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DIABETIC Medicine

SYSTEMATIC REVIEW OR META-ANALYSIS

The bidirectional longitudinal association between depressive symptoms and HbA_{1c}: A systematic review and meta-analysis

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Abstract

Aim: To investigate whether there is a bidirectional longitudinal association of depression with HbA_{1c}.

Methods: We conducted a systematic literature search in PubMed, PsycINFO, CINAHL and EMBASE for observational, longitudinal studies published from

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January 2000 to September 2020, assessing the association between depression and HbA_{1c} in adults. We assessed study quality with the Newcastle-Ottawa-Scale. Pooled effect estimates were reported as partial correlation coefficients (r_p) or odds ratios (OR).

Results: We retrieved 1642 studies; 26 studies were included in the systematic review and eleven in the meta-analysis. Most studies (16/26) focused on type 2 diabetes. Study quality was rated as good (n = 19), fair (n = 2) and poor (n = 5). Of the meta-analysed studies, six investigated the longitudinal association between self-reported depressive symptoms and HbA_{1c} and five the reverse longitudinal association, with a combined sample size of n = 48,793 and a mean follow-up of 2 years. Higher levels of baseline depressive symptoms were associated with subsequent higher levels of HbA_{1c} (partial r = 0.07; [95% CI 0.03, 0.12]; $I^2$38%). Higher baseline HbA_{1c} values were also associated with 18% increased risk of (probable) depression (OR = 1.18; [95% CI 1.12,1.25]; $I^2$0.0%).

Conclusions: Our findings support a bidirectional longitudinal association between depressive symptoms and HbA_{1c}. However, the observed effect sizes were small and future research in large-scale longitudinal studies is needed to confirm this association. Future studies should investigate the role of type of diabetes and depression, diabetes distress and diabetes self-management behaviours. Our results may have clinical implications, as depressive symptoms and HbA_{1c} levels could be targeted concurrently in the prevention and treatment of diabetes and depression.

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KEYWORDS
depression, diabetes mellitus, glycated haemoglobin A, longitudinal studies, meta-analysis, systematic review

1 | INTRODUCTION

Depression and diabetes mellitus are among the leading causes of disability worldwide. The most recent estimates, available for 2017, suggest worldwide 264 million people living with depression and 476 million with diabetes; these figures are expected to rise.[1] The co-occurrence of type 2 diabetes and depression is frequently reported, and their association is suggested to be bidirectional.[2-7] Meta-analyses report a 15% increased risk of depression in individuals with diabetes.[2] For incident diabetes in individuals with depression, risk estimates in meta-analyses vary from% 38 to 60%.[2,8] Individuals with comorbid depression and diabetes have shown a greatly reduced health-related quality of life, compared to individuals with only depression or only diabetes.[9] Moreover, depression in the presence of diabetes has been linked to an increased risk of incident diabetes complications such as retinopathy, neuropathy, and nephropathy,[10] as well as cardiac events,[11] cardiovascular mortality[11,12] and all-cause mortality.[12]

Novelty Statement

- The association between depression and diabetes has been suggested to be bidirectional. A possible mechanism linking depression and diabetes are suboptimal HbA_{1c} levels. Prior studies regarding the association between depression and HbA_{1c} levels showed mixed results and have not been systematically summarised.
- The present meta-analysis suggests a bidirectional longitudinal association between depressive symptoms and HbA_{1c}. Due to the low number of eligible studies, further research in large-scale longitudinal studies is needed to confirm this association.
- Depressive symptoms and HbA_{1c} levels may be targeted concurrently by prevention and treatment efforts.

A possible mechanism linking depression to these adverse health outcomes are suboptimal blood glucose levels, measured with HbA_{1c}. HbA_{1c} levels are a key target in diabetes therapy because persistent or recurrent high glucose levels can damage blood vessels resulting in vascular complications. However, prior studies that investigated the association between depression and HbA_{1c} have yielded inconsistent findings and faced methodological limitations. A landmark meta-analysis by Lustman and colleagues[13] reported a small to moderate association between depression and suboptimal HbA_{1c} for type 1 and type 2 diabetes. However, the meta-analysis included mainly cross-sectional studies, limiting the ability to infer temporality. This seminal review was published in 2000; since then, a substantial number of new studies has become available.

