (84/114)	*-0.25 (-0.68 to 0.17) 70.6%	Very low
	6	myCompass/Healthy Lifestyles Internet-Guided Self-Help/Usual care plus web psychoeducation Healthy Outcomes through Patient Empowerment/ Enhanced Usual Care	3 (431/413)	-0.24 (-0.39 to -0.08) 18.6%	Moderate
PAID/DDS	12	myCompass/Healthy Lifestyles Coach Primary Care Provider/Usual care Healthy Outcomes through Patient Empowerment/ Enhanced Usual Care	3 (341/291)	-0.12 (-0.37 to 0.12) 63.7%	Very low
K-10	3	iCBT/Usual care	1 (31/45)	-1.08 (-1.57 to -0.59) NA	Moderate
Improvement in quality of life					
SF-12 Mental composite	3	iCBT/Usual care	1 (31/45)	0.67 (0.20 to 1.14) NA	Moderate
SF-12 Physical composite	3	iCBT/Usual care	1 (31/45)	-0.15 (-0.61 to 0.31) NA	Low
SF-12 Mental composite	12	Telephone-Delivered CBT/Usual care	1 (145/146)	0.02 (-0.21 to 0.25) NA	Low
SF-12 Physical composite	12	Telephone-Delivered CBT/Usual care	1 (145/146)	0.20 (-0.03 to 0.43) NA	Low
Glycaemic control					
Glycemic control (HbA1c values)	3	iCBT/Usual care	1 (31/45)	0.17 (-0.29 to 0.63) NA	Very low
	6	myCompass/Healthy Lifestyles Pharmacist-Led Telehealth/Nurse-Led Telehealth Internet-Guided Self-Help/Usual care plus web psychoeducation	3 (308/338)	**0.29 (-0.07 to 0.65) 69.7%	Low
	12	myCompass/Healthy Lifestyles Telephone-Delivered CBT/Usual care	2 (293/302)	0.08 (-0.08 to 0.24) 0%	Low

Medication adherence					
Table 3 *(Continued)* **Drugs for diabetes**	6 and 12	Pharmacist-Led Telehealth/Nurse-Led Telehealth Telephone-Delivered CBT/Usual care	2 (158/158)	-0.02 (-0.24 to 0.20) 0%	Low
Drugs for depression	6 and 12	Pharmacist-Led Telehealth/Nurse-Led Telehealth Telephone-Delivered CBT/Usual care	2 (151/153)	0.01 (-0.21 to 0.24) 0%	Low
All drug combined	6	Pharmacist-Led Telehealth/Nurse-Led Telehealth	1 (4/4)	-0.11 (-1.50 to 1.27) NA	Very low

95% IC (95% Confidence Interval). CBT (Cognitive Behavioural Therapy). HbA1c (HemoglobinA1C). iCBT (Internet Cognitive Behavioural Therapy). GRADE (Grading of Recommendations Assessment, Development and Evaluation). NA (Not Applicable). RCT (Randomized Controlled Trial). SMD (Standardized Mean Difference).

*SMD predictive interval: -5.09 to 4.58. **SMD predictive interval: -3.69 to 4.27

Scales that measured depression: BDI (Beck Depression Inventory), CES-D (Center for Epidemiologic Studies Depression Scale), PHQ-9 (Patient Health Questionnaire-9) and PHQ-15 (Patient Health Questionnaire-15).

Scales that measured anxiety: GAD-7 (Generalized Anxiety Disorder Scale), HADS (Hospital Anxiety and depression Scale) and WHO CIDI-auto (World Health Organization Composite International Diagnostic).

Scales that measured improvement of diabetes-specific emotional distress: DDS (Diabetes Distress Scale) K-10 (Kessler 10 item psychological distress scale) and PAID (Problem Areas in Diabetes).

Scale that measured quality of life: SF-12 (Short Form 12 Item Mental Health Subscale and Physical Health subscale).

Discussion

Summary of the main findings

This study summarized the evidence available on e-Health interventions to treat psychological disorders, in people with diabetes mellitus. RCT included mainly adults with T2DM and depression, there was no specific study of adults, children, or adolescents with T1DM. In general, the studies had high methodological quality.

Web-based programs were addressed in 5 studies [20,22,24,26,29]. Three studies showed superior results compared to control groups. ICBT shown to be an effective treatment compared to usual care in improving diabetes-specific emotional distress, in people with diabetes mellitus and major depressive disorder [24]. Diabetes-Specific CBT (DbG.nl) was superior to waiting list in reducing anxiety in people with diabetes mellitus [26]. Internet-Guided Self-Help intervention was superior to usual care in improving depression, anxiety and diabetes-specific emotional distress, in people with T1DM or T2DM [22].

Of studies that explored telehealth interventions [21,23,25,27,28], four of them demonstrated benefits in improving psychological disorders [21,23,25]. Minimal Psychological Intervention was superior to usual care in decreasing diabetes-specific emotional distress and achieving better glycemic control, in people with T2DM, especially in those with poor glycemic control [21]. BAT was superior to usual care in improving depression and decreasing HbA1c values, in people with T2DM [23]. CBT (combined with a walking program) decreased depressive symptoms compared to usual care, but showed no difference in improving on quality of life, HBA1c values and medication adherence [25]. Reductions in diabetes-related emotional distress was observed in Healthy Outcomes through Patient Empowerment intervention compared to control group [27].

Meta-analysis shown improvement in depression outcomes with the use of Internet-Guided Self-Help intervention [22] and Telephone-Delivered CBT, both compared to usual care [25]. It was observed improvement of anxiety with the use of Internet-Guided Self-Help compared to usual care [22], as well as Diabetes-Specific CBT compared to waiting-list [26]. Improvement of diabetes-related emotional distress was observed with the use of Internet-Guided Self-Help [22], Diabetes-Specific CBT [26], myCompass [20], Internet-Guided Self-Help [22], Healthy Outcomes through Patient Empowerment [27] compared to usual care, waiting-list, Healthy

Lifestyles,Usual care plus web psychoeducation and Enhanced Usual Care, respectively. Likewise, iCBT improved this outcome compared to usual care [24].

In studies that reported quality of life [24, 25], no change was observed for this outcome. In relation glycemic control, it was observed no improvement with the use of interventions [17, 22, 24, 25, 28]. Likewise, no change was observed in adherence to drugs for diabetes, drugs for depression and all drug combined [25, 28]. Safety outcomes were not reported. Too improvement on quality of life, satisfaction with the intervention or its acceptability were poor reported. In general, the follow-up ranged from 3, 6 and 12 months between the studies, the quality of the evidence was considered very low or low.

Although there are systematic reviews of e-Health interventions to treat depression, anxiety, and diabetes-specific emotional distress [9,12,13,30], their findings did not address the specific population of our study. In this studies, or the population was not specific to people with psychological diseases [12] or the population was not restricted to diabetes mellitus [9,13,30].

CBT demonstrated effective results in improving depression, anxiety and diabetes-related emotional distress [24–26]. CBT is an organized and time-limited approach, with content such as psychoeducation, behavioral activation, cognitive restructuring, and relapse prevention. This intervention can be useful for people with chronic illnesses by improving self-care skills and learning to adjust to the disease and its impact on their daily lives [31,32].

Strengths and limitations of the study

This systematic review summarizes the findings of published RCT on e-Health interventions in people with diabetes mellitus, focusing on measures of psychological outcomes. It offered a view digital mental health resource available and examined the effectiveness and safety of telehealth and mobile health interventions. Furthermore, although we identified a limited number of clinical trials, we are confident that our findings represent the research conducted to date.

This study was carried out with methodological rigor and explicit eligibility criteria, a comprehensive and extensive search in several databases, no language restriction, independent and peer reviewers for the selection and extraction of data, and an evaluation of the risk of bias.

In general, clinical trials differed in terms of the interventions evaluated, populations studied, follow-up time, as well as in terms of outcome measures and their

measurement methods. These divergences restricted our findings considering the low comparability between the studies, small sample size in most clinical trials, and the fact that psychological illness can manifest differently in people with T1DM and T2DM.

Implications for clinical practice and research

In general, the interventions Internet-Guided Self-Help intervention [22] and Telephone-Delivered CBT [25] for depression outcomes; Internet-Guided Self-Help [22] and Diabetes-Specific CBT [26] for anxiety and diabetes-related emotional distress; and iCBT and Healthy Outcomes through Patient Empowerment [24, 27] for emotional distress can contribute to tratment of mental health problems in this population.

The use of e-Health interventions reduced infrastructure requirements and the travel and time burden for patients. Due to the convenience and flexibility of this format, it was observed patient greater involvement in the telehealth format than in face-to-face meetings CBT [25].

It is important to note that when participants are interviewed at home, via telephone, it is possible that their family members have affected their reports of psychological symptoms [18]. Patients may have cell phones and other phone services that are incompatible with the apps and therefore ineligible for enrollment [23]. Too, not all people may be willing to use Internet-Guided Self-Help, then this intervention, for example, should be offered as just a treatment option alongside already established interventions for depression, in people with diabetes mellitus [16].

According to the literature, clinical trials on digital mental health programs have focused on establishing effectiveness rather than assessing patient acceptance and the adoption of programs [9]. In fact, only one clinical trial evaluated this outcome [22]. In addition, future clinical trials would assess disease recurrence rates on m-Health interventions [30] as well as other clinically relevant outcomes for the patient.

Alternatively, one barrier commonly present in this topic should be highlighted, since the applications are more commercially driven than scientifically derived and evaluated [30]. Furthermore, for these programs to be effective, they must be implemented successfully and sustainably within the range of available mental health services [33]. It can take years to design, develop, and evaluate the effectiveness of web-based applications using rigorous scientific measures. Therefore, such scientifically validated interventions will always be one step behind commercially

unregulated applications unless there are financial resources for larger-scale studies [30].

Although e-Health interventions seem to contribute to the improvement of mental health in people with diabetes mellitus and depression, anxiety, or emotional distress, it is important to note that there are few clinical trials, that limit the confidence of our findings. The follow-up period was relatively short in some studies, and some studies were restricted to evaluating only few outcomes. In addition, the RCT were conducted in high-income countries, making it difficult to determine the effectiveness of these interventions for people living in low-income countries. Although still incipient, the findings of this study can guide patients and health professionals with alternatives for the management of these psychological disorders.

Given the growing number of people with diabetes worldwide and the fact that they are likely to develop psychological problems, the possibility of having interventions that are more economical and easier to access for this population can contribute to better clinical results. Digital interventions can complement traditional face-to-face care support for this population and help bridge the gap between diabetes support and psychological disorders, such as depression, anxiety and diabetes-specific emotional distress.

Conclusion

This study suggested that most interventions e-Health were effective in improving depression, anxiety, and diabetes-specific emotional distress in people mainly with T2DM. Due to divergences in interventions, populations, follow-up time, small sample size, type of measures outcomes, absence of safety outcomes, future clinical trials may confirm these findings. Patients and health professionals can use this information in the choice of alternatives for the management of these psychological disorders.

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Competing interests

The authors report no competing of interest in this study.

Author contributions

Reginaldo Franquez (RF) designed the search, performed the systematic electronic searches, identified relevant articles for inclusion, extracted the data, performed the study quality assessment, and drafted parts of the manuscript. Mariana Paglia (MP), identified relevant articles for inclusion, extracted the data, and performed the study quality assessmen. Delaine McClung (DM) identified relevant articles for inclusion, and extracted the data. Silvio Barberato-Filho, Luciane Lopes, Marcus Silva, Fernando de Sá Del-Fiol identified relevant articles for inclusion or extracted the data and drafted parts of the results of manuscript. Cristiane Bergamaschi (CB) designed the search, identified relevant articles for inclusion, performed the study quality assessment and drafted parts of the manuscript.

All authors were involved in the development of the study concept, critically reviewed the manuscript, and gave permission for publication.

Appendices

Appendix 1. Search strategy

Appendix 2. Characteristics of excluded studies

Appendix 3. Meta-analyses of the evaluated outcomes

Appendix 4. Grading of Recommendations Assessment, Development, and Evaluation – GRADE

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Mental Health Interventions for Depression , Anxiety , and Enhancement of Psychological Well-Being Among College Students : Systematic Review Corresponding Author : J Med INTERNET Res. 2019;21: 1–27. doi:10.2196/12869

Appendix 1. Search strategy

MEDLINE (via PubMed) (n=734)

#1Diabetes [MeSH] + Entry Terms	(Diabetes) OR (Autoimmune Diabetes) OR (Brittle Diabetes Mellitus) OR (IDDM) OR (Insulin Dependent Diabetes Mellitus) OR (Insulin Dependent Diabetes Mellitus 1) OR (Insulin-Dependent Diabetes Mellitus) OR (Insulin-Dependent Diabetes Mellitus 1) OR (Juvenile Onset Diabetes) OR (Juvenile Onset Diabetes Mellitus) OR (Juvenile-Onset Diabetes) OR (Juvenile-Onset Diabetes Mellitus) OR (Ketosis Prone Diabetes Mellitus) OR (Ketosis-Prone Diabetes Mellitus) OR (Sudden Onset Diabetes Mellitus) OR (Sudden-Onset Diabetes Mellitus) OR (Type 1 Diabetes) OR (Type 1 Diabetes Mellitus) OR (Type I Diabetes Mellitus) OR (Adult Onset Diabetes Mellitus) OR (Adult-Onset Diabetes Mellitus) OR (Ketosis Resistant Diabetes Mellitus) OR (Ketosis-Resistant Diabetes Mellitus) OR (Maturity Onset Diabetes) OR (Maturity Onset Diabetes Mellitus) OR (Maturity-Onset Diabetes) OR (Maturity-Onset Diabetes Mellitus) OR (MODY) OR (NIDDM) OR (Non Insulin Dependent Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Slow Onset Diabetes Mellitus) OR (Slow-Onset Diabetes Mellitus) OR (Stable Diabetes Mellitus) OR (Type 2 Diabetes) OR (Type 2 Diabetes Mellitus) OR (Type II Diabetes Mellitus)
#2Depression [MeSH] + Entry Terms	(Depression) OR (Depressions) OR (Depressive Symptom) OR (Depressive Symptoms) OR (Emotional Depression) OR (Emotional Depressions) OR (Depressive Disorder) OR (Depressive Disorders) OR (Depressive Neuroses) OR (Depressive Neurosis) OR (Depressive Syndrome) OR (Depressive Syndromes) OR (Endogenous Depression) OR (Endogenous Depressions) OR (Melancholia) OR (Melancholias) OR (Neurotic Depression) OR (Neurotic Depressions) OR (Unipolar Depression) OR (Unipolar Depressions)
#3 Anxiety [MeSH] + Entry Terms	(Anxiety) OR (Hypervigilance) OR (Nervousness) OR (Social Anxieties) OR (Social Anxieties) OR (Social Anxiety) OR (Anxiety Disorder) OR (Anxiety Disorders) OR (Neurotic Anxiety State) OR (Neurotic Anxiety States)
#4 Digital Technology [MeSH] + Entry Terms	(Digital Technology) OR (Telemedicine) OR (Telehealth*) OR (mobile telehealth) OR (Telecommunication*) OR (Internet Intervention) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Mobile Device) OR (Mobile) OR (Mobile App) OR (Mobile Phone) OR (App*) OR (Application*) OR (Web-based) OR (Web-based intervention) OR (Online-based) OR (Interactive) OR (Online) OR (On-line) OR (Website*) OR (Electronic Health*)
#5	**(#1 AND (#2 OR #3) AND #4)**
#6	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[tiab]) NOT (animals[mh] NOT humans [mh])
#7	**#5 AND #6**

LILACS (via Virtual Health Library) (n=36)

#1	(diabetes) OR (autoimmune diabetes) OR (insulin dependent diabetes mellitus) OR (insulin-dependent diabetes mellitus) OR (juvenile onset diabetes) OR (juvenile-onset diabetes) OR (type 1 diabetes) OR (type 1 diabetes mellitus) OR (non insulin dependent diabetes mellitus) OR (noninsulin dependent diabetes mellitus) OR (noninsulin-dependent diabetes mellitus) OR (non-insulin-dependent diabetes mellitus) OR (type 2 diabetes) OR (type 2 diabetes mellitus)
#2	(depression) OR (depressive symptom) OR (depressive symptoms) OR (depressive disorder) OR (depressive disorders) OR (depressive syndrome) OR (anxiety) OR (social anxiety) OR (anxiety disorder)
#3	(digital technology) OR (telemedicine) OR (telehealth*) OR (mobile telehealth) OR (telecommunication*) OR (internet intervention) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (mobile health) OR (mobile device) OR (mobile) OR (mobile app) OR (mobile phone) OR (app*) OR (application*) OR (web-based) OR (web-based intervention) OR (online-based) OR (interactive) OR (online) OR (on-line) OR (website*) OR (electronic health*)
#4	*(db:("LILACS") AND type_of_study:(" clinical_trials"))*
#5	*#1 AND #2 AND #3 AND #4*

Cochrane CENTRAL (n=1082)

#1	(Diabetes Complications) OR (Diabetes Mellitus, Type 1) OR (Diabetes Mellitus, Type 2)
#2	(Depression) OR (Depressive Disorder) OR (Anxiety) OR (Anxiety Disorders)
#3	(Digital Technology) OR (Telemedicine) OR (Telehealth*) OR (mobile telehealth) OR (Telecommunication*) OR (Internet Intervention) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Mobile Device) OR (Mobile) OR (Mobile App) OR (Mobile Phone) OR (App*) OR (Application*) OR (Web-based) OR (Web-based intervention) OR (Online-based) OR (Interactive) OR (Online) OR (On-line) OR (Website*) OR (Electronic Health*)
#4	#1 AND #2 AND #3 in Trials

Web of Science (n=1665)

