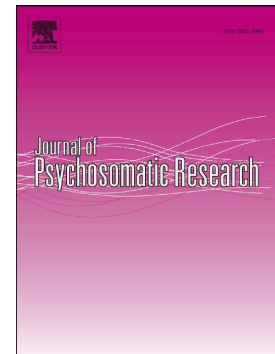


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Depression is linked to hyperglycaemia via suboptimal diabetes self-management: A cross-sectional mediation analysis

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Depression is linked to hyperglycaemia via suboptimal diabetes self-management: A cross-sectional mediation analysis

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Abstract

Objective

To analyse if the association between depressive symptoms and hyperglycaemia is mediated by diabetes self-management.

Methods

430 people with diabetes (57.7% type 1, 42.3% type 2) were cross-sectionally assessed using validated self-report scales for depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D)) and diabetes self-management (Diabetes Self-Management Questionnaire (DSMQ)); HbA_{1c} was analysed simultaneously in a central laboratory. Structural equation modelling was used to test if the association between depressive symptoms and hyperglycaemia (HbA_{1c}) was mediated by suboptimal self-management in people with type 1 and type 2 diabetes.

Results

The hypothesised model of depressive symptoms, diabetes self-management and hyperglycaemia fit the data well for both diabetes types (SRMR \leq 0.04, TLI \geq 0.99, CFI $>$ 0.99, RMSEA \leq 0.02 for both models). In both the type 1 and type 2 diabetes group, higher depressive symptoms were associated with lower self-management ($P < 0.001$), and lower self-management was associated with higher HbA_{1c} ($P < 0.001$). Results indicated that the association between depressive symptoms and hyperglycaemia was significantly mediated by suboptimal diabetes self-management in both type 1 and type 2 diabetes patients ($P < 0.001$). Significant direct associations

between depressive symptoms and hyperglycaemia, not mediated by self-management, could not be observed.

Conclusions

This study provides good evidence supporting that depression is linked to hyperglycaemia via suboptimal diabetes self-management in both major diabetes types.

Keywords

Depressive symptoms; mood disorder; HbA_{1c}; hyperglycaemia; diabetes self-care; mediation

ACCEPTED MANUSCRIPT

Introduction

Depression is a frequent comorbid condition in people with diabetes of both major diabetes types. According to evidence from three epidemiologic meta-analyses, it is likely that about 11 to 12% of all people with diabetes meet the criteria for a major depressive disorder and another 10 to 20% are affected by minor forms of depression [1–3].

Depression is considered to be an adverse condition in people with diabetes because of evidence supporting significantly elevated risks of developing long-term complications of diabetes [4–6] as well as significantly increased cardiovascular and all-cause mortality [7,8]. Furthermore, a meta-analysis by Gonzalez et al. [9] based on 47 studies and over 17,000 subjects showed depression to be associated with significantly reduced diabetes treatment adherence. Certainly, the estimated mean correlations between depression and non-adherence of 0.18 for diet, 0.14 for medication intake, 0.14 for exercise, 0.10 for glucose monitoring and 0.21 for composite measures indicate rather small effects. Nevertheless, they confirm increased risks of poorer self-management behaviours in people with diabetes and comorbid depression.

Depression in diabetes has also been associated with impaired glycaemic control. A meta-analysis by Lustman et al. [10], based on 24 studies and about 2,800 subjects, estimated a mean correlation between depression and hyperglycaemia of 0.17; type-specific values were 0.19 for type 2 and 0.16 for type 1 diabetes. Furthermore, a longitudinal study including over 11,000 people with type 2 diabetes showed that depression predicted consistently worse glycaemic control over a time span of 9 years [11]. These as well as other findings support an association between comorbid depression and hyperglycaemia.

Theoretically, depression, self-management and glycaemic control have been linked in that depression might lead to hyperglycaemia through suboptimal diabetes self-management [12]. This assumption is usually called the behavioural hypothesis of depression-related hyperglycaemia (as opposed to a biological one, focussing on stress-induced endocrine and inflammatory reactions). However, few studies have actually sought to test the hypothesis (which requires employing a mediational approach), and, even more importantly, those few ones which did yielded only little insight into the mechanisms mediating depression into hyperglycaemia [13–17].

Lustman et al. [13] assessed 188 people with type 1 diabetes for depression using the Symptom Checklist-90 and for diabetes self-management using the Summary of Diabetes Self-Care Activities Measure; HbA_{1c} was estimated simultaneously. Their cross-sectional study demonstrated depressive symptoms to be significantly correlated with both lower self-management ($r = -0.26$, $P < 0.001$) and higher HbA_{1c} ($r = 0.23$, $P < 0.01$). However, evidence supporting that the association between depression and HbA_{1c} was indeed mediated by impaired self-management was not found. Instead, the authors concluded that ‘other pathways [besides behaviour] should be investigated’.

Egede et al. [14] analysed the putative mediation using structural equation modelling and cross-sectional data from 126 people with type 2 diabetes. Depressive symptoms were assessed using the Patient Health Questionnaire-9, diabetes self-management behaviours using the Summary of Diabetes Self-Care Activities Measure and HbA_{1c} values were gained from contemporary medical records. The results confirmed a negative association between depressive symptoms and diabetes self-management ($\beta = -0.28$, $P = 0.004$). However, a significant association between diabetes self-management and HbA_{1c} was not observed. Correspondingly, a mediating role for self-management could not be supported.

