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ORIGINAL ARTICLE

The affective and somatic side of depression: subtypes of depressive symptoms show diametrically opposed associations with glycemic control in people with type 1 diabetes

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Abstract
Aims While depression has been linked to serious adverse outcomes in diabetes, associations with glycemic control are not conclusive. Inconsistencies could be due to the complex symptomatology of depression. Aim of this study was to analyze the associations of depressive subtypes with glycemic control in people with type 1 and type 2 diabetes.
Methods Patients completed the Center for Epidemiological Studies-Depression scale which comprises affective, somatic, and anhedonic symptoms. These subtypes were analyzed in a joint linear regression analysis with glycemic control as a dependent variable. Subtype scores were calculated as mean item scores. Separate analyses for people with type 1 and type 2 diabetes were conducted. All analyses were controlled for demographic and medical confounders.
Results The sample comprised 604 patients with type 1 and 382 patients with type 2 diabetes. In people with type 1 diabetes, the somatic and affective subtype showed diametrically opposed associations with glycemic control (somatic: $\beta = +0.23$, $p < .05$; affective: $\beta = -0.23$, $p < .05$). Anhedonia was not significantly associated with glycemic control. In people with type 2 diabetes, none of the depressive subtypes was significantly associated with glycemic control.
Conclusions For people with type 1 diabetes, the distinction of subtypes offered a detailed picture of the associations of depressive symptoms with glycemic control. However, due to the cross-sectional design, inferences about the direction of these associations cannot be made. In clinical practice, instead of focusing on overall depression, healthcare providers should examine the nature of depressive symptoms and how they might be related to having diabetes.

Keywords Depressive symptoms · Glycemic control · Subtypes · Psychosocial aspects

Background and introduction

Depression is of special interest in people with diabetes because its prevalence is nearly doubled compared to people without diabetes [1, 2] and because depression is a well-established vulnerability factor in people with diabetes [3]. The detrimental effects of not only depression but also elevated depressive symptoms in people with diabetes can be seen in a reduced quality of life [4], poorer self-care behavior [5], an increased risk for micro- and macrovascular complications [6], and early mortality [7].

In contrast, the associations of depression with glycemic control are not as conclusive. In a meta-analysis by Lustman et al. [8], depression was found to be associated with worse glycemic control. However, effect sizes of the analyzed studies ranged from 0.04 to 0.46, indicating a rather heterogeneous association. In addition, several studies could not find a significant association at all [9–11] or

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found that blood glucose monitoring [12] and diabetes-related distress [10, 13, 14] were significant mediators of the association between depression and glycemic control. Also, intervention studies aiming to reduce depression or depressive symptoms in people with diabetes failed to consistently demonstrate a corresponding reduction in HbA1c levels [15–19]. Moreover, a recent systematic review by Baumeister et al. [15] showed moderate effects of anti-depressants on glycemic control, especially selective serotonin reuptake inhibitors, but found no clear effect of psychotherapy on glycemic control. These inconsistencies in epidemiological and interventional studies may contradict the assumption of a general, direct link between depression and glycemic control.

A potential explanation for the inconclusive findings regarding the association of depression and glycemic control may be the complex symptomatology and heterogeneity of depression. Depression is a diagnosis based on a syndrome of symptoms ranging from primarily somatic symptoms such as fatigue, change in sleep, or change in appetite to primarily affective symptoms such as depressed mood, worthlessness, or guilt to symptoms of dysphoria or anhedonia. Both leading classification systems for the diagnosis of mental disorders (ICD-10 or DSM-5) require the presence of at least two out of three core symptoms (ICD-10) or one out of two core symptoms (DSM-5), respectively. Additionally, the ICD-10 requires at least two additional depressive symptoms, while the DSM-5 requires four for a diagnosis of clinical or major depression. This implies that different symptom profiles are summarized under the same depression diagnosis. For example, a mild depressive episode according to the ICD-10 can be potentially defined by 63 different profiles of depressive symptoms. In fact, according to the ICD-10 and DSM-5, it is possible for two people diagnosed with depression to share just one symptom, otherwise having completely different symptoms. This shows the complex definition of the construct "depression." The same problem persists when depression is assessed by self-report questionnaires as there are multiple possible combinations of symptoms that can lead to an elevated depression score.

