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# Reduced heart rate variability in people with type 1 diabetes and elevated diabetes distress: Results from the longitudinal observational DIA-LINK1 study

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## Abstract

**Aims:** People with type 1 diabetes have a higher risk for cardiovascular disease (CVD). Reduced heart rate variability (HRV) is a clinical marker for CVD. In this observational study using continuous HRV measurement across 26 days, we investigated whether psychological stressors (diabetes distress, depressive symptoms) and glycaemic parameters (hypo- and hyperglycaemic exposure, glycaemic variability and $HbA_{1c}$) are associated with lower HRV in people with type 1 diabetes.

**Methods:** Data from the non-interventional prospective DIA-LINK1 study were analysed. At baseline, depressive symptoms and diabetes distress were assessed. Glucose values and HRV were recorded daily for 26 days using continuous glucose monitoring (CGM) and a wrist-worn health tracker respectively. Multilevel modelling with participant as nesting factor was used to analyse associations between day-to-day HRV and diabetes distress, depressive symptoms and CGM-derived parameters.

**Results:** Data from 149 participants were analysed (age: 38.3 ± 13.1 years, $HbA_{1c}$: 8.6 ± 1.9%). Participants with elevated diabetes distress had a significantly lower

HRV across the 26 days compared to participants without elevated distress ($\beta = -0.28$; $p = 0.004$). Elevated depressive symptoms were not significantly associated with HRV ($\beta = -0.18$; $p = 0.074$). Higher daily exposure to hyperglycaemia ($\beta = -0.44$; $p = 0.044$), higher average exposure to hypoglycaemia ($\beta = -0.18$; $p = 0.042$) and higher $HbA_{1c}$ ($\beta = -0.20$; $p = 0.018$) were associated with reduced HRV across the 26 days. Sensitivity analysis with HRV averaged across all days corroborated these results.

**Conclusions:** Diabetes distress is a clinically meaningful psychosocial stressor that could play a role in the cardiovascular health of people with type 1 diabetes. These findings highlight the need for integrated psychosocial care in diabetes management.

**KEYWORDS**

cardiovascular health, depression, diabetes distress, heart rate variability, type 1 diabetes

## 1 | INTRODUCTION

People with type 1 diabetes have a substantially increased risk for cardiovascular disease (CVD)[1,2] that can be attributed to hyperglycaemia[3] and hypoglycaemia.[4] Furthermore, people with type 1 diabetes have an almost 4.5 times higher risk to die from cardiovascular causes compared to matched controls without diabetes.[5] A recent population-based study found a ninefold increased risk of acute myocardial infarction in people with type 1 diabetes compared to matched controls.[6] Additionally, CVD events occur 10–15 years earlier on average in people with type 1 diabetes.[7] Thus, early identification of risk factors and establishing at-risk groups is important for the prevention and timely management of CVD in people with type 1 diabetes.[8]

An early subclinical marker of impaired cardiovascular health is reduced heart rate variability (HRV).[8,9] HRV refers to the beat-to-beat variation in intervals between consecutive heartbeats and is a marker of autonomic function.[10] The ability of the human body to constantly adjust the heart rate is a prerequisite for adaptation to sudden changes or stressors and has, therefore, long been considered an indicator of a healthy cardiorespiratory control system.[10,11] In turn, HRV has been implemented as a clinically useful marker[12] based on a body of research demonstrating the effects of cardiovascular risk factors such as diabetes, smoking, obesity, work stress and hypertension, on reduced HRV.[11] For people with diabetes, evidence suggests that parasympathetic autonomic activity is reduced even before clinical symptoms of neuropathy are reported.[10] Thus, HRV can be used to detect autonomic neuropathy in people with diabetes.[10,11] In addition, hyperglycaemia as well as hypoglycaemia are associated with changes in HRV.[13,14]

**What's new?**

- People with type 1 diabetes have an increased risk of cardiovascular disease. Little is known about the role of psychosocial stressors in the cardiovascular health of people with type 1 diabetes.
- Across 26 days, daily heart rate variability (HRV) was significantly lower in participants with elevated diabetes distress compared to those without elevated diabetes distress. Depression was not significantly associated with HRV.
- Daily exposure to hyperglycaemia (>180 mg/dl), average exposure to hypoglycaemia (<70 mg/dl) and elevated $HbA_{1c}$ were associated with reduced HRV.
- The effect sizes for the association of diabetes distress and HRV were small to moderate but were comparable to those for the associations of glycaemic parameters and HRV.
- Diabetes distress may be regarded as a relevant parameter with regard to cardiovascular health highlighting the need for integrated psychosocial care into diabetes management.