The reverse association on impaired glucose metabolism and the risk of incident depression has been recently addressed by Tong et al.[14] In this meta-analysis, individuals with previously diagnosed diabetes had a higher risk of developing depressive symptoms compared to individuals with normal glucose metabolism. For individuals with newly diagnosed diabetes or impaired glucose metabolism, no significant association with depression was found. However, the numbers of individuals with incident depression within the impaired glucose metabolism or newly diagnosed type 2 diabetes groups were relatively small and thus confidence intervals were wide and the power to detect differences was low. Furthermore, this meta-analysis explored categories of glucose metabolism as opposed to continuous glucose measures and did not include individuals with type 1 diabetes.

In summary, prior evidence regarding depression as a risk factor for suboptimal HbA_{1c} levels revealed mixed findings, is mainly based on cross-sectional data and needs updating, whereas the evidence regarding suboptimal HbA_{1c} levels as a risk factor for depression needs increased power to assess the association of early hyperglycaemia with depression. Further, there is a need to assess whether the association is truly bidirectional which requires (large scale) longitudinal data. Therefore, we conducted a systematic review and meta-analysis to investigate (I) whether there is a longitudinal association between depression and HbA_{1c} levels, and (II) whether there is a longitudinal association between HbA_{1c} levels and depression. We hypothesised that higher HbA_{1c} levels will be associated with a higher risk for depression, and vice versa.

2 | METHODS

2.1 | Search strategy

We performed a systematic literature search in the following databases: PubMed, PsycINFO (Ebsco), CINAHL (Ebsco) and EMBASE (OVID). Searches were conducted for studies indexed between January 1, 2000 to July 29, 2019 and were updated until September 30, 2020. We restricted to articles written in English, Dutch, German, Spanish or French. Studies published before January 2000 were not included due to the previous meta-analysis by Lustman et al. including studies up until that date.[13]

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42019147551) and is performed in accordance with the MOOSE guidelines[15] and the PRISMA guidelines.[16] A search strategy was developed based on the following search terms including their variants: (I) glycaemic/glycaemic control, (II) depression/depressive symptoms and (III) cohort/longitudinal studies. The search terms are provided in detail in Table S1.

2.2 | Selection criteria

Two pairs of reviewers (MB and MS, RM and AG) independently screened the titles and abstracts retrieved. Subsequently, full-text screening was performed in parallel by MB and RM based on predefined in- and exclusion criteria (Table S2). Any disagreement was resolved by consulting a third reviewer. Additionally, we handsearched reference lists of papers eligible for inclusion. The core criteria for inclusion were a prospective cohort study design with two or more measurements, a study sample size of >50 participants, and an adult (≥18 years) study population. Only studies that partially or solely included individuals with type 1 or type 2 diabetes were eligible for inclusion. Studies had to include a variable for depression (all types) or depressive symptoms, and a continuous variable for HbA_{1c} levels, and report an estimate of the longitudinal association between them. The determinant had to be assessed at one or more time points and the outcome at two or more time points. As we looked at both depressive symptoms based on self-report questionnaires and clinical diagnosis of major depressive disorder, we use the term 'depression' to refer to both. Randomised controlled trials and other intervention studies were excluded because they would answer a different research question and require different methodology.

2.3 | Data extraction

We pilot tested the data extraction form independently (MB and RM) using six studies to minimise bias and errors. As the extractions were highly comparable, one reviewer (MB) completed the data extraction. AG extracted the data from the new studies identified during

the repeated search. The following characteristics of the included studies were extracted: Authors, year of publication, country, age, sex, detailed description of the study population, sample size, assessment method for depression, diabetes type, assessment method for HbA_{1c}, use of medication for depression/diabetes, diabetes distress, study duration, number and time of follow-up measurements, reasons for exclusion/loss to follow up, statistical analysis, effect measures (crude and adjusted) with confidence intervals, standard errors or p-values, confounding factors, and stratified analyses including results.

