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ORIGINAL ARTICLE

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Somatic and mental symptoms associated with dysglycaemia, diabetes-related complications and mental conditions in people with diabetes: Assessments in daily life using continuous glucose monitoring and ecological momentary assessment

Norbert Hermanns PhD[1,2,3,4] | Dominic Ehrmann PhD[1,2,3] | Bernhard Kulzer PhD[1,2,3,4] | Laura Klinker MA[1,3,4] | Thomas Haak MD[4] | Andreas Schmitt PhD[1,3,4]

[1]Research Institute of the Diabetes-Academy Mergentheim (FIDAM), Bad Mergentheim, Germany

[2]Department of Clinical Psychology and Psychotherapy, University of Bamberg, Bamberg, Germany

[3]German Center for Diabetes Research (DZD), Neuherberg, Germany

[4]Diabetes Center Mergentheim (DZM), Diabetes Clinic, Bad Mergentheim, Germany

Correspondence
Norbert Hermanns, PhD, Research Institute of the Diabetes Academy Mergentheim (FIDAM), Johann-Hammer-Str. 24, 97980 Bad Mergentheim, Germany.
Email: hermanns@fidam.de

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Abstract

Aim: To analyse the potential drivers (glucose level, complications, diabetes type, gender, age and mental health) of diabetes symptoms using continuous glucose monitoring (CGM) and ecological momentary assessment.

Materials and Methods: Participants used a smartphone application to rate 25 diabetes symptoms in their daily lives over 8 days. These symptoms were grouped into four blocks so that each symptom was rated six times on 2 days (noon, afternoon and evening). The symptom ratings were associated with the glucose levels for the previous 2 hours, measured with CGM. Linear mixed-effects models were used, allowing for nested random effects and the conduct of $N = 1$ analysis of individual associations.

Results: In total, 192 individuals with type 1 diabetes and 179 with type 2 diabetes completed 6380 app check-ins. Four symptoms showed a significant negative association with glucose values, indicating higher ratings at lower glucose (speech difficulties, $P = .003$; coordination problems, $P = .00005$; confusion, $P = .049$; and food cravings, $P = .0003$). Four symptoms showed a significant positive association with glucose values, indicating higher scores at higher glucose (thirst, $P = .0001$; urination, $P = .0003$; taste disturbances, $P = .021$; and itching, $P = .0120$). There were also significant positive associations between microangiopathy and eight symptoms. Elevated depression and diabetes distress were associated with higher symptom scores.

Norbert Hermanns and Dominic Ehrmann share first-authorship.

$N = 1$ analysis showed highly idiosyncratic associations between symptom reports and glucose levels.

Conclusions: The $N = 1$ analysis facilitated the creation of personalized symptom profiles related to glucose levels with consideration of factors such as complications, gender, body mass index, depression and diabetes distress. This approach can enhance precision monitoring for diabetes symptoms in precision medicine.

KEYWORDS
continuous glucose monitoring, hypoglycaemia, patient-reported outcomes, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Disease symptoms constitute a significant dimension of the affected individual's quality of life.[1,2] Consequently, effective management of disease symptoms is crucial for maintaining a good quality of life for those with chronic diseases. Hence, medical treatments not only aim to improve clinical parameters, but also to reduce symptom burden. Person-reported outcome measures, such as disease-specific symptom checklists, are commonly used to assess how a disease or its treatment affects symptom burden, providing vital insights into the perspective of the affected individual and enabling tailored treatment.[3,4]

In diabetes, symptoms play a complex and critical role. Symptoms related to glucose levels, including hypoglycaemia (e.g. shakiness, sweating and confusion) and hyperglycaemia (e.g. increased thirst and frequent urination), are particularly important.[5] Hypoglycaemia is a common side effect of glucose-lowering treatments,[6] while hyperglycaemia occurs when diabetes is not controlled well.[7] Glucose-related symptoms serve a dual purpose: on the one hand, they act as early warnings to prevent dangerous blood glucose levels; on the other, they significantly contribute to the overall symptom burden, impacting daily functioning.

Besides glucose-related symptoms, diabetes-related complications such as microangiopathic and macroangiopathic complications also contribute to symptom burden.[8] Other factors, including obesity, age and gender, can also contribute to symptom burden. Additionally, impaired emotional functioning (e.g. depression and diabetes distress) can affect symptom reporting, leading to an amplification of perceived symptoms.[9,10]

Symptom burden is a comparatively undervalued outcome in diabetes research. A recent review discovered that only 34% of studies used diabetes symptoms as a relevant outcome compared with mental health (76%), physical functioning (67%) and psychological functioning (47%).[11] Continuous glucose monitoring (CGM) may have reduced the emphasis on glucose-symptom recognition, as it provides continuous glucose values and alerts. The retrospective nature of symptom assessment, typically using questionnaires, does not take into account the glucose level at the time of symptom assessment.[12] Thus, there has been no evaluation of how glucose values that directly precede the reporting of a symptom affect the symptom burden and whether glucose affects various symptoms differently. Furthermore, retrospective symptom assessment using questionnaires may be subject to memory or recall bias.[5,13]

Considering the importance of diabetes symptoms in determining symptom burden and evaluating treatment efficacy, our study aims to clarify the determinants of symptom perception using the ecological momentary assessment (EMA) alongside CGM. With EMA, diabetes symptoms can be assessed in one's daily life using a smartphone application.[13] This study analyses the independent impact of glucose on diabetes symptoms when both are assessed contemporaneously, while controlling for other factors such as complications, diabetes type, gender, age, body mass index (BMI), depression and diabetes distress. The subsequent $N = 1$ analyses explore the individual associations between EMA-derived symptoms and CGM metrics. By addressing these complexities, we aim to improve the understanding of symptom perception in the daily lives of people with diabetes and improve their diabetes management.