Importantly, HRV is not only negatively affected by somatic conditions or stressors, but also by emotional stressors and can thus be considered a marker of psychological health and an important psychophysiological parameter.[9,15] The meta-analysis by Koch et al. demonstrated that HRV was substantially lower in people with major depression, with effect sizes up to 0.46.[9]

As the prevalence of depression in people with diabetes is two to threefold higher than in people without diabetes,[16] these findings on depression and reduced HRV are particularly relevant to people with diabetes. Although depression is an established risk factor for morbidity and early mortality,[16] little is known about the association between depression and HRV among people with diabetes.[17,18] An observational study has shown a mediating effect of depression in association between parasympathetic activation and $HbA_{1c}$ among people with type 2 diabetes,[18] while another study in people with type 2 diabetes found no association between depression and HRV.[17] Studies in people with type 1 diabetes are still lacking.

A construct closely related to depression is diabetes distress. Diabetes distress is an expectable emotional reaction to having diabetes and having to manage this condition 24/7.[19] Elevated diabetes distress occurs when diabetes-specific stressors are perceived as greater than the person's resources for coping and is present in 20–40% of people with diabetes.[19] Common sources of diabetes distress in people with type 1 diabetes are worries about long-term complications, fear of hypoglycaemia, feeling powerless and burnt out, and worries about the future.[19] The clinical relevance of elevated diabetes distress on diabetes management has been demonstrated as diabetes distress is associated with impaired quality of life, suboptimal diabetes self-management and depression.[19] There is also evidence suggesting that diabetes distress may be more strongly associated with glucose levels than depression[20] indicating the relevance to consider condition-specific stressors and their association to somatic outcomes besides more general stressors such as depression.

Taken together, this evidence suggests that diabetes distress is another clinically relevant psychosocial stressor besides depression. Thus, it can be hypothesized that elevated diabetes distress, like depression, might also be associated with a reduced HRV. However, to the best of our knowledge, no study has analysed the association between diabetes distress and HRV in people with type 1 diabetes. One study found longitudinal associations between HRV and negative affect, a composite score including diabetes distress, though this study was conducted in a very selected group of people with type 2 diabetes.[21]

To test the hypothesis that both depression and diabetes distress are associated with lower HRV in people with type 1 diabetes, data from the prospective observational DIALINK1 study in which HRV was measured daily across a 26-day period were analysed. Furthermore, the impact of sensor detected hyperglycaemic and hypoglycaemic exposure as well as glucose variability on a given day on concurrent HRV was analysed.

## 2 | RESEARCH DESIGN AND METHODS

The non-interventional, prospective, observational DIALINK1 Study was designed to analyse the relationships between diabetes distress, depressive symptoms and somatic markers of diabetes management. Glucose values and HRV were recorded daily for 26 days using continuous glucose monitoring (CGM) and a wrist-worn health tracker respectively. A detailed description of the study is available elsewhere,[22] and the full study protocol is available from ClinicalTrials.gov (Reg. No. NCT03811132). Ethical approval was obtained from the Ethics Committee of the German Psychological Society (file number NH082018).

### 2.1 | Participants

Recruitment took place between March 2019 and March 2020 among inpatients who were treated at the Diabetes Centre Mergentheim (Bad Mergentheim, Germany). People with diabetes are referred to this clinic because of problems with their diabetes management such as sustained hyperglycaemia or occurrence of complications, education, initiation of insulin pump therapy or psychosocial issues complicating diabetes management. A total sample of 200 people with type 1 diabetes was targeted. To involve an equal number of participants with and without depression and/or diabetes distress, a stratified recruitment approach was chosen: 50 people with elevated diabetes distress and elevated depressive symptoms, 50 people with elevated diabetes distress only, 50 people with elevated depressive symptoms only and 50 people with neither elevated distress nor depressive symptoms. Inpatients were pre-screened and then informed about the study (orally and in writing). Additionally, those who screened positive for elevated diabetes distress and/or depressive symptoms were informed about the psychosocial services offered by the Diabetes Centre Mergentheim. For study inclusion, the following eligibility criteria had to be fulfilled: diagnosis of type 1 diabetes, diabetes duration ≥1 year, age between 18 and 70 years, sufficient German language skills, having a smartphone compatible with the research app collecting Garmin Vivosmart 4 data and informed consent. People were excluded if any of the following exclusion criteria were present: inability to consent, severe somatic illness or mental disorder likely to confound results (e.g. heart disease, schizophrenia and

bipolar disorder), significant cognitive impairment, being bedridden or terminal illness.