2.4 | Quality assessment

The quality of the included studies was assessed by use of the Newcastle-Ottawa-Scale (NOS) which examines three domains: selection, comparability and outcome. The slightly adjusted version of the NOS including a rationale for adjustments can be found in the Supporting Information. One reviewer (MB) conducted the quality assessment which was independently assessed by a second reviewer for 30% of the included articles (RM). In order to judge the overall quality of a study, results were converted to the Agency for Healthcare Research and Quality Standards (see Supporting Information–Methods).

2.5 | Statistical analysis

All statistical analyses were conducted in R by use of the metafor package (R version 3.6.2).[17] Studies were stratified based on whether HbA_{1c} or depression was used as outcome variable and two meta-analyses were conducted by use of a random-effects model. If both the crude and adjusted effect estimate were presented in the article, the adjusted effect estimate was chosen, as advised by the COSMOS-E guidelines.[18] In order to enable pooling of the results, regression coefficients were transformed into partial correlation coefficients (r_p).[19,20] Fisher's r-to-z transformation was applied to stabilise variances of the r_p.[21] For studies with depression as outcome variable, effect measures were transformed into ORs, if needed. For this purpose, ORs were log-transformed to normalise their distribution. The pooled estimates and 95% CI were displayed in forest plots. We assessed heterogeneity using I^2 statistics (low (25%), moderate (50%), high (75%)) and determined the risk of publication bias by visual inspection of funnel plots. We explored heterogeneity and the robustness of our results by iteratively removing one study to assess each study's influence on the pooled estimate for both outcomes. We also intended conducting sensitivity analyses such as comparing studies with different types of depression assessment and exploring heterogeneity using meta-regression. However, the limited number of available studies did not allow for such exploration.

3 | RESULTS

3.1 | Study selection and characteristics

We retrieved 1642 studies, of which 173 full-text articles were assessed for eligibility. Of these, 26 studies met the inclusion criteria and were included in the systematic review. Inter-rater reliability for the full-text screening was 0.68 (Cohen's kappa). The results of 11 studies could be subjected to meta-analysis. Fifteen studies[22–36] had to be excluded from the meta-analysis as the reported effect measures could not be pooled in a meta-analysis. The exact reasons for exclusion can be found in Tables S5 and S6. Of the studies included in the meta-analysis, six investigated the longitudinal association between depressive symptoms and HbA_{1c}[24,37-41] and five assessed the longitudinal association between HbA_{1c} and major depressive disorder/depressive symptoms[42–46] (see Figure 1). Thereof, two studies assessed the reciprocal association.[37,38] For these two studies, we only considered the association between depressive symptoms and HbA_{1c} as an outcome due to missing information for the transformation of the effect measure on the reversed association.

Table S3 presents the characteristics of the 26 studies in the systematic review. Sixteen studies consisted of individuals with type 2 diabetes,[24-26,29-33,37-40,43-46] six with type 1 diabetes,[22,28,34-36,41] two included a mixed population[27,47] and two did not specify the type of diabetes.[23,42] The mean age of participants ranged from 22.6 to 67.9 years. Study sample sizes varied with a range from 79 to 40,214 participants with a median of 598 individuals. Study duration varied from 6 months up to twelve years with two to six follow-up time points. Three studies used a retrospective study design[30,32,46]; nonetheless, we decided to include them as neither depression nor HbA_{1c} were relevant for the selection of the exposed and non-exposed study participants. Six studies did not report adjusted outcome measures, and 13 studies did not report 95% CI.

3.2 | Quality assessment

For studies with HbA_{1c} as the outcome variable, we rated thirteen as having *good* quality, one as *fair* and five as having *poor* quality according to NOS. Inter-rater reliability for quality assessment was 0.79 (Gwet's Agreement Coefficient 1). For studies with depression as outcome variable, eight were evaluated as *good*, one as *fair* and