A study by Dirmaier et al. [15] analysed the associations between depression, self-management and HbA_{1c} in a prospective design with measurement time points at baseline and 12-month follow up. A population-based sample of 866 people with type 2 diabetes was assessed using the Depression Screening Questionnaire; adherence to medication and diabetes-related health behaviours (diet, physical activity and smoking) were measured using Likert type questions; HbA_{1c} values were reported by the treating physicians. The study once more supported significant associations between depression and both suboptimal self-management and impaired glycaemic control. However, neither cross-sectional nor prospective analyses supported the supposed mediating role for self-management.

Chiu et al. [16] analysed associations between depressive symptoms, health behaviours and HbA_{1c} using a structural equation modelling approach and prospective data from 998 patients with type 2 diabetes. At baseline, depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale. At 2-year follow up, a composite measure of health behaviours was established (based on questions regarding physical exercise and smoking status as well as patients' BMI, which was used to rate their weight control behaviour). At 5-year follow up, HbA_{1c} was self-reported. The study was able to demonstrate a small but significant association between depressive symptoms at baseline and poorer health behaviour at 2-year follow up ($\beta = -0.09$, $P < 0.001$). Poorer health behaviour at 2-year follow up in turn predicted higher HbA_{1c} at 5-year follow up ($\beta = -0.17$, $P < 0.001$). However, the mediated effect of depressive symptoms on HbA_{1c} came to no more than $\beta = 0.015$, explaining roughly 0.02% of glycaemic variation.

Finally, McGrady et al. [17] analysed the putative mediation using cross-sectional data from 276 adolescents with type 1 diabetes. Variables were depressive symptoms (Children's Depression Inventory), glucose monitoring frequency (gained

from meters or by self-report) and HbA_{1c} (estimated in one laboratory). The study found depressive symptoms significantly associated with a lower monitoring frequency ($P = 0.02$) and marginally significantly associated with higher HbA_{1c} ($P = 0.05$). When depressive symptoms and monitoring frequency were included into a single regression model of HbA_{1c}, only monitoring was a significant statistical predictor ($P < 0.001$) while depressive symptoms was not ($P = 0.19$). A Sobel test supported the mediating role for glucose monitoring with $P = 0.05$.

Although this last study provides some interesting results, there are several limitations: First, since standardised coefficients were not provided, the size of the effect is unclear. Second, since only a single behaviour rather than overall diabetes self-management was analysed, the inferability for self-management is limited. Third, since separate regression analyses were used without Bonferroni correction, the risk of type I error is increased. The last point is particularly important since the mediation only bordered on significance.

To sum up the present evidence, not a single study has provided satisfactory evidence for the behavioural hypothesis of depression-related hyperglycaemia, and there is currently little evidence supporting that the association between depression and poor glycaemic control is mediated by impaired diabetes self-management.

For this reason, we conducted the present study using data from a convenience sample of people with type 1 and type 2 diabetes. We aimed to analyse the direct and indirect (i. e. mediated) associations between depressive symptoms and glycaemic control using structural equation modelling (which has the advantage of testing the significance of all associations within one model; hence, type I error probability does not increase). To account for differences between the two diabetes types, the analyses were conducted separately for these groups. We hypothesised to find 1) significant negative associations between depressive symptoms and diabetes

self-management, II) significant negative associations between self-management and HbA_{1c} (meaning that better self-management is associated with better glycaemic control) and III) significant mediation effects between depressive symptoms and HbA_{1c} via self-management.

Materials and methods

Data acquisition was performed as part of a larger study focussing affective symptoms in diabetes (identifier NCT01812291), approved by the Ethics Committee of the State Medical Chamber of Baden-Wuerttemberg. All data were collected from patients at a German in-patient diabetes centre (Diabetes Center Mergentheim), yielding a convenience sample of people with type 1 and type 2 diabetes. Inclusion criteria were: diabetes mellitus type 1 or 2 (diagnosis confirmed at the centre); age \geq 18 years; sufficient German language skills; written informed consent. 58% of the sample were enrolled into a clinical trial, for which elevated affective symptoms (CES-D score \geq 16 and/or PAID score \geq 40) were an additional inclusion criterion. Exclusion criteria were: terminal illness; being bedbound; being under guardianship. Eligible persons were approached at the centre and informed about the study. Those who consented to participate (62%) were assessed using validated self-report scales for depression (Center for Epidemiologic Studies Depression Scale) and diabetes self-management (Diabetes Self-Management Questionnaire), and provided venous blood for HbA_{1c} analysis in a central laboratory. Demographic data were collected by nurses. Long-term complications were diagnosed by the centre's physicians. The study was carried out in accordance with the Declaration of Helsinki. All participants were informed about the study procedures and aims and provided written informed consent prior to enrolment.