## 2.2 | Study phases

After study inclusion, all participants were equipped with an unblinded, intermittently scanned CGM system (FreeStyle Libre 2) and the Garmin Vivosmart 4 health tracker (Garmin International, Inc., Olathe, USA). The inpatient stay was used to familiarize participants with both devices and to ensure data were collected as intended. Collection of HRV and glucose data started after discharge from the hospital. Thus, although participants were recruited in an inpatient setting, data were collected in an outpatient setting in people's everyday life.

## 2.3 | Assessments

For baseline assessments, electronic health records and case report forms were used to assess demographic and medical data. $HbA_{1c}$ was measured in a central laboratory. To achieve the stratified recruitment, diabetes distress and depressive symptoms were assessed via questionnaires. Diabetes distress was assessed with the German version of the Problem Areas in Diabetes (PAID) questionnaire.[23] A cut-off score ≥ 40 was used to categorize elevated diabetes distress.[23] Depressive symptoms were assessed with the Centre for Epidemiological Studies Depression (CES-D) scale.[24] A cut-off score ≥ 22 was used to categorize elevated depressive symptoms in line with recommendations by Bailer et al.[24]

Heart rate was measured continuously over a 26-day period (day and night) with the Garmin Vivosmart 4, a wrist-worn device which has shown acceptable accuracy and validity to assess HRV.[25,26]

## 2.4 | HRV and glucose processing

All available inter-beat intervals between 0:00 h and 23:59 h were extracted from the Garmin device and used as the basis for calculating HRV per participant, per day. Missing values due to motion artefacts and wear time (e.g. removing the device due to discomfort or inconvenience) are a considerable problem with wearable devices.[27] To compensate for this and ensure reliable data, HRV calculations were done for ultra-short time windows of 30 consecutive seconds for which complete data were present. The use of such ultra-short time windows has been validated to accurately reflect HRV.[27,28] The Root Mean Square of Successive RR interval Differences (RMSSD) was used as a marker for HRV as it has been established as the preferred time-domain measure of HRV when using such ultra-short time windows[27] and is less affected by respiratory influences.[28] Following the recommendations of Laborde et al.,[28] the daily median RMSSD of all valid 30 sec intervals per day was calculated and used as a marker of HRV for each participant on that day. Data cleaning and processing were conducted using R version 2021.10.1.

Similarly, glucose values from 0:00 to 23:59 h were used to calculate the daily percentages of glucose values below 70 mg/dl (<3.9 mmoL/L) and above 180 mg/dl (>10 mmoL/L) as well as the daily coefficient of variation (CV) as marker of glycaemic variability. Additionally, the means of these CGM metrics across the 26-day period were calculated per person.

## 2.5 | Statistical analyses

To take advantage of the longitudinal daily measurement of HRV and glucose, a multilevel modelling approach with participant as nesting factor was employed. The dependent variable was HRV, measured with the daily median RMSSD per person. Within-level predictors were the daily percentages of hypoglycaemic glucose values: <70 mg/dl (<3.9 mmol/L) and hyperglycaemic glucose values: >180 mg/dl (>10 mmol/L), as well as daily CV. Thus, both HRV and glucose data were indicative of the same time frame and were only considered for within-person effects when both were not missing. These within-level predictors were allowed to vary between persons. Between-level predictors were elevated diabetes distress (PAID-score ≥ 40: yes/no), elevated depressive symptoms (CES-D score ≥ 22: yes/no) and the interaction of both. The analysis was controlled for the following variables included as between-level predictors: age, sex, body-mass index (BMI), diabetes duration, number of long-term complications (retinopathy, nephropathy, neuropathy, diabetic foot syndrome, CVD, stroke and arterial vascular disease), $HbA_{1c}$ and the person-average (mean across all study days) hypo- and hyperglycaemic exposure and CV. A sensitivity analysis was conducted with continuous questionnaire scores of diabetes distress and depressive symptoms as between-level predictors. Study day and first autoregressive parameter were controlled in each analysis. Missing data were not replaced. Bayes estimation was used, and raw estimates and standardized regression coefficients (β) are reported. Analyses were conducted with Mplus 8.6. In further sensitivity analysis, a mean HRV value across all study days was calculated per person. Analysis of covariance (ANCOVA) was used

to test the difference in HRV between groups with (vs without) elevated diabetes distress and elevated depressive symptoms, controlling for the above-mentioned factors. Mediation analyses were conducted to evaluate whether glycaemia-related variables mediated the relationship between psychological variables and HRV. The PROCESS (v4.2) macro for SPSS by Andrew F. Hayes was used for mediation analyses. $p < 0.05$ were considered statistically significant.