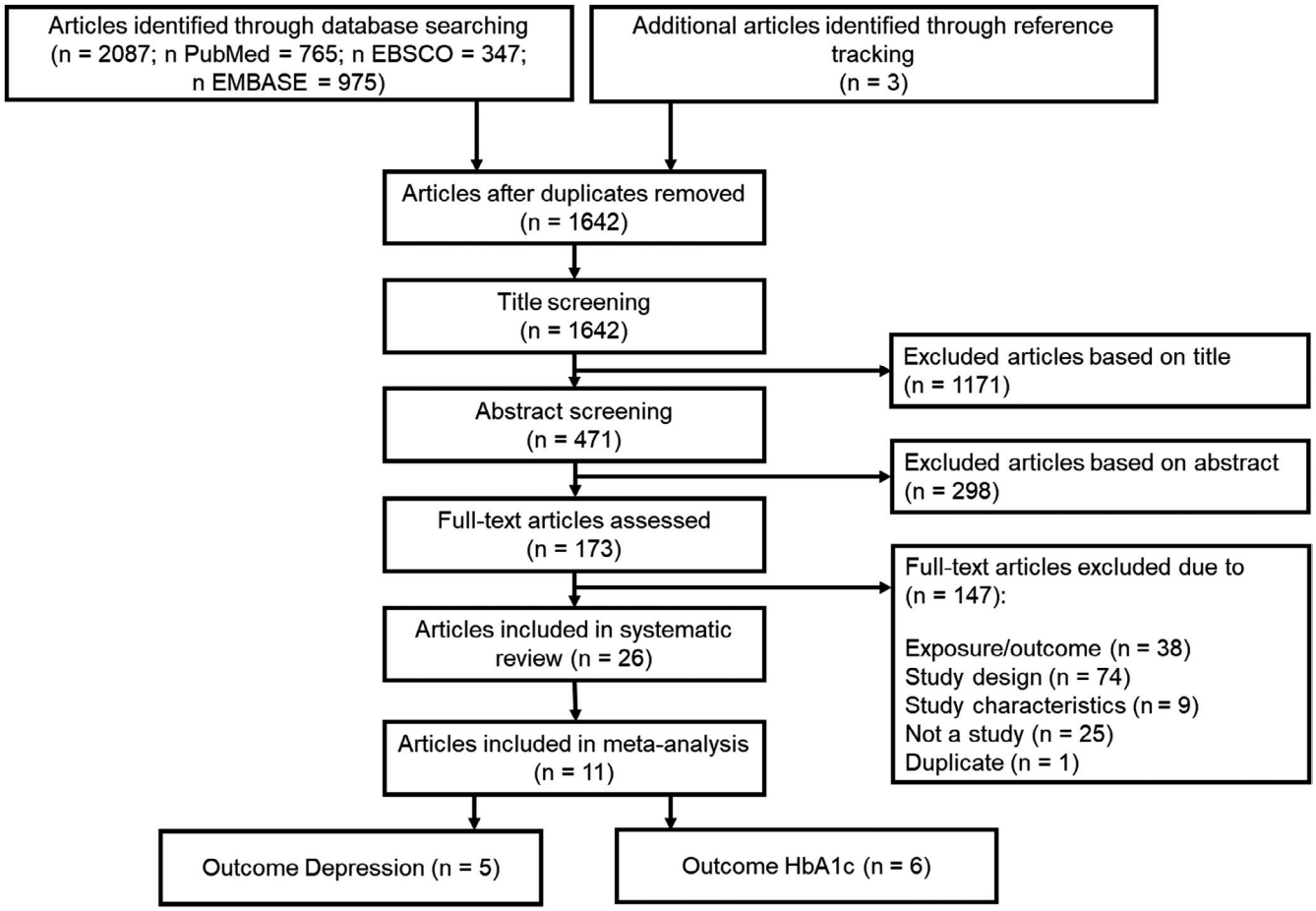

FIGURE 1 Flowchart of the study selection process

three received a *poor* rating (see Table S4). The main reason for a poor rating was lack of adjustments for sex, age, BMI or antidepressant medication use, or not adjusting for baseline values or disease status of the relevant dependent variable. Three studies used a selective study population such as only including men,[24] mainly including women with microalbuminuria,[45] or individuals with a longer disease duration and a low prevalence of probable depression in the study sample,[47]

3.3 | Longitudinal association of depressive symptoms with HbA_{1c}

Six studies that investigated the longitudinal association of depressive symptoms with HbA_{1c} with a combined sample size of 3,683 individuals were included in the meta-analysis. The follow-up periods ranged from six months to five years with a mean follow-up period of 37 months. Results showed a small significant association between depressive symptoms (at baseline) and HbA_{1c} levels (at follow-up) ($r_p = 0.07$; [95% CI 0.03, 0.12], $p = 0.002$; Figure 2). Between-study heterogeneity was found to be moderate and non-significant ($I^2 = 38\%$, [95% CI 00.00, 91.88], $p = 0.159$). When we removed one study at a time, r_p ranged from 0.05 to 0.09. We saw no indication of publication bias at visual inspection of the funnel plot.

