



## High Glycaemic Variability is Associated with Worse Diabetes-related Well-being in Type 2 Diabetes Patients on Insulin Therapy, an Observational Study

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### Abstract

**Aims:** Patients with diabetes have a reduced quality of life, especially those with high HbA1c. This study investigates if high glycaemic variability also negatively influences diabetes-related well-being.

**Methods:** This cross-sectional observational study was conducted at the University Medical Centre Utrecht (UMCU), the Netherlands (February 2010 - July 2013). Type 2 diabetes patients attending the (outpatient) clinic of the UMCU were approached to participate in a nationwide biobank study. In the UMCU, patients were also approached to participate in a local add-on study (this study), which required separate consent. Glycaemic variability was measured by continuous glucose monitoring in 124 patients with type 2 diabetes by standard deviation of glucose data from 48 hours. The Problem Areas in Diabetes Scale (PAID) was used to assess diabetes distress. Health status was assessed by 12-item short-form general health survey and EuroQoL of life-5 dimensions visual analogue scale. Association of glycaemic variability and quality of life was analysed in the entire study population and in pre-defined subgroups (insulin treatment (n = 68); other treatment (n = 56)). Associations were investigated using linear regression.

**Results:** A higher glycaemic variability tended to be associated ( $p = 0.07$ ) with a worse PAID score in the entire study population ( $\beta0.20$  (95% CI 0.01-0.42)), but this attenuated when adjusted for confounders. High glycaemic variability was associated with worse PAID score in insulin-treated patients ( $\beta0.33$  (95% CI 0.01-0.65)), especially in the domains treatment-related problems ( $\beta0.29$  (95% CI 0.09-0.50)) and diabetes-related emotional problems ( $\beta0.32$  (95% CI 0.03-0.61)). These associations attenuated ( $\beta0.24$  (95% CI 0.04-0.44);  $\beta0.24$  (95% CI -0.06-0.54)) after correction for confounders and after correction for HbA1c ( $\beta0.15$  (95% CI 0.07-0.38);  $\beta0.17$  (95% CI 0.17-0.52)). Glycaemic variability was not consistently associated with parameters from other questionnaires.

**Conclusions:** High glycaemic variability was associated with diabetes distress albeit not independent of HbA1c. Since this association was found in insulin-treated type 2 diabetes patients only; glycaemic variability could be a potential treatment goal for this particular group.

### Keywords

Glycaemic variability, Diabetes-related well-being, PAID, Diabetes distress

### Introduction

Patients with diabetes mellitus have a decreased quality of life as compared to the general population, especially when diabetes complications and hypoglycaemia are present [1-4]. In addition, poor glycaemic control (as measured by elevated HbA1c) is associated with worse quality of life in most studies [1,5-7]. One study suggests that the relation between HbA1c and quality of life is not strictly linear, but that quality of life is best in patients with HbA1c levels between 7 and 8% (53 and 64 mmol/mol) [1].

Increased glycaemic variability is an additional characteristic of the diabetic state. Glycaemic variability and its possible association with diabetes complications has been researched thoroughly. However, this association remains controversial because studies showed inconsistent results [8-14]. Some studies did show that glycaemic variability was associated with diabetes complications, for instance with retinopathy [13], neuropathy [8] and coronary artery calcification [14]. Whereas other studies could not confirm this association [10,11].

Considering this ongoing controversy about the association between glycaemic variability and diabetes organ complications, we used a different approach in this study. We investigated if glycaemic variability itself is bothersome for a patient and if it is associated with health status, diabetes-related well-being or diabetes distress. If so, this would emphasize that glycaemic variability emerges as a clinical problem.

Our hypothesis is that increased glycaemic variability might not only lead to more frequent (symptomatic) hypo- and hyperglycaemia but also to a feeling of non-predictability of the disease and a decrease in perceived ability to control it, which might lead to more

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diabetes distress. With large glycaemic variability the daily effort to approximate a non-diabetic metabolic state can seem futile and patients can feel resigned, possibly leading to worse diabetes-related well-being.