Variables and measures

Depressive symptoms

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [18]. The CES-D assesses the frequencies of 20 common symptoms of depression during the previous week. Responses are given on a four-point Likert scale ranging from 0 – ‘rarely or never’ to 3 – ‘most of the time’. Total scores range between 0 and 60, with higher values indicating more depressive symptoms. The CES-D has very good reliability and validity in assessing depression [18,19], which was also confirmed for people with diabetes [20]. In the present study, Cronbach’s α amounted to 0.88., indicating adequate reliability.

Diabetes self-management

Diabetes self-management was assessed using the Diabetes Self-Management Questionnaire (DSMQ) [21]. The scale consists of 16 items assessing behaviours related to the self-management of the condition. Respondents rate the extent to which each item applies to them on a four-point Likert scale (3 – ‘applies to me very much’ to 0 – ‘does not apply to me’), referring to the previous eight weeks. Item scores are summed and transformed to five scale scores with ranges from 0 to 10 and higher scores indicating better behaviour. The scales reflect people with diabetes’s ‘dietary control’ (3 items), ‘medication adherence’ (2 items), ‘blood glucose monitoring’ (3 items), ‘physical activity’ (3 items) and ‘physician contact’ (3 items). The DSMQ has good reliability and validity [21–23]. In the present study, Cronbach’s coefficients α were 0.79, 0.75, 0.83, 0.74 and 0.72 (scales in above order).

Glycaemic control

To estimate glycaemic control, glycated haemoglobin (HbA_{1c}) was assessed. All blood samples were analysed in one central laboratory at the same time as the psychometric assessments were conducted. HbA_{1c} values were determined using high performance liquid chromatography, performed with the Bio-Rad Variant II Turbo analyser (meeting the current standards of HbA_{1c} measurement; DCCT standard). The laboratory normal range is 4.3 – 6.1% (24 – 43 mmol/mol).

Statistical Analyses

The statistical analyses were performed using SPSS 22.0.0 including AMOS 22.0.0 (IBM SPSS Statistics, New York, USA). Structural equation modelling was performed using maximum likelihood estimation. The hypothesised model was based on previous works in the field [14,16,22,24] and included the variables depressive symptoms, diabetes self-management and HbA_{1c} (see Figure 1). To enable the analysis of diabetes self-management as a composite measure, it was modelled as latent variable operationalised by the DSMQ's five behaviour scales. This type of modelling was effectively employed in previous studies [14,22,24], and a recent study showed that self-management as assessed by the DSMQ can be modelled with good fit to the data using this approach [22].

The hypothesised model was then tested separately on the subsamples with type 1 and type 2 diabetes (to account for the differences between these conditions, e.g. different relevancies of specific behaviours such as diet or exercise). Following relevant modification indices (threshold = 4.0), we successively modelled significant correlations between the variables' error terms. Model fit was evaluated based on the criteria suggested by Hu and Bentler [25]: Standardised Root Mean Square Residual (SRMR) \leq 0.08, Tucker Lewis Index (TLI) \geq 0.95, Comparative Fit Index (CFI) \geq 0.95

and Root Mean Square Error of Approximation (RMSEA) ≤ 0.06 (90% CI upper bound ≤ 0.08).

Associations between the independent and dependent model variables were assessed in the form of standardised regression coefficients (β). Levels of explained variation (i. e. statistical variance) in the dependent variables were estimated as squared multiple correlations (R^2). Effect size appraisal for these outcomes can be made according to the established standards by Cohen [26].

The size of the hypothesised mediation effect was evaluated based on the appraisal criteria by Kenny [27], considering an indirect effect of $\beta = 0.01$ as small, $\beta = 0.09$ as medium and $\beta = 0.25$ as large (these values represent squared correlations of small, medium and large size according to the Cohen standards [26], referring to the fact that an indirect effect is the product of two single effects, which decreases its size). To test the hypothesised mediation effect for statistical significance using AMOS, boot strapping was applied using 5000 bootstrap samples.

To account for potential confounding by socio-demographic variables, the tested models were fully adjusted for gender, age, BMI and education by modelling associations between these covariates and the three main variables, depressive symptoms, diabetes self-management and HbA_{1c}.

Since testing the hypothesised associations for both major types of diabetes separately required the use of two distinct model tests, leading to increased risk of a type I error, the p value was adjusted using the Bonferroni method as follows: $P = 0.05 / 2 = 0.025$. Accordingly, a P value < 0.025 was used as criterion of statistical significance.

Data exploration revealed non-normal distributions of three of the DSMQ scales (medication adherence, blood glucose monitoring and physician contact) as well as the CES-D. To warrant adequate normality, these variables were converted using

Templeton's two-step transformation, involving percentile ranking (first step; resulting in uniformly distributed probabilities) followed by applying the inverse-normal transformation (second step; yielding normally distributed z-scores) [28].

Results

Characteristics of the study sample

The sample comprised 430 people with diabetes; 248 were diagnosed with type 1 diabetes (58%) and 182 with type 2 diabetes (42%). The sample characteristics are displayed in Table 1.

People with type 1 diabetes were on average 39 years old and had a mean BMI of 27 kg/m². With a prevalence of 60%, females were slightly overrepresented. The average diabetes duration amounted to approximately 17 years. Glycaemic control was clearly improvable as 71% of the patients had HbA_{1c} values above 7.5% (60 mmol/mol), the standard for acceptable control of the German Diabetes Association. 31% of the patients were diagnosed with one or more long-term complications.