Thirteen studies with HbA_{1c} as an outcome could not be included in the meta-analysis due to the reported effect measures (e.g. regression coefficient not standardised, depression as binary outcome variable, or no formula available for transformation). The results of these studies and reasons for exclusion are summarised in Table S5. Out of these thirteen studies, five reported that major depressive disorder/higher levels of depressive symptoms were longitudinally associated with higher levels of $HbA_{1c,}$[26,28–30,36] while eight did not find an association.[22,25,27,32–35,47] One study described their results without reporting an effect estimate.[47]

3.4 | Longitudinal association of HbA_{1c} with major depressive disorder/depressive symptoms

Five studies that investigated the longitudinal association of HbA_{1c} with major depressive disorder/depressive

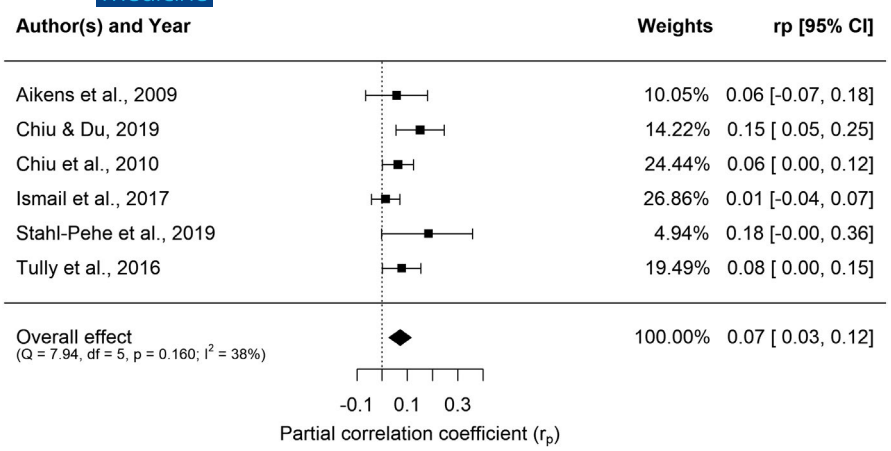

FIGURE 2 Forest plot showing the weighted mean partial correlation between depressive symptoms and HbA1c values

symptoms with a combined sample size of 45,110 individuals were included in the meta-analysis. The follow-up periods ranged from six months to three years with a mean follow-up period of 19.7 months. A one-point higher baseline HbA_{1c} level was associated with a 18% increased risk of (probable) depression at follow-up (pooled OR =1.18; [95% CI 1.12, 1.25], $p < 0.001$; Figure 3). The heterogeneity of the included studies was low and non-significant ($I^2 = 0.04\%$; [95% CI 0.00, 98.33], $p = 0.237$). When we removed one study at a time, ORs ranged from 1.18 to 1.25. We saw no indication of publication bias at visual inspection of the funnel plot.

Seven studies could not be included in the meta-analyses due to the reported effect measures (e.g. results presented for quintiles of HbA_{1c}). Of these, three found that higher HbA_{1c} levels were associated with an increased risk for subsequent (probable) depression[23,26,31]; four reported no significant association.[22,35,37,38] The results and reasons for exclusion are presented in detail in Table S6.

4 | DISCUSSION

In this meta-analysis and systematic review, we extensively and systematically assessed the longitudinal association between depression and HbA_{1c} levels, and between HbA_{1c} levels and depression. We found a significant bidirectional association, despite the relatively small number of studies that could be included in the meta-analysis. Our findings support the temporality of both associations. Due to the methodological issues observed in meta-analysing data from the available literature, we consider this work as a first step in exploring the longitudinal and bidirectional association between depression and HbA1c levels.