2 | MATERIALS AND METHODS

The DIA-LINK1[5] and DIA-LINK2[5,14] studies constitute a pair of non-interventional, prospective observational studies analysing the links between mental health symptoms and glycaemic levels in people with type 1 diabetes and type 2 diabetes, respectively. The analysis in the current study focuses on an 8-day EMA period during which diabetes symptoms were assessed three times daily; the full study protocol is available at ClinicalTrials.gov (clinical trial reg. no. NCT03811132 and no. NCT04438018).

2.1 | Recruitment

The study participants were recruited at the Diabetes Center Mergentheim, Bad Mergentheim, Germany, which is an inpatient facility that people with diabetes are referred to because of sustained hyperglycaemia, the occurrence of complications, or psychosocial issues complicating the treatment and course of diabetes. After participant recruitment in the inpatient setting and subsequent discharge from the clinic, data collection began. Recruitment took place from March

2019 to March 2022. The following inclusion criteria were applied: type 1 diabetes or type 2 diabetes, diabetes duration longer than 1 year, age 18-70 years, sufficient German language skills, compatible smartphone and having provided informed consent.

Individuals were excluded if they exhibited any of the following: an inability to provide consent, significant cognitive impairment, severe somatic illness or a diagnosed mental disorder (according to International Classification of Diseases 10 criteria), terminal illness or bedriddenness. The recruited participants were provided with information on the study, both orally and in writing. Written informed consent was obtained. Both studies were approved by the Ethics Committee of the German Psychological Society (NH082018).

2.2 | Procedure

After their enrolment, participants completed a baseline assessment by responding to questionnaires. They were then fitted with an unblinded, intermittently scanned CGM system (FreeStyle Libre 2) for the duration of the study. For EMA, a smartphone application (mEMA, Ilumivu Software for Humanity, Asheville, NC) was installed on participants' personal smartphones. The actual EMA phase was conducted in an outpatient, ambulatory setting.

The EMA period started on the first Saturday postdischarge from the hospital, with questions being asked daily for 18 consecutive days. These EMA questions were primarily related to diabetes distress and glucose-related distress (for further information, see Ehrmann et al.[5,14]). The diabetes symptom assessment via EMA took place from day 19 to day 26. The participants rated diabetes symptoms three times per day (noon, afternoon and evening). The items on the list were selected from both the diabetes symptom checklist[12] and a hypoglycaemia symptom list.[15] The diabetes symptom checklist contains many symptoms related to potential diabetes complications, whereas the hypoglycaemia symptom checklist primarily contained symptoms related to the glucose level. The interdisciplinary team of psychologists and an endocrinologist (AS, DE, NH, BK and TH) selected the final symptom list presented with EMA based on their clinical and psychometric experience. They combined the lists to create a shorter, more focused set of symptoms suitable for daily assessment. This approach ensured a balance between symptoms related to current glucose levels and potential complications. Overall, 25 symptoms were included and were grouped into four blocks, each containing different symptoms. Each block was presented on 2 days. A maximum of six symptom ratings could be obtained per participant. The following symptoms were presented: speech difficulties, concentration problems, food cravings, mood swings, coordination problems, increased thirst, confusion, heartburn, tingling, shortness of breath, headache, palpitations, altered taste, an urge to urinate, weakness, sweating, thinking difficulties, nausea, itching, irritability, anxiety, shakiness, strange feeling, dizziness and vision problems.

The participants were asked whether they had experienced any of these symptoms in the previous 2 hours and, if so, how intense they were. Symptom intensity was rated on an 11-point visual analogue scale using a sliding scale from 0 (no symptom experienced) to 10 (very intense symptom experienced).

Every symptom rating and every glucose reading had a time stamp, so that both datapoints could be matched. This allowed to select the glucose readings in the 120 minutes prior to each symptom rating. For the period of 120 minutes prior to each symptom rating, the mean glucose level based on CGM data was computed.

2.3 | Statistical analysis

Multilevel regressions were key models for the statistical analysis used for two reasons. First, these multilevel regression models can account for autoregression of dependent and independent variables (e.g. symptoms ratings and glucose values). Second, these models can deal with the complexity of our data, which include different levels of variability between study participants. There are between-level predictors that influence symptom perception that remain constant within a person and only differ between individuals, such as age, gender, the presence of macroangiopathic or microangiopathic complications, type and duration of diabetes, BMI, and levels of depression and diabetes distress. In addition, there are within-level predictors that vary within participants throughout the study. One example is the relationship between blood glucose levels in the 2 hours before symptom assessment and actual symptom perception. It is known that symptoms of hypoglycaemia, for example, can be perceived differently even when glucose levels are similarly low. These are within-person differences. The mixed-effect models allowed us to adequately model both the stable between-person differences and the dynamic within-person variation over time.

For assessing the associations between diabetes symptoms and CGM-derived variables, a linear mixed-effects model was used for each symptom, allowing for nested random effects. The participant was the nested factor. Thus the model allowed for each individual to vary in their association between symptom perception and glucose level. Consequently, an individual association per participant was modelled, which was then aggregated to achieve an overall estimate of this association. The within-level predictor was the mean glucose level in the 2 hours preceding the respective symptom rating.