People with type 2 diabetes had a mean age of 57 years and a mean BMI of 34 kg/m². With a rate of 46% of the sample being female, the gender distribution was relatively balanced. The majority (80%) was treated with insulin, corresponding to the rather long diabetes duration of 14 years. Glycaemic control was comparable to that of the type 1 diabetes group; approximately 73% had HbA_{1c} values above 7.5% (60 mmol/mol). Long-term complications were present in 62% of the patients.

Study participants were generally comparable to typical clinic population, as there were no significant differences regarding gender, age, diabetes types, illness duration, glycaemic control and long-term complications. However, since part of the

sample was selected for elevated affective symptoms specifically, the sample's mean CES-D score was significantly higher (22 ± 11 vs. 17 ± 12).

- Table 1 here -

Structural equation model of depression-related hyperglycaemia for people with type 1 diabetes

The structural equation model for people with type 1 diabetes is displayed in Figure 1. The model showed very good fit to the data, as indicated by the following fit indices: SRMR = 0.04; TLI = 0.99; CFI > 0.99; RMSEA = 0.02 (90% CI < 0.001 – 0.06). The variable diabetes self-management was significantly operationalised by the assessed self-management behaviours (all path coefficients $P < 0.001$). Based on the related path coefficients (i. e. standardized regression coefficients), the most relevant behaviours were medication adherence, blood glucose monitoring and dietary control (see Figure 1).

Higher depressive symptoms were significantly related to lower diabetes self-management, explaining 6.3% of self-management variation, and lower diabetes self-management was significantly related to hyperglycaemia (i. e. higher HbA_{1c}), explaining 28% of variation in HbA_{1c} (both $P < 0.001$). The bootstrapping test confirmed a significant indirect association between depressive symptoms and hyperglycaemia mediated by lower diabetes self-management ($P < 0.001$). The size of this indirect association amounted to $\beta = 0.13$ – medium to large according to Kenny [27] – indicating that an increase of depressive symptoms by 1 standard deviation (approx. 10 points on the CES-D) was associated with an increase of HbA_{1c} by 0.13 of a standard deviation (i. e. 0.21 % points or 2.3 mmol/mol). While controlling for this indirect link between depressive symptoms and HbA_{1c} in the

model, a significant concomitant direct association between depressive symptoms and HbA_{1c} could not be observed ($P = 0.13$).

- Figure 1 here -

Structural equation model of depression-related hyperglycaemia for people with type 2 diabetes

The model for type 2 diabetes is displayed in Figure 2. The results were generally comparable to those for the type 1 diabetes group: The model fit the data quite well (SRMR = 0.03; TLI > 0.99; CFI > 0.99; RMSEA < 0.001 [90% CI < 0.001 – 0.03]); diabetes self-management was significantly operationalised by all assessed behaviours (all path coefficients $P < 0.001$); and the hypothesised associations between depressive symptoms, self-management and HbA_{1c} were supported. Again, higher depressive symptoms were significantly related to lower diabetes self-management, explaining 16.6% of variation in self-management, and lower self-management was significantly related to hyperglycaemia, explaining 28.1% of variation in HbA_{1c} (both $P < 0.001$).

As hypothesised, higher depressive symptoms were indirectly linked to hyperglycaemia (i. e. higher HbA_{1c}) via lower diabetes self-management, and the bootstrapping test confirmed this association as significant ($P < 0.001$). The revealed indirect effect of $\beta = 0.22$ – large according to Kenny [27] – indicated that an increase of depressive symptoms by 1 standard deviation (approx. 10 CES-D points) was associated with an increase of HbA_{1c} by 0.22 standard deviations (i. e. 0.36 % points or 3.9 mmol/mol). Again, while controlling for the indirect path, a significant direct association between depressive symptoms and HbA_{1c} could not be observed ($P = 0.24$).

Notably, the type 2 diabetes model suggested a higher association between depressive symptoms and diabetes self-management compared to type 1 diabetes. However, testing this potential difference using multi-group analysis suggested no significant difference across groups ($P = 0.32$).

- Figure 2 here -

Discussion

This study provides evidence supporting that depression relates to hyperglycaemia based on an indirect relationship via suboptimal diabetes self-management. While the small number of previous studies which addressed this aspect found either no [13–15] or very little [16,17] support for a behavioural mediation between depression and poor glycaemic control, the results of our study are clearly in favour of the behavioural hypothesis of depression-related hyperglycaemia. In fact, the indirect associations observed here had moderate to large sizes, and could thus be uncovered with high significance using samples of relatively limited size.

The lack of supportive evidence from previous studies is striking and needs to be discussed. We suppose that a reason for this might be suspected in the operationalisation of the variable self-management and potential limitations of the used measurement instruments. Lustman et al. as well as Egede et al. [13,14] utilised the Summary of Diabetes Self-Care Activities Measure, which was found to explain relatively little variation in glycaemic outcomes in several studies [21,22,29]. The analyses by Dirmaier et al. and Chiu et al. [15,16] were both based on self-management aspects assessed using single questions which had not been rigorously

psychometrically tested. Furthermore, the behaviours analysed in these studies included smoking, alcohol consumption and physical activity which may not be regarded to directly affect blood glucose. In comparison, our study used the DSMQ, a validated psychometric tool which was supported as significant statistical predictor of glycaemic control, thus being more suitable for mediation analysis.