As a consequence, considerable effort has been made to deconstruct the depression construct in order to acknowledge the heterogeneity of symptoms and challenge their equivalence [20, 21]. Recent studies took into account possible differences in depressive symptomatology when looking at important clinical outcomes in diabetes [22] as well as in cardiovascular diseases [23].

Two studies investigating the effects of different depressive symptoms on glycemic control found intriguing associations of single symptoms with glycemic control and offered a more comprehensive understanding [24, 25]. However, both studies used the PHQ-9 questionnaire to assess depressive symptoms according to DSM-5 and included every single item of the PHQ-9 as a predictor in separate linear regression analyses, therefore missing a multivariate analysis necessary to account for the co-occurrence of depressive symptoms. In addition, despite the PHQ-9 being a well-validated questionnaire [26], the reliability and validity of each individual item has not been evaluated and leads to worse diagnostic performance than using a sum score [27].

Based on the results of Bot et al. [24] as well as Baechle et al. [25], we analyzed the associations between glycemic control and clusters of depressive symptoms rather than single depressive symptoms. Therefore, we used the Center for Epidemiological Studies-Depression Scale (CES-D) [28] for which the symptom profiles or subtypes "affective symptoms," "somatic symptoms" and "anhedonia" were established in a meta-analytic factor analysis [29].

Research design and methods

The analyses relied on a combined sample of three studies; one study was conducted in the inpatient setting of the Diabetes Clinic Mergentheim [19], and two studies were conducted in an outpatient setting [30, 31]. Inpatients were recruited during their stay; outpatients were recruited during education classes in their respective diabetes care practice throughout Germany (over 40 practices comprising both rural and urban areas). All three studies combined, the duration of the enrollment period comprised three years. Demographic and medical data (e.g. late complications) used as covariates were retrieved either from case report forms completed by physicians or from medical files. HbA1c concentration was measured in a central laboratory [normal range 4.3–6.1% (24–43 mmol/l)]. Blood sampling and psychometric assessments were conducted concomitantly. This study was conducted as a retrospective analysis; therefore, specific inclusion or exclusion criteria for this particular analysis were not applied. For all three studies, ethical approval was obtained prior to data collection and written informed consent was obtained from every patient in these studies.

Patients completed the CES-D questionnaire which contains 20 items assessing the frequency of depressive symptoms. The items can be clustered to different subtypes of depressive symptoms [29]: seven items assessing affective symptoms (feeling blue, sad, depressed, fearful, lonely, thought of life as a failure, having crying spells); seven items assessing somatic symptoms (poor appetite, feebleness, lack of concentration, being bothered, less talkative, lack in drive, restless sleep); four items assessing hedonic symptoms (enjoyed life, feeling good, hopeful, happy) which are inverted to assess anhedonia.

Additionally, the CES-D contains two items assessing interpersonal problems (people were unfriendly, people disliked me) which, however, were not clustered to a subtype due to their low congruence with the depression construct. The frequency of the symptom each item depicts is scored on a scale of 0 (occurs not at all or on < 1 day) to 3 (occurs on 5–7 days). A total score (all 20 items) and mean item scores for the "affective," "somatic," and "anhedonic" subtypes were calculated.

Because of previously demonstrated mediating effects of diabetes-related distress [10, 13, 14], patients additionally completed the Problem Areas in Diabetes scale (PAID) which consists of 20 items depicting specific issues for people with diabetes (e.g. fear of long-term complications, hypoglycemia problems, motivational problems) [32]. Items are scored on a five-point Likert scale from 0 (not a problem) to 4 (serious problem). A total score was derived and transformed to a scale from 0 to 100 (higher values indicate higher distress).