4.1 | Longitudinal association of depressive symptoms with HbA_{1c}

We found a small, but significant association between depressive symptoms and HbA_{1c} levels at follow-up as an outcome in our meta-analysis. Importantly, these results suggest temporality of this association. Our finding extends previous research on cross-sectional studies by Lustman and colleagues where the authors found a small-to-moderate significant association.[13] A possible explanation for the somewhat reduced magnitude of the effect could be that longitudinal studies are often subject to attrition bias with healthier individuals less likely to drop-out, leading to an underestimation of the effect size.

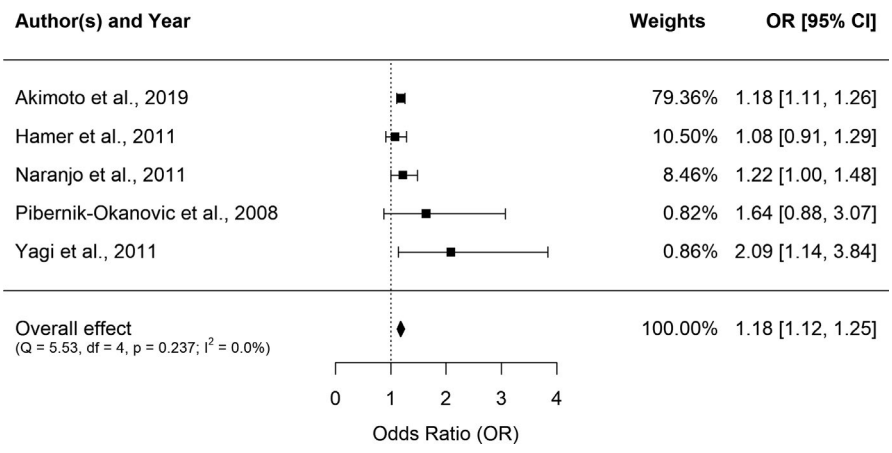

FIGURE 3 Forest plot showing the association of higher HbA_{1c} values with increased probable depression risk in weighted odds

Five out of six studies had a fair-to-good quality, supporting the credibility of our results. In addition, studies from our systematic review that found an association between lower depression scores and higher HbA_{1c} levels were of good quality whereas the studies that did not support an association received mixed quality ratings.

A potential pathway linking depression to the development of hyperglycaemia could be via behavioural mediation. Higher depressive symptoms have been associated with less optimal diabetes self-management which has in turn been related to hyperglycaemia.[48] A meta-analysis found a moderate association between depression and reduced diabetes self-management with the strongest association found for keeping medical appointments and dietary self-care.[49] In addition, depressed mood may lead to physical inactivity and unhealthy dietary behaviour.[6,50] Physical inactivity and an unhealthy diet may further lead to weight gain which in turn negatively affects blood glucose levels.[S51,52] Furthermore, pharmacological therapies for depression can also lead to weight gain. Prior evidence demonstrated a 5% increased risk of weight gain in individuals on antidepressant treatment compared to those without.[S53]

Since associations with depressive symptoms were often measured as a secondary analysis, most studies in this review did not report on adjustments for diabetes self-management and health behaviours. The studies that did adjust for these factors mentioned that depressive symptoms might improve with better glycaemic control once barriers to insulin treatment have been addressed.[29] Chiu et al. found that a variety of health behaviours explained a large part of the association of depressive symptoms with HbA_{1c}. However, they still found a significant direct association of baseline depressive symptoms on HbA_{1c} levels at follow-up above and beyond health behaviours.[39] Based on a mediation analysis, Schmitz et al. suggested that cardiometabolic factors and lifestyle-related behaviours might mediate the association between depressive symptoms and HbA_{1c}.[26]

4.2 | Longitudinal association of HbA_{1c} with depression

Our meta-analysis on the association between HbA_{1c} and depression as an outcome yielded a significant association between higher HbA_{1c} and higher risk for (probable) depression. This finding contradicts results from a previous meta-analysis,[14] which concluded that hyperglycaemia or hyperinsulinemia is unlikely to be related to the development of depression. However, this study did not investigate a linear contribution of HbA1c to the incidence of depression. The use of HbA_{1c} as a continuous measure gave us more statistical power to detect a difference. Moreover, the size of our pooled effect estimate was within the range reported by Tong et al.[14] Four out of five studies in our meta-analysis were of good quality, supporting the credibility of our results. The studies that were excluded from the meta-analysis showed mixed results with two studies supporting and four studies failing to support our findings. Studies which found an association had a good quality rating. One study with a poor, two studies with a fair and one study with a good quality rating did not find an association. A lower quality rating was based on lack of adjustment for important confounding factors and baseline values of HbA_{1c} or depression.