In this study, we analysed depression as a metric variable (i. e. depressive symptoms) rather than diagnostic category. Therefore, the generalisation of our findings to a clinical disorder such as major depression might be seen problematic. However, it has been argued by others that levels of depressive symptoms could be of greater relevance for predicting diabetes outcomes than a criteria-based diagnosis [e.g. 16,30], and a number of studies support this hypothesis regarding both outcomes, self-management behaviour [31] and glycaemic control [32–34]. Therefore, the measurement approach chosen here appears not only valid but may also improve our understanding of associations between depression and suboptimal diabetes outcomes across the range of depressive symptomatology.

Interestingly, we observed a difference between the type 1 and type 2 diabetes groups: The association between depressive symptoms and diabetes self-management was somewhat larger for type 2 diabetes, accordingly leading to a larger mediated association between depressive symptoms and glycaemic control. This finding corresponds to the meta-analytic results by Lustman et al. [10], which also observed a smaller association between depression and hyperglycaemia in the type 1 diabetes group. However, comparing the associations between depressive symptoms and self-management across diabetes groups yielded no significant effect, thus a systematic difference is not supported.

Besides self-management behaviour, other potential mechanisms to mediate depression-related hyperglycaemia have been discussed. Particularly stress-induced

endocrine or inflammatory responses to depressive symptoms may constitute a pathway [35], which is supported by findings confirming that comorbid depression in diabetes is associated with increased inflammation [36] and in turn with poorer glycaemic control [37]. However, the results presented here do not support this pathway because the direct associations between depressive symptoms and HbA_{1c}, not mediated by behaviour, were non-significant. On the other hand, neither biological markers of stress nor psychological stress were assessed in our study which limits our claims regarding a direct HPA axis link between stress and glycaemic control. Thus, our findings may be best considered as evidence supporting the behavioural hypothesis rather than evidence against other putative mechanisms.

Importantly, recent studies focussing on the relationship between depression and glycaemic control found evidence supporting that depression may not generally predict hyperglycaemia, but there may be attenuating factors. An aspect of potential importance appears to be diabetes-specific distress, as several studies found depression associated with hyperglycaemia particularly when diabetes distress was present concomitantly [38–40]. These issues require further investigation. Nevertheless, the present findings support that the association between depression and hyperglycaemia – whether attenuated by diabetes distress or not – is mediated by self-management.

Our results have to be qualified by several limitations of the study: Firstly, the data were cross-sectional; hence, the study does not warrant causal inferences. Although the findings are in line with the assumption of a causal effect of depression leading to impaired diabetes self-management and in turn to hyperglycaemia, prospective studies are needed to support causality. Secondly, the sample consisted of patients with diabetes enrolled into the study during the stay at an in-patient diabetes care centre. People are usually referred there for problems regarding

diabetes treatment and control. Additionally, affective symptoms were overrepresented. Thus, the sample may not be representative for the primary care patient group. Thirdly, the hypothesised mediation was tested for patients with type 1 and type 2 diabetes separately, leading to reduced sample sizes. Future studies should try to replicate our findings on the basis of larger and more representative samples. Finally, the performed modelling permitted significant correlations between error terms which is regarded as a statistical sleight of hand by some. On the other hand, it has been argued that failure to include such correlations may generate misleading results [41]. However, since only few correlations between residuals were actually observed, it appears unlikely that this aspect may have biased the results.

The strengths of our study lie in a) the standardised methods (in-patient setting; validated psychometric scales; HbA_{1c} analysis in central laboratory; blood sampling at the same time as the psychometric assessment; standardised multiple variable modelling analysis), warranting high internal validity, and b) the testing of the hypotheses on distinct samples of people with type 1 and type 2 diabetes, enabling generalisation to both major diabetes types. Furthermore, the revealed mediation effects were large enough to reach high significance within study samples of rather limited size, which supports the validity of the mediation. Finally, our adjusting for potential confounders such as gender, age and education supports the validity of our drawn conclusions.

In sum, our findings support that depression in people with diabetes can be associated with hyperglycaemia due to suboptimal diabetes self-management. Following this evidence, it is reasonable to assume that the successful treatment of comorbid depression may facilitate the provision of optimal diabetes care to this high-risk patient group (and support of self-care) [4–10], and the established risks of

subsequent long-term morbidity based on comorbid depression in diabetes [4–6] might be effectively reduced.

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A. S. collected the data, researched the data and wrote the manuscript. A. R. collected the data, contributed to the discussion and reviewed the manuscript. N. H., B. K., D. E., M. K., J. H. and T. H. contributed to the discussion and reviewed the manuscript.