The following variables were included as between-level predictors: microangiopathic complications (yes vs. no; at least one of the following: retinopathy, neuropathy or nephropathy), presence of macroangiopathic complications (yes vs. no; at least one of the following: coronary heart disease, stroke or peripheral arterial occlusive disease), sex, age, type of diabetes, BMI, elevated depression score at baseline (yes vs. no; score of > 22 on the Center for Epidemiological Studies-Depression scale)[16] and elevated diabetes distress score at baseline (yes vs. no; score of > 39 on the Problem Areas in Diabetes questionnaire).[17] In each analysis, we controlled for time between the measurements and the first autoregressive parameter. For the between- and within-level predictors, estimates, *T*-values and *P* values were obtained and reported.

We extracted the random effects from the linear mixed-effects model. The random effects represent the deviations of individual participants from the overall estimate (across participants) of the association between a specific symptom score and the mean glucose level. Thus we were able to calculate the individual estimate of the association between the respective symptom score and the mean glucose level in the previous 2 hours for each participant. By calculating the difference between the individual deviations from intercept and

TABLE 1 Sample characteristics.

Characteristic	Type 1 diabetes, $N = 192$	Type 2 diabetes, $N = 179$	P
Age, y (± SD)	38.7 (± 12.7)	53.3 (± 9.4)	< .001
Gender			
Male, *N* (%)	80 (41.7%)	105 (58.7%)	< .001
Female, *N* (%)	112 (58.3%)	74 (41.3%)	
Other, *N* (%)	0 (0%)	0 (0%)	
Years of education (± SD)[a]	12.2 (± 3.0)	11.6 (± 3.1)	.043
BMI, kg/m^2 (± SD)	26.1 (± 5.2)	35.3 (± 6.6)	< .001
Migration background[b]			
No migration background reported, *N* (%)	176 (91.7%)	166 (92.7%)	.701
Migration background reported, *N* (%)	16 (8.3)	13 (7.3%)	
Duration of diabetes, y (± SD)	18.9 (±11.6)	12.0 (±7.6)	< .001
HbA1c, % (± SD)	8.7 (±1.9)	9.0 (±1.7)	.072
Treatment			
Diet and/or oral medication and/or incretins, number (%)	0 (0%)	30 (16.88%)	< .001
Oral medication or insulin incretins and basal insulin/mixed insulin, number (%)	4 (2.1%)	36 (20.1%)	
Intensive insulin therapy (pen or syringe), number (%)	77 (40.1%)	112 (62.5%)	
Intensive insulin therapy (CSII), number (%)	111 (57.8%)	1 (0.6%)	
Complications			
CHD, number (%)[c]	5/192 (2.1%)	20/179 (10.7%)	< .001
Arterial occlusive disease, *N* (%)	6/192 (3.1%)	10/177 (5.6%)	.308
Macroangiopathy, *N* (%)[d]	11/192 (5.7%)	30/177 (16.9%)	< .001
Retinopathy, *N* (%)	45/192 (23.4%)	39/178 (21.9%)	.726
Nephropathy, *N* (%)	7/192 (3.6%)	25/179 (14.0%)	< .001
Neuropathy, *N* (%)	64/192 (33.3%)	94/179 (52.5%)	< .001
Microangiopathy, *N* (%)	88/192 (45.8%)	109/179 (60.9%)	.005
Hypoglycaemia unawareness			
Clarke score (± SD)	1.7 (±1.6)	1.5 (±1.2)	.210
CGM metrics: whole EMA period (day 0-day 26)			
< 54 mg/dL (< 3.0 mmol/L)	1.0%	0.2%	< .001
< 70 mg/dL (< 3.9 mmol/L)	3.8%	1.2%	< .001
> 70 and ≤ 180 mg/dL (> 3.9 mmol/L and ≤ 10.0 mmol/L)	55.2%	75.1%	< .001
> 180 mg/dL (> 10.0 mmol/L)	41.0%	23.7%	< .001
> 250 mg/dL (> 13.9 mmol/L)	15.1%	7.0%	< .001
Mean glucose, mg/dL (± SD)	175.3 (± 37.9)	152,4 (± 38.4)	< .001
Mean glucose, mmol/L (± SD)	9.7 (± 2.1)	8.5 (± 2.1)	< .001
Glucose management index, % (± SD)	7.5 (± 0.9)	7,0 (± 0.9)	< .001
Glucose variability, CV% (± SD)	36% (± 5.6%)	26.8% (± 6.2%)	< .001
Mean glucose in the 2-h period prior to each symptom rating			
< 54 mg/dL (< 3.0 mmol/L)	0.6%	0.0%	< .001
< 70 mg/dL (< 3.9 mmol/L)	3.1%	0.4%	< .001
> 70 and ≤ 180 mg/dL (> 3.9 mmol/L and ≤ 10.0 mmol/L)	58.2%	71.9%	< .001

TABLE 1 (Continued)

Characteristic	Type 1 diabetes, $N = 192$	Type 2 diabetes, $N = 179$	P
> 180 mg/dL (> 10.0 mmol/L)	38.7%	27.7%	< .001
> 250 mg/dL (> 13.9 mmol/L)	12.9%	7.0%	< .001
Mean glucose, mg/dL (± SD)	171.3 (±65.9)	159.7 (±53.7)	< .001
Mean glucose, mmol/L (± SD)	9.5 (±3.7)	8.9 (±3.0)	< .001

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; CHD, coronary heart disease; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; EMA, ecological momentary assessment; SD, standard deviation.
[a]Years of education refers to number of years in school or university.
[b]Born in Germany = no migration background; not born in Germany = migration background.
[c]Coronary infarction, angina pectoris, stroke, cardiovascular intervention or procedure.
[d]Stroke and/or CHD and/or arterial occlusive disease.

coefficient and the overall intercept and coefficient, we were able to provide an individual intercept and coefficient of the association between symptoms and glucose levels.