## 3 | RESULTS

### 3.1 | Sample characteristics

A total of 203 people with type 1 diabetes participated in the study and HRV data could be gained from 149 of them. Reasons for unavailable HRV data included technical problems when transferring data from the Garmin device to the research platform ($n = 49$) and participants not wearing the Garmin device at all ($n = 5$). Sample characteristics are provided in Table 1. Participants had a mean age of 38 years and had lived with diabetes for 18 years on average. The stratified recruitment was generally successful as 44% of participants had elevated depressive symptoms and 54% had elevated diabetes distress at baseline. Comparisons of participant characteristics between those with versus without HRV data revealed no significant differences (see Table 1), indicating no substantial drop out bias for those whose HRV could not be analysed.

### 3.2 | Associations between depressive symptoms, diabetes distress and HRV

Table 2 contains the estimates and standardized regression coefficients for the model predicting daily HRV from within- and between-level predictors. Multilevel regression analysis revealed that participants with elevated diabetes distress at baseline had a nearly 4 milliseconds lower HRV compared to participants without elevated diabetes distress at baseline ($\beta = -0.28$; $p = 0.004$). Figure 1 shows that this effect of lower HRV when diabetes distress was present can be seen across all study days. Elevated depressive symptoms at baseline showed a marginal but statistically non-significant association with HRV ($\beta = -0.18$; $p = 0.074$).

### 3.3 | Associations between glycaemic parameters and HRV

Three different measures of dysglycaemia had an adverse impact on concurrent daily HRV. First, higher exposure to hyperglycaemic values on a given day was associated with reduced HRV on that day ($\beta = -0.44$; $p = 0.044$). On a between-person level, a higher average exposure to hypoglycaemic values ($\beta = -0.18$; $p = 0.042$) across the 26-day study period as well as a higher $HbA_{1c}$ ($\beta = -0.20$; $p = 0.018$) was significantly associated with reduced HRV.

### 3.4 | Sensitivity analyses

Table 3 shows the sensitivity analysis with continuous questionnaire scores for diabetes distress and depressive symptoms. Results were confirmative as higher scores on the PAID questionnaire at baseline were associated with lower HRV ($\beta = -0.31$; $p = 0.010$) and daily hyperglycaemic exposure, average hypoglycaemic exposure and $HbA_{1c}$ remained significant predictors of reduced HRV; whereas higher CES-D scores (depressive symptoms) were not significantly associated with HRV. ANCOVA with HRV averaged across all study days also demonstrated a significant and moderate main effect of elevated diabetes distress on reduced HRV ($F_{(1, 130)} = 6.14$; $p = 0.015$; Cohen's $d = 0.43$) as well as significant effects of $HbA_{1c}$ and average exposure to hypoglycaemic values (Table 4). Mediation analyses indicated a significant direct association between elevated diabetes distress and reduced HRV that was not substantially mediated by $HbA_{1c}$ or exposure to hyper- or hypoglycaemia (Figures S1–S3).

## 4 | DISCUSSION

Over a 26-day period, baseline diabetes distress, exposure to hypoglycaemia and hyperglycaemia, and elevated $HbA_{1c}$ were associated with lower HRV as measured with RMSSD. This indicates that, alongside somatic markers, diabetes distress is a clinically meaningful psychosocial stressor that could play a role in the cardiovascular health of people with type 1 diabetes. The association of diabetes distress with HRV remained significant after controlling for demographic and clinical risk factors. Interestingly, diabetes distress seemed to be more strongly associated with reduced HRV than depressive symptoms which showed no association with HRV. This highlights the relative importance of condition-specific psychosocial stressors beyond general, condition-unspecific depression and further reinforces diabetes distress as an important factor in diabetes therapy.