Statistical analysis

Multivariate linear regression analyses were performed with HbA1c as a dependent variable. Separate analyses were performed for patients with type 1 and type 2 diabetes, as Bot et al. [24] found substantial differences between these patient groups. Independent variables of interest were the three depressive subtypes (somatic, affective, anhedonic). All analyses were controlled for demographic (age, gender, BMI, education years) and medical variables [diabetes duration, insulin therapy (only type 2 diabetes), insulin pump therapy (only type 1 diabetes), frequency of self-monitored blood glucose measurements per day, late complications [retinopathy, nephropathy, neuropathy, coronary heart disease, diabetic foot syndrome)] as well as for inpatient/outpatient status as these might be independent predictors confounding the associations between depressive subtypes and glycemic control. Diabetes-related distress was included as an additional control variable due to mediating effects demonstrated in recent studies [10, 13, 14]. Threshold for significance was set at an alpha level of 0.05. Standardized coefficients (β) as well as non-standardized coefficients (B) with standard errors (SE) are reported for the linear regression analyses. Statistical analyses were conducted with SYSTAT 12.0 (Systat Software, Inc., Chicago, IL).

Results

A total sample of 986 patients with type 1 and type 2 diabetes mellitus participated in the study (61% type 1 diabetes). Sample characteristics are displayed in Table 1. As expected, patients with type 1 diabetes were significantly younger and had diabetes for a longer time. Glycemic control was suboptimal in people with type 1 [8.1 ± 1.4% (65 ± 15.3 mmol/mol)] and type 2 diabetes [8.5 ± 1.5% (69 ± 16.4 mmol/mol)]. Furthermore, mean item scores of depressive symptoms were comparable except for anhedonia which was higher in patients with type 2 diabetes (Table 2). Interestingly, anhedonia had the highest mean item score that was nearly doubled compared to somatic symptoms and nearly tripled (for type 1) or quadrupled (for type 2) compared to affective symptoms. Overall, one-third of the total sample had elevated depressive symptoms and nearly 40% had elevated levels of diabetes distress; there were no differences between people with type 1 and type 2 diabetes (Table 2).

In people with type 1 diabetes, the depressive subtypes showed differential associations with glycemic control (see Fig. 1): Affective symptoms were negatively associated with glycemic control ($\beta = -0.23$, $B = -0.35$, SE = 0.1, $p < .001$), while somatic symptoms showed a positive association with glycemic control ($\beta = 0.24$, $B = 0.36$, SE = 0.09, $p < .001$). In this multivariate analysis, greater somatic symptoms were associated with higher HbA1c levels, but greater affective symptoms were associated with lower HbA1c levels. Anhedonia showed no significant association with glycemic control, while greater diabetes distress was significantly positively associated with higher HbA1c levels ($\beta = 0.15$, $B = 0.01$, SE = 0.004, $p = .005$).

The results for type 2 diabetes are displayed in Fig. 2. None of the depressive subtypes were significantly associated with glycemic control. However, the covariate diabetes distress was marginally associated with glycemic control ($\beta = 0.12$, $B = 0.01$, SE = 0.005, $p = .053$). Among the other covariates, age, gender, and years of education and being inpatient/outpatient status showed a significant association.

Additional analyses with the CES-D sum score as an independent variable (instead of the depressive subtypes; but same covariates) showed that depressive symptoms in general were not associated with glycemic control; neither for patients with type 1 ($\beta = 0.02$, $B = 0.004$, SE = 0.008, $p = .65$) nor for patients with type 2 ($\beta = -0.06$, $B = -0.01$, SE = 0.01, $p = .32$) diabetes.

Conclusions

This study tried to shed some light on the association between depression and glycemic control in people with diabetes. The initial hypothesis was that the complex symptomatology of depression may be responsible for the inconsistent findings regarding the association between