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References

- [1] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001; 24: 1069-1078. DOI: 10.2337/diacare.24.6.1069
- [2] Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with Type 1 diabetes: systematic literature review. *Diabet Med* 2006; 23: 445-448. DOI: 10.1111/j.1464-5491.2006.01814.x
- [3] Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med* 2006; 23: 1165-1173. DOI: 10.1111/j.1464-5491.2006.01943.x
- [4] Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, Ludman EJ, Young BA, Williams LH, McCulloch DK, Von Korff M. Depression and advanced complications of diabetes: a prospective cohort study. *Diabetes Care* 2010; 33: 264-269. DOI: 10.2337/dc09-1068
- [5] Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care* 2003; 26: 2822-2828. DOI: 10.2337/diacare.26.10.2822
- [6] Clouse RE, Lustman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. *Psychosom Med* 2003; 65: 376-383.
- [7] Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. *Gen Hosp Psychiatry* 2013; 35: 217-225. DOI: 10.1016/j.genhosppsy.2013.01.006
- [8] Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. *PLoS One* 2013; 8: e79809. DOI: 10.1371/journal.pone.0079809

- [9] Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, Safren SA. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care* 2008; 31: 2398-2403. DOI: 10.2337/dc08-1341
- [10] Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; 23: 934-942. DOI: 10.2337/diacare.23.7.934
- [11] Richardson LK, Egede LE, Mueller M, Echols CL, Gebregziabher M. Longitudinal effects of depression on glycemic control in veterans with Type 2 diabetes. *Gen Hosp Psychiatry* 2008; 30: 509-514. DOI: 10.1016/j.genhosppsych.2008.07.001
- [12] Egede LE. Effect of depression on self-management behaviors and health outcomes in adults with type 2 diabetes. *Curr Diabetes Rev* 2005; 1: 235-243. DOI: 10.2174/157339905774574356
- [13] Lustman PJ, Clouse RE, Ciechanowski PS, Hirsch IB, Freedland KE. Depression-related hyperglycemia in type 1 diabetes: a mediational approach. *Psychosom Med* 2005; 67: 195-199.
- [14] Egede LE, Osborn CY. Role of motivation in the relationship between depression, self-care, and glycemic control in adults with type 2 diabetes. *Diabetes Educ* 2010; 36: 276-283. DOI: 10.1177/0145721710361389
- [15] Dirmaier J, Watzke B, Koch U, Schulz H, Lehnert H, Pieper L, Wittchen HU. Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control. *Psychother Psychosom* 2010; 79: 172-178. DOI: 10.1159/000296135
- [16] Chiu CJ, Wray LA, Beverly EA, Dominic OG. The role of health behaviors in mediating the relationship between depressive symptoms and glycemic control in type 2 diabetes: a structural equation modeling approach. *Soc Psychiatry Psychiatr Epidemiol* 2010; 45: 67-76. DOI: 10.1007/s00127-009-0043-3

- [17] McGrady ME, Laffel L, Drotar D, Repaske D, Hood KK. Depressive symptoms and glycemic control in adolescents with type 1 diabetes: mediational role of blood glucose monitoring. *Diabetes Care* 2009; 32: 804-806. DOI: 10.2337/dc08-2111
- [18] Hautzinger M, Bailer M, Hofmeister D, Keller F. ADS: Allgemeine Depressionsskala (2., überarbeitete und neu normierte Auflage) [ADS: General depression inventory (2nd revised, newly standardised edition)] (in German). Hogrefe, Göttingen, 2012.
- [19] Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* 1997; 12: 277-287. DOI: 10.1037/0882-7974.12.2.277
- [20] Schmitt A, Hermanns N, Kulzer B, Gahr A, Haak T. Depressionsscreening mit der Allgemeinen Depressionsskala (ADS) bei Diabetespatienten im stationären Setting [Depression screening among patients with diabetes in an in-patient setting using the Center for Epidemiologic Studies Depression Scale] [abstract in German]. *Diabetologie & Stoffwechsel* 2013; 8 (Suppl 1): 77. DOI: 10.1055/s-0033-1341892
- [21] Schmitt A, Gahr A, Hermanns N, Kulzer B, Huber J, Haak T. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. *Health Qual Life Outcomes* 2013; 11: 138. DOI: 10.1186/1477-7525-11-138
- [22] Schmitt A, Reimer A, Hermanns N, Huber J, Ehrmann D, Schall S, Kulzer B. Assessing diabetes self-management with the Diabetes Self-Management Questionnaire (DSMQ) can help analyse behavioural problems related to reduced glycaemic control. *PLoS ONE* 2016; 11: e0150774. DOI: 10.1371/journal.pone.0150774

- [23] Schmitt A, Hermanns N, Kulzer B, Reimer A, Schall S, Haak T. The Diabetes Self-Management Questionnaire (DSMQ) can detect inadequate self-care behaviour and help identify patients at risk of a negative diabetes prognosis [abstract]. In: Proceedings of the 50th EASD Annual Meeting; 2014 Sep 15–19; Vienna, Austria. Düsseldorf, 2014: EASD. Abstract #1041.
- [24] Osborn CY, Bains SS, Egede LE. Health literacy, diabetes self-care, and glycemic control in adults with type 2 diabetes. *Diabetes Technol Ther* 2010; 12: 913-919. DOI: 10.1089/dia.2010.0058
- [25] Hu L, Bentler PM. Fit indices in covariance structure modeling: Sensitivity to underparameterized model misspecification. *Psychol Methods* 1998;3:424-53.
- [26] Cohen J. A power primer. *Psychol Bull* 1992; 112: 155-159. DOI: 10.1037/0033-2909.112.1.155
- [27] Kenny D. Mediation. <http://davidakenny.net/cm/mediate.htm>, 2016 (accessed 01.08.2016).
- [28] Templeton GF. A Two-Step Approach for Transforming Continuous Variables to Normal: Implications and Recommendations for IS Research. *CAIS* 2011; 28: 4. Available from <http://aisel.aisnet.org/cais/vol28/iss1/4/>
- [29] Toobert DJ, Glasgow RE. Assessing diabetes self-management: the summary of diabetes self-care activities questionnaire. In: Bradley C, editor. *Handbook of Psychology and Diabetes: a guide to psychological measurement in diabetes research and practice*. Switzerland: Harwood Academic; 1994; 351-375.
- [30] Fisher L, Skaff MM, Mullan JT, Arean P, Mohr D, Masharani U, Glasgow R, Laurencin G. Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. *Diabetes Care* 2007; 30: 542-548. DOI: 10.2337/dc06-1614