#1	ALL=((Diabetes) OR (Autoimmune Diabetes) OR (Insulin Dependent Diabetes Mellitus) OR (Insulin-Dependent Diabetes Mellitus) OR (Juvenile Onset Diabetes) OR (Juvenile-Onset Diabetes) OR (Type 1 Diabetes) OR (Type 1 Diabetes Mellitus) OR (Non Insulin Dependent Diabetes Mellitus) OR (Noninsulin Dependent Diabetes Mellitus) OR (Noninsulin-Dependent Diabetes Mellitus) OR (Non-Insulin-Dependent Diabetes Mellitus) OR (Type 2 Diabetes) OR (Type 2 Diabetes Mellitus))
#2	ALL=((Depression) OR (Depressive Symptom) OR (Depressive Symptoms) OR (Depressive Disorder) OR (Depressive Disorders) OR (Depressive Syndrome) OR (Anxiety) OR (Social Anxiety) OR (Anxiety Disorder))
#3	**ALL=((Digital Technology) OR (Telemedicine) OR (Telehealth*) OR (mobile telehealth) OR (Telecommunication*) OR (Internet Intervention) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Mobile Device) OR (Mobile) OR (Mobile App) OR (Mobile Phone) OR (App*) OR (Application*) OR (Web-based) OR (Web-based intervention) OR (Online-based) OR (Interactive) OR (Online) OR (On-line) OR (Website*) OR (Electronic Health*))**
#4	#3 AND #2 AND #1
#5	**ALL=((Randomized controlled trial) OR (randomization))**

#6	#4 AND #5

EMBASE (n=1466)

#1	'non insulin dependent diabetes mellitus'/exp AND [embase]/lim
#2	'insulin dependent diabetes mellitus'/exp AND [embase]/lim
#3	'depression'/exp AND [embase]/lim
#4	'major depression'/exp AND [embase]/lim
#5	'anxiety'/exp AND [embase]/lim
#6	'anxiety disorder'/exp AND [embase]/lim
#7	'telehealth'/exp AND [embase]/lim
#8	'mhealth'/exp AND [embase]/lim
#9	'web-based intervention'/exp AND [embase]/lim
#10	#1 OR #2
#11	#3 OR #4 OR #5 OR #6
#12	#7 OR #8 OR #9
#13	#10 AND #11 AND #12 AND ('controlled study'/exp OR 'controlled study' OR 'randomized controlled trial'/exp OR 'randomized controlled trial')

ISRCTN (n=34)

#1	(Diabetes) OR (Diabetes Mellitus)
#2	(Depression) OR (Depressive Disorder) OR (Anxiety)
#3	(Digital Technology) OR (Telehealth*) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Web-based)
#4	#1 AND #2 AND #3
#5	#4 in Condition Category: Nutritional, Metabolic, Endocrine

CLINICAL TRIALS (n=8)

#1	(Diabetes) OR (Diabetes Mellitus)
#2	(Depression) OR (Depressive Disorder) OR (Anxiety)
#3	(Digital Technology) OR (Telehealth*) OR (ehealth) OR (e-health) OR (mhealth) OR (m-health) OR (Mobile Health) OR (Web-based)
#4	#1 AND #2 AND #3

Appendix 2. Characteristics of excluded studies

Study	Reason for exclusion
Aburizik A, Dindo L, Kaboli P, Charlton M, Dawn K, Turvey C. A pilot randomized controlled trial of a depression and disease management program delivered by phone. J Affect Disord. 2013 Nov;151(2):769–74.	Other population
Aguilera A, Figueroa CA, Hernandez-Ramos R, Sarkar U, Cemballi A, Gomez-Pathak L, et al. mHealth app using machine learning to increase physical activity in diabetes and depression: clinical trial protocol for the DIAMANTE Study. BMJ Open. 2020 Aug;10(8):e034723.	Other design of study
Aikens JE, Rosland A-M, Piette JD. Improvements in illness self-management and psychological distress associated with telemonitoring support for adults with diabetes. Prim Care Diabetes. 2015 Apr;9(2):127–34.	Other population
Al-Ozairi E, Ridge K, Taghadom E, de Zoysa N, Tucker C, Stewart K, et al. Diabetes and TelecommunicationS (DATES) study to support self-management for people with type 2 diabetes: a randomized controlled trial. BMC Public Health. 2018 Nov;18.	Other population
Araya R, Menezes PR, Claro HG, Brandt LR, Daley KL, Quayle J, et al. Effect of a Digital Intervention on Depressive Symptoms in Patients With Comorbid Hypertension or Diabetes in Brazil and Peru: Two Randomized Clinical Trials. JAMA. 2021 May;325(18):1852–62.	Other population
Baron JS, Hirani S, Newman SP. A randomised, controlled trial of the effects of a mobile telehealth intervention on clinical and patient-reported outcomes in people with poorly controlled diabetes. J Telemed Telecare. 2017 Feb;23(2):207–16.	Other population
Baumeister H, Nowoczin L, Lin J, Seifferth H, Seufert J, Laubner K, et al. Impact of an acceptance facilitating intervention on diabetes patients' acceptance of Internet-based interventions for depression: a randomized controlled trial. Diabetes Res Clin Pract. 2014 Jul;105(1):30–9.	Other population
Bender MS, Cooper B. A feasible and effective mobile health weight loss lifestyle intervention for filipinos with type 2 diabetes. Circulation [Internet]. 2017;135.	Other population
Bendig E, Bauereiss N, Schmitt A, Albus P, Baumeister H. ACTonDiabetes-a guided psychological internet intervention based on Acceptance and Commitment Therapy (ACT) for adults living with type 1 or 2 diabetes: results of a randomised controlled feasibility trial. BMJ Open. 2021 Jul;11(7):e049238.	Other population
Berghmans C, Godard R, Joly J, Tarquinio C, Cuny P. Effects of the Mindfulness Based Stress Reduction (MBSR) approach on psychic health (stress, anxiety, depression) and coping mode of diabetic patients: a controlled and randomized pilot study. Ann Med Psychol (Paris) [Internet]. 2012;170(5 CC-Complementary Medicine):312-317.	Other outcomes
Bisno DI, Reid MW, Fogel JL, Pyatak EA, Majidi S, Raymond JK. Virtual Group Appointments Reduce Distress and Improve Care Management in Young Adults with Type 1 Diabetes. J Diabetes Sci Technol. 2021 Jul;19322968211035770.	Other population
Bohingamu Mudiyanselage S, Stevens J, Watts JJ, Toscano J, Kotowicz MA, Steinfort CL, et al. Personalised telehealth intervention for chronic disease management: A pilot randomised controlled trial. J Telemed Telecare. 2019 Jul;25(6):343–52.	Other population
Bond GE, Burr RL, Wolf FM, Feldt K. The effects of a web-based intervention on psychosocial well-being among adults aged 60 and older with diabetes: a randomized trial. Diabetes Educ. 2010;36(3):446–56.	Other population
Boucher E, Moskowitz JT, Kackloudis GM, Stafford JL, Kwok I, Parks AC. Immediate and Long-Term Effects of an 8-Week Digital Mental Health Intervention on Adults With Poorly Managed Type 2 Diabetes: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2020 Aug;9(8):e18578.	Other population
Burner E, Lam CN, Deross R, Kagawa-Singer M, Menchine M, Arora S. Using Mobile Health to Improve Social Support for Low-Income Latino Patients with Diabetes: A Mixed-Methods Analysis of the Feasibility Trial of TExT-MED + FANS. Diabetes Technol Ther [Internet]. 2018;20(1):39–48.	Other population
Burner E, Mercado J, Hernandez-Saenz A, Peters A, Baezconde-Garbanati L, Arora S, et al. Design and patient characteristics of the randomized controlled trial TExT-MED plus FANS A test of mHealth augmented social support added to a patient-focused text-messaging intervention for emergency department patients with poorly controlled diabetes. Contemp Clin Trials. 2019;80:1–8.	Other population
Cartwright M, Hirani SP, Rixon L, Beynon M, Doll H, Bower P, et al. Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. BMJ. 2013 Feb;346:f653.	Other population
Cassimatis M, Kavanagh DJ, Hills AP, Smith AC, Scuffham PA, Gericke C, et al. The On Track Diabetes Web-Based Program for Type 2 Diabetes and Dysphoria Self-Management: A Randomized Controlled Trial Protocol. JMIR Res Protoc. 2015;4(3).	Other population
Chew BH, Vos RC, Stellato RK, Ismail M, Rutten GEHM. The effectiveness of an emotion-focused educational programme in reducing diabetes distress in adults with Type 2 diabetes mellitus (VEMOFIT): a cluster randomized controlled trial. Diabet Med. 2018 Jun;35(6):750–9.	Other outcomes
Clarke J, Vatiliotis V, Verge CF, Holmes-Walker J, Campbell L V, Wilhelm K, et al. A mobile phone and web-based intervention for improving mental well-being in young people with type 1 diabetes: design of a randomized controlled trial. JMIR Res Protoc. 2015 May;4(2):e50.	Other design of study
Clarke J, Sanatkar S, Baldwin PA, Fletcher S, Gunn J, Wilhelm K, et al. A Web-Based Cognitive Behavior Therapy Intervention to Improve Social and Occupational Functioning in Adults With Type 2 Diabetes (The SpringboarD Trial): Randomized Controlled Trial. J Med Internet Res. 2019 May;21(5):e12246.	Another study selected with the same population
Cohn MA, Pietrucha ME, Saslow LR, Hult JR, Moskowitz JT. An online positive affect skills intervention reduces depression in adults with type 2 diabetes. J Posit Psychol. 2014 Jan;9(6):523–34.	Other population

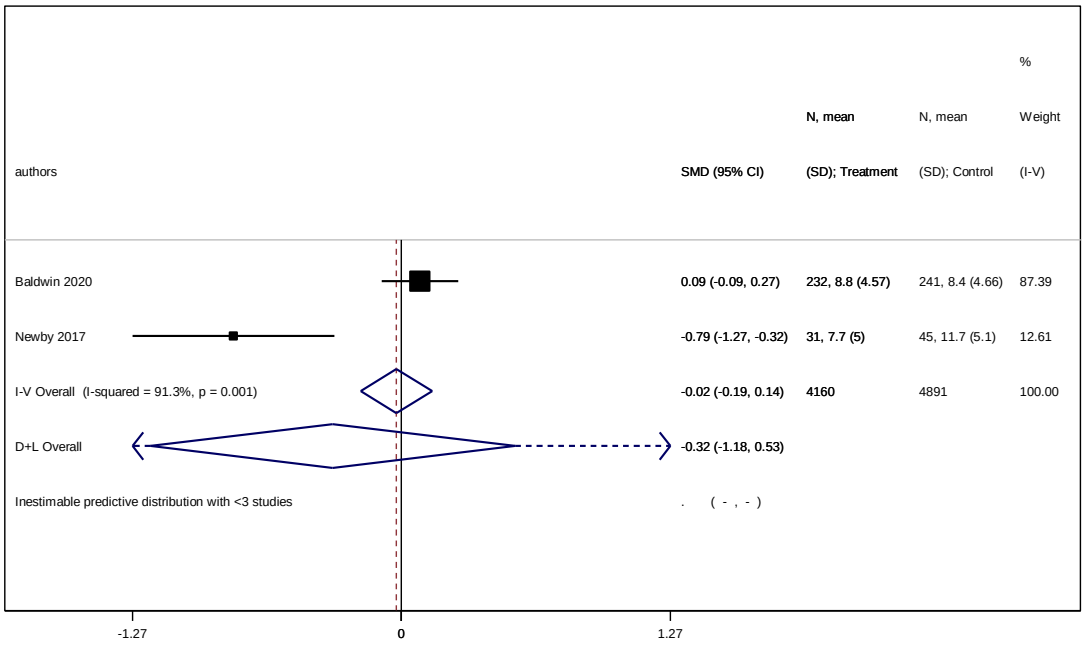
Crawford J, Wilhelm K, Robins L, Proudfoot J. Writing for Health: Rationale and Protocol for a Randomized Controlled Trial of Internet-Based Benefit-Finding Writing for Adults With Type 1 or Type 2 Diabetes. JMIR Res Protoc. 2017 Mar;6(3):e42.	Other design of study
Crawford J, Wilhelm K, Proudfoot J. Web-Based Benefit-Finding Writing for Adults with Type 1 or Type 2 Diabetes: Preliminary Randomized Controlled Trial. JMIR diabetes. 2019 Jun;4(2):e13857.	Other population
Cummings DM, Lutes LD, Littlewood K, DiNatale E, Hambidge B, Schulman K. EMPOWER: A randomized trial using community health workers to deliver a lifestyle intervention program in African American women with Type 2 diabetes: Design, rationale, and baseline characteristics. Contemp Clin Trials. 2013;36(1):147–53.	Other outcomes
DRKS00004748. Internet-based programme to treat depressive symptoms of patients with diabetes mellitus type 1 and type 2. http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00004748 [Internet]. 2013; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01810830/full	Other design of study
DRKS00013193. ACTonDiabetes - A randomised-controlled feasibility trial of an acceptance and commitment therapy-based internet intervention for people with diabetes mellitus. http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00013193 [Internet]. 2017; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01890306/full	Other population
DRKS00016714. Feasibility trial of an online intervention for symptoms of depression and anxiety in adolescents with chronic medical conditions (youthCOACH-CD). http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00016714 [Internet]. 2019; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01973003/full	Other population
DRKS00017161. Effectiveness and cost-effectiveness of guided internet-and mobile-based CBT for adolescents and young adults with chronic somatic conditions and comorbid depression and anxiety symptoms (youthCOACHcd): a multicentre randomized controlled trial with a 12-. http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00017161 [Internet]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02067289/full	Other design of study
Duruturk N, Özköslü MA. Effect of tele-rehabilitation on glucose control, exercise capacity, physical fitness, muscle strength and psychosocial status in patients with type 2 diabetes: A double blind randomized controlled trial. Prim Care Diabetes. 2019 Dec;13(6):542–8.	Other population
Evanson O, Wu S. Comparison of Satisfaction With Comorbid Depression Care Models Among Low-Income Patients With Diabetes. J patient Exp. 2020 Oct;7(5):734–41.	Other population
Fletcher S, Clarke J, Sanatkar S, Baldwin P, Gunn J, Zwar N, et al. Recruiting to a Randomized Controlled Trial of a Web-Based Program for People With Type 2 Diabetes and Depression: Lessons Learned at the Intersection of e-Mental Health and Primary Care. J Med Internet Res. 2019 May;21(5):e12793.	Other outcomes
Fortmann AL, Garcia MI, Skidmore J, Clark T, Ruiz M, Hernandez M, et al. Diabetes distress affects responsiveness to an mhealth self-management intervention among hispanics with type 2 diabetes (dulce digital). Diabetes [Internet]. 2016;65:A202.	Not found full text
Franco P, Gallardo AM, Urtubey X. Web-Based Interventions for Depression in Individuals with Diabetes: Review and Discussion. JMIR diabetes. 2018 Sep;3(3):e13.	Other design of study
Gustafson DHS, Mares M-L, Johnston DC, Mahoney JE, Brown RT, Landucci G, et al. A Web-Based eHealth Intervention to Improve the Quality of Life of Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2021 Feb;10(2):e25175.	Other population
Hay JW, Lee P-J, Jin H, Guterman JJ, Gross-Schulman S, Ell K, et al. Cost-Effectiveness of a Technology-Facilitated Depression Care Management Adoption Model in Safety-Net Primary Care Patients with Type 2 Diabetes. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2018 May;21(5):561–8.	Other population
Hofmann M, Dack C, Barker C, Murray E. The Impact of an Internet-Based Self-Management Intervention (HeLP-Diabetes) on the Psychological Well-Being of Adults with Type 2 Diabetes: A Mixed-Method Cohort Study. J Diabetes Res. 2016;2016.	Other population
Holland-Carter L, Tuerk PW, Wadden TA, Fujioka KN, Becker LE, Miller-Kovach K, et al. Impact on psychosocial outcomes of a nationally available weight management program tailored for individuals with type 2 diabetes: Results of a randomized controlled trial. J Diabetes Complications. 2017 May;31(5):891–7.	Other outcomes
Kobe EA, Edelman D, Tarkington PE, Bosworth HB, Maciejewski ML, Steinhauser K, et al. Practical telehealth to improve control and engagement for patients with clinic-refractory diabetes mellitus (PRACTICE-DM): Protocol and baseline data for a randomized trial. Contemp Clin Trials. 2020 Nov;98:106157.	Other population
Lunkenheimer F, Domhardt M, Geirhos A, Kilian R, Mueller-Stierlin AS, Holl RW, et al. Effectiveness and cost-effectiveness of guided Internet- And mobile-based CBT for adolescents and young adults with chronic somatic conditions and comorbid depression and anxiety symptoms (youthCOACHCD): study protocol for a multicentre randomized control. Trials [Internet]. 2020;21(1 CC-Cystic Fibrosis and Genetic Disorders).	Other population
Magee MF, Kaltman SI, Mete M, Nassar CM. A Prospective, Non-randomized Feasibility and Preliminary Efficacy Study of a Telemedicine-Enabled Co-management Intervention for Adults With Type 2 Diabetes and Moderate Anxiety and/or Depression. Sci diabetes self-management care. 2021 Apr;47(2):144–52.	Other design of study
McCusker J, Cole M, Yaffe M, Sussman T, Lavoie KL, Strumpf E, et al. A feasibility study of a telephone-supported self-care intervention for depression among adults with a comorbid chronic physical illness in primary care. Ment Health Fam Med. 2012 Dec;9(4):257–73.	Other population
Menezes P, Quayle J, Garcia Claro H, da Silva S, Brandt LR, Diez-Canseco F, et al. Use of a Mobile Phone App to Treat Depression Comorbid With Hypertension or Diabetes: A Pilot Study in Brazil and Peru. JMIR Ment Heal. 2019 Apr;6(4):e11698.	Other population
Mochari-Greenberger H, Vue L, Luka A, Peters A, Pande RL. A Tele-Behavioral Health Intervention to Reduce Depression, Anxiety, and Stress and Improve Diabetes Self-Management. Telemed E-HEALTH. 2016;22(8):624–30.	Other design of study