Table 1 Sample characteristics

	Type 1 diabetes	Type 2 diabetes	*p*
n	604	382	
Age (in years)	43.8 ± 14.2	60.7 ± 9.4	<.001
Gender (% female)	44%	39%	.17
BMI in kg/m^2	26.3 ± 4.9	32.3 ± 5.9	<.001
Years of education	11.2 ± 3.1	10.4 ± 2.9	<.001
Duration of diabetes (in years)	16.0 ± 12.6	12.8 ± 8.7	<.001
Self-monitored blood glucose measurements per day	4.9 ± 1.7	2.9 ± 1.6	<.001
HbA1c (%, mmol/mol)	8.1 ± 1.4	8.5 ± 1.5	<.001
	65 ± 15.3	69 ± 16.4	
Insulin therapy (%)	100%	65%	<.001
Insulin pump therapy (%)	18%	0%	n.a.
Late complications (% with at least one)	38%	71%	<.001

Table 2 Psychological characteristics

	Type 1 diabetes	Type 2 diabetes	*p*
n	604	382	
Depressive symptoms (CES-D sum score: range 0–60)	13.8 ± 8.9	14.1 ± 8.0	.63
Affective symptoms (mean item score: range 0–3)	0.46 ± 0.53	0.40 ± 0.49	.09
Somatic symptoms (mean item score: range 0–3)	0.69 ± 0.51	0.71 ± 0.53	.54
Anhedonia (mean item score: range 0–3)	1.29 ± 0.78	1.50 ± 0.81	<.001
Diabetes distress (PAID sum score: range 0–100)	27.1 ± 17.0	25.9 ± 16.1	.26
Elevated depressive symptoms (CES-D sum score ≥ 16)	35.6%	35.6%	.99
Elevated diabetes distress (PAID sum score ≥ 30)	41.3%	39.9%	.47

depression and glycemic control and that depressive symptom clusters might show differential associations. Therefore, depressive symptoms were categorized into three distinct and established subtypes [29], and their associations with glycemic control were analyzed.

For people with type 1 diabetes, the hypothesis could be confirmed as the affective and somatic subtype showed diametrically opposed associations with glycemic control; while somatic symptoms showed a positive association, affective symptoms showed a negative association. Interestingly, the absolute numbers and hence the effect sizes of these associations were nearly identical. This suggests that when analyzed together, the associations of both subtypes may offset each other. Hence, this might explain the observed lack of association between depressive symptoms in general (CES-D sum score) and glycemic control found in this and other studies [9–11].

For people with type 1 diabetes, the negative association of affective symptoms with glycemic control is counterintuitive. In order to understand this complex association, a deeper look at the analysis is necessary. The observed standardized beta coefficient of affective symptoms in this model represents the unique association that is free from co-variation of the other variables in the model. This means that the association with glycemic control reflects the relationship with affective symptoms that cannot be accounted for by any somatic symptoms (and vice versa). Hence, affective symptoms (which were not due to somatic discomfort) in this model might reflect a level of diabetes-unspecific concern and conscientiousness that might be necessary to adequately take care of a chronic condition like diabetes which in turn may translate into better glycemic control. In contrast, diabetes-specific concern (i.e. diabetes distress) was associated with worse glycemic control. Another explanation for the counterintuitive finding could be that the display of affective symptoms is more salient to healthcare providers and thus results in more intensive support or recommendations for psychosocial interventions. Future research should focus on the characterization of patients with elevated affective symptoms and how these affect the course of glycemic control.

Somatic symptoms could be regarded as a possible risk factor for worse glycemic control. Considering the cross-sectional nature of this study, however, somatic symptoms might also be a consequence of high HbA1c levels. Nonetheless, the positive association of somatic symptoms with HbA1c is in line with studies that found a positive association between depression and HbA1c [8, 33].