Based on the random effects (i.e. individual associations), a separate regression equation for every symptom for every person was generated. This process allowed us to predict a specific symptom intensity at different glucose levels. We estimated the individual symptom score at a very low glucose level (54 mg/dL [3.0 mmol/L]) and at a very high glucose level (250 mg/dL [13.9 mmol/L]) for all symptoms showing a significant association with the mean glucose level. We chose the low and high glucose levels to express the individual difference and, in turn, the individual responsiveness of this symptom to low compared with high glucose levels. This difference illustrates how much of the full-scale range of the symptom score is influenced by the glucose level.

Missing data were excluded. The level of significance was set at .05 because of the exploratory nature of the analyses. All the analyses were performed with SPSS 29 (IBM, Armonk, NY) and R statistics (LME-package).

3 | RESULTS

A total of 371 out of 413 participants (89.8%) rated the symptoms on 8 days using the EMA app, resulting in a total of 6380 noon, afternoon and evening check-ins. The participants completed an average of 71.6% total check-ins (noon: 70.6%; afternoon: 67.8%; evening: 76.6%).

Table 1 presents the sample characteristics of the participants who rated the symptoms. Significant differences are expected between the participants with type 1 diabetes and those with type 2 diabetes. The individuals with type 2 diabetes were significantly older and had a higher BMI, less intensive diabetes treatment and more complications. Furthermore, during the total assessment period between day 0 and day 26, the participants with type 2 diabetes showed more favourable CGM metrics (more time in range, less glucose variability and less time below or above range) than those with type 1 diabetes. Notably, the individuals with type 2 diabetes had significantly more years of education and were more probable to be female, while there were no significant differences between the participants with type 1 diabetes and type 2 diabetes in terms of immigrant background.

3.1 | Associations between symptoms and glycaemic, medical and demographic variables

Figure 1 shows a heatmap of the associations between symptom scores and glycaemic, medical and demographic variables. Eight symptoms showed a significant association with glucose in the previous 2 hours. Four symptoms—speech difficulties, coordination problems, confusion and food cravings—showed a negative association, indicating higher symptom intensity in response to lower glucose levels. Four symptoms—increased thirst, an urge to urinate, itching and taste disturbances—showed a positive association between higher symptom intensity and higher glucose readings. There were also significant positive associations between the presence of microangiopathy and the intensity of eight symptoms: tingling, shortness of breath, palpitations, taste disturbances, weakness, nausea, irritability and strange feeling. The presence of macroangiopathy appeared not to be a significant driver of symptoms; the only significant association was observed between the presence of macroangiopathy and a low intensity of sweating. Notably, participants with elevated depression scores reported significantly higher intensity in 24 out of the 25 symptoms studied. The only exception was the symptom of sweating, which displayed a non-significant positive association with elevated depression scores. A similar pattern was noted for elevated diabetes distress and symptom intensity. The participants with elevated diabetes distress scores reported significant higher symptom intensity in 17 out of 25 symptoms.

The multilevel regression model was also adjusted for participants' type of diabetes, sex, age and BMI. There was only one significant association between type of diabetes and heartburn (individuals with type 2 diabetes reported a higher symptom intensity). Female participants reported considerably higher anxiety levels than male participants. Age was associated with significantly higher shakiness, and a higher BMI was associated with greater shortness of breath. The specific coefficients and P values are reported in Table S1 in Data S1.