In a previous small study in type 1 diabetes patients (n = 32), only an association between mood and actual level of glucose (measured real-time) was found, but no association of mood with glycaemic variability in the previous hour [15]. In contrast, two prior cross-sectional studies in type 2 diabetes had reported an association between reduced glycaemic variability and improved health-related quality of life and health status in patients with type 2 diabetes [16,17]. However, both studies investigated only a small sample of patients (n = 23 - 54) and neither adjusted for HbA1c.

In our study, we aim to investigate this association in a large sample of type 2 diabetes patients and determine whether or not glycaemic variability is associated with diabetes-related well-being, independent of HbA1c.

## Materials and Methods

### Study design and patients

This observational prospective study was conducted at the University Medical Centre Utrecht (UMCU), the Netherlands, from February 2010 till July 2013 as part of a nationwide long-term bio bank initiative for patients with type 2 diabetes (Diabetes Pearl). The Diabetes Pearl is a large cohort of patients diagnosed with type 2 diabetes, covering different geographical areas in the Netherlands. The aim of the study is to create a research infrastructure that will allow the study of risk factors, including biomarkers and genetic determinants for severe diabetes complications [18]. The current study was a local add-on to this national database study. It was conducted according to Good Clinical Practice and the protocol was approved by the ethics committee of the (UMCU). Written informed consent was obtained from all patients. Type 2 diabetes patients, able to speak and understand Dutch and attending the (outpatient) clinic of the UMCU were approached to participate in a nationwide biobank study. All patients that participated in the biobank study in the UMCU were also approached to participate in the local add-on study (this study), which required separate consent. Patients filled in quality of life questionnaires, and at their first visit lab results (for HbA1c) were taken and continuous glucose monitoring was started. All health questionnaires were taken before start of continuous glucose monitoring (CGM).

### Assessment of glycaemic variability

Patients wore an off-line continuous glucose monitoring system (CGMS) for > 48 hours (*iPro®2 Professional CGM, Medtronic*). With this CGMS glucose levels were recorded subcutaneously every 5 minutes (288 readings per day), and all data was blinded for the patients. The first 48 hours (2 days) from midnight till midnight were used to calculate glycaemic variability. Glycaemic variability was calculated as the standard deviation (SD) of all glucose data from 48 hours. The glucose data was complete (576 glucose data) for 81% of the patients. Patients with less than 50% recorded glucose data (< 288 readings) were defined as inadequate data and were excluded from the analysis (n = 2). We specified SD as the parameter of choice to describe glycaemic variability, since our previous study showed that SD is highly correlated to other parameters of variability, which is further discussed in our discussion section.

### Quality of life questionnaires

Several questionnaires were used to assess health status and diabetes-related well-being. These questionnaires were filled in by the patients just before wearing CGM. First, the Dutch version of the Problem Areas in Diabetes Scale (PAID) questionnaire was used to measure diabetes-related well-being or diabetes distress [6]. The questionnaire consists of 20 items, which are scored by the patient on a 5 point Likert scale (0 = no problem, 4 = severe problem). The total score is then amplified by 1.25, rendering a score from 0 - 100

[19] with 0 being the best achievable score and 100 the worst score. The PAID score is known to have consistently high internal reliability  $\alpha = 0.90$  and a sound test-retest reliability in stable patients ( $r = 0.83$ ) [19]. The questionnaire can be divided into four subdomains: diabetes-related emotional problems, treatment-related problems, food-related problems and social support-related problems [6].

Furthermore, two generic measures of health status were used. The first was the Dutch version of the 12-item short-form general health survey (SF-12) [20,21]. The SF-12 contains 12 items derived from the more extensive SF-36 health related quality of life form. This questionnaire is reported as two separate scores for health status, considering a physical component score and a mental component score. Scores range from 0 to 100, with 100 being the best health status achievable and 0 the worst. Second, the EuroQuality of life-5 dimensions visual analogue scale (EQ5D-VAS) was used. This questionnaire consists of an overall score on a visual analogue scale (VAS) from 0 (worst) to 100 (best), on which a patient estimates his or her own health state. A list of five questions within separate dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) is added to this VAS. Patients can score 1 indicating no problem, 2 indicating some problems or 3 indicating extreme problems. A health state can be derived from the answers to the questions, which can be further translated into a single index value.