Morgan MAJ, Coates MJ, Dunbar JA, Reddy P, Schlicht K, Fuller J. The TrueBlue model of collaborative care using practice nurses as case managers for depression alongside diabetes or heart disease: a randomised trial. BMJ Open. 2013;3(1).	Other outcomes
Muijs LT, de Wit M, Knoop H, Snoek FJ. Feasibility and user experience of the unguided web-based self-help app "MyDiaMate" aimed to prevent and reduce psychological distress and fatigue in adults with diabetes. INTERNET Interv Appl Inf Technol Ment Behav Heal. 2021;25.	Other design of study
Naika AD, Lawrence B, Kiefer L, Ramos K, Utech A, Masozera N, et al. Building a primary care/research partnership: lessons learned from a telehealth intervention for diabetes and depression. Fam Pract [Internet]. 2015;32(2):216-223.	Other design of study
NCT01328639. TeamCare PCN: collaborative Care for Diabetes and Depression. https://clinicaltrials.gov/show/NCT01328639 [Internet]. 2011; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02022631/full	Other outcomes
NCT01985711. Web-Based Collaborative Care for Patients With Diabetes and Depression. https://clinicaltrials.gov/show/NCT01985711 [Internet]. 2013; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01479048/full	Other design of study
NCT03371940. Program ACTIVE II: behavioral Depression Treatment for Type 2 Diabetes. https://clinicaltrials.gov/show/NCT03371940 [Internet]. 2017; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01566657/full	Other design of study
NCT03473704. Telematic Program for the Treatment of Depression in Type 1 Diabetes. https://clinicaltrials.gov/show/NCT03473704 [Internet]. 2018; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01567404/full	Other design of study
NCT03655067. Internet-Based Cognitive Behavioral Therapy for Depressive Symptoms in Adolescents With Type 1 Diabetes Mellitus. https://clinicaltrials.gov/show/NCT03655067 [Internet]. 2018; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01662865/full	Other design of study
NCT03734367. Evaluation of the Effectiveness of a Program of Emotional Intelligence in Adolescents With Type 1 Diabetes (INTEDI). https://clinicaltrials.gov/show/NCT03734367 [Internet]. 2018; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01918339/full	Other outcomes
NCT04888780. Effects of Web-Based Training on HbA1c, Quality of Life and Depression Levels in Adolescents With Type 1 Diabetes. https://clinicaltrials.gov/show/NCT04888780 [Internet]. 2021; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02270476/full	Other design of study
NCT05000021. Telemedicine-Delivered Cognitive Behavioral Therapy to Reduce Diabetes Distress. https://clinicaltrials.gov/show/NCT05000021 [Internet]. 2021; Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02297513/full	Other design of study
Nobis S, Lehr D, Ebert DD, Berking M, Heber E, Baumeister H, et al. Efficacy and cost-effectiveness of a web-based intervention with mobile phone support to treat depressive symptoms in adults with diabetes mellitus type 1 and type 2: design of a randomised controlled trial. BMC Psychiatry. 2013 Nov;13:306.	Other design of study
Nobis S, Lehr D, Ebert DD, Baumeister H, Snoek F, Riper H, et al. Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: a randomized controlled trial. Diabetes Care. 2015 May;38(5):776–83.	Another study selected with the same population
Nobis S, Ebert DD, Lehr D, Smit F, Buntrock C, Berking M, et al. Web-based intervention for depressive symptoms in adults with types 1 and 2 diabetes mellitus: a health economic evaluation. Br J Psychiatry. 2018 Apr;212(4):199–206.	Another study selected with the same population
Proudfoot J, Clarke J, Gunn J, Fletcher S, Sanatkar S, Wilhelm K, et al. A Web-Based Public Health Intervention to Reduce Functional Impairment and Depressive Symptoms in Adults With Type 2 Diabetes (The SpringboarD Trial): Randomized Controlled Trial Protocol. JMIR Res Protoc. 2017 Aug;6(8):e145.	Other design of study
Robins L, Newby J, Wilhelm K, Smith J, Fletcher T, Ma T, et al. Internet-delivered cognitive behaviour therapy for depression in people with diabetes: study protocol for a randomised controlled trial. BMJ open diabetes Res care. 2015;3(1):e000144.	Other design of study
Sarda A, Munuswamy S, Sarda S, Subramanian V. Using Passive Smartphone Sensing for Improved Risk Stratification of Patients With Depression and Diabetes: Cross-Sectional Observational Study. JMIR mHealth uHealth. 2019 Jan;7(1):e11041.	Other design of study
Van-Bastelaar KMP, Pouwer F, Cuijpers P, Twisk JWR, Snoek FJ. Web-based cognitive behavioural therapy (W-CBT) for diabetes patients with co-morbid depression: design of a randomised controlled trial. BMC Psychiatry. 2008 Feb;8:9.	Other design of study
Van-Bastelaar KMP, Pouwer F, Cuijpers P, Riper H, Snoek FJ. Web-based depression treatment for type 1 and type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2011 Feb;34(2):320–5.	Another study selected with the same population
Van-Bastelaar K, Cuijpers P, Pouwer F, Riper H, Snoek FJ. Development and reach of a web-based cognitive behavioural therapy programme to reduce symptoms of depression and diabetes-specific distress. Patient Educ Couns. 2011 Jul;84(1):49–55.	Another study selected with the same population
White V, Linardon J, Stone JE, Holmes-Truscott E, Olive L, Mikocka-Walus A, et al. Online psychological interventions to reduce symptoms of depression, anxiety, and general distress in those with chronic health conditions: a systematic review and meta-analysis of randomized controlled trials. Psychol Med. 2020 Jul;1–26.	Other design of study
Whittemore R, Jaser SS, Faulkner MS, Murphy K, Delamater A, Grey M. Type 1 diabetes eHealth psychoeducation: youth recruitment, participation, and satisfaction. J Med Internet Res. 2013 Jan;15(1):e15.	Other population
Wilczynska M, Lubans DR, Plotnikoff RC. The effects of the eCoFit RCT on depression and anxiety symptoms among adults with or at risk of Type 2 Diabetes. Psychol Health Med. 2021 Mar;1–10.	Other population
Wu S, Ell K, Gross-Schulman SG, Sklaroff LM, Katon WJ, Nezu AM, et al. Technology-facilitated depression care management among predominantly Latino diabetes patients within a public safety net care system: comparative effectiveness trial design.	Other population

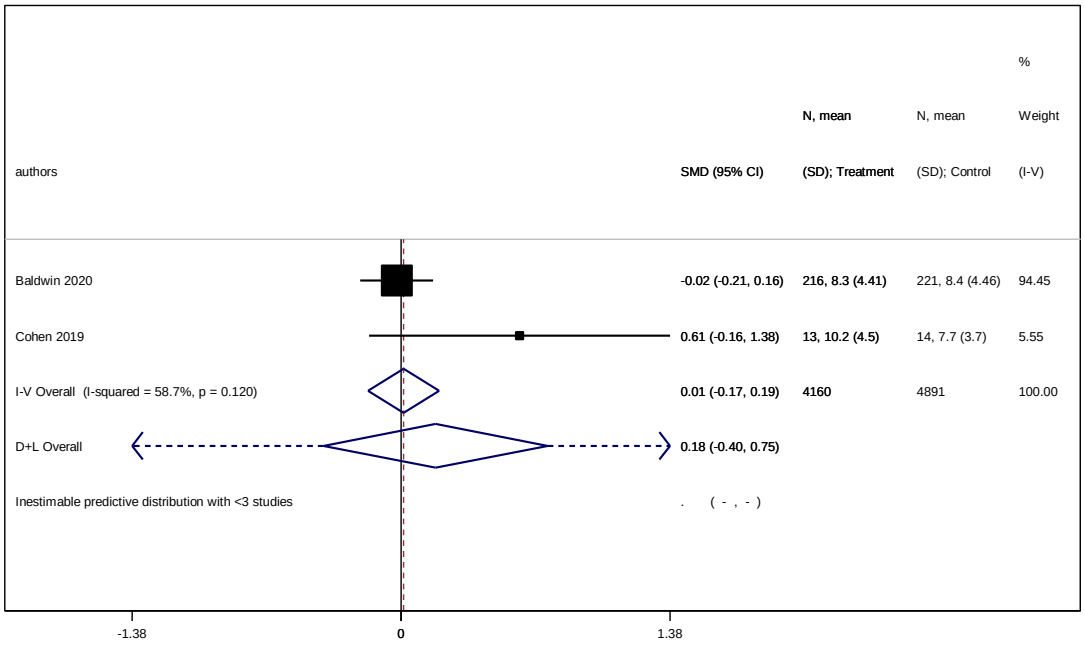
Young HM, Miyamoto S, Dharmar M, Tang-Feldman Y. Nurse Coaching and Mobile Health Compared With Usual Care to Improve Diabetes Self-Efficacy for Persons With Type 2 Diabetes: Randomized Controlled Trial. JMIR mHealth uHealth. 2020 Mar;8(3):e16665.	Other population
Yuan Z, Jiao N, Liu X, Liu C. The effect of web-based educational intervention on psychological status and blood glucose in newly diagnosed patients with diabetes type 2 in rural China: A protocol for randomized trial. Medicine (Baltimore). 2021 Feb;100(8):e24937.	Other population
Zamanifard M, Soltanian M, Edraki M, Moravaj H, Sharifi N. The Effects of Virtual Directed Painting Therapy on Anxiety, Depression, and Self-efficacy of Children with Type 1 Diabetes: a Randomized Controlled Clinical Trial. Int J community based Nurs midwifery. 2022;10(3):210-222.	Other outcomes

Appendix 3. Meta-analyses of the evaluated outcomes

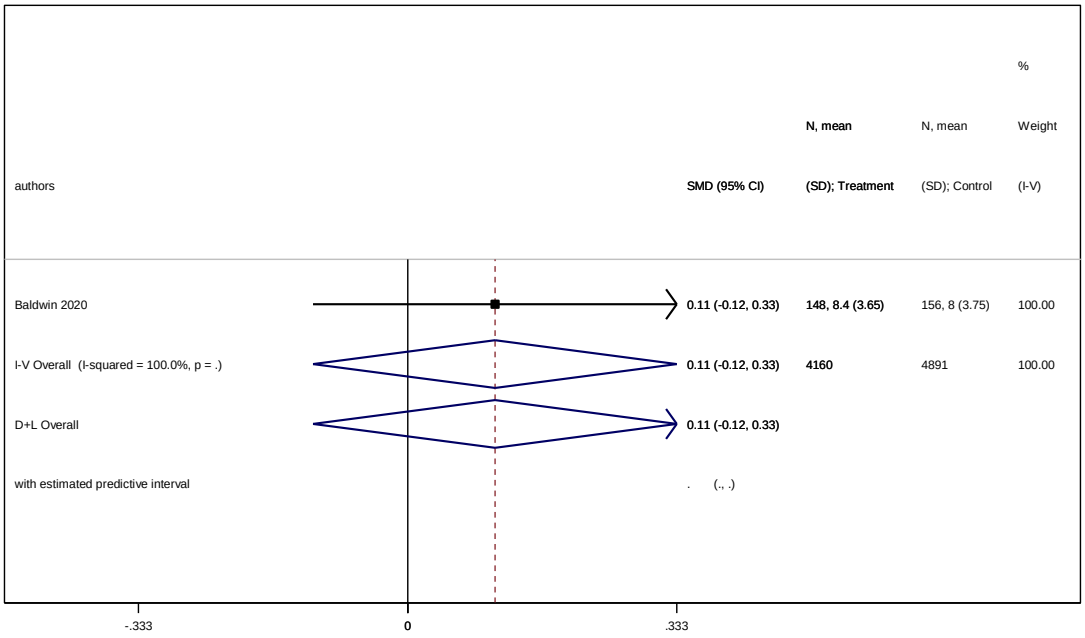
Outcome: *Improvement and/or clinical remission of depression*