	Within-level predictors	Between-level predictors							
Symptoms	Glucose	Diabetes type	Sex[1]	Age	BMI	Macroangiopathy[2]	Microangiopathy[3]	Depression[4]	Diabetes distress[5]
Speech difficulties	**−3.014471**	−0.038315	1.273189	1.267001	−0.696931	0.71815080	0.196258	**3.340051**	**2.613009**
Concentra on problems	−1.394134	−0.038315	0.828238	−0.169068	0.868931	1.33556580	1.021909	**5.811116**	**3.033298**
Cravings	**−3.015577**	1.779027	1.484205	0.025938	1.161226	0.06291294	0.372264	**2.713227**	**4.179859**
Mood swings	**−2.579206**	0.635273	0.656183	0.485991	−0.352569	−0.51246254	1.379459	**6.524933**	**2.969632**
Coordination	**−4.114131**	−0.519955	0.522249	1.289245	0.319406	0.34094990	0.914246	**4.397455**	1.729502
Thirst	**4.150969**	1.229961	−1.235050	−1.284547	0.925243	−0.30187410	−0.437672	**3.362856**	**2.497997**
Confusion	−1.848832	−0.863822	−1.805768	−0.079071	0.158899	1.24911610	0.226734	**4.024503**	**2.624419**
Heartburn	1.713158	**2.725747**	0.562512	0.469657	−0.679956	−0.62077880	0.220074	**2.738600**	1.402571
Tingling	0.132503	1.721265	−0.433446	0.326338	0.634177	0.36344140	**3.313297**	**4.535603**	1.584938
Shortness of breath	1.480133	0.343936	−0.834015	0.631142	**2.628307**	−0.56749660	**2.566321**	**2.153567**	1.657474
Headaches	0.664330	0.230084	−0.093261	−1.761736	1.116822	0.18569504	1.093429	**2.500096**	**3.427892**
Palpita ons	−1.815731	1.116384	0.117339	−0.410854	−0.224103	0.63822536	**2.323043**	**2.327216**	**3.714701**
Taste disturbance	**2.486017**	−0.567058	−1.914327	0.847075	1.364735	0.40845885	**2.210825**	**2.381789**	**2.555313**
Urge to urinate	**4.170660**	0.406144	−1.165316	1.143093	1.654023	−1.55735480	0.242448	**3.586957**	1.713414
Weakness	−1.748980	−0.295115	1.464583	−0.179911	−0.148173	−1.94280470	**2.970455**	**4.798275**	**3.360652**
Swea ng	0.017199	−0.309650	0.717077	−0.070045	−0.105720	**−2.44041980**	1.459495	1.744896	1.706281
Thinking difficul es	−0.974938	0.247716	1.621263	0.590783	−0.018376	−0.44987050	1.464580	**6.145698**	**4.090683**
Nausea	−0.730268	0.473922	1.856452	−1.418966	1.707325	−0.91459320	**2.752532**	**2.021182**	1.864566
Itching	**2.544186**	1.680816	0.146657	0.575059	0.738711	−0.28895770	1.443926	**4.211977**	1.494606
Irritability	−0.427471	0.545754	−0.355013	−1.225277	−0.506665	−1.57674570	**2.088853**	**6.375898**	**3.944313**
Anxiousness	−0.276000	1.603000	**2.570000**	1.284000	−1.259000	−1.49150750	0.718000	**6.550000**	**3.259000**
Shakiness	**−2.092166**	0.806638	0.652729	**2.225984**	−0.790820	−1.24940150	0.411110	**3.531107**	**3.750092**
Strange feeling	−1.640837	−0.733872	−0.084694	−0.640065	1.107132	−1.71759530	**2.651141**	**5.226073**	**4.684288**
Dizziness	0.014448	−0.633527	−0.137849	1.537469	−0.050588	−0.38443220	1.420718	**4.064862**	**4.210013**
Visual disturbances	1.307572	1.228719	0.348120	0.725072	−1.619670	0.12648380	1.615557	**4.101376**	**3.261568**

[1] 1 = male; 2 = female; [2] yes vs. no; yes = at least one of the following: coronary heart disease, stroke, or peripheral arterial occlusive disease; [3] yes vs. no, yes=at least one of the following:

FIGURE 1 Heatmap of the association of medical, demographic and psychological determinants of diabetes symptoms. [1]1 = male; 2 = female; [2]yes versus no; yes = at least one of the following: coronary heart disease, stroke or peripheral arterial occlusive disease; [3]yes versus no, yes = at least one of the following: retinopathy, neuropathy or nephropathy; [4]yes = CES-D score ≥ 23, no = CES-D score < 23; [5]yes = PAID score ≥ 40, no = PAID score < 40. Depicted values are *t*-scores; *t*-scores > 1.96 indicate significant associations; negative *t*-scores indicate negative associations, while positive *t*-scores indicate positive associations. Bold *t*-scores indicate a significant association between symptoms and predictors. Blue colour indicates negative associations, with a darker shade indicating a higher association. Red colour indicates positive associations, with a darker shade indicating a higher association. BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; PAID, Problem Areas in Diabetes.

3.2 | The *N* = 1 analysis of the associations between symptoms and glucose levels

Because of the repeated assessment of symptoms and glucose levels with EMA and CGM, respectively, we were able to calculate the individual associations between glucose levels and symptoms for each participant. As *pars pro toto*, Figure 2 presents a heatmap of these individual beta coefficients for 10 participants with type 1 diabetes. Darker blues indicate that lower glucose levels were associated with a higher intensity of a particular symptom. Visual inspection reveals a high degree of idiosyncrasy among the 10 participants in terms of which symptoms are more intense at lower glucose levels. For example, participants 7 and 8 reported a rather high association between many symptoms' increase in intensity and lower glucose levels, whereas participants 2 and 10 reported no clear association between higher symptom intensity and lower glucose levels. Hence, participants 7 and 8 may be more aware of lower glucose levels than participants 2 and 10.

In Figure 2, darker reds indicate that higher glucose levels were associated with higher intensity of a particular symptom. Fewer symptoms seem to indicate higher glucose levels in the study participants. Increased thirst and urination appeared to increase in all participants when glucose levels were higher.

This heatmap also provides a profile for each participant, indicating the symptoms that are individually associated with low and high glucose levels. This heatmap may be helpful in advising people with diabetes regarding which symptoms are individually indicative of lower and higher glucose levels.

3.3 | Responsiveness of the glucose-dependent symptoms based on individual regression equations

Using the individual regression equations for predicting symptom intensity at different glucose levels, we predicted the intensity of the eight symptoms that were significantly associated with mean glucose levels. The mean absolute difference in the predicted intensity at glucose levels of 54 mg/dL (3.0 mmol/L) versus 250 mg/dL (13.9 mmol/L) is depicted in Figure 3. The highest responsiveness to glucose changes was observed for the following symptoms: an urge to urinate ($\Delta = 0.85$), increased thirst ($\Delta = 0.82$) and food cravings ($\Delta = 0.75$). In general, the absolute difference in symptom intensity at glucose levels of 54 mg/dL (3.0 mmol/L) and 250 mg/dL (13.9 mmol/L) ranged from 0.26 to 0.85. This corresponds to an absolute difference of 2.6%-8.5% of the total symptom scale range (0-10), and can be considered the glucose-related difference in symptom scores for these eight symptoms.