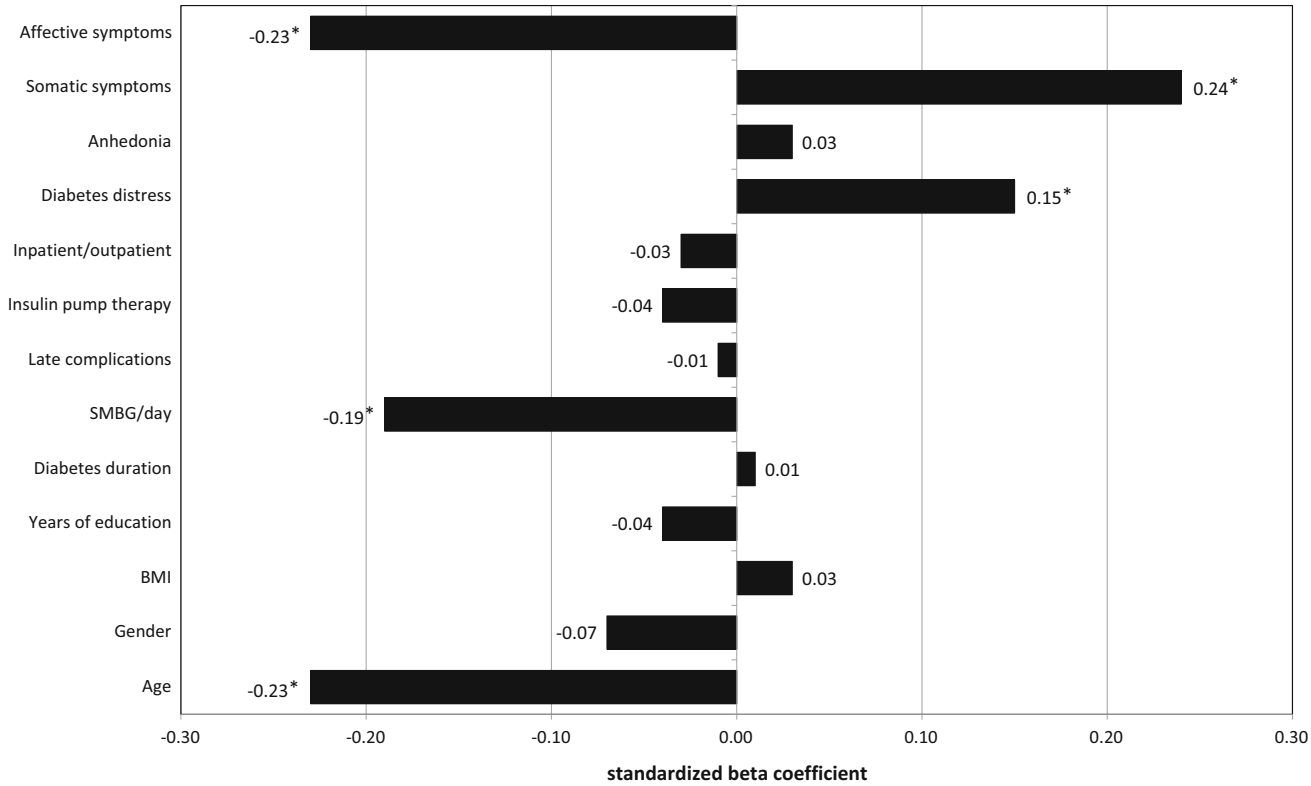

Fig. 1 Associations of the depressive subtypes and possible confounders with HbA1c in a linear regression analysis for people with type 1 diabetes. $*p < .05$

Support for the importance of somatic symptoms comes from Bot et al. [24] who found significant associations of glycemic control with sleeping difficulties ($\beta = 0.16$) and appetite problems ($\beta = 0.15$) as well as Baechle et al. [25] who found a significant association with glycemic control only for lethargy ($\beta = 0.23$) and appetite problems ($\beta = 0.27$). Problems with appetite might manifest directly in problems with prandial insulin dosages and thus prandial glucose control. Besides in studies on depression, hours of sleeping, sleep quality, and obstructive sleep apnea have previously been linked to worse glycemic control [34, 35]. In addition, somatic symptoms were found to explain the association between depression and treatment non-adherence [36]. Taken together, this might help to explain the association of the somatic subtype with worse glycemic control in this study. Furthermore, somatic symptoms and not affective symptoms were found to predict the long-term increase in proinflammatory cytokines [37] which can have a negative impact on achieving optimal glycemic control [38].

In clinical practice, it is often difficult to distinguish between somatic symptoms of depression and symptoms due to poor glycemic control. However, new diabetes technology such as continuous glucose measurement (CGM) or flash glucose measurement (FGM) facilitates the identification of possible glycemic sources for problems with sleep, appetite, or concentration (e.g., blood glucose fluctuations, frequency and timing of hypo- and hyperglycemic episodes). This in turn can lead to a better understanding of the somatic symptoms of depression.