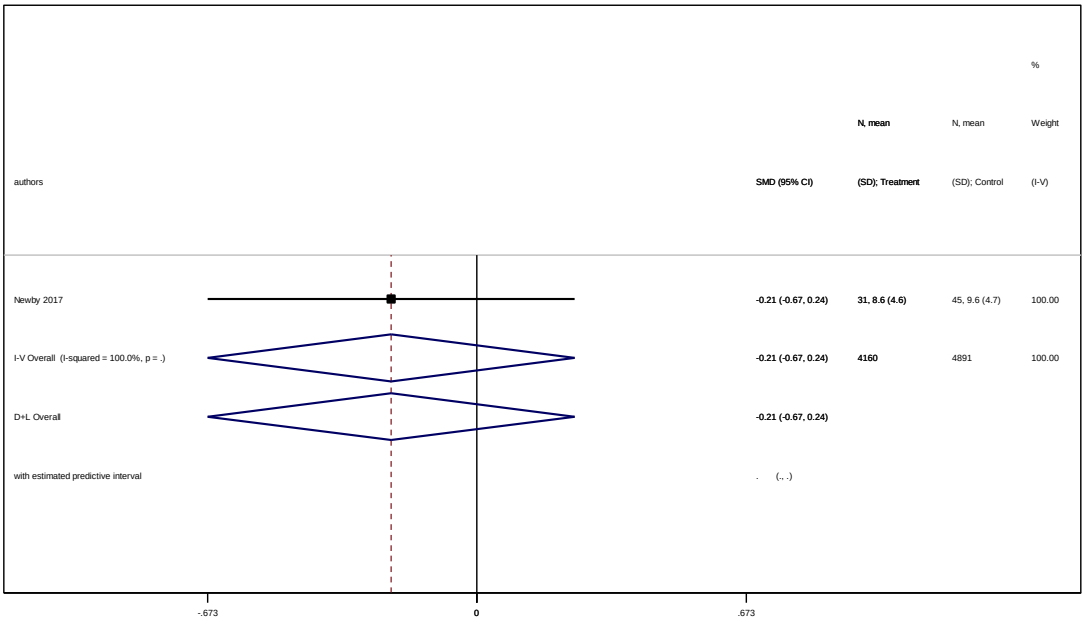
Follow up months: Three
Tools: PHQ-9



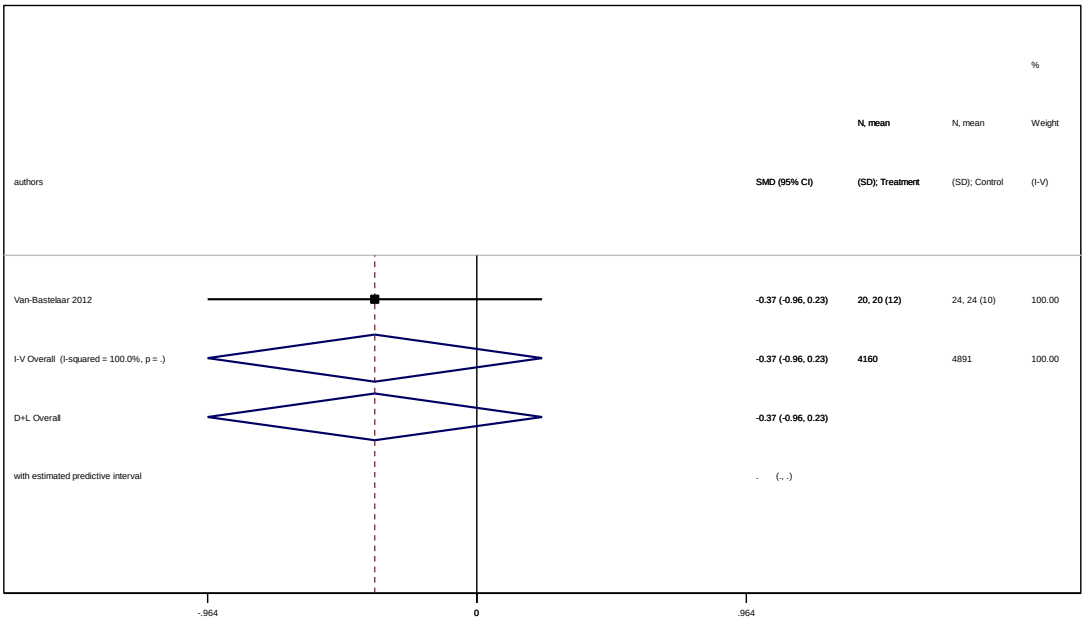
Follow up months: Six
Tools: PHQ-9



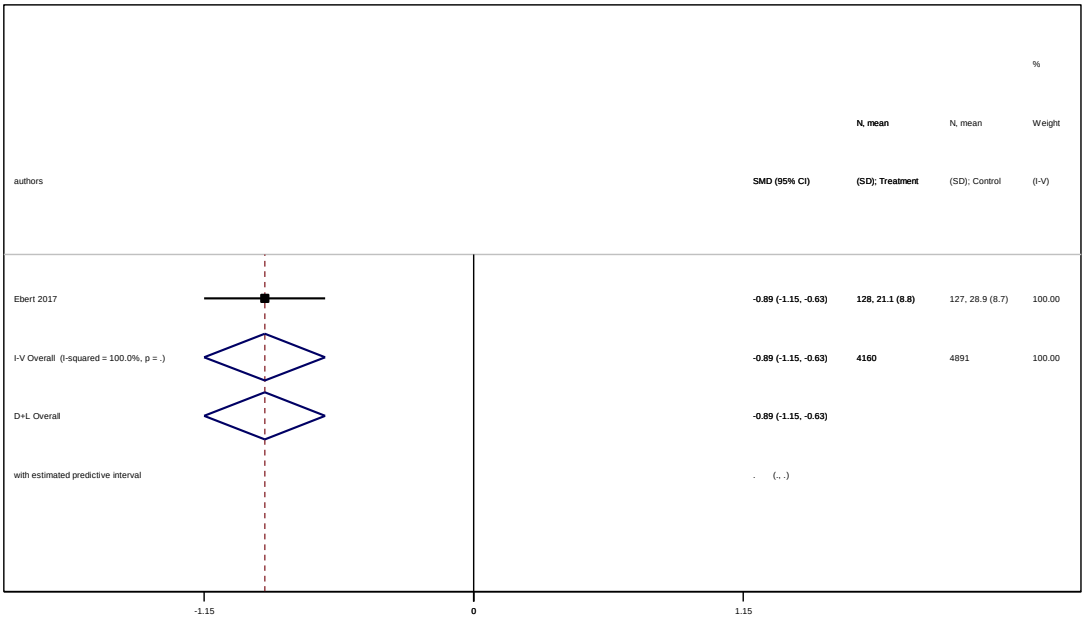
Follow up months: Twelve
Tools: PHQ-9



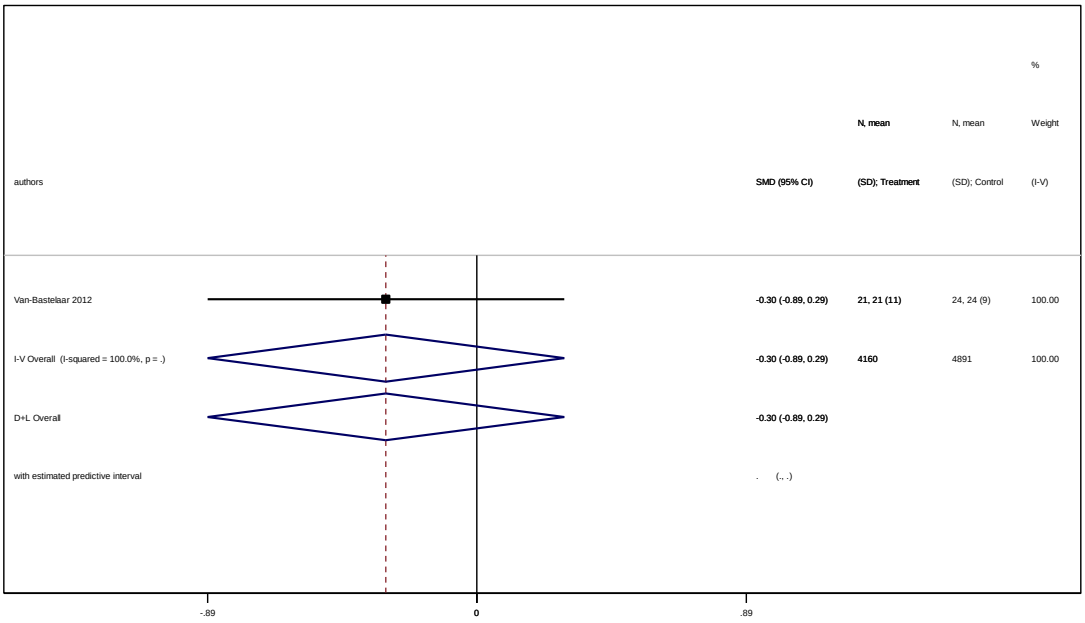
Follow up months: Three
Tools: PHQ-15



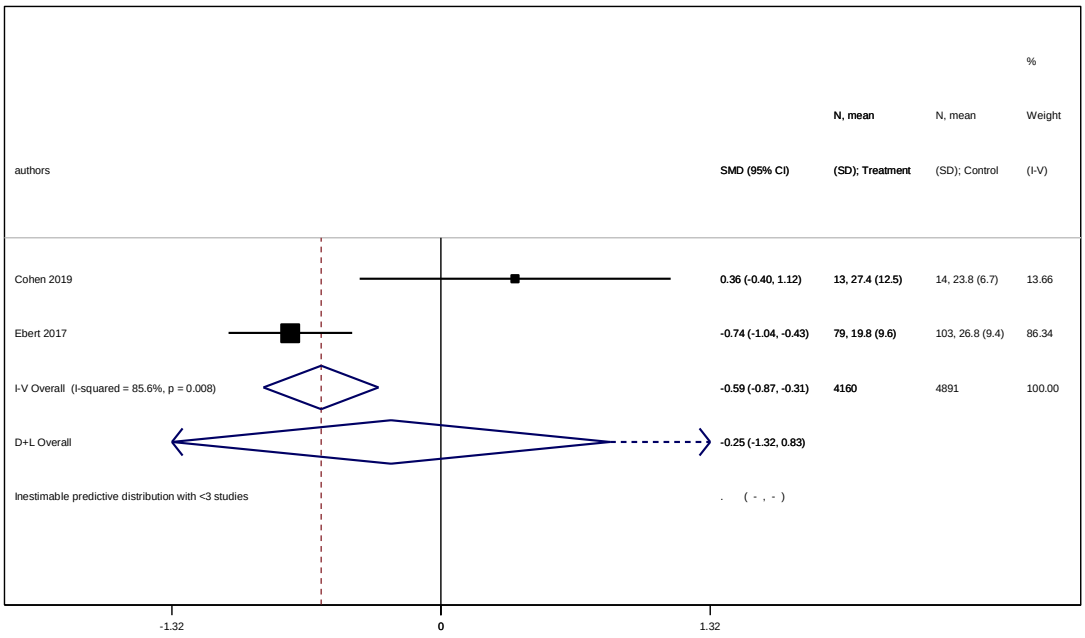
Follow up months: One
Tools: CES-D



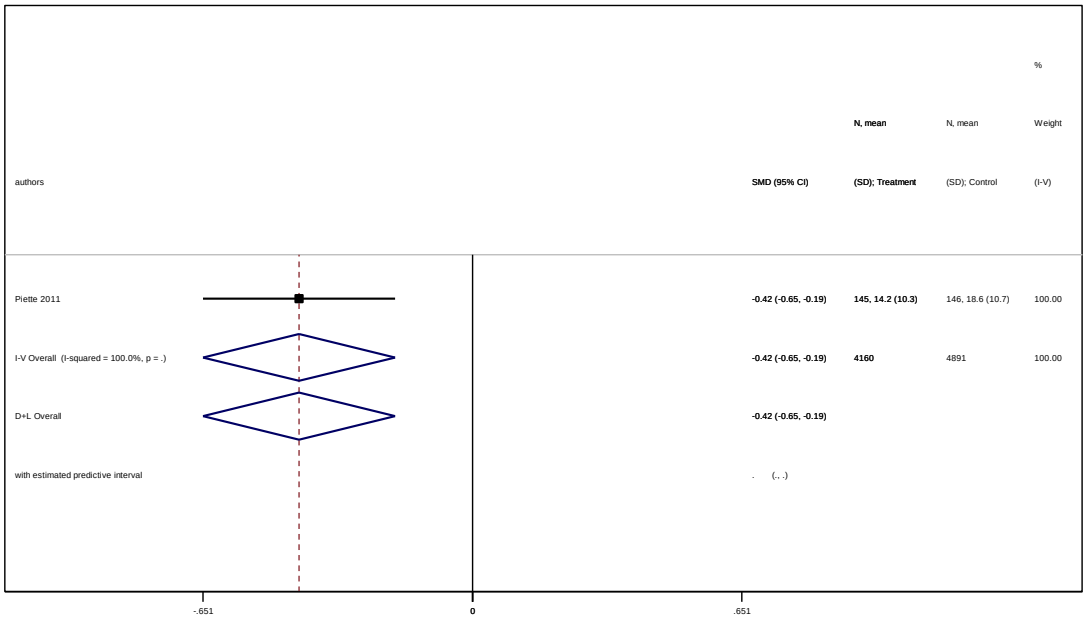
Follow up months: Two
Tools: CES-D



Follow up months: Three
Tools: CES-D

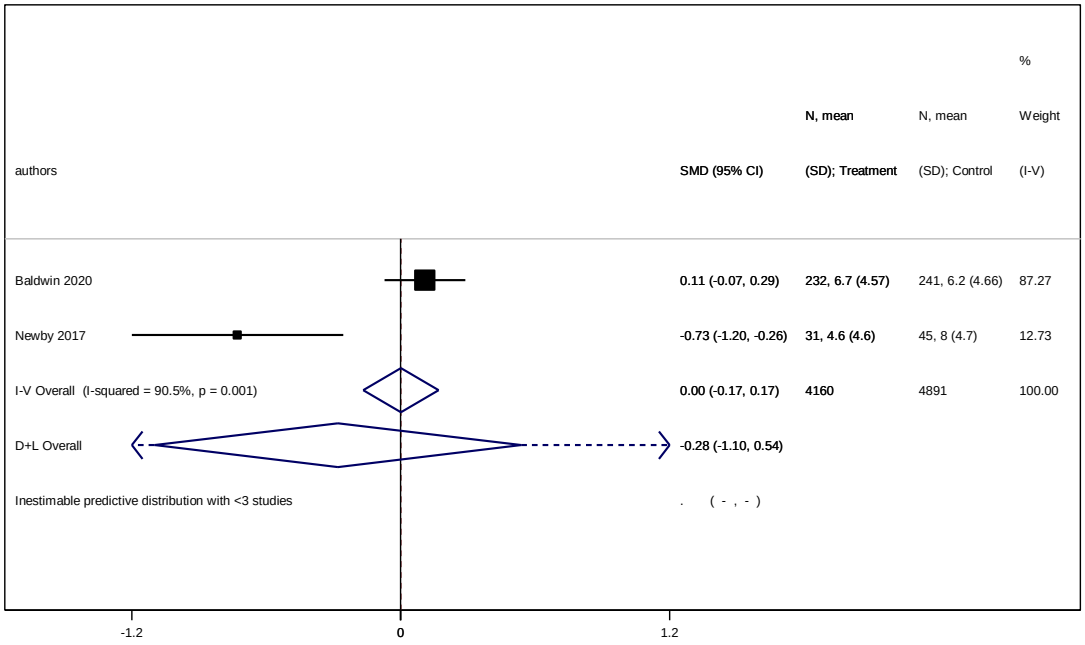


Follow up months: Six
Tools: CES-D

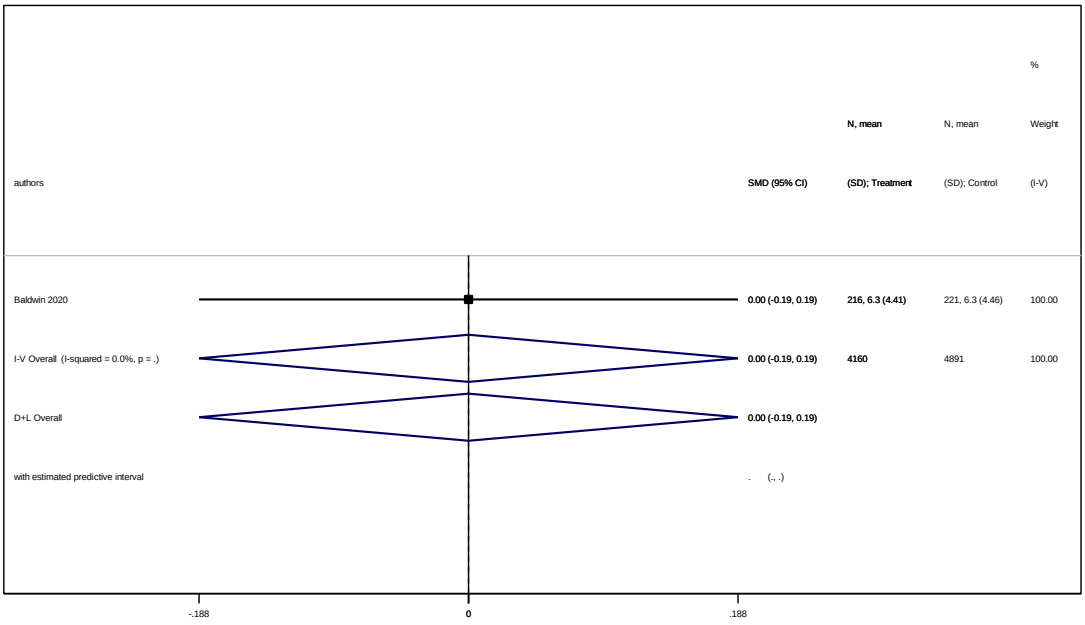


Follow up months: Twelve
Tools: BDI

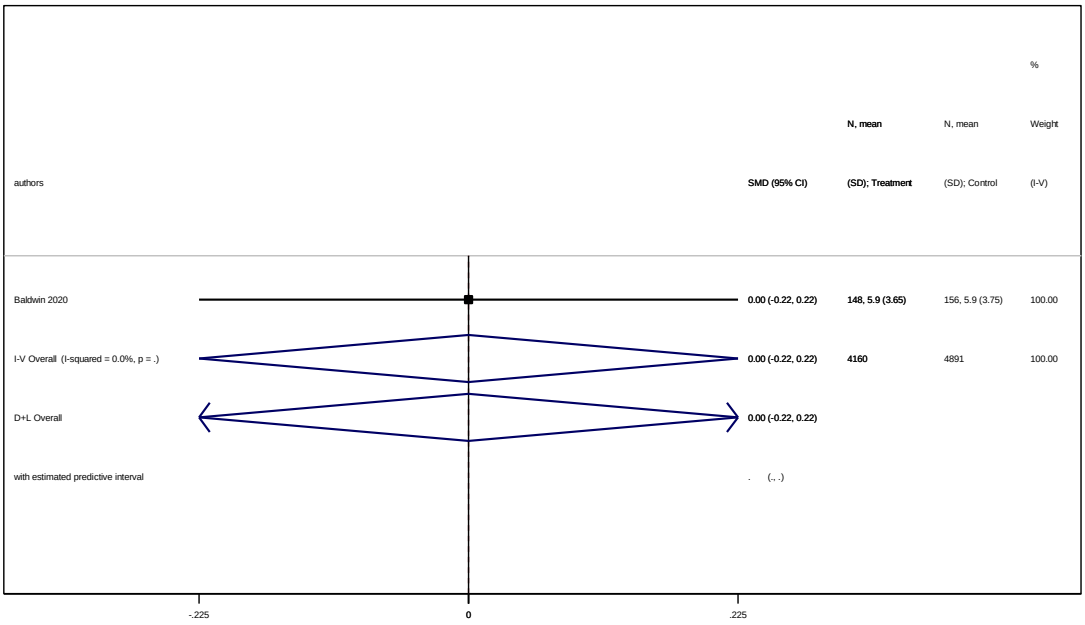
Outcome: *Improvement and/or clinical remission of anxiety*