### Statistical analysis

Results are presented as mean and SD for normally-distributed variables and median and range for non-normally distributed parameters. A student's t-test was used to compare between two groups with normal distribution. Linear regression analysis was used to identify parameters associated with outcome of interest. If the variables were non-normally (right-skewed) distributed, then they were log-transformed and in case of left-skewed distribution, they were exponentially transformed. Regression analyses were adjusted for pre-defined confounders; age, sex, duration of DM, educational level or use of antidepressant drugs. Although we do not regard HbA1c as a confounder, we adjusted for HbA1c in a separate model to investigate whether the results for glycemic variability were independent of HbA1c. Missing values of confounders were imputed, using the mean value (HbA1c 1 missing value, duration of diabetes 20 missing values). Association of glycaemic variability with scores on different questionnaires was analysed in the whole group, and in pre-defined subgroups based on treatment regimen (insulin treatment (n = 68) versus other treatment (n = 56). These subgroups had been predefined because glycaemic variability was expected to be higher in insulin users than in non-insulin users. The interaction between glycaemic variability and treatment group was tested by including an interaction term in the model. Standardised  $\beta$ 's were used to compare the associations of HbA1c and SD with outcome (scores on PAID questionnaire) separately. The different domains of the PAID score were also analysed as an additional outcome. Because the distribution of residuals from linear regression for the domains problems with food and lack of social support was not entirely normal, these analyses were repeated using logistic regression (after dichotomizing data below or above mean). Finally, a sensitivity analysis was performed on all analyses to adjust for selection bias due to patients not consenting separately to CGM using inverse probability weighting. Level of significance was set at  $p < 0.05$ .

## Results

From February 2010 till July 2013, 1372 patients were screened and 508 patients were included in the nation-wide biobank study, 5 withdrew consent, leaving 503 patients for analysis. Continuous glucose monitoring (CGM) data were not available in all 503 patients since an additional informed consent was necessary for wearing the CGMs and the majority of the patients only consented to questionnaires and laboratory measurements. A total of 126 patients signed the additional consent for CGM and from these patients 124 (98%) had adequate data and could be included for analysis in this

**Table 1:** Baseline characteristics of the 124 Type 2 diabetes patients included, compared to 377 patients, who did not consent to CGM.

	Patients included N = 124	Patients that did not consent to CGM N = 377
Age	58 (11)	61 (12)*
Sex (% female)	46 %	38%
Ethnicity (% caucasian)	90 %	85%
BMI	32 (6)	31 (6)
HbA1c (mmol/mol)	58 (18)	58 (14)
Duration of DM (years)	11 (8)	13 (10)*
Blood pressure (MAP in mmHg)	98 (10)	97 (12)
Current smoking	20 %	16%
Use of antidepressant drugs	6%	9%
<b>Complications</b>		
- microvascular		
- neuropathy	26 %	30%
- retinopathy	20 %	25%
- nephropathy	19 %	20%
- macrovascular	32 %	38%
<b>Therapy</b>		
- None	5 %	5%
- Oral agents only/ GLP-1 analogs	40 %	39%
- Insulin	55 %	56%
o Long-acting	6 %	6%
o Premix	4 %	8%
o Intensive	38 %	35%
o CSII	7 %	7%
Glycaemic variability (SD)	2.2 (1.0)	Not determined
<b>Questionnaires</b>		
PAID	12.5 (0-75)	7.5 (0-67.5)*
SF-12		
Physical component score	39 (11)	41 (11)
Mental component score	46 (10)	48 (10)*
EQ5D		
VAS score	64 (18)	65 (19)
Index Value	0.78 (-0.13 – 1.00)	0.81 (-0.26 - 1.00)

Results are described as mean (SD) or median (range) or percentage

HbA1c 58 mmol/mol equals 7.5%

Neuropathy is defined as a score on the neurothesiometer of > 25 V

Retinopathy is defined as any degree of retinopathy (as assessed by fundus photographs)