- [31] Gonzalez JS, Safren SA, Cagliero E, Wexler DJ, Delahanty L, Wittenberg E, Blais MA, Meigs JB, Grant RW. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care* 2007; 30: 2222-2227. DOI: 10.2337/dc07-0158
- [32] Aikens JE, Perkins DW, Lipton B, Piette JD. Longitudinal analysis of depressive symptoms and glycemic control in type 2 diabetes. *Diabetes Care* 2009; 32: 1177-1181. DOI: 10.2337/dc09-0071
- [33] Fisher L, Mullan JT, Arean P, Glasgow RE, Hessler D, Masharani U. Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. *Diabetes Care* 2010; 33: 23-28. DOI: 10.2337/dc09-1238
- [34] Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. *Diabetes Care* 2010; 33: 1034-1036. DOI: 10.2337/dc09-2175
- [35] Stuart MJ, Baune BT. Depression and type 2 diabetes: inflammatory mechanisms of a psychoneuroendocrine co-morbidity. *Neurosci Biobehav Rev* 2012; 36: 658-676. DOI: 10.1016/j.neubiorev.2011.10.001
- [36] Laake JP, Stahl D, Amiel SA, Petrak F, Sherwood RA, Pickup JC, Ismail K. The association between depressive symptoms and systemic inflammation in people with type 2 diabetes: findings from the South London Diabetes Study. *Diabetes Care* 2014; 37: 2186-2192. DOI: 10.2337/dc13-2522
- [37] Gohel MG, Chacko AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: An evidence linking oxidative stress, inflammation and glycemic control. *J Diabetes Metab Disord* 2013; 12: 56. DOI: 10.1186/2251-6581-12-56

- [38] van Bastelaar KM, Pouwer F, Geelhoed-Duijvestijn PH, Tack CJ, Bazelmans E, Beekman AT, Heine RJ, Snoek FJ. Diabetes-specific emotional distress mediates the association between depressive symptoms and glycaemic control in Type 1 and Type 2 diabetes. *Diabet Med* 2010; 27: 798-803. DOI: 10.1111/j.1464-5491.2010.03025.x
- [39] Schmitt A, Reimer A, Kulzer B, Haak T, Gahr A, Hermanns N. Negative association between depression and diabetes control only when accompanied by diabetes-specific distress. *J Behav Med* 2015; 38: 556-564. DOI: 10.1007/s10865-014-9604-3
- [40] Pibernik-Okanovic M, Grgurevic M, Begic D, Szabo S, Metelko Z. Interaction of depressive symptoms and diabetes-related distress with glycaemic control in Type 2 diabetic patients. *Diabet Med* 2008; 25: 1252-1254. DOI: 10.1111/j.1464-5491.2008.02553.x
- [41] Cole DA, Ciesla JA, Steiger JH. The Insidious Effects of Failing to Include Design-Driven Correlated Residuals in Latent-Variable Covariance Structure Analysis. *Psychol Methods* 2007; 12: 381-398. DOI: 10.1037/1082-989X.12.4.381

Table 1. Characteristics of the study samples

	Type 1 DM	Type 2 DM	<i>P</i>
	<i>n</i> = 248	<i>n</i> = 182	value*
	(57.7%)	(42.3%)	
<i>Demographic variables</i>			
Female gender	149 (60.1%)	84 (46.2%)	0.004
Age (years)	39.0 ± 13.2	57.0 ± 8.9	< 0.001
BMI (kg/m ²)	26.9 ± 11.0	34.1 ± 6.6	< 0.001
<i>Diabetes-related variables</i>			
Diabetes duration (years)	16.6 ± 12.1	13.5 ± 7.5	0.001
Diabetes treatment:			
Insulin treatment	248 (100%)	146 (80.2%)	< 0.001
Other medical treatment [†]	0 (0%)	36 (19.8%)	< 0.001
HbA _{1c}			
Value in %	8.5 ± 1.6	8.6 ± 1.5	0.71
Value in mmol/mol	70 ± 18	70 ± 17	0.71
Patients with values > 7.5% (60 mmol/mol)	176 (71.0%)	132 (72.5%)	0.72
Long-term complications:			
Retinopathy	57 (23.0%)	43 (23.6%)	0.88
Neuropathy	36 (14.5%)	87 (47.8%)	< 0.001
Nephropathy	11 (4.4%)	33 (18.1%)	< 0.001
Foot ulcer	5 (2.0%)	18 (9.9%)	< 0.001
CES-D score	22 ± 11	22 ± 10	0.74

Data are n (%) or $M \pm SD$.