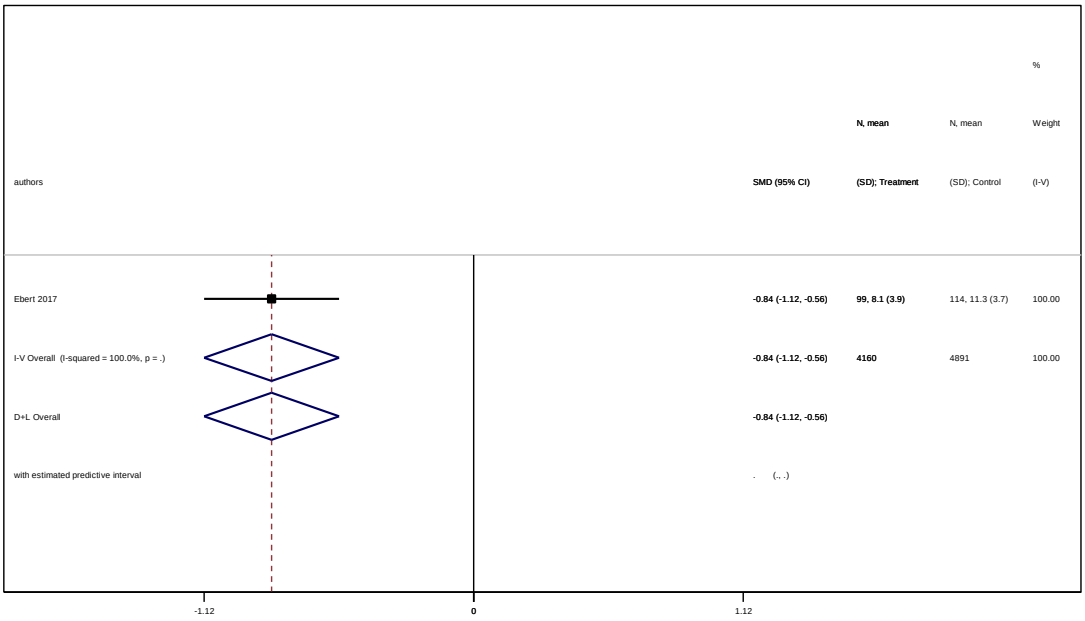
Follow up months: Three
Tools: GAD-7



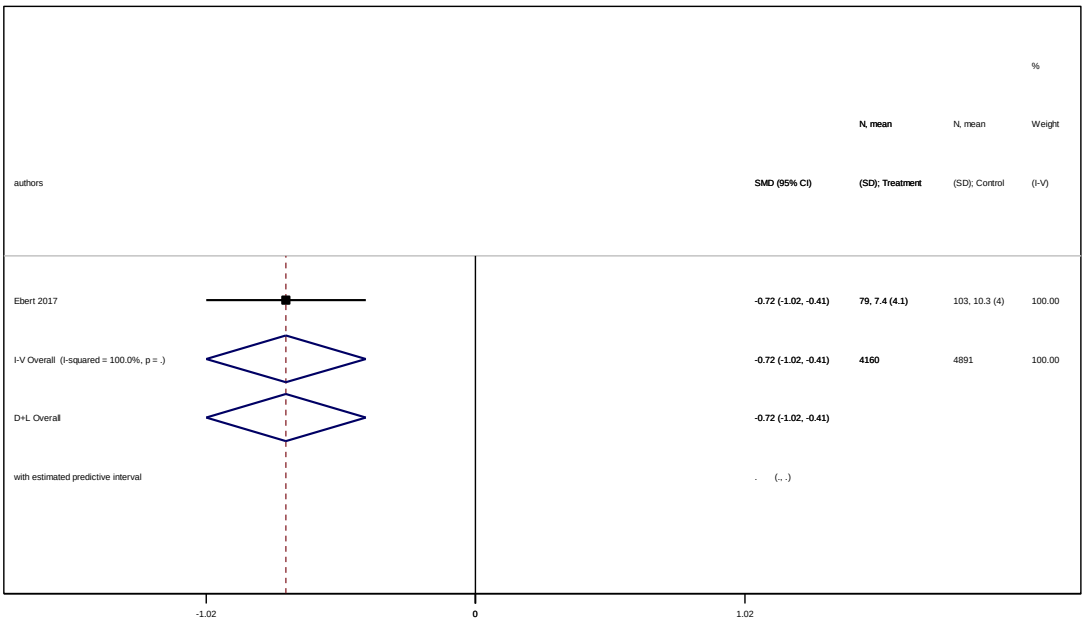
Follow up months: Six
Tools: GAD-7



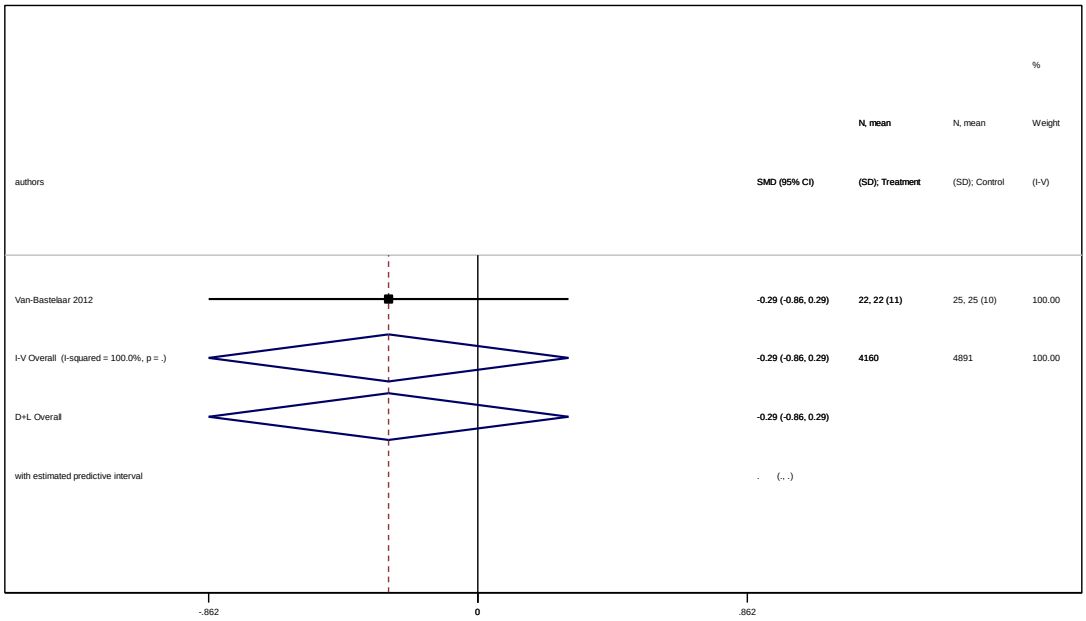
Follow up months: Twelve
Tools: GAD-7



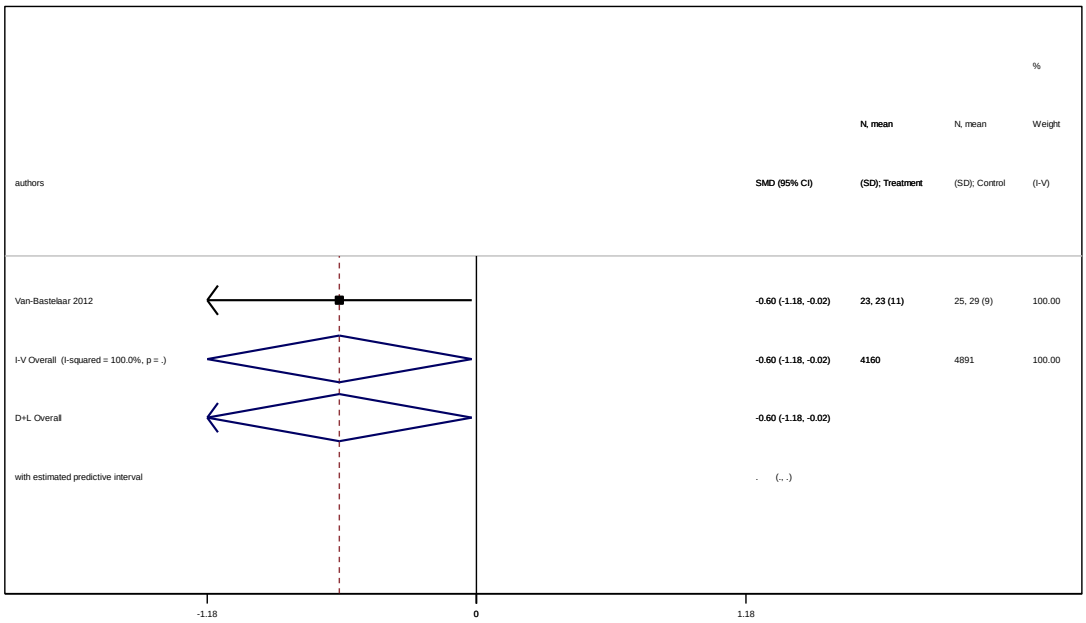
Follow up months: Two
Tools: HADS



Follow up months: Six
Tools: HADS

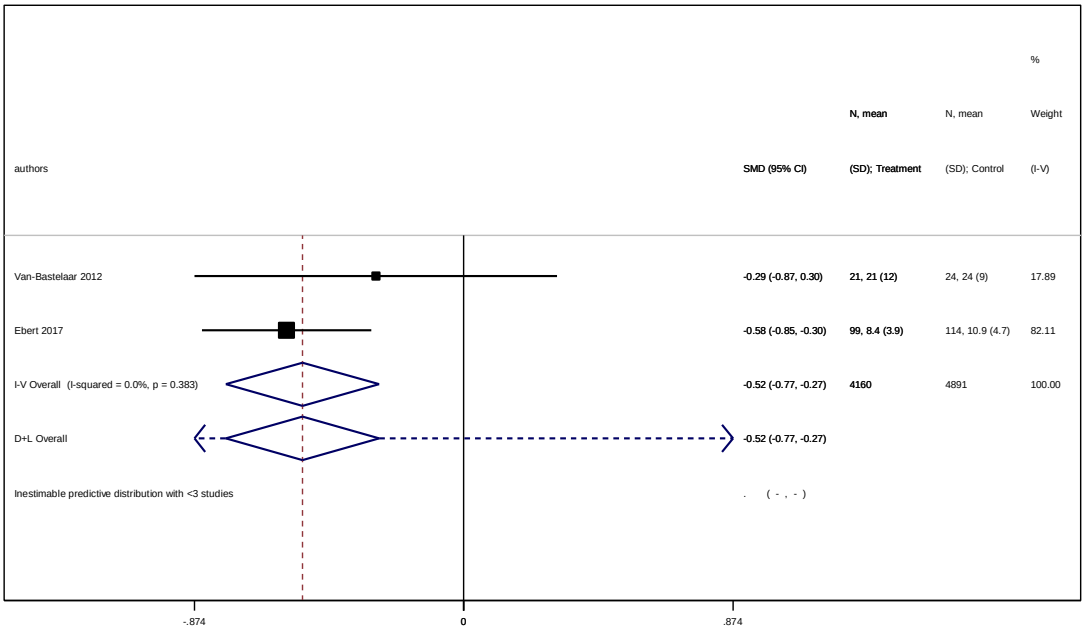


Follow up months: One
Tools: WHO CIDI-auto

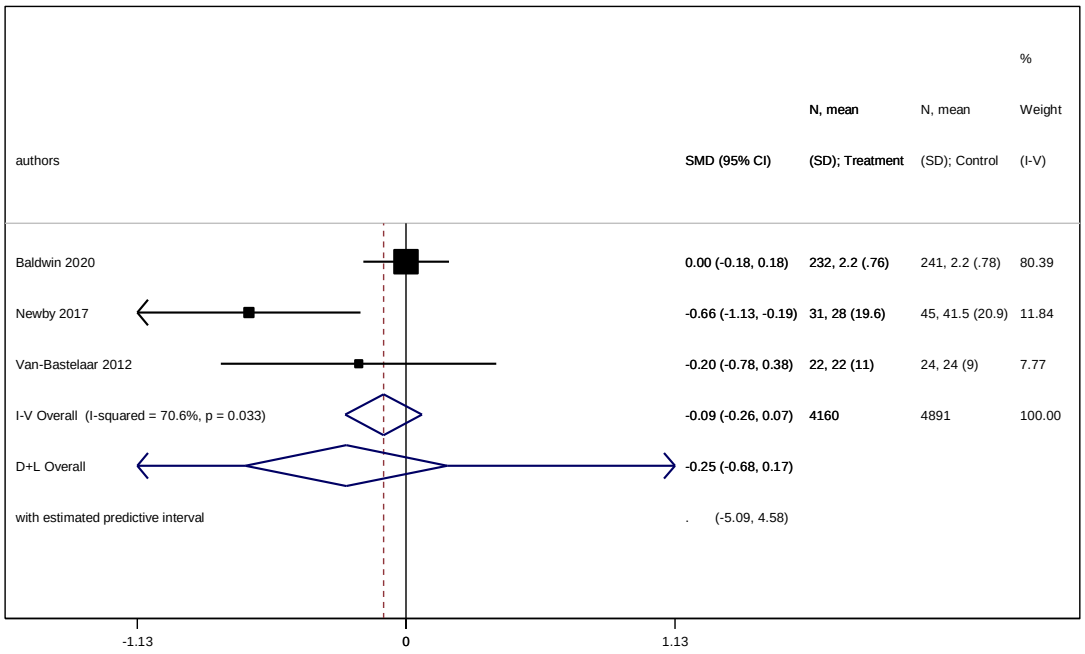


Follow up months: Three
Tools: WHO CIDI-auto

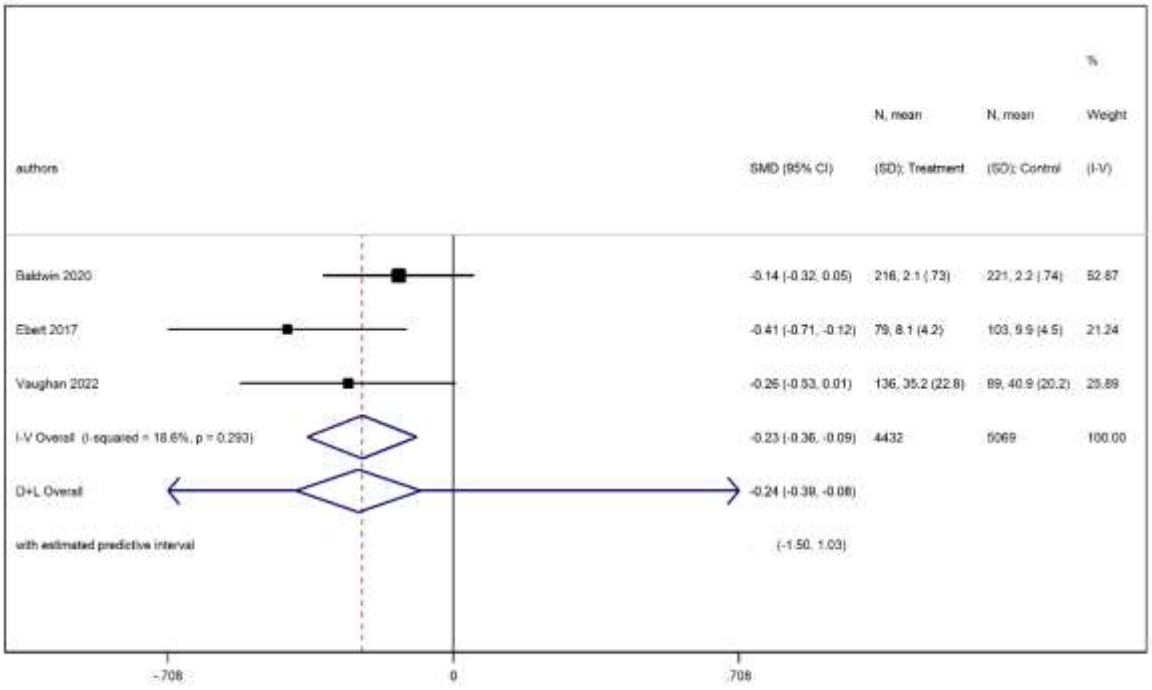
Outcome: *Remission of diabetes-related emotional distress*