Nephropathy is defined as GFR (MDRD) < 60

Macro-vascular complication is defined as a composite endpoint (MI or CVA or angioplasty or vascular surgery (coronary, carotid, femoral, iliacal, aortal)

Antidepressants drugs were defined as drugs that are indicated for depression, however drugs commonly prescribed for neuropathic pain were excluded (amitriptyline, duloxetine, nortriptilene)

\*Significant difference (p < 0.05)

study. The mean glycaemic variability (SD) in the total group was 2.2 (1.0). This was significantly higher in the subgroup of patients on intensive insulin scheme (SD 2.7) compared to the glycaemic variability in the subgroup of patients on oral agents or diet only (SD 1.7, p < 0.001). HbA1c was associated with glycaemic variability (Pearson coefficient r = 0.46 p = <0.001) and with the score on the PAID questionnaire (r = 0.30, p = 0.01), but not with scores on other questionnaires.

Baseline characteristics are shown in [Table 1](#). Included patients were predominantly of Caucasian origin, and had a median age of 58 years, BMI 32, and HbA1c 7.5% (58 mmol/ mol). Duration of diabetes was approximately 11 years and most patients (55%) used insulin. Baseline characteristics of included patients were compared to characteristics of patients that did not consent to CGM. The latter were older, had longer duration of diabetes and scored better on the PAID and SF 12 mental component score ([Table 1](#)).

A higher glycaemic variability tended to be associated (p = 0.067) with worse PAID score ( $\beta$  0.2; 95% CI-0.014 - 0.41). The association attenuated after correction for pre-defined confounders (age, sex, duration of diabetes, educational level or use of antidepressant drugs)

( $\beta$  0.17 (95% CI-0.06-0.40) p = 0.158) and after adjusting for HbA1c ( $\beta$  0.03 (95% CI-0.24-0.30) p = 0.817) ([Table 2](#)).

The association of glycaemic variability with the PAID score was also analyzed in pre-defined subgroups based on treatment regimen (interaction term for SD\* treatment p = 0.14). A higher glycaemic variability was associated with a worse PAID score in the insulin-treated patients only ( $\beta$  0.33 (95% CI0.01-0.65), p = 0.042), whereas variability was not related to scores on PAID questionnaires among patients on other treatment. The association in the insulin-treated patients attenuated to non-significance after correction for confounders ( $\beta$  0.26 (95% CI-0.09-0.61) p = 0.139) and adjustment for HbA1c ( $\beta$  0.20 (95% CI-0.20-0.59) p = 0.316) ([Table 2](#)).

Glycaemic variability was associated with two of the four domains of the PAID score (treatment-related problems and diabetes-related emotional problems). These associations were found in the total and in the insulin-treated group, but not in the subgroup on oral treatment or diet ([Table 3](#)). The associations were significant after correction for confounders in the domain treatment-related problems domain ( $\beta$  0.24 (0.04-0.44) p = 0.021), but attenuated in the domain diabetes-related emotional problems ( $\beta$  0.24 (95% CI-0.06-0.54) p = 0.108).

**Table 2:** Linear regression analysis showing association of glycaemic variability (SD) with (log)PAID score in patients on different therapeutic regimen.

	Total group (n = 124)		Diet or oral agents only (n = 56)		Insulin treatment (n = 68)	
	B (CI)	P	B (CI)	P	B (CI)	P
SD	0.20 (-0.01–0.42)	0.067	-0.03 (-0.42–0.35)	0.858	0.33 (0.01 - 0.65)	0.042
MV	0.16 (-0.07–0.38)	0.167	-0.02 (-0.41–0.38)	0.926	0.26 (-0.07 – 0.59)	0.119
MV + HbA1c	0.00 (-0.26–0.26)	0.977	-0.28 (-0.71–0.15)	0.201	0.17 (-0.21 – 0.54)	0.371

PAID = Problem Areas in Diabetes Scale

MV = Adjusted for pre-defined covariates (age, sex, duration of diabetes, use of antidepressant drugs and education level)

MV + HbA1c = Also adjusted for HbA1c

**Table 3:** Linear regression analysis showing association of glycaemic variability (SD) with (log)PAID score in different pre-defined domains of the PAID questionnaire.