Interestingly, the previously found the mediating effect of diabetes distress [10, 13, 14] could not be supported by this study. Adding diabetes distress to the model did not substantially change the results.

In people with type 2 diabetes, none of the depressive subtypes were associated with glycemic control. However, this is in line with other cross-sectional studies which only found an association of depression with glycemic control in patients with type 1 but not type 2 diabetes [39, 40]. This lack of associations could be due to the multi-morbidity of this patient group which can be characterized by multiple therapy regimens (i.e. multiple medications), different requirements for self-care behavior (more medical control, less autonomous), and the influence of comorbidities on metabolism and glycemic control. These factors might prevent a direct association between depression and glycemic control. Thus, the association might be more complex and should be investigated further. Nevertheless, depression has been established as an independent risk factor in patients with type 2 diabetes [6] and should not be

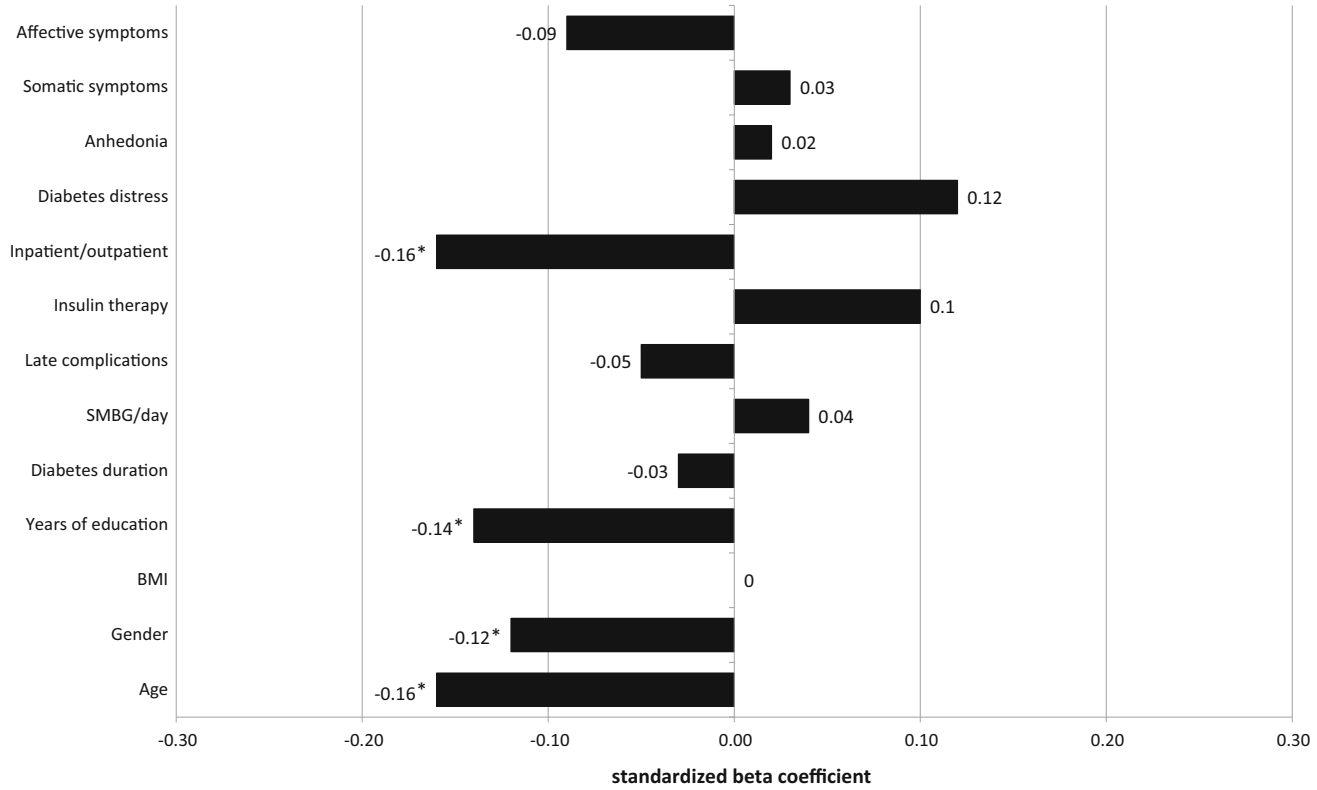

Fig. 2 Associations of the depressive subtypes and possible confounders with HbA1c in a linear regression analysis for people with type 2 diabetes. *$p < .05$

overlooked in these patients. Another factor that should be considered when interpreting the missing association between depressive subtypes and glycemic control in people with type 2 diabetes is the smaller statistical power compared to the type 1 sample due to the smaller sample size of people with type 2 diabetes. However, post hoc power analysis showed that the sample size of 384 people with type 2 diabetes was sufficient to detect significant associations with a statistical power of >99% when the same magnitude of associations between depressive subtypes and glycemic control would have been observed in type 2 diabetes as in type 1 diabetes. Therefore, the effect size of the associations between depressive subtypes and glycemic control for people with type 2 diabetes might be a more important cause for the nonsignificant findings than the lack of statistical power.

Anhedonia seems to be of special interest in people with diabetes as anhedonic symptoms were by far the most prominent in this study. Furthermore, a study by Nefs et al. [41] found a significant association between anhedonia and worse glycemic control in people with type 2 diabetes. However, in the present study anhedonia was not associated with glycemic control. Further research is needed to clarify the role of anhedonia in diabetic patients and compare the magnitude of anhedonic symptoms with other chronic conditions or the general population.