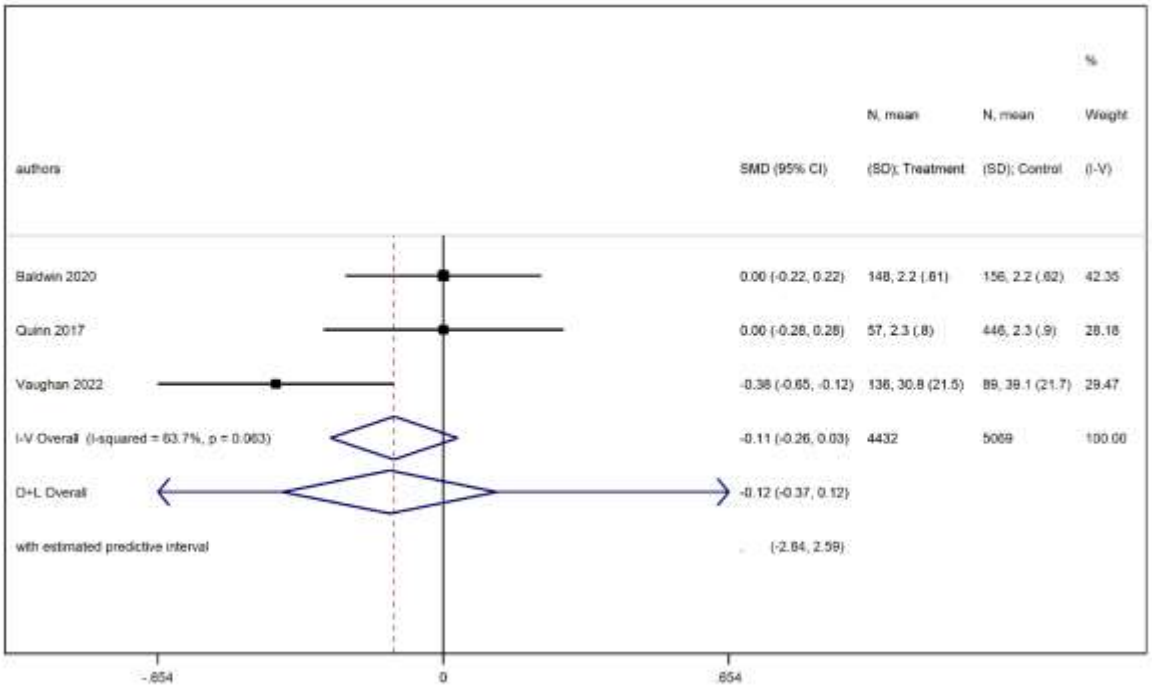
Follow up months: One/ Two
Tools: PAID



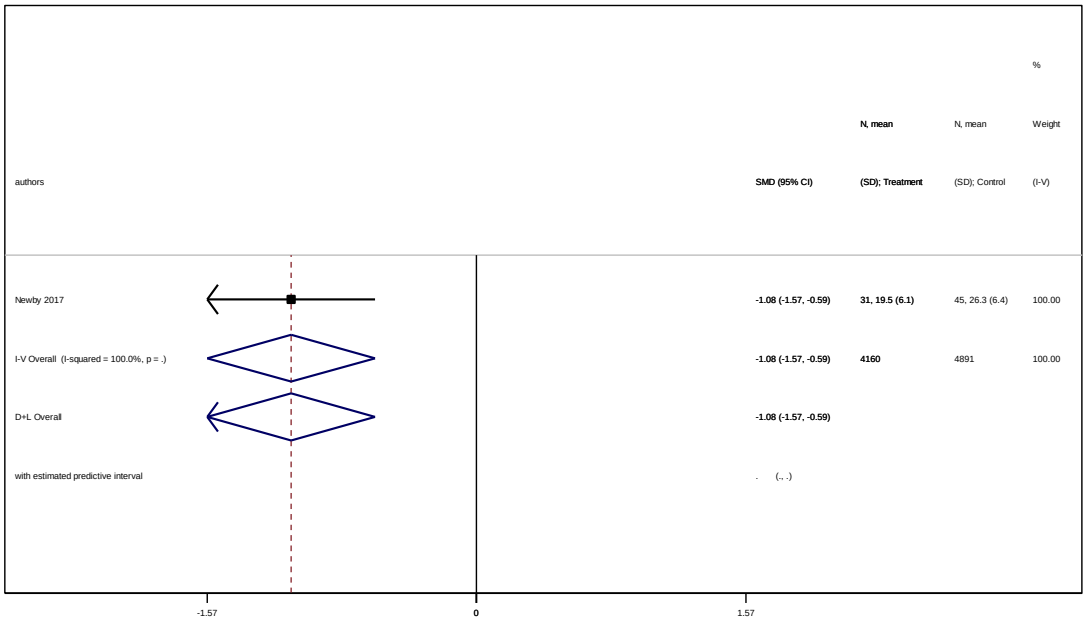
Follow up months: Three
Tools: PAID/DDS



Follow up months: Six
Tools: PAID/DDS

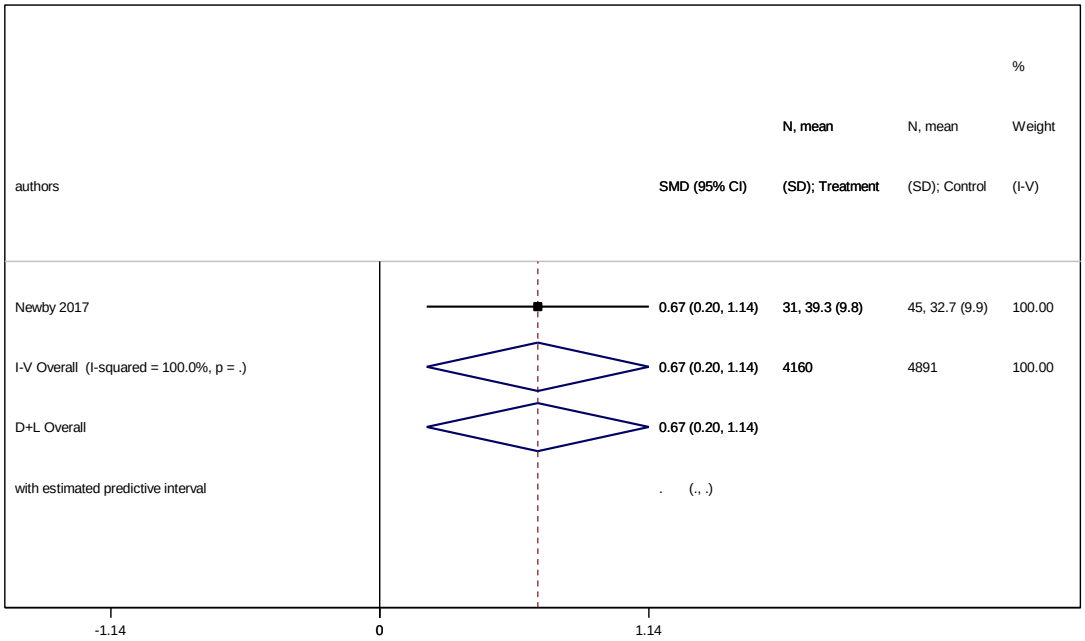


Follow up months: Twelve
Tools: DDS

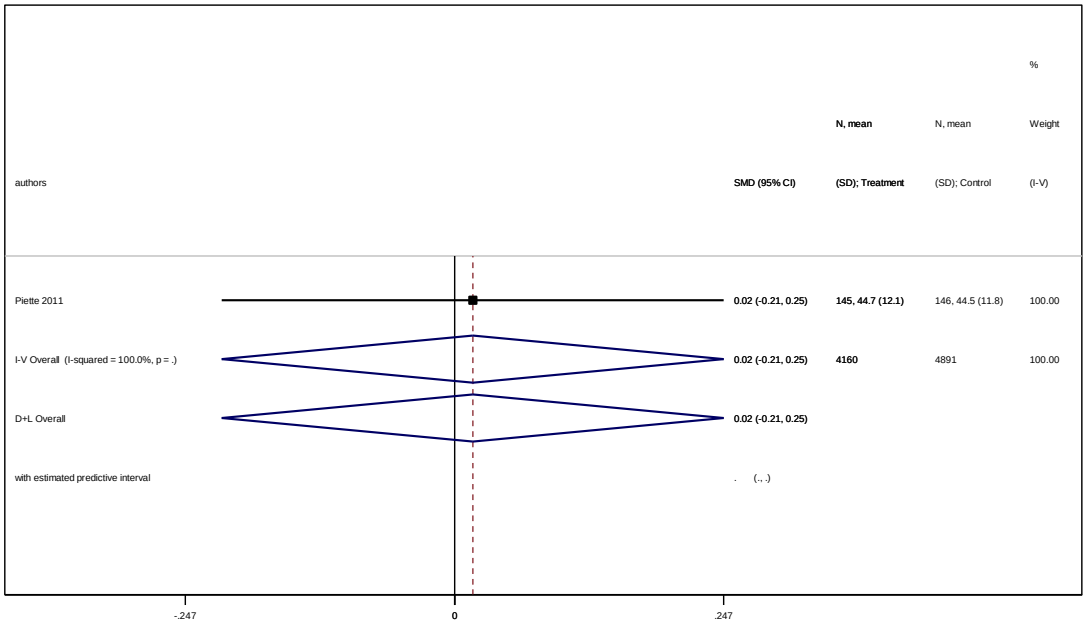


Follow up months: Three
Tools: K-10

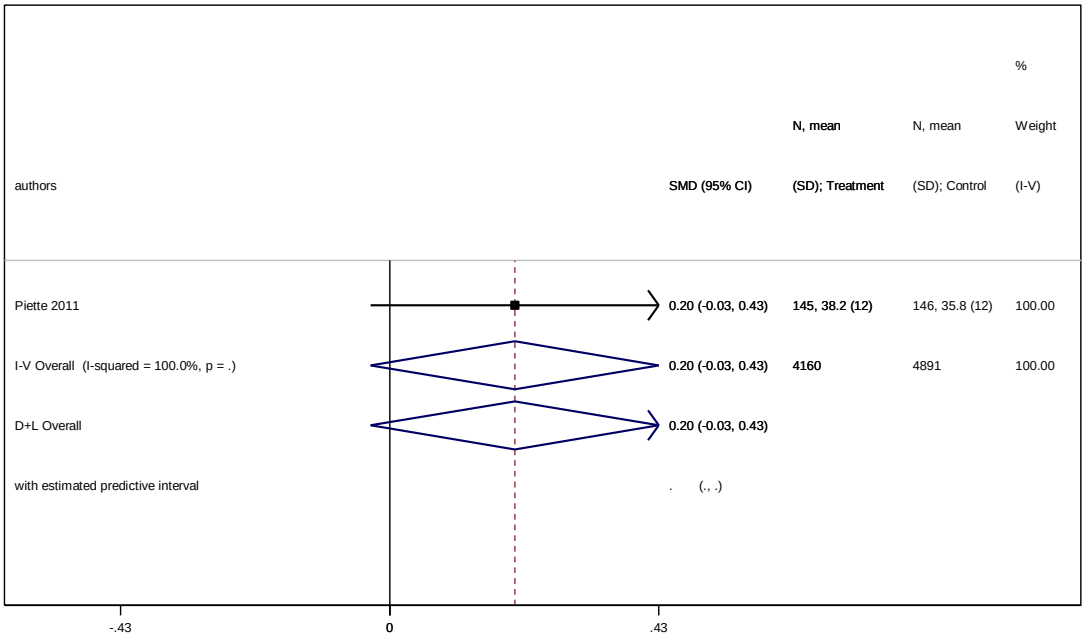
Outcome: *Improvement in quality of life*



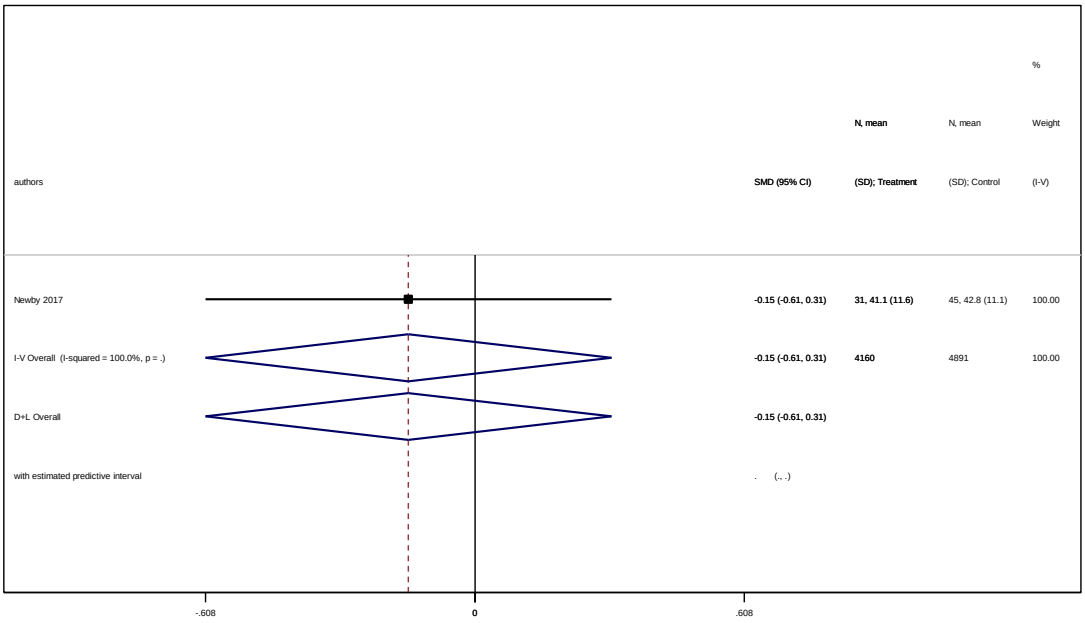
Follow up months: Three
Tools: SF-12 MCS