	Total group (n = 124)		Diet or oral agents only (n = 56)		Insulin treatment (n = 68)	
	$\beta$ (CI)	P	$\beta$ (CI)	P	$\beta$ (CI)	P
<b>Domains of PAID</b>						
Diabetes-related emotional problems	<b>0.23 (0.04-0.43)</b>	<b>0.021</b>	-0.02 (-0.38-0.35)	0.934	<b>0.32 (0.03-0.61)</b>	<b>0.031</b>
- MV	0.18 (-0.03-0.38)	0.096	0.00 (-0.38-0.38)	0.995	0.24 (-0.06-0.54)	0.108
- MV + HbA1c	0.04 (-0.21-0.28)	0.754	-0.21 (-0.63-0.21)	0.313	0.17 (-0.17-0.52)	0.320
Treatment-related problems	<b>0.23 (0.09-0.37)</b>	<b>0.001</b>	0.15 (-0.09-0.40)	0.211	<b>0.29 (0.09-0.50)</b>	<b>0.006</b>
- MV	<b>0.22 (0.08-0.37)</b>	<b>0.003</b>	0.15 (-0.12-0.43)	0.270	<b>0.24 (0.04-0.44)</b>	<b>0.021</b>
- MV + HbA1c	0.11 (-0.06-0.27)	0.211	-0.02 (-0.32-0.27)	0.943	0.15 (-0.07-0.38)	0.171
Food-related problems	-0.01 (-0.15-0.13)	0.879	-0.05 (-0.28-0.19)	0.684	0.07 (-0.14-0.28)	0.504
- MV	-0.03 (-0.18-0.11)	0.639	-0.05 (-0.30-0.20)	0.694	0.01 (-0.21-0.22)	0.935
- MV + HbA1c	-0.12 (-0.29-0.04)	0.144	-0.18 (-0.46-0.10)	0.201	-0.06 (-0.32-0.19)	0.617
Social support-related problems	0.05 (-0.07-0.16)	0.410	-0.12 (-0.28-0.04)	0.151	0.09 (-0.10-0.27)	0.366
- MV	0.03 (-0.09-0.14)	0.628	-0.11 (-0.28-0.07)	0.226	0.03 (-0.16-0.22)	0.740
- MV + HbA1c	-0.03 (-0.17-0.11)	0.677	-0.14 (-0.34-0.06)	0.165	-0.02 (-0.24-0.20)	0.850

PAID = Problem Areas in Diabetes Scale

MV = Adjusted for pre-defined covariates (age, sex, duration of diabetes, use of antidepressant drugs and education level)

MV + HbA1c = Also adjusted for HbA1c

None of the associations were significant after correction for HbA1c ( $\beta$  0.15 (95% CI-0.07-0.38)  $p = 0.171$ ,  $\beta$  0.17 (95% CI-0.17-0.52)  $p = 0.320$ ) data for insulin-treated patients)). When analyses were repeated with logistic regression analysis, results were comparable.

Comparison of the standardized  $\beta$ 's for association of HbA1c or SD with PAID scores showed that these were comparable in the insulin-treated group (SD  $\beta$  0.26  $p = 0.042$ ; HbA1c  $\beta$  0.27  $p = 0.034$  (univariate) SD  $\beta$  0.13  $p = 0.371$ ; HbA1c  $\beta$  0.15  $p = 0.331$  (multivariate)), whereas in the total group (SD  $\beta$  0.17  $p = 0.067$ ; HbA1c  $\beta$  0.26  $p < 0.001$ ) and other treatment group (SD  $\beta$  -0.03  $p = 0.858$ ; HbA1c  $\beta$  0.32  $p = 0.017$ ) HbA1c was the most important or even only factor (multivariate HbA1c  $\beta$  0.25-0.38, SD not significant).

Glycaemic variability was not associated with scores on generic measures of health status (SF12 or EQ5D) with the exception of a significant association between higher glycaemic variability and worse scores on SF12 physical component score in the insulin-treated group ( $\beta$  -3.29 (95% CI-6.42- -0.17),  $p = 0.039$ ) after correction for confounders and HbA1c, whereas the opposite was found in patients with other treatment for the SF12 mental component score ( $\beta$  3.52 (95% CI 0.08-6.96)  $p = 0.045$ ) (Supplement 1).