It was found that the findings were not dependent on a specific cut-off score of elevated diabetes distress. Sensitivity analysis using the continuous score of the PAID questionnaire demonstrated that a higher PAID score was associated with lower HRV. Thus, with increasing severity

**TABLE 1** Baseline characteristics for the sample with and without HRV data

| | Participants with HRV data ($n = 149$) | Participants without HRV data ($n = 54$) | $p$- value |
|---|---|---|---|
| Age (in years) | 38.3 ± 13.1 | 39.0 ± 12.1 | 0.745 |
| Female sex | 59% (88/149) | 57% (31/54) | 0.805 |
| BMI (in kg/m$^2$) | 26.0 ± 5.0 | 26.4 ± 5.7 | 0.619 |
| Years of education | 13.2 ± 2.5 | 12.5 ± 2.6 | 0.088 |
| Duration of diabetes (in years) | 18.2 ± 11.5 | 19.2 ± 12.4 | 0.588 |
| $HbA_{1c}$ (in % [mmol/mol]) | 8.6 ± 1.9 [70 ± 21] | 8.8 ± 2.0 [73 ± 22] | 0.407 |
| Long-term complications (mean per person)[a] | 0.7 ± 0.8 | 0.8 ± 0.9 | 0.520 |
| Depressive symptoms | | | |
| CES-D sum score, range 0–60) | 20.6 ± 11.8 | 23.6 ± 10.2 | 0.100 |
| Elevated depressive symptoms (CES-D ≥ 22) | 44% (66/149) | 63% (34/54) | |
| Diabetes distress | | | |
| PAID sum score, range 0–100 | 40.3 ± 18.4 | 40.0 ± 17.9 | 0.909 |
| Elevated diabetes distress (PAID ≥40) | 54% (80/149) | 50% (27/54) | |
| Heart rate variability (RMSSD) | 43.8 ± 5.4 | – | – |
| CGM metrics across the 26-day study period | | | |
| Mean glucose (mg/dl) | 176.8 ± 40.9 | 178.1 ± 31.4 | 0.838 |
| % of glucose <70 mg/dl (<3.9 mmoL/L) | 3.9 ± 4.2 | 3.4 ± 2.9 | 0.421 |
| % of glucose 70–180 mg/dl (3.9–10 mmoL/L) | 54.5 ± 17.4 | 54.0 ± 16.1 | 0.833 |
| % of glucose >180 mg/dl (> 10 mmoL/L) | 41.6 ± 18.9 | 42.7 ± 17.7 | 0.718 |
| Glucose fluctuations (CV) | 32.2 ± 4.9 | 32.4 ± 4.7 | 0.792 |

*Note*: Data are means ± SD or % ($n/N$).

[a]List of complications: retinopathy, neuropathy, nephropathy, diabetic foot syndrome, cardiovascular disease, apoplexy and arterial vascular disease. Between-group differences were calculated via $t$-test or chi$^2$ test.

of diabetes distress, HRV became more affected indicating a possible dose–response relationship.

The results demonstrate the potential importance of assessing and addressing diabetes distress in clinical practice. There are several questionnaires that enable systematic screening for elevated diabetes distress and offer starting points for addressing problem areas in diabetes management.[19] Several studies and meta-analyses have shown that various intervention strategies exist to treat elevated diabetes distress such as structured diabetes education[29] and psychological interventions.[30] In clinical practice, elevated diabetes distress can be addressed with several strategies, such as exploring feelings, attitudes and expectations about diabetes management; initiating a change in perspective; developing a specific and realistic plan of action; and ongoing monitoring.[31] However, while HRV has been shown to be a clinically meaningful screener for autonomic neuropathy in people with diabetes,[10,11] these findings do not indicate the use of HRV as a screener for diabetes distress. Further research is needed to determine whether it is meaningful to screen for HRV in people with elevated diabetes distress.

The analyses also demonstrated associations between glucose values and HRV. Increased $HbA_{1c}$, exposure to hyperglycaemic values and exposure to hypoglycaemic values were associated with lower HRV. This might be seen in line with findings showing that prolonged hyperglycaemia and hypoglycaemia can negatively affect cardiovascular health.[3,4] Besides, the associations of the rather cumulative glycaemic parameters of $HbA_{1c}$ and average