3.4 | Robustness check

We also performed a robustness check to assess the impact of missing prompts on the results by excluding all EMA prompts with less than three prompts; the results are shown in Figure S1. There is a similar pattern of symptoms responding to glucose levels and other interperson predictors as in the analysis using all available prompts. In particular, seven out of eight significant associations between symptoms and glucose levels could be replicated in this robustness check. In contrast

Association between glucose levels and diabetes symptoms (within person effects)										
	Pbn1	Pbn2	Pbn3	Pbn4	Pbn5	Pbn6	Pbn7	Pbn8	Pbn9	Pbn10
Speech difficul es	−0.0020820	−0.0016305	−0.0017799	−0.0011627	−0.0017693	−0.0008542	−0.0007058	−0.0007709	−0.0006145	−0.0015636
Concentra on problems	−0.0020157	−0.0013355	−0.0035286	−0.0038280	−0.0020109	−0.0022643	−0.0036332	−0.0028351	−0.0034533	−0.0018268
Cravings; ravenous appetite	−0.0013114	−0.0024187	−0.0070029	−0.0016119	−0.0033482	0.0000821	0.0022856	−0.0156031	−0.0011984	−0.0036224
Mood swings	−0.0055563	0.0019935	−0.0093874	−0.0076908	−0.0036863	−0.0080572	−0.0130146	−0.0113882	−0.0129631	−0.0032415
Coordina on	−0.0017043	−0.0015284	−0.0024111	0.0003057	−0.0020780	−0.0002201	0.0010793	−0.0004514	0.0006625	−0.0016823
Thirst	0.0063027	0.0030122	0.0023445	0.0024729	0.0034826	0.0029732	0.0016493	0.0035080	0.0017630	0.0033390
Confusion	−0.0014997	−0.0008980	−0.0013407	−0.0005184	−0.0012130	−0.0006066	−0.0004785	−0.0002066	−0.0005173	−0.0012334
Heartburn	0.0009431	0.0008884	0.0010680	0.0007797	0.0008718	0.0008278	0.0011030	0.0012072	0.0010747	0.0008843
Tingling	0.0017869	−0.0002561	−0.0007506	0.0005748	0.0004914	0.0014879	0.0009839	−0.0002819	−0.0018196	0.0006282
Shortness of breath	0.0075982	0.0096934	−0.0023763	−0.0019246	−0.0003866	−0.0013641	−0.0049477	−0.0037104	−0.0022438	−0.0003084
Headaches	0.0005001	−0.0066181	0.0027469	−0.0001814	0.0002597	−0.0000020	0.0000436	0.0018816	0.0009279	−0.0004560
Palpita ons	−0.0013755	−0.0012555	−0.0008073	−0.0011263	−0.0013422	−0.0009578	−0.0008544	−0.0010120	−0.0014347	−0.0013354
Taste disturbance	−0.0031760	0.0010271	0.0031996	−0.0004944	0.0001888	0.0019844	−0.0009239	0.0015240	−0.0040562	0.0045239
Urge to urinate	0.0027546	0.0037959	0.0040155	0.0002888	0.0025469	0.0039024	0.0002337	0.0075020	0.0034545	0.0018132
Weakness	−0.0023615	0.0008092	−0.0079501	−0.0039334	−0.0034287	−0.0040541	−0.0090780	−0.0065853	−0.0018174	−0.0038870
Swea ng	−0.0026980	0.0021204	−0.0003227	−0.0015488	−0.0024379	−0.0015973	−0.0048809	−0.0030157	0.0065459	−0.0026917
Thinking difficul es	0.0000042	−0.0003022	−0.0029926	−0.0018611	−0.0010384	−0.0021387	−0.0035112	−0.0027486	−0.0002234	−0.0012879
Nausea	−0.0006001	−0.0007931	−0.0000677	−0.0001920	−0.0003536	−0.0000992	0.0002292	−0.0007507	−0.0010007	−0.0001564
Itching	0.0026311	0.0012328	−0.0014769	−0.0005695	0.0009654	0.0012188	−0.0028610	−0.0016828	0.0162143	0.0007281
Irritability	−0.0032088	0.0008778	−0.0045955	−0.0043117	−0.0026199	−0.0038259	−0.0073791	−0.0052128	0.0039279	−0.0025240
Anxiousness	−0.0009991	0.0004843	−0.0023909	−0.0005307	−0.0001122	−0.0010218	−0.0029504	−0.0025538	−0.0032437	−0.0005289
Shakiness	−0.0014104	−0.0013765	−0.0001306	−0.0006644	−0.0013339	−0.0005083	0.0001179	−0.0000619	−0.0050026	−0.0014182
Strange feeling	−0.0035320	−0.0020691	−0.0024845	−0.0022778	−0.0025070	−0.0021770	−0.0041652	−0.0028821	−0.0077817	−0.0023777
Dizziness	−0.0004490	−0.0021786	−0.0069515	−0.0065823	−0.0017654	−0.0059815	−0.0089497	−0.0093173	0.0051956	−0.0009921
Visual disturbances	0.0008637	0.0007262	−0.0010767	−0.0003016	0.0003996	−0.0003226	−0.0007406	0.0001990	0.0018807	0.0005685

FIGURE 2 Individual beta coefficients of 10 study participants (Ppt) between glucose level and diabetes symptom intensity.