BMI, Body Mass Index; HbA_{1c}, glycated haemoglobin; CES-D, Center for Epidemiologic Studies Depression Scale; M, mean; SD, standard deviation.

* testing differences between patients with type 1 versus type 2 diabetes using Student's t -Test for scaled variables or Pearson's χ^2 -Test for frequencies.

† oral antidiabetic agents and/or incretin mimetics

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Figure legends**Figure 1. Structural equation model of depressive mood, diabetes self-management and glycaemic control for people with type 1 diabetes (N = 248)**

Data are standardised regression coefficients (β) for paths or squared multiple correlations (R^2) for variables, adjusted for gender, age, BMI and education.

Boxes indicate manifest measurement variables; ovals indicate latent variables operationalised by manifest indicators; error terms are not displayed for ease of presentation.

SRMR, Standardised Root Mean Square Residual; TLI, Tucker Lewis Index; CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation.

Indication of two-sided significance: * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$; ^{ns} not significant.

Figure 2. Structural equation model of depressive mood, diabetes self-management and glycaemic control for people with type 2 diabetes (N = 182)

Data are standardised regression coefficients (β) for paths or squared multiple correlations (R^2) for variables, adjusted for gender, age, BMI and education.

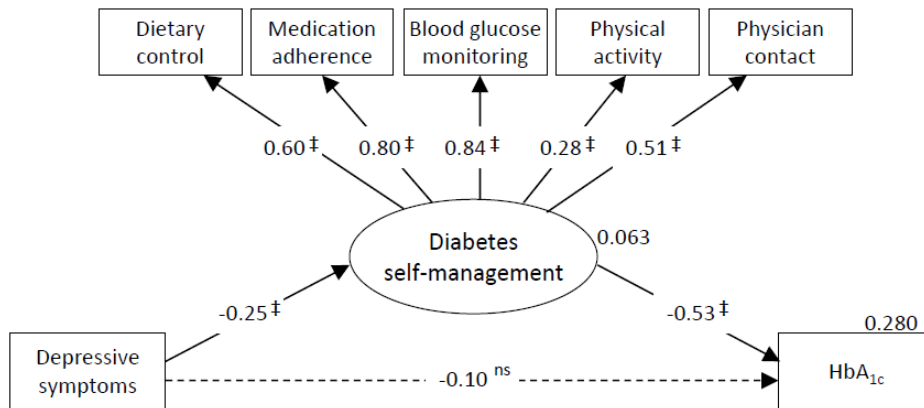
Boxes indicate manifest measurement variables; ovals indicate latent variables operationalised by manifest indicators; error terms are not displayed for ease of presentation.

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Indication of two-sided significance: * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$; ^{ns} not significant.

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Figure 1

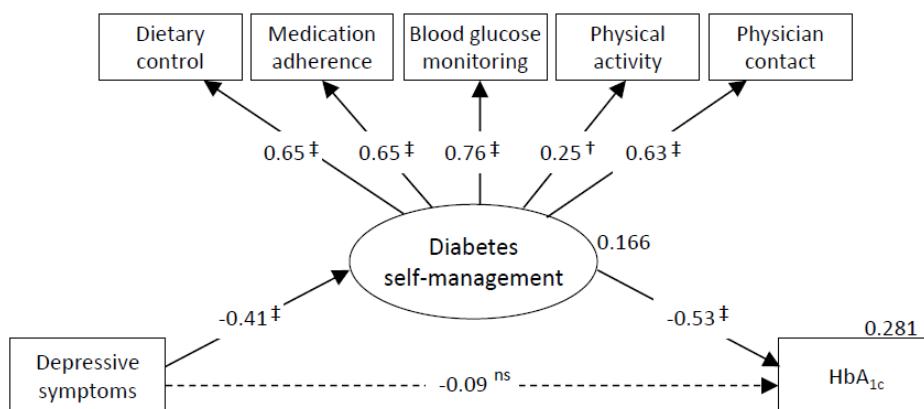


Model fit indices: SRMR = 0.04, TLI = 0.99, CFI > 0.99, RMSEA = 0.02 (90% CI < 0.001 – 0.06)

Indirect effect of depressive mood on HbA_{1c} via self-management: $\beta = 0.13$ (95% CI 0.05 – 0.21), $P < 0.001$

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Figure 2



Model fit: SRMR = 0.03, TLI > 0.99, CFI > 0.99, RMSEA < 0.01 (90% CI < 0.001 – 0.03)

Indirect effect of depressive mood on HbA_{1c} via self-management: $\beta = 0.22$ (95% CI 0.12 – 0.35), $P < 0.001$

Highlights:

- The study supports a behavioural mediation between depression and hyperglycaemia
- The mediation was observed in both type 1 and type 2 diabetes
- Depression explained up to 17% of the variation of diabetes self-management
- Diabetes self-management explained up to 28% of the variation of HbA_{1c}
- Behavioural mediation effects were of moderate to large size.

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