Several biological mechanisms could explain an association between hyperglycaemia and incident depression. Neurons in the brain do not possess active glucose transporters. Consequently, prolonged high levels of plasma glucose directly affect intraneuronal glucose levels. These high glucose concentrations can activate the polyol pathway, inducing an overgeneration of reactive oxygen species, and cause the generation of advanced glycation end products.[S54] These processes induce oxidative stress which may lead to neuronal apoptosis. Neuronal apoptosis may subsequently lead to brain atrophy which could eventually cause depression.[S54–55] Moreover, hyperglycaemia might lead to increased cortisol levels,[S54] which has been associated with incident depression.[S56] Other potential mechanisms include low-grade inflammation,[S57] reductions in serum brain-derived neurotrophic factor[S57] or vascular damage in brain regions implicated in mood regulation.[S54] The association between hyperglycaemia and incident depression may also be explained by psychological demands or psychological factors (e.g. social support, coping skills) related to the illness or its treatment. Depression may also be triggered from seeing high blood glucose levels all the time, resulting in a sense of personal failure to get the number down.[S58]

Importantly, both HbA_{1c} levels and depression have been linked to diabetes distress.[S59] Diabetes distress refers to negative behavioural and emotional reactions due to suffering from diabetes. It can be induced by the diagnosis itself, fear or experience of complications, struggle with self-management or other factors that are specific to the disease.[S60] Evidence from cross-sectional analyses suggests that diabetes-distress might mediate the association between depression and glycaemic control.[S61,62] From the studies included in this review, seven analysed the role of diabetes distress.[22,29,33-35,40,41] Thereof, three did not find evidence for an association for depressive symptoms or diabetes distress with HbA_{1c}[22,35,40] and two found an association for both depressive symptoms and diabetes distress.[29,41] In one study, the association between depressive symptoms and HbA1c attenuated when diabetes distress

was entered into the model.[41] In two studies, neither depressive symptoms nor major depressive disorder showed an association with HbA_{1c}.[33,34] Interestingly, diabetes distress was associated with HbA_{1c} levels cross-sectionally and in the time-varying analysis but not in the prospective analysis in both studies. Based on these results, no firm conclusion on mediation can be drawn. Further research in longitudinal studies is needed to entangle this complex relationship.

4.3 | Limitations and strengths

The quality of our meta-analyses is highly dependent on the quality of available literature. We only found a few studies that have investigated the association between depression and HbA_{1c} and vice versa. Based on the limited number of studies, we could not formally assess publication bias,[S63] conduct meta-regression or sensitivity analyses that would discriminate between type of diabetes, assessment of depression (clinical diagnosis of major depressive disorder versus self-reported depressive symptoms), adjustment for diabetes distress, or between users and non-users of insulin, antidepressants or other types of medication. As the majority of pooled studies were in individuals with type 2 diabetes, conclusions about individuals with type 1 diabetes are limited. With regards to comparing users and non-users of insulin, potential differences were only analysed in the study by Aikens et al. The results suggested that HbA1c is only associated with depressive symptoms among insulin-users compared to individuals on oral medication alone.[37]

Moreover, most studies in the meta-analysis assessed depression by use of a self-report questionnaire. Self-report questionnaires are widely used in research to assess 'depression' because clinical diagnoses are often not available.[S59] Although cut-off scores on self-report questionnaires have been validated to identify depressive symptoms, a one-point increase or decrease in score of a questionnaire is difficult to clinically interpret. Aside from that, self-report questionnaires have a lower specificity to identify depression.[S64] Structured clinical interviews remain the gold standard method to establish a diagnosis of major depressive disorder.