Follow up months: Twelve
Tools: SF-12 MCS Mental composite

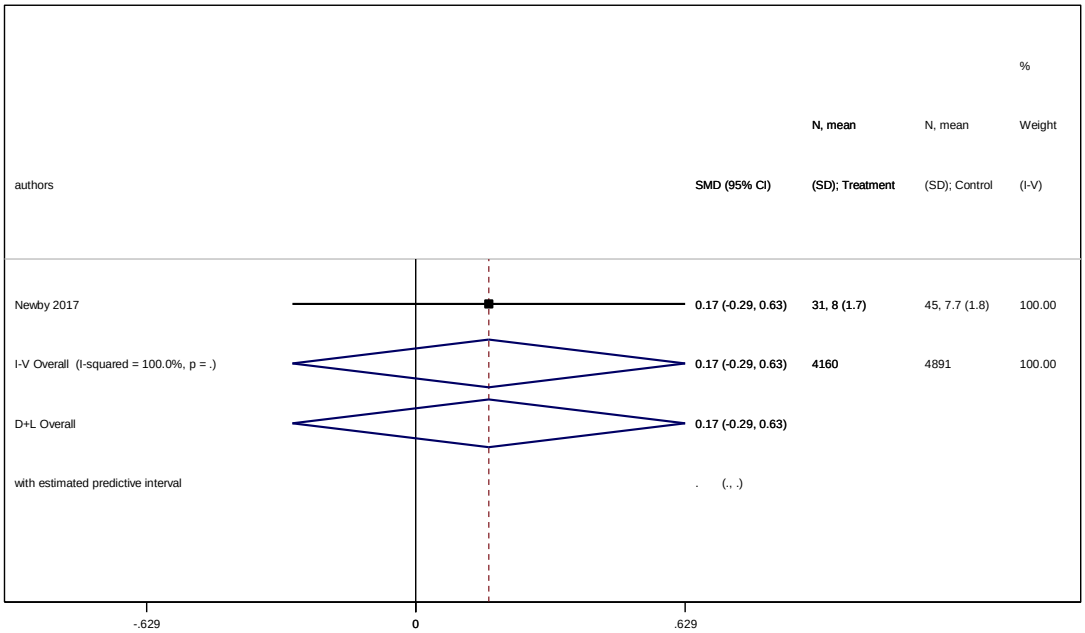


Follow up months: Twelve
Tools: SF-12 MCS Physical composite

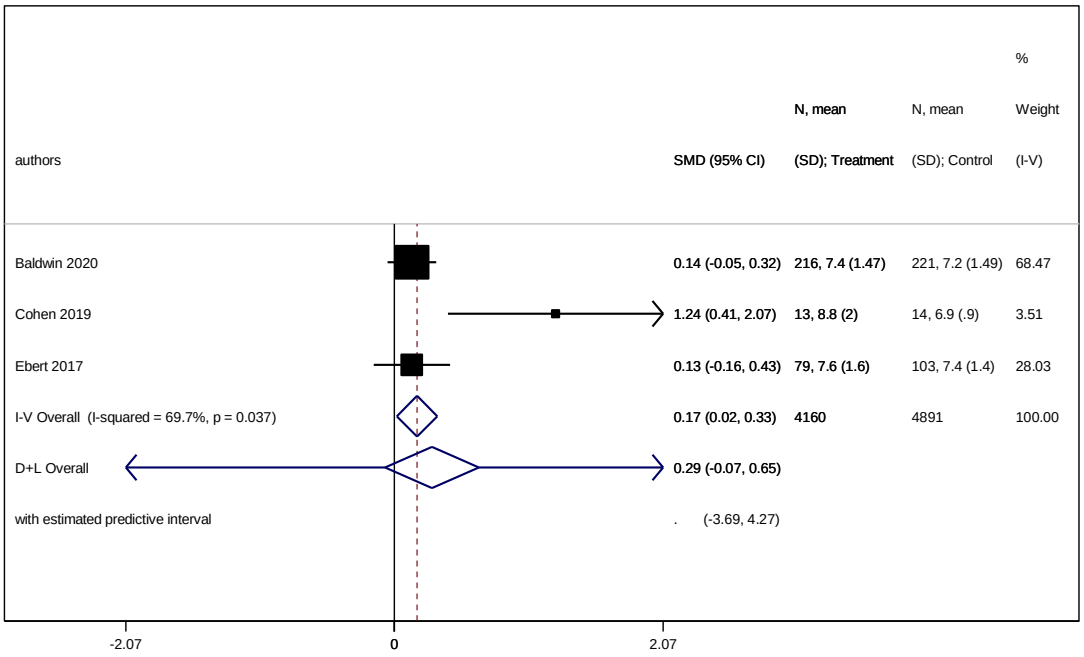


Follow up months: Three
Tools: SF-12 PCS

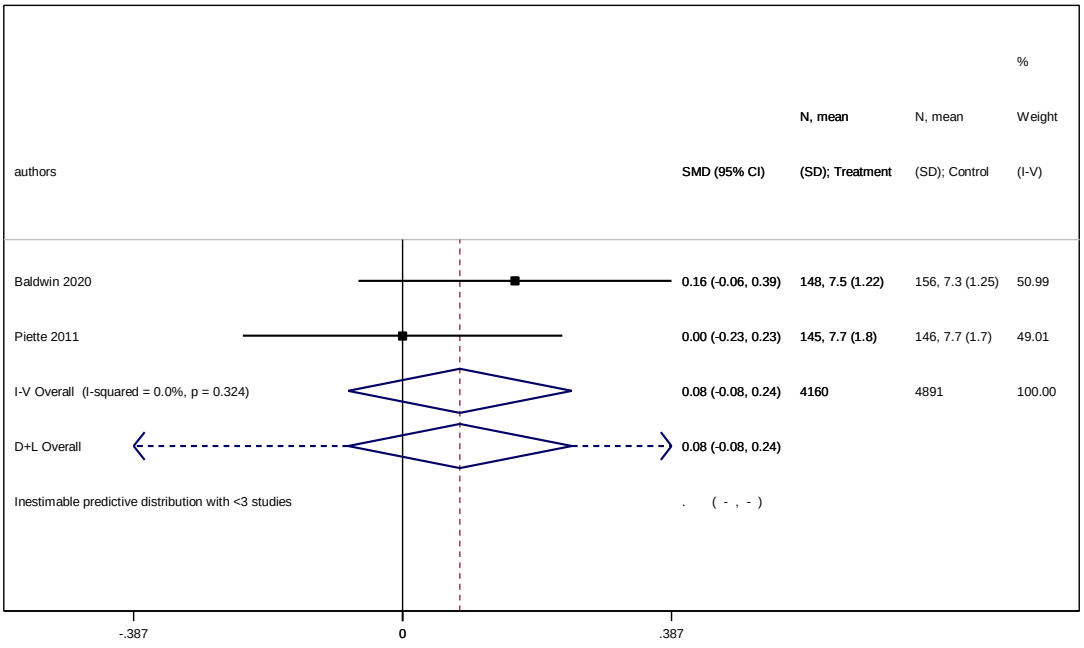
Outcome: *Glycemic control*



Follow up months: Three
Tools: HbA1c

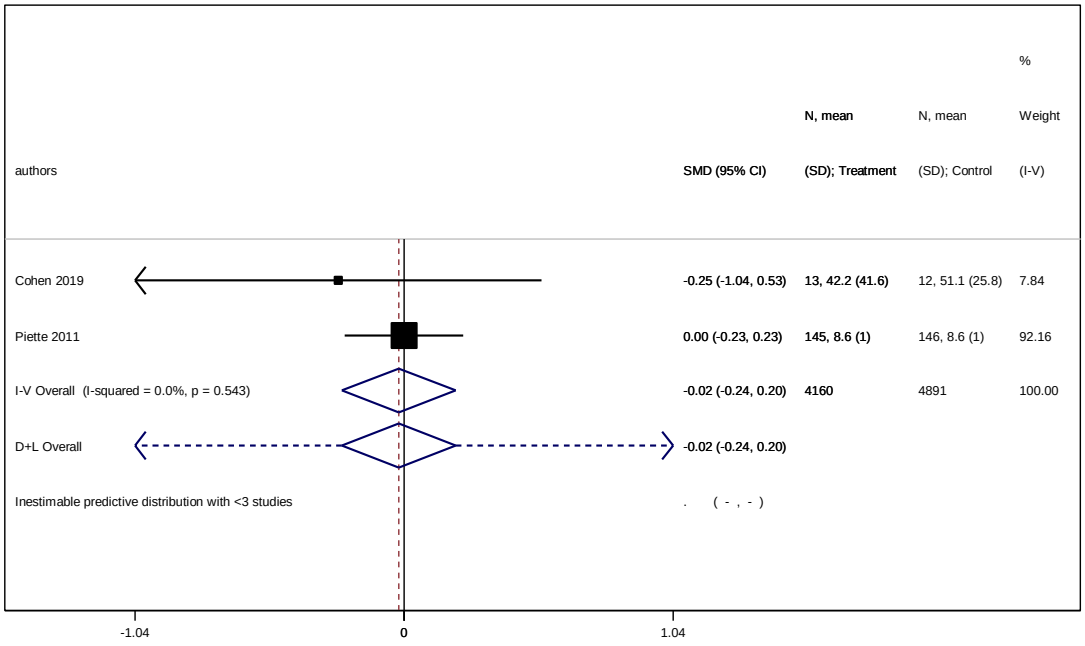


Follow up months: Six
Tools: HbA1c

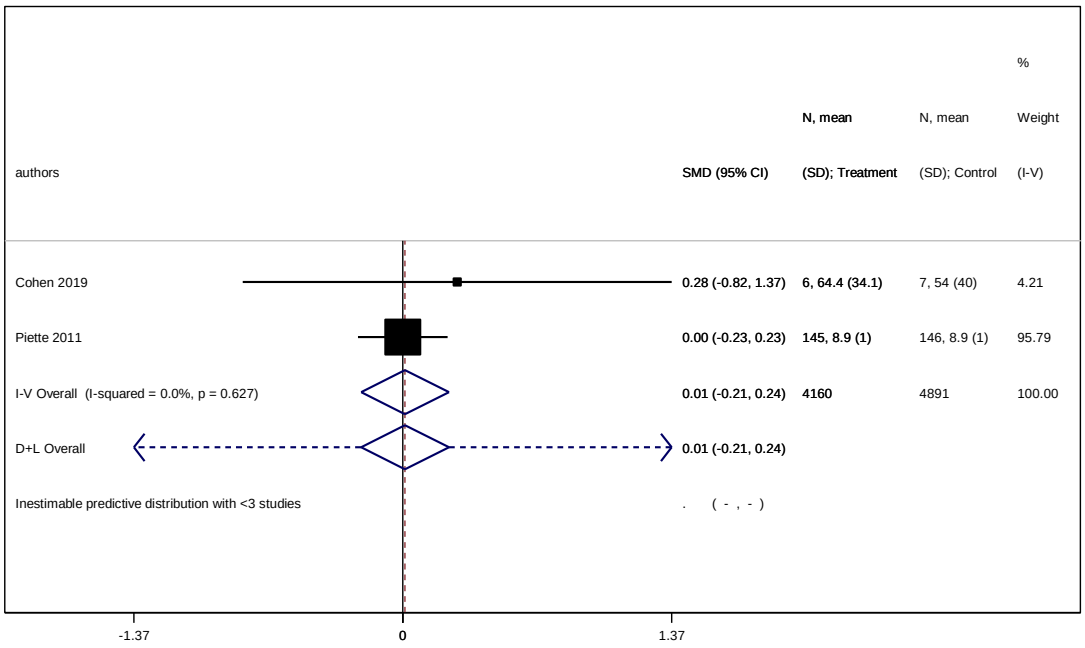


Follow up months: Twelve
Tools: HbA1c

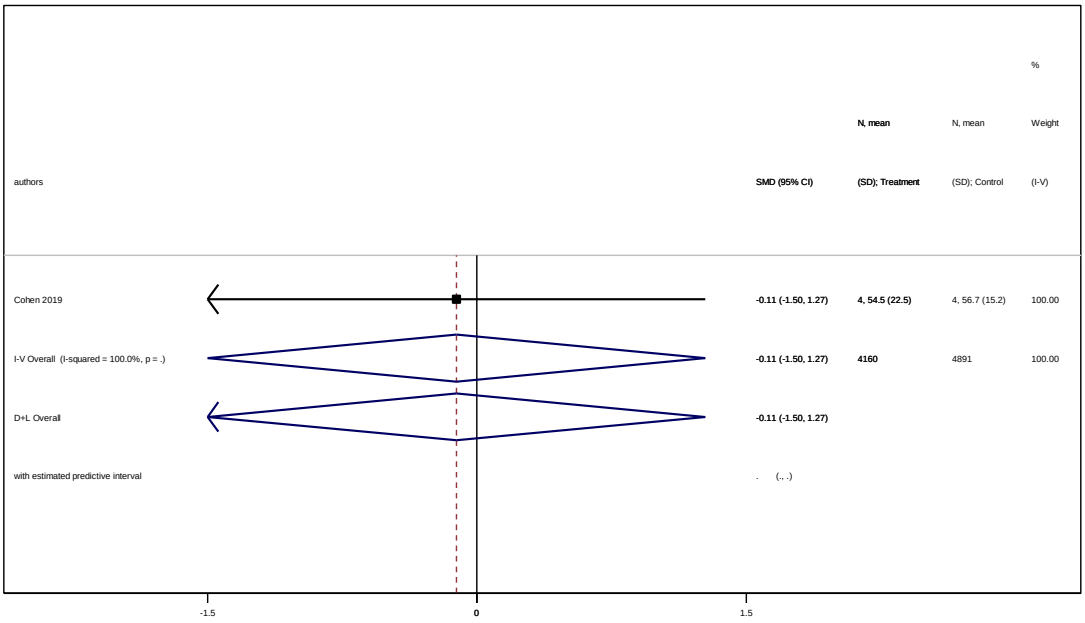
Outcome: *Medication adherence*



Follow up months: Six/Twelve
Tools: Drugs for diabetes



Follow up months: Six/Twelve
Tools: Drugs for depression



Follow up months: Twelve
Tools: All drugs combined

Appendix 4. Grading of Recommendations, Assessment, Development and Evaluation - GRADE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervenção e-health para tratar depressão, ansiedade	outras intervenções	Relative (95% CI)	Absolute (95% CI)		
improvement or remission of depression (PHQ-9) - My Compass or iCBT compared to healthy Lifestyles or usual care (follow-up: 3 months)												
2	randomised trials	not serious	very serious[a,b]	not serious	serious[c]	none	263	289	-	SMD **0 SD** (1.18 fewer to 0.53 more)	⨁◯◯◯ Very low	
Improvement and/or clinical remission of depression (PHQ-9) - My Compass/Healthy Lifestyles Pharmacist-led telehealth/Nurse-led telehealth (follow-up: 6 months)												
2	randomised trials	serious	not serious	not serious	serious[c]	none	229	235	-	SMD **0 SD** (0.4 lower to 0.75 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of depression (PHQ-9) - My Compass/Healthy Lifestyles (follow-up: 12 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	148	156	-	SMD **0 SD** (0.12 lower to 0.33 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of depression (PHQ-15) - iCBT/Usual care (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	31	45	-	SMD **0 SD** (0.64 lower to 0.27 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of depression (CES-D) - Diabetes-specific CBT /Waiting-list (follow-up: 1)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	21	24	-	SMD **0 SD** (0.93 lower to 0.23 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of depression (CES-D) - Internet-guided self-help intervention /Usual care plus web psychoeducation (follow-up: 2 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	128	127	-	SMD **0 SD** (1.15 lower to 0.63 lower)	⨁⨁⨁◯ Moderate	
Improvement and/or clinical remission of depression (CES-D) - Diabetes-specific CBT/Waiting-list (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	21	24	-	SMD **0 SD** (0.89 lower to 0.29 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of depression (CES-D) - Pharmacist-led telehealth/Nurse-led telehealth Guided web-based self-help/Usual care plus web psychoeducation (follow-up: 6 months)												
2	randomised trials	serious	very serious[a,b]	not serious	serious[c]	none	92	117	-	SMD **0 SD** (1.32 lower to 0.83 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervenção e-health para tratar depressão, ansiedade	outras intervenções	Relative (95% CI)	Absolute (95% CI)		
Improvement and/or clinical remission of depression (BDI) - Telephone-delivered CBT/Usual Care (follow-up: 12 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	146	146	-	SMD **0 SD** (0.65 lower to 0.19 lower)	⨁⨁⨁◯ Moderate	
Improvement and/or clinical remission of anxiety (GAD-7) - My Compass/Healthy Lifestyles iCBT/Usual care (follow-up: 3 months)												
2	randomised trials	not serious	very serious[a,b]	not serious	serious[c]	none	263	286	-	SMD **0 SD** (1.1 lower to 0.54 higher)	⨁◯◯◯ Very low	
Improvement and/or clinical remission of anxiety (GAD-7) - My Compass/Healthy Lifestyles (follow-up: 1 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	216	221	-	SMD **0 SD** (0.19 lower to 0.19 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of anxiety (GAD-7) - My Compass/Healthy Lifestyles (follow-up: 12 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	148	156	-	SMD **0 SD** (0.22 lower to 0.22 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of anxiety (HADS) - Internet-guided self-help intervention /Usual care plus web psychoeducation (follow-up: 2 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	99	114	-	SMD **0 SD** (1.12 lower to 0.56 lower)	⨁⨁⨁◯ Moderate	
Improvement and/or clinical remission of anxiety (HADS) - Internet-guided self-help intervention /Usual care plus web psychoeducation (follow-up: 6 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	79	103	-	SMD **0 SD** (1.02 lower to 0.41 lower)	⨁⨁⨁◯ Moderate	
Improvement and/or clinical remission of anxiety (WHO CIDI-auto) - Diabetes-specific CBT/Waiting-list (follow-up: 1 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	22	25	-	SMD **0 SD** (0.86 lower to 0.29 higher)	⨁⨁◯◯ Low	
Improvement and/or clinical remission of anxiety (WHO CIDI-auto) - Diabetes-specific CBT/Waiting-list (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	23	25	-	SMD **0 SD** (1.18 lower to 0.02 lower)	⨁⨁⨁◯ Moderate	
Remission of diabetes-related emotional distress (PAID/DDS) - Diabetes-specific CBT/Waiting-list Internet-guided self-help intervention /Usual care plus web psychoeducation (follow-up: 1-2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervenção e-health para tratar depressão, ansiedade	outras intervenções	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious[c]	none	120	138	-	SMD **0 SD** (0.77 lower to 0.27 lower)	⨁⨁⨁◯ Moderate	
Remission of diabetes-related emotional distress (PAID/DDS) - iCBT/Usual care Diabetes-specific CBT/Waiting-list My Compass/Healthy Lifestyles (follow-up: 3 months)												
3	randomised trials	not serious	very serious[b,e]	not serious	serious[c]	none	285	310	-	SMD **0 SD** (0.68 lower to 0.17 higher)	⨁◯◯◯ Very low	
Remission of diabetes-related emotional distress (PAID/DDS) - My Compass/Healthy Lifestyles Internet-guided self-help intervention/Usual care plus web psychoeducation (follow-up: 6 months)												
3	randomised trials	not serious	not serious	not serious	serious[c]	none	431	413	-	SMD **0 SD** (0.39 lower to 0.08 lower)	⨁⨁⨁◯ Moderate	
Remission of diabetes-related emotional distress (DDS) - My Compass/Healthy Lifestyles Coach Primary Care Provider/Usual care (follow-up: 12 months)												
3	randomised trials	serious	serious[e]	not serious	serious[c]	none	341	291	-	SMD **0 SD** (0.37 lower to 0.12 higher)	⨁◯◯◯ Very low	
Remission of diabetes-related emotional distress (K-10) - iCBT/Usual care (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	31	45	-	SMD **0 SD** (1.57 lower to 0.59 lower)	⨁⨁⨁◯ Moderate	
Improvement in quality of life (SF-12 MCS) - iCBT/Usual care (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	not serious	not serious	none	31	45	-	SMD **0 SD** (0.2 higher to 1.14 higher)	⨁⨁⨁◯ Moderate	
Improvement in quality of life (SF-12 MCS Mental composite) -Telephone-delivered CBT/Usual Care (follow-up: 12 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	145	146	-	SMD **0 SD** (0.21 lower to 0.25 higher)	⨁⨁◯◯ Low	
Improvement in quality of life (SF-12 MCS Physical composite) - Telephone-delivered CBT/Usual Care (follow-up: 12 months)												
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	145	146	-	SMD **0 SD** (0.03 lower to 0.43 higher)	⨁⨁◯◯ Low	
Improvement in quality of life (SF-12 PCS) - iCBT/Usual care (follow-up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervenção e-health para tratar depressão, ansiedade	outras intervenções	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	serious[d]	not serious	serious[c]	none	31	45	-	SMD **0 SD** (0.61 lower to 0.31 higher)	⨁⨁◯◯ Low	
Glycaemic control (HbA1c) - iCBT/Usual care (follow-up: 3 months)												
1	randomised trials	not serious	serious[d]	serious[f]	serious[c]	none	31	45	-	SMD **0 SD** (0.29 lower to 0.63 higher)	⨁◯◯◯ Very low	
Glycaemic control (HbA1c) - My Compass/Healthy Lifestyles Pharmacist-led telehealth/Nurse-led telehealth Internet-guided self-help intervention /Usual care plus web psychoeducation (follow-up: 6 months)												
3	randomised trials	serious	not serious	serious[f]	serious[c]	none	308	338	-	SMD **0 SD** (0.07 lower to 0.65 higher)	⨁◯◯◯ Very low	
Glycaemic control (HbA1c) - My Compass/Healthy Lifestyles Telephone-delivered CBT/Usual care (follow-up: 12 months)												
2	randomised trials	not serious	not serious	serious[f]	serious[c]	none	193	302	-	SMD **0 SD** (0.08 lower to 0.24 higher)	⨁⨁◯◯ Low	
Medication Adherence (Drugs for diabetes) - Pharmacist-led telehealth/Nurse-led telehealth Telephone-delivered CBT/Usual care (follow-up: 6-12 months)												
2	randomised trials	serious	not serious	not serious	serious[c]	none	158	158	-	SMD **0 SD** (0.24 lower to 0.2 higher)	⨁⨁◯◯ Low	
Medication Adherence (Drugs for depression) - Pharmacist-led telehealth/Nurse-led telehealth Telephone-delivered CBT/Usual care (follow-up: 6-12 months)												
2	randomised trials	serious	not serious	not serious	serious[c]	none	151	153	-	SMD **0 SD** (0.21 lower to 0.24 higher)	⨁⨁◯◯ Low	
Medication Adherence (All drug combined) -Pharmacist-led telehealth/Nurse-led telehealth (follow-up: 6 months)												
1	randomised trials	serious	serious[d]	not serious	serious[c]	none	4	4	-	SMD **0 SD** (1.5 lower to 1.27 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **SMD:** standardised mean difference

4.3 Artigo técnico publicado na revista Boletim Farmacoterapêutico do Conselho Federal de Farmácia (CFF)

10.14450/2763-7654.v25.e3.a2021.pp5-13

DEPRESSÃO EM PACIENTES COM DIABETES MELITO: CONTEXTO, DIAGNÓSTICO E TRATAMENTO

Reginaldo Tavares Franquez (https://orcid.org/0000-0001-5538-2200)[1]
Marcus Tolentino Silva (https://orcid.org/0000-0002-7186-9075)[1]
Cristiane de Cássia Bergamaschi (https://orcid.org/0000-0002-6608-1806)[1]
[1]Programa de Pós-graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso)

Características gerais da depressão em pacientes com diabetes melito

A Federação Internacional de Diabetes (*International Diabetes Federation*), em 2017, estimou que 8,8% da população mundial com 20 a 79 anos de idade (424,9 milhões de pessoas) viviam com diabetes melito. Se as tendências atuais persistirem, a projeção no ano de 2045 será superior a 628,6 milhões de pessoas com a doença[1].

Tanto a frequência de novos casos (incidência) como a de casos existentes (prevalência) são informações importantes para o conhecimento da carga que o diabetes representa para os sistemas de saúde. O Brasil está entre os 10 países com maior número de indivíduos com diabetes no mundo[1].

Dados da Pesquisa Nacional de Saúde (PNS), coletados em 2013 e 2015, demonstraram uma prevalência de 6,0% e 6,6%, respectivamente, em adultos brasileiros com diabetes melito, sendo maior no sexo feminino, naqueles com idade superior a 30 anos e em populações com baixa escolaridade, excesso de peso e obesidade[2,3].

1034450/2763-7654.v25.e3.a2021.pp5-13

O diabetes melito tipo 1 é associado a uma maior prevalência de transtornos psicológicos comparado ao diabetes melito tipo 2[4,5]. Também, a depressão parece ser duas vezes mais comum em pessoas com diabetes melito tipo 1 ou tipo 2, comparado à população sem a doença[6]. Existe uma ligação biológica entre diabetes melito e depressão na qual acredita-se que alterações metabólicas e inflamatórias compensatórias à destruição autoimune de células beta sejam agravadas pela depressão[7].

Transtornos psicológicos, tais como depressão, ansiedade e distúrbios de personalidade podem agravar o quadro clínico de pessoas que convivem com diabetes melito, sendo a depressão o mais frequentemente encontrado nesses indivíduos[8].

A depressão esteve presente em 22% da população brasileira com diabetes melito, segundos dados da PNS coletados em 2013. Os sintomas depressivos eram considerados leves a moderadamente graves. Maior gravidade da depressão foi associada ao uso de insulina e em pessoas que apresentavam complicações da doença, como amputação de membros, coma, problemas circulatórios, infarto, pé diabético e problemas renais[2].

Diagnóstico da depressão em pacientes com diabetes melito

Pessoas com diabetes melito parecem ser mais propensas a transtornos psicológicos[6,9,10], fato que impacta não apenas no controle glicêmico, mas sobretudo no funcionamento físico, psicológico, social, ocupacional e na qualidade de vida dos indivíduos e encargos socioeconômicos[11].

O diagnóstico do diabetes e/ou a autogestão inadequada da doença podem contribuir para a presença de quadros de depressão e ansiedade, e piora da qualidade de vida[12]. A presença

concomitante de ambos, em comparação com as pessoas que apresentam apenas uma delas, resulta em inúmeras complicações de curto e longo prazo e no aumento da mortalidade[11].

Os profissionais envolvidos no cuidado devem considerar a triagem anual dos casos de diabetes melito e de depressão ou de outros transtornos psicológicos, a fim de encaminhá-las ao serviço de saúde mental ou profissional especializado. Deve-se ter presente a avaliação para o diagnóstico da depressão, quando há complicações do diabetes ou mudanças significativas no estado clínico desses indivíduos[9].

Na vigência da identificação de pessoas com diabetes melito e com sintomas de transtornos psicológicos e que apresentem as situações descritas no Quadro 1, as boas práticas recomendam o encaminhamento ao profissional de saúde mental.

Quadro 1. Situações nas quais pessoas com diabetes melito podem necessitar de encaminhamento a um profissional de saúde mental

Sofrimento significativo relacionado ao controle do diabetes melito
Medo persistente de hipoglicemia
Resistência psicológica à insulina
Transtornos psicológicos (a exemplo da depressão, ansiedade e transtornos alimentares)

Fonte: *The Royal Australian College of General Practitioners*, 2020, p.99.

10.14450/2763-7654.v25.e3.a2021.pp5-13

É importante que os profissionais da saúde incluam na anamnese perguntas sobre o bem-estar do paciente durante as consultas e/ou os atendimentos. O rastreamento da presença de depressão nos pacientes com diabetes pode ser feito por meio de duas perguntas:

1. No último mês, você, frequentemente, tem se sentido deprimido, triste ou sem esperança?
2. No último mês, você, frequentemente, tem sentido pouco interesse ou prazer pelas coisas em geral?