Sensitivity analyses to adjust for selection bias due to patients that did not consent separately to CGM using inverse probability weighting showed comparable results. The association between glycaemic variability and PAID score in the entire study population ( $\beta$  0.20,  $p = 0.067$ ) did not change after sensitivity analysis ( $\beta$  0.20,  $p = 0.053$ ); nor did the association in the insulin-treated group ( $\beta$  0.33  $p = 0.042$ , after inverse probability weighting  $\beta$  0.31,  $p = 0.043$ ).

## Discussion

This study shows that increased glycaemic variability is associated with more diabetes distress and reduced diabetes-related well-being, measured by a diabetes-specific questionnaire, in insulin-treated patients with type 2 diabetes. These associations were present in the sub-domains considering diabetes-related emotional problems and treatment-related problems, but these were not independent from HbA1c.

Our findings are in concordance with two previous smaller studies in type 2 diabetes patients, which also showed an association between reduced glycaemic variability and improved health-related quality of life and health status [16,17]. However these studies did not correct for HbA1c. Our data suggest that the association of glycaemic variability with worse quality of life is not independent from HbA1c.

Associations of higher glycaemic variability with reduced diabetes-related well-being were only found in the insulin-treated patients. This was expected since this particular group has higher glycaemic variability. The strength of associations of HbA1c or SD with PAID scores was comparable in the insulin-treated group, whereas in the group with patients on other treatment, HbA1c was the most important factor. These results suggest that treating glycaemic variability in clinical practice should be considered for insulin-treated patients only. Glycaemic variability could be reduced by optimizing education, dietary advice and (pre-prandial) insulin doses, or by intervention in the incretin pathway (GLP1-analoga or DPP4-inhibitors), which improve alpha and beta cell function in a glucose dependent manner. Another way to reduce glycemic variability could be by (real-time) continuous glucose monitoring, enabling patients to react to minor glucose changes, and in doing so, and keep variability as low as possible. The exact target of lowering glycaemic variability should be individualized and depends on the glycaemic variability measured and the score on the PAID questionnaire for the individual patient.

Associations of glycaemic variability were mainly found with scores on the PAID questionnaire. This was expected since the PAID questionnaire is a disease-specific questionnaire, consisting of questions that could be specifically affected by glycaemic variability. Glycaemic variability will inevitably mean more hyper- and/or hypoglycaemia, which could produce symptoms, possibly decreasing quality of life. Furthermore, we hypothesized that a high degree of glycaemic variability can lead to more problems with the manageability and controllability of the disease. Moreover, the daily effort to approximate normal glucose levels can seem futile to patients with large glycaemic variability, which can result in frustration

**Supplement 1:** Linear regression analysis showing association of glycemic variability (SD) with SF-12 scores and EQ5D

	Total group		Diet or oral agents only		Insulin treatment	
	$\beta$ (CI)	P	$\beta$ (CI)	P	$\beta$ (CI)	P
SF12 physical	-1.46 (-3.40-0.49)	0.140	0.86 (-2.84-4.56)	0.643	-2.48 (-5.08-0.12)	0.061
- MV	-0.53 (-2.58-1.52)	0.611	1.88 (-2.19-5.95)	0.357	-2.16 (-4.82-0.50)	0.110
- MV + HbA1c	-1.17 (-3.56-1.21)	0.334	1.39 (-3.29-6.08)	0.552	<b>-3.08 (-6.07-0.09)</b>	<b>0.044</b>
SF12 mental	0.31 (-1.45-2.07)	0.727	1.32 (-2.11-4.74)	0.445	-0.12 (-2.46-2.21)	0.917
- MV	0.42 (-1.36-2.19)	0.644	0.21 (-3.27-3.68)	0.906	0.72 (-1.59-3.04)	0.534
- MV + HbA1c	1.86 (-0.15-3.86)	0.069	<b>3.52 (0.08-6.96)</b>	<b>0.045</b>	1.14 (-1.50-3.78)	0.390
EQ5D VAS	-1.00 (-4.32-2.33)	0.555	1.66 (-4.57-7.88)	0.595	-1.20 (-5.67-3.37)	0.603
- MV	-0.65 (-4.15-2.86)	0.715	-0.25 (-6.98-6.48)	0.941	-0.10 (-4.83-4.63)	0.967
- MV + HbA1c	-0.20 (-4.31-3.91)	0.925	2.20 (-5.43-9.81)	0.565	-0.81 (-6.21-4.58)	0.764
EQ5D index value	-0.01 (-0.10-0.07)	0.770	0.07 (-0.08-0.21)	0.389	0.00 (-0.12-0.12)	0.970
- MV	0.02 (-0.07-0.11)	0.662	0.08 (-0.08-0.25)	0.332	0.04 (-0.08-0.16)	0.490
- MV + HbA1c	0.03 (-0.08-0.13)	0.603	0.09 (-0.10-0.28)	0.351	0.04 (-0.10-0.17)	0.601