**TABLE 2** Prediction of heart rate variability across the 26-day period from within- and between-level predictors

| | Estimate[b] | Standardized coefficients (95% CI) | *P*-value |
|---|---|---|---|
| Within-level predictors (daily assessments) | | | |
| Daily hypoglycaemic exposure (<70 mg/dl)[a] | −0.03 | −0.18 (−0.62; 0.47) | 0.598 |
| Daily hyperglycaemic exposure (>180 mg/dl)[a] | **−0.05** | **−0.44 (−0.67; −0.03)** | **0.044** |
| Daily glucose fluctuations (CV)[a] | −0.07 | −0.30 (−0.73; 0.44) | 0.564 |
| Between-level predictors (baseline assessment) | | | |
| Elevated diabetes distress | **−3.75** | **−0.28 (−0.43; −0.10)** | **0.004** |
| Elevated depressive symptoms | −2.42 | −0.18 (−0.35; 0.02) | 0.074 |
| Interaction between distress and depression | 2.83 | 0.19 (−0.06; 0.38) | 0.124 |
| Person-average hypoglycaemic exposure[a] | **−2.95** | **−0.18 (−0.36; −0.01)** | **0.042** |
| Person-average hyperglycaemic exposure[a] | −0.54 | −0.15 (−0.34; 0.03) | 0.106 |
| Person-average glucose fluctuations[a] | 1.30 | 0.09 (−0.07; 0.25) | 0.254 |
| $HbA_{1c}$ | **−0.73** | **−0.20 (−0.37; −0.03)** | **0.018** |

*Note*: $N = 149$. Two-level regression analysis using Bayes estimation with participant as nesting factor. Analysis was controlled for study day, first autoregressive parameter, age, sex, BMI, diabetes duration and mean number of long-term complications. Significant findings ($p < 0.05$) appear in boldface type.

[a]Unit of glucose parameters in increments of 10%.

[b]Estimate refers to the unstandardized coefficients from the multilevel regression.

hypoglycaemic exposure on a between-person level, the daily exposure to hyperglycaemic values within an individual also showed an association to HRV. This suggests that daily, not only cumulative, glucose values, may directly affect HRV. Further analyses are needed to replicate this association and confirm its direction. Interestingly, average hypoglycaemic exposure was significantly associated with HRV independent of $HbA_{1c}$ while average hyperglycaemic exposure was not. This difference may be due to the stronger association of average hyperglycaemic exposure with $HbA_{1c}$ ($r = 0.59$) compared to the association of average hypoglycaemic exposure with $HbA_{1c}$ ($r = -0.20$). As such, we would argue that average hypoglycaemic exposure cannot be explained by $HbA_{1c}$ and thus contributes independently to HRV. Compared with average hyperglycaemic exposure, daily hyperglycaemic exposure seems to contain additional information not fully explained by $HbA_{1c}$, leading to the significant association with daily HRV in multilevel models. Daily hypoglycaemic events may have been too few resulting in lower statistical power in contrast to average hypoglycaemic exposure. Only 48% of the observed days had a CGM reading within hypoglycaemic range, whereas 97.9% of participants had at least one hypoglycaemic event across the study days.

One strength of our study is that the identified associations appeared to be rather stable as they were corroborated in sensitivity analyses. Even when the multilevel data structure of daily HRV values nested within a person was not considered, and just one HRV value per person was calculated by averaging HRV across all eligible study days, the same significant variables were identified using ANCOVA. This indicates that the effect of elevated diabetes distress on reduced HRV is not a chance finding or a statistical artefact and represents a statistically robust and clinically meaningful effect. Elevated diabetes distress showed small-to-moderate associations with reduced HRV that were descriptively larger than the associations of $HbA_{1c}$ and hypoglycaemic exposure with HRV. In addition, mediation analyses indicate that elevated diabetes distress was independently associated with reduced HRV and that dysglycaemia was not a substantial mediator of this association. This provides support for