When interpreting the results of this study, the following limitations should be considered. The cross-sectional nature of the study does not allow for any causal inferences. Depressive symptoms were assessed via self-report and not via diagnostic interviews; however, many studies analyzing the association between depression and glycemic control used self-report measures (e.g., the CES-D) [8]. In addition, by using the CES-D, subtypes as defined in the DSM-5 or ICD-10 could not be analyzed. Nonetheless, using somatic and affective symptom clusters yielded clinically relevant results. Strengths of the study were the large sample size which enabled the separate analysis of type 1 and type 2 diabetes and the multivariate analyses in order to account for co-occurrences of depressive symptoms. In addition, including outpatients from over 40 secondary care units from all over Germany as well as inpatients from a tertiary care unit increases the generalizability of the results.

For people with type 1 diabetes, the results indicate that the complex symptomatology of depression has a differential impact on medical outcomes such as glycemic control. By thinking of depression as a homogenous construct, important associations or effects may be overlooked. In this

study, analyzing depressive symptoms without differentiation would have led to the result that an association with glycemic control was non-existent. Differentiating three main symptom clusters, however, offered a more detailed picture of the association. In clinical practice and further research, this means that two people with diagnosed depression or elevated depressive symptoms might have less in common than the label "depression" might suggest. Especially with a chronic somatic condition like diabetes, distinguishing somatic and affective symptoms of depression might help reveal the specific reciprocal relationship between the two conditions. Comparable efforts made in other somatic conditions such as coronary artery disease showed differential associations of depressive symptoms clusters with important medical outcomes [23, 42]. While affective symptoms might be more representative of the common understanding of depression, these results highlight the role of somatic symptoms and demonstrate that the somatic side of depression should be taken into consideration in clinical practice.

In summary, special attention in routine care should be directed at somatic symptoms of depression as they might be indicative of problems with achieving good glycemic control. Further research on the longitudinal relationship of the somatic and affective subtypes with glycemic control is needed in order to clarify the impact of depressive symptoms on the course of glycemic control.

Authors' contribution DE and NH researched the data and wrote the manuscript. AS and AR contributed to the discussion and reviewed/edited the manuscript. TH and BK contributed to the discussion. DE is the guarantor of the article, therefore taking full responsibility for the contents of the article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard As this was a retrospective analysis, formal consent is not required. The three studies which were combined for this analysis were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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