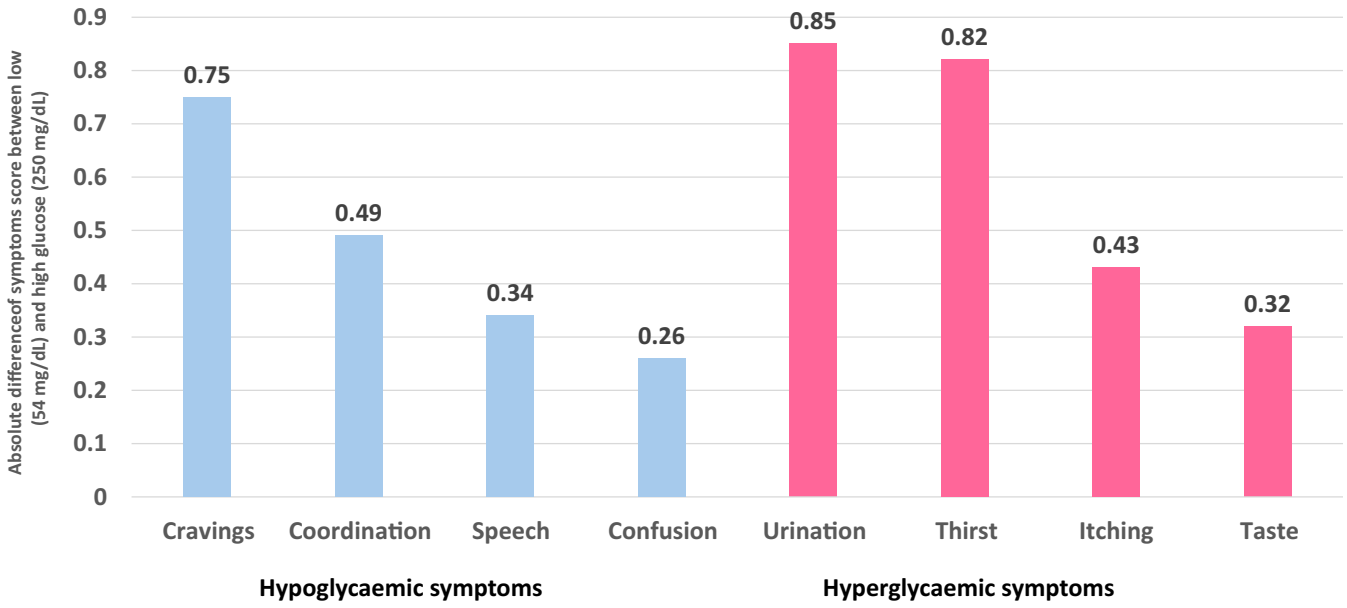

FIGURE 3 Absolute difference of symptom scores between glucose levels of 54 and 250 mg/dL (3.0 mmol/L and 13.9 mmol/L) based on the between-level predictors, as well as individual within-level predictors.

to considering all available prompts, hypoglycaemic symptom shakiness was significantly associated with low glucose levels when only symptom ratings with at least four prompts were considered. The hyperglycaemic symptom taste disturbances only showed significant associations with high glucose when all prompts were considered. We also repeated the $N = 1$ analysis with symptoms that had at least four prompts. The modelled absolute difference in symptom score between very high glucose (> 250 mg/dL [> 13.9 mmol/L]) and low glucose (< 54 mg/dL [< 3.0 mmol/L]) compared with the analysis including all available prompts is shown in Figure S2 in Data S1. This figure shows a very similar result in the comparisons between the whole sample and participants with at least four prompts.

Glucose-related changes in symptom reporting ranged from 2.9% to 9.0% of the full-scale range. In summary, this robustness check suggests that the bias caused by fewer prompts for certain symptoms was rather small.

4 | DISCUSSION

In this study, we used multilevel regression models to analyse the determinants of diabetes symptom intensity in people with type 1 diabetes and type 2 diabetes. The $N = 1$ analysis allowed us to identify individual determinants and create individual associations between high and low glucose levels and symptom intensity for each participant. Consequently, we developed personalized profiles of glucose-related symptoms. This detailed profiling indicates the symptoms that may signal low or high glucose levels for each person.

We found that eight symptoms showed glucose dependence, with their intensity ratings being significantly predicted by the mean glucose in the previous 2 hours. Four symptoms—food cravings, coordination problems, speech difficulties and confusion—had a higher intensity when glucose levels were low, indicating an association with hypoglycaemia. The other four symptoms—an urge to urinate, increased thirst, itching and taste disturbances—were stronger in intensity for hyperglycaemic values. Overall, these eight symptoms may be specifically responsive to changes in glucose control and can be used to indicate a reduction in symptom burden when problems with hypoglycaemia or hyperglycaemia are alleviated. This information can be useful for clinical studies that assess the effect of improved glucose control on person-reported outcomes, such as symptom burden.

For clinical practice, the individualized associations between glucose levels and symptom intensity are particularly useful. By determining which symptoms are responsive to hypoglycaemia and hyperglycaemia, individual symptom profiles can be created, and the individual can be advised to focus on these specific symptoms. Doing so can improve person-centred care with the help of a structured assessment. However, for interpreting individual heatmaps, a minimum number of prompts should be available, to increase the precision of these idiosyncratic symptom patterns.