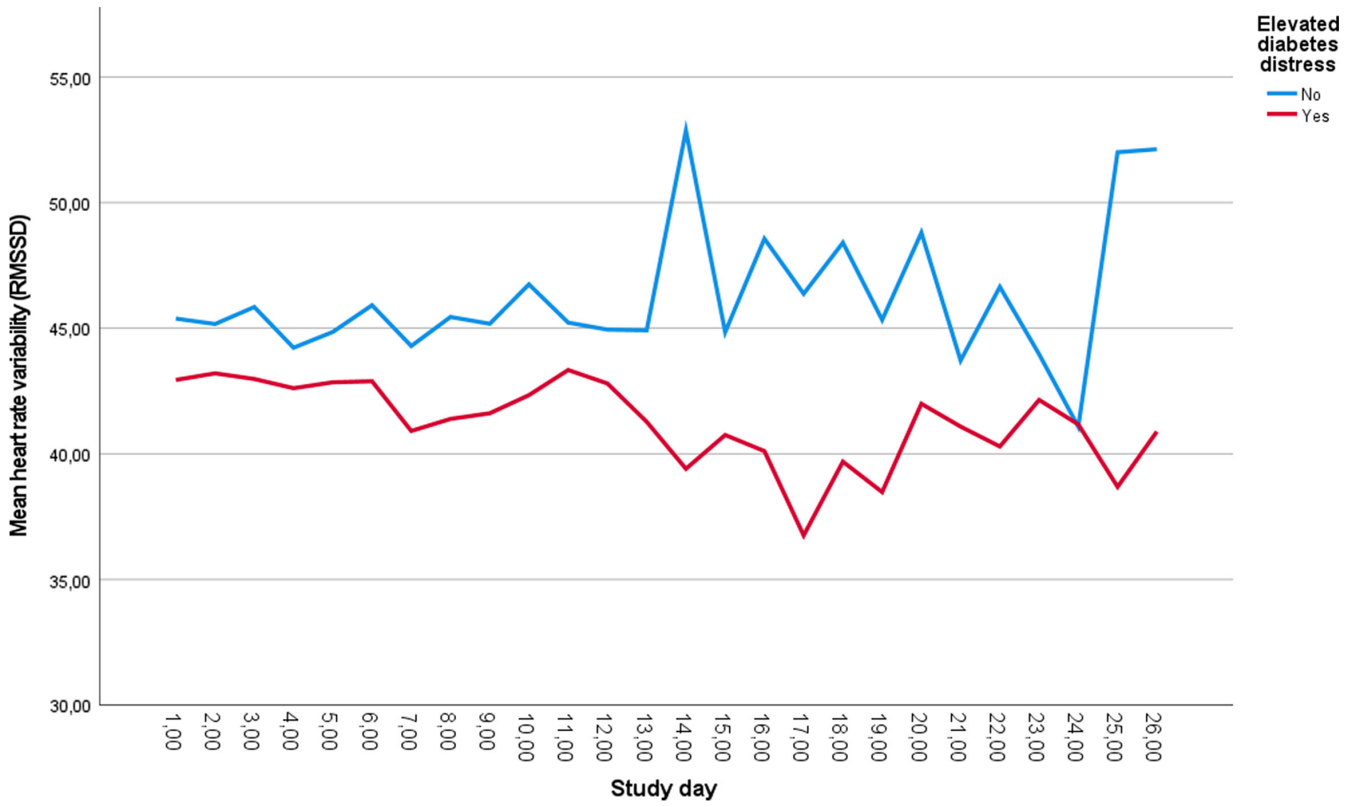


**FIGURE 1** Mean heart rate variability (RMSSD) across the study days for people with and without elevated diabetes distress.

**TABLE 3** Sensitivity analysis: Prediction of heart rate variability across the 26-day period from within- and between-level predictors with continuous questionnaire scores

| | Estimate[b] | Standardized coefficients (95% CI) | *P*-value |
|---|---|---|---|
| Within-level predictors (daily assessments) | | | |
| Daily hypoglycaemic exposure (<70 mg/dl)[a] | −0.02 | −0.11 (−0.58; 0.45) | 0.726 |
| Daily hyperglycaemic exposure (>180 mg/dl)[a] | **−0.04** | **−0.36 (−0.62; −0.01)** | **0.049** |
| Daily glucose fluctuations (CV)[a] | −0.07 | −0.28 (−0.70; 0.43) | 0.570 |
| Between-level predictors (baseline assessment) | | | |
| Continuous diabetes distress score (PAID) | **−0.13** | **−0.31 (−0.47; −0.08)** | **0.010** |
| Continuous depressive symptoms score (CES-D) | −0.14 | −0.22 (−0.42; 0.09) | 0.144 |
| Interaction between distress and depression | 0.003 | 0.36 (−0.07; 0.59) | 0.094 |
| Person-average hypoglycaemic exposure[a] | **−3.21** | **−0.18 (−0.35; −0.02)** | **0.034** |
| Person-average hyperglycaemic exposure[a] | −0.50 | −0.12 (−0.32; 0.05) | 0.146 |
| Person-average glucose fluctuations[a] | 1.63 | 0.11 (−0.04; 0.25) | 0.146 |
| $HbA_{1c}$ | **−0.79** | **−0.19 (−0.35; −0.05)** | **0.008** |

*Note*: $N = 149$. Two-level regression analysis using Bayes estimation with participant as nesting factor. Analysis was controlled for study day and first autoregressive parameter, age, sex, BMI, diabetes duration and mean number of long-term complications. Significant findings ($p < 0.05$) appear in boldface type.