SF12 physical = SF12 physical component score

SF12 mental = SF12 mental component score

EQ5D VAS = EQ5D visual analogue scale

MV = Adjusted for pre-defined covariates (age, sex, duration of diabetes, use of antidepressant drugs and education level)

MV + HbA1c = also adjusted for HbA1c

and negative feelings about diabetes. Our results are in line with this hypothesis since we observed associations with the domains treatment-related problems and diabetes-related emotional problems particularly. However, we have to consider the possibility that it could also be the other way around, that patients with better diabetes-related well-being are more capable of adequate self-management and hence experience less glycaemic variability.

We did not find associations of glycaemic variability with scores on health-related questionnaires, not specifically designed for diabetes patients (SF12, EQ5D), with the exception of the adjusted positive association between variability and SF 12 physical component score in the insulin-treated group, whereas the opposite was found for the mental component score in the non-insulin-treated patients. This is in contrast to the analysis with the PAID questionnaires, in which the association attenuated to non-significance after correction for HbA1c. We cannot explain the different and contradictory outcome after correcting for HbA1c in the associations with the SF12. However, since these are the only significant outcomes for the health-specific questionnaires and no consistent significant results were found at all for the other regression analyses, these associations are considered chance findings.

Measurement of glycaemic variability is complicated. More than 20 criteria to measure glycaemic variability are available and one standardized parameter used in literature is lacking [22]. A priori we specified SD as the parameter of choice to describe glycaemic variability, since our previous study showed that SD is highly correlated to other parameters of variability [23,24] and our choice for SD is supported by literature [22,25]. We did not investigate associations of quality of life with all other different parameters of glycaemic variability to prevent multiple testing [26].

The most important limitation of the study is its relative low percentage of patients consenting to the CGM. Although 503 patients were included in this nationwide long-term biobank initiative study, only 25% consented to also wearing a CGM. This separate consent could have generated a selection bias. However, from the 126 patients which were included in this sub-study 98% (124) completed the sub-study and could be used for this analysis. Although patients were not told the hypothesis of the study, it remains possible that patients who expected high variability or had more diabetes distress or worse well-being participated in the study more often. This was indeed partly reflected by slightly worse scores on the questionnaires in the included group of patients wearing CGM. Such selection bias could in theory overestimate the associations. However, we adjusted for such selection bias using inverse probability weighting and this did not change our results. We therefore think it did not largely influence our results. Secondly, we measured glycaemic variability during 48 hours

to make an estimation of the magnitude of variability in a specific patient. Maybe our estimation would have been more accurate if this period had been longer (HbA1c is a reflection of glucose levels for a much longer period), however, a longer period of wearing the CGM was not feasible in this study. Finally, because of the cross-sectional design of this study we can only speculate on the causative effect of glycaemic variability on diabetes distress.

In conclusion, high glycaemic variability was associated with worse quality of life, albeit not independent of HbA1c. Since this association was found in insulin-treated type 2 diabetes patients only, glycaemic variability could be a potential treatment goal in this particular group.

## Conflict of Interest

All authors declare there is no conflict of interest.

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