However, using individual regression coefficients to predict symptom intensity at glucose levels of 250 mg/dL (13.9 mmol/L) and 54 mg/dL (3.0 mmol/L), we determined that only a small proportion of the total symptom scale range (2.6%-8.5%) was directly related to glucose. This limited glucose-related proportion of the total symptom scale range suggests that showing the benefits of new interventions for reducing diabetes symptoms can be challenging. An early meta-analysis also showed that interventions aimed at improving glucose control could only reduce symptoms of bodily pain by 3.6% of the total scale range.[18]

The modest increase in hypoglycaemic symptoms at low glucose levels observed in this study may be a result of the real-life symptom assessment compared with older laboratory studies. In the 1990s, when hypoglycaemia was identified as a limiting factor in intensive insulin therapy, researchers used insulin clamp techniques to study symptomatic changes during controlled hypoglycaemia in comparatively young, healthy participants.[19] These studies showed significant increases in symptoms at low glucose levels, with symptom scores rising substantially more than those observed in our study. For example, in one of their insulin clamp studies, Fanelli et al. showed that autonomic and neuroglycopenic symptoms increased by 30%-33% of the total symptom scale range.[20] Unlike research conducted in such experimental settings, our study assessed glucose-related symptoms in individuals with type 1 diabetes and type 2 diabetes in real-life conditions, where various factors such as distractions, attention to external cues, stress and overall mental and physical health can affect symptom perception more than blood glucose levels.[21] Thus, our study provides a more realistic estimate of the impact of glucose levels on symptoms. Our results also expand on previous work by Svensson et al.,[22] who could not show significant associations between CGM-detected hypoglycaemia and symptom scores. Therefore, the combination of CGM and EMA to create longitudinal data for a person provided a more granular insight into the associations between glucose levels and symptom intensity.

The presence of microangiopathic complications was associated with increased intensity for eight symptoms (tingling, palpitations, taste disturbances, weakness, itching, shortness of breath, irritability and strange feeling), indicating that these complications, in addition to glucose levels, significantly drive symptom burden. The regression coefficients showed that microangiopathic complications may increase symptom scores by up to 6.4% of the scale range. Many of these symptoms are also associated with sensory and autonomic neuropathy.[23,24]

Elevated baseline depression and diabetes distress scores were significant drivers of diabetes symptoms, with individuals reporting a higher intensity of almost all the symptoms. This relationship was pronounced, with elevated depression or diabetes distress increasing symptom scores by as much as 1.2 points or 12% of the total possible scale range. This finding suggests that high levels of depressive symptoms or diabetes distress can increase symptom perception or reporting.[17,25] Individuals who are more depressed or distressed may perceive their diabetes symptoms as more intense than those with lower levels of emotional distress. Elevated depressive symptoms or diabetes distress may not only exacerbate the actual physical symptoms, but also heighten the individual's awareness and reporting of these symptoms. This heightened symptom perception may be caused by a variety of factors, including increased sensitivity to physical sensations, a lower threshold for reporting discomfort, or a cognitive bias in which psychological distress amplifies the perceived severity of physical health issues.[26] Managing depression and diabetes distress may, therefore, improve overall individuals' well-being and reduce the perceived burden of diabetes symptoms, leading to better health outcomes and quality of life.

However, some limitations should be considered. There were only six assessments of each symptom with corresponding CGM outcomes in participants' daily lives, which may have reduced the statistical power of the multilevel regression analysis. Additionally, because the

participants were enrolled in a tertiary care centre, there may be a selection bias of over-representing people with more complicated diabetes, reducing the generalizability of the results. A further limitation was that intake of medication was not adjusted for. Despite these limitations, the study's strengths include a comparatively large sample of clinically well-defined participants with type 1 diabetes and type 2 diabetes, providing more than 6000 symptom ratings in their daily life. The proportions of individuals in the sample with elevated depression and diabetes distress scores were well balanced.

In conclusion, this study showed the glucose dependency of eight symptoms that were either indicative of hypoglycaemia or hyperglycaemia. Furthermore, the importance of elevated depressive symptoms and diabetes distress for an increased symptom burden was shown. The combination of CGM and EMA facilitated the conduct of the $N = 1$ analysis, which helped to identify idiosyncrasies in the relationship between symptoms and daily glucose levels. The $N = 1$ analysis enabled the creation of personalized symptom profiles that specifically concerned glucose levels, considering other factors such as complications, gender, BMI, baseline depression and diabetes distress. This approach can improve precision monitoring in precision medicine[14,26] by identifying personalized symptoms specific to hypoglycaemic and hyperglycaemic excursions.

AUTHOR CONTRIBUTIONS

NH and DE analysed the data and wrote the manuscript. AS collected the data, contributed to the interpretation of the data and revised the manuscript for important intellectual content. LK, TH and BK contributed to the interpretation of the data and revised the manuscript for important intellectual content. DE, AS, BK and NH designed the study. NH and DE are the guarantors of this work and, as such, had full access to all the data and take responsibility for the integrity and accuracy of the data.

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CONFLICT OF INTEREST

All the authors declare no conflicts of interest with regard to the content of the manuscript.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15983.

DATA AVAILABILITY STATEMENT

The following data can be shared: individual participant data underlying the results reported in this article after de-identification (text, tables, figures, and appendices). Additionally, the study protocol can be made available. Data sharing can commence immediately following publication and continue until 10 years of publication. The data will be shared with researchers who provide a methodologically sound proposal. The sharing of the data needs to fulfil the purpose of achieving the aims of the approved proposal. Proposals should be directed to hermanns@fidam.de. To gain access to the data, the requestors will need to sign a data access agreement.

ORCID

Norbert Hermanns https://orcid.org/0000-0002-2903-2677
Dominic Ehrmann https://orcid.org/0000-0002-5794-5596
Bernhard Kulzer https://orcid.org/0000-0001-9120-4479
Laura Klinker https://orcid.org/0000-0002-9484-3257
Andreas Schmitt https://orcid.org/0000-0002-5913-1457

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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