[a]Unit of glucose parameters in increments of 10%.

[b]Estimate refers to the unstandardized coefficients from the multilevel regression.

**TABLE 4** Results from analysis of covariance with HRV averaged across all study days as dependent variable

| Predictors | F | *p* | Partial Eta$^2$ (Cohen's *d*) |
|---|---|---|---|
| Elevated diabetes distress | **6.136** | **0.015** | **0.045 (0.43)** |
| Elevated depressive symptoms | 2.214 | 0.139 | |
| Interaction between distress and depression | 1.752 | 0.188 | |
| Person-average hypoglycaemic exposure | **4.257** | **0.041** | **0.032 (0.36)** |
| Person-average hyperglycaemic exposure | 3.128 | 0.079 | |
| Person-average glucose fluctuations | 0.887 | 0.348 | |
| $HbA_{1c}$ | **6.640** | **0.011** | **0.049 (0.45)** |

*Note*: $N = 149$. Analysis was controlled for age, sex, BMI, diabetes duration and mean number of long-term complications. Significant findings ($p < 0.05$) appear in boldface type. Partial Eta$^2$ depicts the effect size of significant effects and was converted to Cohen's *d* to aid interpretation.

previous findings that HRV is affected both by physiological and psychological states and has thus been considered a marker of 'psychological resiliency'.[15] Thus, dysglycaemia and elevated diabetes distress may exist in absence of each other and have an independent but also potentially additive effect on reduced HRV. This further highlights the role of psychosocial stressors such as diabetes distress for the clinical management of diabetes and the importance of prioritizing psychosocial care as a standard component of diabetes care. While the role of diabetes distress in the development of long-term complications is unclear,[32] this analysis may provide first evidence for an association or potential mechanism that might link diabetes distress to cardiovascular health via lower adaptation of the beat-to-beat variability and autonomic function.

When interpreting the findings, the following limitations should be considered. First, due to practical reasons, HRV was assessed via a wearable fitness tracker using photoplethysmography which may be less accurate than electrocardiogram or electrodes, limiting reliability to a certain degree. Second, participants were recruited from an inpatient setting with rather suboptimal glycaemic management and increased psychosocial issues as per the stratified recruitment strategy. Thus, participants might not be representative of the broader population of people with type 1 diabetes in other healthcare settings. Third, due to the observational nature of the analysis, a potential causal link cannot be inferred. Lastly, potential confounders of HRV such as pregnancy, sleep, caffeine or alcohol consumption, and heart medication were not controlled. More work is needed to understand the exact mechanisms and temporal relationships linking HRV and diabetes distress, the influence of different sources of diabetes distress, and the associations in other groups (e.g. people with type 2 diabetes).

In summary, the analysis supports the clinical importance of diabetes distress, as a significant association with reduced HRV was found among people with type 1 diabetes. This effect of a diabetes-specific psychosocial stressor stands alongside glycaemic risk factors of reduced HRV such as daily hyperglycaemic exposure, increased $HbA_{1c}$ and average hypoglycaemic exposure. Given that reduced HRV is a surrogate marker for decreased cardiovascular health, these findings have clinical relevance and highlight the need for integrated psychosocial care in diabetes management. However, further research is needed to elucidate the possible role of diabetes distress in the development of CVD. More research is also needed to investigate the biological and behavioural mechanisms that link diabetes distress and HRV and to determine whether a reduction in diabetes distress or increased HRV is clinically relevant for reducing cardiovascular risk.

## AUTHOR CONTRIBUTIONS

D.E. and N.H. wrote the manuscript. D.E., H.C. and N.H. analysed data. H.C., U.S. and J.L.A. prepared HRV data for statistical analysis. A.S. collected data, revised the manuscript and contributed to the discussion. B.K., H.C., U.S., J.L.A., M.B., T.H. and F.P. revised the manuscript and contributed to the discussion. D.E., A.S., B.K. and N.H. designed the study. D.E. and N.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported. U.S. works for Novo Nordisk A/S (the work for this manuscript was undertaken prior to this employment).

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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