Se ambas as perguntas forem respondidas afirmativamente e se estas respostas permanecerem constantes por um período de pelo menos duas semanas, um possível diagnóstico da depressão deve ser considerado e investigada a necessidade de tratamento[15].

A triagem do status psicossocial de pacientes com diabetes melito pode contribuir para verificar a presença de problemas psicológicos. O Quadro 2 descreve os itens que podem ser considerados na realização da triagem psicossocial e as principais preocupações relatadas pela pessoa com diabetes melito.

Quadro 2. Triagem psicossocial e preocupações comuns reportadas pelos pacientes com diabetes melito

Triagem psicossocial	Preocupações comuns do paciente
Atitudes sobre o diagnóstico de diabetes melito	Preocupação com o futuro e com as possíveis complicações da doença
Expectativas de gestão da doença e resultados	Culpa e ansiedade por não estar no caminho certo com os objetivos do tratamento
Humor ou afeto	Não saber se o humor ou os sentimentos estão relacionados ao diabetes
Qualidade de vida geral e diabetes	Medo de viver com viver com a doença
	Estar constantemente preocupado com alimentação (qualidade, quantidade e horário)
	Sentir-se privado de certos alimentos
Recursos (sociais, emocionais e financeiros)	Incapaz de lidar com o diagnóstico do diabetes
Histórico psiquiátrico	Sentir-se deprimido por viver com diabetes

Fonte: *Diabetes Task Group, 2009, p. 27* [2].

Na realização de uma avaliação clínica que busque identificar pacientes com depressão, é importante que se use ferramentas padronizadas e validadas, como por exemplo questionário de Saúde do Paciente-9 (*Patient Health Questionnaire-9* – PHQ-9)[15], Inventário de Depressão de Beck II (*Beck Depression Inventory II*)[16], Escala Hospitalar de Ansiedade e Depressão (*Hospital Anxiety and Depression Scale* - HADS)[17], Escala de Avaliação de Depressão de Hamilton (*Hamilton Rating Scale for Depression* - HAM-D)[18], Inventário de Depressão Maior (*Major Depression Inventory* – MDI)[19], Escala de Avaliação de Depressão para Crianças (*Children Depression Evaluation Scale* – CDRS)[20] e Escala de Depressão Geriátrica (*Geriatric Depression Scale* – GDS)[21].

O instrumento pode ser aplicado na visita inicial, em intervalos periódicos, e quando

1034450/2763-7654.v25.e3.a2021.pp5-13

há uma mudança na doença, no tratamento ou nas circunstâncias de vida[22]. O Inventário de Depressão de Beck II, por exemplo, é comumente utilizado em adolescentes e adultos para avaliar os sintomas depressivos e sua gravidade. O instrumento contém 21 itens que analisa os sintomas de depressão por autorrelato, de acordo com os critérios de diagnósticos listados no Manual de Diagnóstico e Estatística para Transtornos Mentais (*Diagnostic and Statistical Manual for Mental Disorders* - DSM). Pontuações mais altas indicam níveis mais altos de depressão. O instrumento é aplicado para fins de pesquisa e para a prática clínica, sendo um dos mais utilizados entre os profissionais da saúde[23].

Tratamento da depressão em pacientes com diabetes melito

Recomenda-se que o tratamento da depressão no paciente com diabetes melito seja abrangente e multidisciplinar, incluindo adequado suporte emocional e comportamental. As intervenções psicológicas são recomendadas quando o paciente apresenta sintomas leves de depressão. Cabe ao profissional da saúde avaliar a indicação do tratamento, bem como encaminhar o paciente para a psicoterapia[1].

Entre as intervenções encontradas na literatura destacam-se como principais: psicológicas, psicossociais e farmacológicas. É importante ressaltar que as intervenções não farmacológicas demonstram ser efetivas no tratamento da depressão leve a moderada nos pacientes com diabetes melito[24].

Feito o diagnóstico de depressão maior, intervenções farmacológicas podem ser utilizadas combinadas ou não com psicoterapia[25]. Os antidepressivos devem ser usados para tratar a depressão aguda em pessoas com diabetes melito e como tratamento de manutenção para prevenir a sua recorrência nesses pacientes[10].

Revisão sistemática que avaliou o efeito de intervenções farmacológicas e não farmacológicas na depressão em pacientes com diabetes melito tipo 1 e tipo 2 mostrou que, em comparação com tratamento usual, placebo ou lista de espera, as intervenções (uso de medicamentos, terapia de grupo, psicoterapia e cuidado colaborativo) mostraram um efeito

10.14450/2763-7654.v25.e3.a2021.pp5-13

significativo na melhora da depressão e no controle glicêmico desses pacientes[26].

Intervenções psicológicas

Estudo que sintetizou informações de diretrizes de prática clínica e consensos para pacientes com diabetes melito tipo 2 mostrou que intervenções psicológicas são indicadas como parte do tratamento da depressão e podem contribuir para mudanças significativas no estilo de vida[26]. Recomenda-se como intervenções a terapia cognitivo-comportamental, a terapia interpessoal, e a intervenção psicoeducacional[9].

Terapia cognitivo-comportamental é uma abordagem organizada e limitada no tempo com conteúdo como psicoeducação, ativação comportamental, reestruturação cognitiva e prevenção de recaídas. Pode reduzir os sintomas depressivos pela capacidade de identificar e avaliar pensamentos negativos. É uma intervenção efetiva para pacientes com doenças crônicas, melhorando as habilidades de autocuidado e favorecendo ajustar a doença com o impacto que ela causa na vida do paciente[27,28].

Revisões sistemáticas demonstraram que a terapia cognitivo-comportamental pode contribuir para a remissão da depressão e melhorar a qualidade de vida em pacientes com diabetes melito[25,29-31]. Ensaio clínico recente avaliou a efetividade dessa terapia em adultos com diabetes melito tipo 1, por meio do uso da intervenção via mensagens *online* e em tempo real, para apoiar a autogestão e melhorar o controle glicêmico nesses pacientes. Observou-se redução nos escores de depressão e nos valores de hemoglobina glicosilada (HbA1c) dos pacientes submetidos à intervenção, por um período de acompanhamento de até 12 meses[32].

Intervenções psicossociais

As intervenções psicossociais fornecem informações e orientações para o diabetes, autogestão da doença e apoio psicológico. Entre elas, o cuidado colaborativo tem demonstrado efetividade em pessoas com diabetes melito[10]. Este é um modelo de gestão coordenada, realizado na atenção primária à saúde, que envolve médicos, enfermeiros, profissionais de saúde mental, entre outros profissionais que proporcionem o manejo ao paciente[33,34].

Revisão sistemática observou que as intervenções psicossociais reduziram sintomas de estresse emocional específico do diabetes e os valores de HbA1c, em adultos com diabetes melito tipo 2, em comparação com os grupos controles (em geral, definidos como grupos de pacientes que receberam cuidados usuais)[35]. O Quadro 3 descreve as intervenções psicossociais reportadas na literatura para depressão em pacientes com diabetes melito.

Quadro 3. Cuidado colaborativo e outras intervenções psicossociais que podem ser utilizadas em pacientes com diabetes melito e depressão

Cuidado colaborativo fornecido ao paciente com diabetes melito e depressão pode melhorar:
Sintomas depressivos
Adesão ao antidepressivo
Controle glicêmico
Outras intervenções psicossociais que podem ser integradas aos planos de tratamento do diabetes melito:
Intervenções motivacionais
Estratégias de gerenciamento de estresse
Treinamento de habilidades de enfrentamento
Terapia familiar
Gestão de caso

Fonte: Mancini et al., 2018, p.178-185[9].

1034450/2763-7654.v25.e3.a2021.pp5-13

Intervenções farmacológicas

Revisões sistemáticas que abordaram o tratamento farmacológico da depressão em pacientes com diabetes melito demonstraram melhora nos escores de gravidade e de remissão da depressão, bem como no controle glicêmico em adultos, com destaque para o uso dos Inibidores Seletivos da Recaptação de Serotonina (ISRS)[15,25].

Há diferentes classes de antidepressivos. No Brasil, o Sistema Único de Saúde (SUS) seleciona e disponibiliza duas classes principais: os tricíclicos (amitriptilina, nortriptilina, clomipramina, etc) e os ISRS (fluoxetina, citalopram, sertralina, etc)[36]. O Quadro 4 descreve os antidepressivos que constam na Relação Nacional de Medicamentos Essenciais (Rename)[16], ou seja, que são os medicamentos selecionados e ofertados pelo SUS no Brasil.

Para que os antidepressivos comecem a produzir seus efeitos, é necessário o tempo de uso de pelo menos duas semanas, conhecido como período de latência, e para que ocorra redução expressiva dos sintomas, os medicamentos devem ser utilizados por pelo menos quatro semanas[37]. O tratamento antidepressivo bem-sucedido deve continuar por 9 a 12 meses, após a remissão dos sintomas, e, em casos em que ocorra recorrências e recidivas frequentes, poderá demandar terapia com duração indefinida[38].

O medicamento deve ser selecionado de acordo com o perfil do paciente e a existência de outras doenças[41,42]. Comorbidades e possíveis interações medicamentosas devem ser consideradas, a fim de minimizar danos e maximizar a resposta terapêutica[37].

É importante destacar que o uso de antidepressivos, também, pode estar relacionado a um maior risco de desenvolver diabetes

melito do tipo 2, especialmente quando utilizados em doses mais altas e por períodos prolongados[39]. Desta forma, histórico de depressão, depressão atual e de uso de antidepressivos são fatores de risco para o desenvolvimento do diabetes melito, especialmente em indivíduos com obesidade e com história familiar de diabetes melito tipo 2[40].

Intervenções no estilo de vida

Revisão sistemática que avaliou intervenções no estilo de vida, incluindo dieta e/ou atividade física, demonstrou diminuição dos escores de depressão em adultos com diabetes melito tipo 2 ou em risco de desenvolver a doença, apenas nos primeiros 6 meses de intervenção. As intervenções por meio de sessões individuais ou em sessões em grupo foram associadas à melhora da depressão. Entretanto, a qualidade das evidências desses achados não foi avaliada pelo estudo, o que limita afirmar sobre a real efetividade dessa intervenção[43].

10.14450/2763-7654.v25.e3.a2021.pp5-13

Quadro 4. Fármacos utilizados no tratamento da depressão presentes na Rename

MEDICAMENTOS ANTIDEPRESSIVOS	CLASSE FARMACOLÓGICA	ESQUEMA DE ADMINISTRAÇÃO	INDICAÇÕES DE USO	EFEITOS ADVERSOS
Amitriptilina (comprimido: 25 mg e 75 mg)	Inibidores Não Seletivos da Recaptação de Monoaminas (Tricíclicos)	1 vez ao dia, ao deitar. Aumentar a dose de acordo com a resposta (dose máxima: 150-300 mg/dia)	• Transtornos e episódios de depressão maior, particularmente quando sedação é necessária • Profilaxia de enxaqueca (tratamento intercrises) **Obs:** pode ser utilizado durante a amamentação e com precaução na gravidez	Boca seca, constipação, retenção urinária, ganho de peso, sedação, disfunção sexual, hipotensão, taquicardia, arritmias.
Bupropiona (comprimido de liberação prolongada: 150 mg)	Inibidores Seletivos da Recaptação de Dopamina (ISRD)	1 vez ao dia. Aumentar gradualmente a dose de acordo com a resposta (dose máxima: 400 mg/dia, administrados em 2 doses fracionadas)	• Transtorno depressivo maior • Tratamento adjuvante na cessação do tabagismo	Cefaleia, insônia, ansiedade, irritabilidade, distúrbios visuais, xerostomia, constipação, náusea e perda moderada de apetite.
Clomipramina (comprimido: 10 mg e 20 mg)	Inibidores Não Seletivos da Recaptação de Monoaminas (Tricíclicos)	2 a 3 vezes ao dia. Aumentar gradualmente a dose de acordo com a resposta (dose máxima: 250 mg/dia, administrado em 2 a 4 doses fracionadas)	• Depressão • Distúrbios do pânico, associados ou não à agorafobia • Transtorno Obsessivo Compulsivo (TOC) **Obs: pode ser utilizado durante a amamentação e com precaução na gravidez	Boca seca, constipação, retenção urinária, ganho de peso, sedação, disfunção sexual, hipotensão, taquicardia, arritmias.
Nortriptilina (cápsula: 10 mg, 25 mg, 50 mg e 75 mg)	Inibidores Não Seletivos da Recaptação de Monoaminas (Tricíclicos)	1 vez ao dia, ao deitar. Aumentar gradualmente de acordo com a resposta (dose máxima: 150 mg/dia, pode ser administrado em doses fracionadas)	• Depressão maior **Obs: pode ser utilizado durante a amamentação e com precaução na gravidez	Boca seca, constipação, retenção urinária, ganho de peso, sedação, disfunção sexual, hipotensão, taquicardia, arritmias.
Fluoxetina (cápsula e comprimido: 20 mg)	Inibidores Seletivos da Recaptação da Serotonina (ISRS)	1 vez ao dia. Aumentar gradualmente de acordo com a resposta. O uso de mais que 20 mg/dia pode ser feito em 2 doses fracionadas.	• Transtorno depressivo • Transtorno Obsessivo Compulsivo (TOC) • *Rigidez comportamental e agressividade • **Redução da compulsão na bulimia e nos quadros de Transtorno Compulsivo Alimentar (TCA) **Obs: não deve ser utilizado durante a gravidez e amamentação	Náuseas, diarreia, azia, disfunção sexual, cefaleia, insônia ou sonolência.

Fonte: *Rename 2020*. Disponível em: < http://conitec.gov.br/images/Rename-2020-final.pdf/>[35]

**Assumpção, et al., 2012*[43]; *Yudofsky et al., 2012*[44]

***Hermelinda et al., 2020*

10.14450/2763-7654.v25.e3.a2021.pp5-13

Participação de profissionais da saúde nos cuidados desses pacientes

As intervenções psicológicas são recomendadas quando o paciente apresenta sintomas leves de depressão. Em quadros mais graves, recomenda-se o uso de antidepressivo associado à intervenção psicológica, sempre que possível. Desta forma, de acordo com as intervenções reportadas pela literatura, diferentes profissionais da saúde podem contribuir nos cuidados de pessoas com diabetes melito e depressão. As informações reportadas neste boletim podem orientar enfermeiros, educadores físicos, farmacêuticos, médicos e psicólogos, a respeito dos cuidados que refletem em melhorias no quadro clínico da depressão nessa população.

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5 CONSIDERAÇÕES FINAIS

Uma vez que os transtornos psicológicos como depressão e ansiedade acometem pessoas com diabetes *mellitus* de todas as idades e que diabetes *mellitus* é um problema de saúde comum e crescente, a presente tese sumarizou e avaliou as intervenções disponíveis na literatura para tratar transtornos psicológicos em pessoas com diabetes *mellitus* tipo 1 e tipo 2;

Foram identificadas revisões sistemáticas que sumarizam a evidência dos achados de intervenções psicológicas (a exemplo da entrevista motivacional, intervenção psicossocial, Terapia Cognitivo Comportamental, dentre outras); intervenção psicoeducacional (como cuidados colaborativos); educação em saúde; e intervenções farmacológicas (uso de ISRS e do fitoterápico *Gardenia Fructus*);

As evidências baseadas nos achados das revisões sistemáticas sugerem que as intervenções Terapia Cognitivo Comportamental, cuidados colaborativos e educação em saúde foram promissoras na melhora de desfechos, principalmente relacionados a depressão e ao controle glicêmico, na população adulta com diabetes *mellitus*. Entretanto, tais achados em geral, tem evidência de baixa a moderada qualidade;

Dentre as intervenções psicológicas, a Terapia Cognitivo Comportamental, oferecida no formato usual ou via *web*, mostrou-se efetiva para a maioria dos desfechos de depressão, ansiedade e controle glicêmico. Esta intervenção foi também a mais estudada na população de adultos ou idosos com diabetes;

Com base nos achados da revisão sistemática, a respeito das intervenções de e-Saúde, foi possível observar melhora da depressão com o uso da intervenção Autoajuda Guiada pela Internet ou da Terapia Cognitivo Comportamental por Telefone; melhora da ansiedade com a Autoajuda guiada pela Internet ou Terapia Cognitivo Comportamental Específica para Diabetes; e melhora do sofrimento emocional com o uso da Autoajuda guiada pela Internet ou da Terapia Cognitivo Comportamental Específica para Diabetes. Entretanto, as evidências também foram aferidas como de baixa a moderada qualidade;

Dados de segurança das intervenções e-Saúde reportados pelos ECR estiveram ausentes nestes estudos, bem como, poucos estudos exploraram os desfechos qualidade de vida, “satisfação” ou “aceitabilidade” dos pacientes com o uso dos aplicativos;

De acordo as limitações observadas na qualidade da evidência reportadas pelas revisões sistemáticas; e as divergências observadas nos ECR desenhados para intervenções de e-Saúde no que se refere as intervenções, população estudada, tempo de acompanhamento dos participantes, e desfechos mensurados; novos ensaios clínicos são necessários para confirmar os achados de efetividade e segurança das intervenções estudadas.

As informações geradas da presente tese podem auxiliar os pacientes com diabetes e seus cuidadores, e orientar os profissionais de saúde na escolha de intervenções para o manejo da depressão, ansiedade e do sofrimento emocional devido ao diabetes *mellitus*.

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APÊNDICE A: ORIENTAÇÕES PARA APRESENTAÇÃO DE TESES DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS DA UNIVERSIDADE DE SOROCABA

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Para aclarar membros da banca que desconhecem esta versão alternativa da dissertação/tese recomenda-se anexar este documento no final das versões encaminhadas aos membros da banca.

A dissertação/tese no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Elementos textuais	*1. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.

	2. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	3. Objetivos: geral e específico
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	5. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	6. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	7. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.
Elementos pós-textuais	*8. Referências:* Devem seguir as normas do “Manual para normalização de trabalhos acadêmicos” da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	9. Apêndices (Opcional)
	10. Anexos (Opcional)