However, several strengths should be acknowledged as well. Our systematic review and meta-analysis were based on a comprehensive search including four databases, addressing both directions of the association between depression and HbA_{1c}. Moreover, searches included papers in Dutch, German, Spanish, and French aside from English language papers, increasing the scope of the review. Another strength of this study is the inclusion of longitudinal studies which are of higher empirical evidence than cross-sectional studies and are able to assess the temporality of events. Most studies were of high quality and adjusted for multiple confounding factors. We also solely included studies that used continuous measures of HbA_{1c}, increasing the power to detect a potential association.

Furthermore, despite the dissent in the current literature on how to best pool regression coefficients (e.g. S65–68) and the lack of information on converting effect sizes, we found a solution for pooling regression coefficients.[19,20] The studies included in our meta-analyses adjusted for different sets of independent variables. The use of partial effect sizes allowed us to account for the influence of these variables. However, caution is needed when making inferences about population effect sizes. The size of the individual partial effects might be influenced by the complexity of the models that the effects derive from.[19]

4.4 | Recommendations and future perspectives

The results of our systematic review and meta-analysis support a bidirectional association between depression/depressive symptoms and HbA_{1c}. Further research is needed to investigate whether this offers treatment opportunities, because improvements in HbA_{1c} levels could have a favourable effect on depression outcomes and vice versa. However, more high-quality, large-scale longitudinal studies on the bidirectional association between depression and HbA_{1c} are firstly needed.

Future observational longitudinal studies on the current topic should pay attention to a coherent reporting of effect estimates, as is already advised for reporting in clinical trials,[S69] as well as to deciding on a commonly reported metric. This would enable the pooling of additional studies and avoid the introduction of noise due to the translation of effect estimates. A way in which the quality of future research can also be improved is through adequate adjustment for important confounding factors, especially age,[S70] sex[S71] and antidepressant medication,[S72] which have been suggested to play an important role in this association. Different mechanisms might be in place that influence the association in individuals with type 1 or type 2 diabetes. Ideally, additional studies should be conducted in individuals with type 1 diabetes to allow for comparison between these important subgroups. Furthermore, assessment of type of diabetes treatment and stratified analyses based on insulin-use are recommended. Another subject that requires attention is the long-term effect of high glucose levels on depression. Based on our systematic search, we conclude that there is a need for studies assessing the impact of high HbA_{1c} levels on depression at multiple time points over a longer follow-up period. Aside

from that, mediation analyses based on longitudinal data could provide further inside into the role of diabetes distress, diabetes self-management and health behaviours in the association between depression and HbA_{1c}.

A bidirectional association between depression and HbA_{1c} levels may also have important clinical implications. Routine screening for depressive symptoms by diabetes health care teams is recommended in individuals with all types of diabetes. Special attention needs to be paid to ensure that, if symptom scores indicate the presence of depressive symptoms, affected individuals actually want help in dealing with them[S73,74] and that processes are in place to ensure appropriate management and treatment.[S75] Prior research suggests that clinical vigilance of HbA_{1c} levels, especially shortly after a diagnosis of major depressive disorder, is particularly important to avoid hospital admissions due to hyper- or hypoglycaemic episodes.[S76] Research has also suggested to simultaneously treat depression and suboptimal HbA_{1c} levels.[S75] In their comprehensive overview of interventions for depression and diabetes, Petrak et al. highlight the need to conduct active comparison studies that elucidate the effectiveness of individual intervention components.[S75] Moreover, depression and suboptimal HbA_{1c} levels might share the same antecedents such as physical inactivity or inflammation. Consequently, prevention efforts could aim at targeting these antecedents to concurrently prevent depression and suboptimal HbA_{1c} levels.

5 | CONCLUSION

This meta-analysis suggests that depressive symptoms are associated with an increased risk for the development of higher HbA_{1c} levels over time and that HbA_{1c} levels are associated with an increased risk for the development of (probable) depression over time. These findings support a longitudinal bidirectional association between depressive symptoms and HbA_{1c}. However, the observed effect sizes were small and the number of eligible studies low. Further research in large-scale longitudinal studies is needed to confirm this association. Future studies should investigate the role of type of diabetes and depression, diabetes distress and diabetes self-management behaviours in the bidirectional association between HbA1c and depression over time. Consistent reporting of effect estimates is crucial in this endeavour. In relation to clinical practice, the findings suggest that depression and HbA_{1c} levels should be targeted concurrently by prevention and treatment efforts.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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