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No association between fear of hypoglycemia and blood glucose variability in type 1 diabetes: The cross-sectional VARDIA study

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ABSTRACT

Aims: In type 1 diabetes (T1D), treatment efficacy is limited by the unpredictability of blood glucose results and glycemic variability (GV). Fear of Hypoglycemia (FOH) remains a major brake for insulin treatment optimization. We aimed to assess the association of GV with FOH in participants with T1D in an observational cross-sectional study performed in 9 French Diabetes Centres (NCT02790060).

Methods: Participants were T1D for ≥5 years, aged 18–75 years, on stable insulin therapy for ≥3 months. The coefficient of variation (CV) of blood glucose and mean amplitude of glycemic excursions (MAGE) were used to assess GV from 7-point self-monitoring of blood glucose (SMBG). FOH was assessed using the validated French version of the Hypoglycemia Fear Survey-II (HFS-II) questionnaire.

Results: Among a total of 570 recruited participants, 298 were suitable for analysis: 46% women, 58% on continuous subcutaneous insulin infusion [CSII], mean age 49 ± 16 years, HbA1c 7.5 ± 0.9%, HFS-II score 67 ± 18 and 12% with recent history of severe hypoglycemia during the previous 6 months, mean CV 39.8 ± 9.7% and MAGE 119 ± 42 mg/dL. CV and MAGE did not significantly correlate with HFS-II score ($R = -0.05$; $P = 0.457$ and $R = 0.08$; $P = 0.170$).

Participants with severe hypoglycemia in the previous 6 months had higher HFS scores. Participants with higher HFS scores presented more hypoglycemias during follow-up.

Conclusions: FOH as determined using the HFS-II questionnaire was not associated with 7-point SMBG variability in participants with T1D, but was associated with a positive history of severe hypoglycemia. Higher FOH was associated with higher frequency of hypoglycemia during follow-up.

1. Introduction

Glycemic control in diabetes helps to delay long-term complications.[1] However, one of the major limitations of intensive glycemic control is the occurrence of hypoglycemia,[2] which can also contribute to acute complications, such as unpleasant symptoms, unconsciousness, as well as impaired quality of life.[3]

Glycemic variability (GV) refers to swings in BG levels and has a broad definition.[4] GV has been hypothesized to be a putative mediator of diabetes complications, through its impact on oxidative stress, an established factor in the pathophysiology of complications.[5] Indeed, it has been shown that oxidative stress markers are generated or amplified by GV.[6,7] Many indexes derived from self-monitoring of BG (SMBG) or from continuous glucose monitoring (CGM) have been

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proposed to assess GV. Long-term GV, beyond glycated hemoglobin (HbA1c), is associated with long-term complications in T1D patients,[8] even though the literature remains controversial.[9–11] Even if modern BG monitoring strategies,[12,13] or modern insulin pumps help to target GV,[14] GV is still a primary barrier to glycemic control optimization. Since GV magnitude has not been defined up until now in a universal manner, it is important to confront GV data in a given population with an external and well-defined reference T1D population such as DCCT participants.

Fear of hypoglycemia (FOH) is a limitation for current diabetes treatment optimization[15] and influences quality of life.[16]

FOH can be assessed with validated and standardized questionnaires that measure behaviors and anxiety related to hypoglycemia in diabetes.[17] FOH is potentially accessible to medical therapy, such as diabetes-specific counseling, BG awareness training[18] and personalized therapy of diabetes.[19,20]

The aim of the present study was to assess the association between GV and FOH in participants with T1D.

2. Materials and methods

We conducted the VARDIA study, an observational study in 9 hospitals in France (NCT02790060). Participants were prospectively enrolled from March 2013 to December 2015. The Poitiers University Hospital Ethics Committee approved the design (CPP Ouest III). All participants in the study gave their informed written consent.

2.1. Participants selection

Inclusion criteria were as the following: participants aged 18–75 years with T1DM treated with insulin therapy (continuous subcutaneous insulin infusion [CSII] or multiple-daily injection [MDI] regimens) for at least 5 years who were able to perform SMBG. Participants with unstable medical situation, <3 months change in insulin treatment or renal failure (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), pregnant/breastfeeding women, or those with a pregnancy within the previous year, were excluded.

2.2. Procedure

Eligible participants were prospectively enrolled in the in-hospital department and/or the outpatient clinic from the participating centers. Participants were then invited to complete the questionnaires.

We defined responders as all those that returned their questionnaire within 3 months and 2 monthly phone reminders and non-responders as those that did not return their questionnaire within that time.

2.3. Fear of hypoglycemia

Fear of hypoglycemia was assessed by using the revised Hypoglycemia Fear Survey version II (HFS-II) to assess participants' worries and behaviors related to hypoglycemia.[21] HFS-II is a 33 5-point (never to very often) Likert item survey that includes an 18-item Worry subscale (HFS-W) and a 15-item Behavior subscale (HFS-B). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes whereas HFS-W items describe specific concerns about their hypoglycemic episodes. Addition of HFS-W and HFS-B gives a Total score for HFS-II (HFS-II Score). Higher scores indicate higher fear of hypoglycemia. We substituted the missing value with the mean of the responder's answered questions for the specific subscale as long as 2 or less of the questions had not been answered.

2.4. Hypoglycemia

History of severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions in the previous 6 months according to the American Diabetes Association[22]. These events were recorded from patient interview and medical record check, by the investigator.

During the 2-week follow-up, clinical hypoglycemia was defined as suggestive hypoglycemia symptoms (i.e. palpitations, sweating, lightheadedness) treated by the participants themselves. Documented symptomatic hypoglycemia was defined as an episode during which typical symptoms of hypoglycemia were accompanied by a plasma glucose value of <3.9 mmol/L (<70 mg/dL), treated by the participants themselves. Severe hypoglycemia was defined as symptoms consistent with severe hypoglycemia (altered cognition, seizures, coma) necessitating third party assistance to actively administer carbohydrate, or glucagon in conjunction with a glucose value <3.0 mmol/L (<54 mg/dL).

2.5. Glycemic measures

For 2 weeks, in addition to the 3 pre-meal usual SMBG, participants were asked to perform and self-report on a paper-based diary three 7-P SMBG profiles with their own home device: pre-breakfast, 2-h post-breakfast, pre-lunch, 2-h post-breakfast post-lunch), pre-dinner, 2-h post-breakfast post-dinner and night-time (4:00 AM).

2.6. Glycemic control and variability

As a marker of glycemic control, HbA1c was measured locally in each hospital by using a certified high-performance liquid chromatography method and mean of BG calculated based on 7-P SMBG profiles. As markers of GV, we calculated the BG coefficient of variation (CV) which is the standard deviation (SD) divided by the mean.[23] In order to limit the impact of missing data in the 7-P SMBG profiles, we only assessed GV in patients who had three full 7-P SMBG profiles (21 points considered) or two full 7-P SMBG profiles (14 points considered). In cases of 3 incomplete profiles we only considered participants with at least 80% of the BG values i.e. with 17 to 19 points. We also calculated the mean amplitude of glycemic excursion (MAGE), a measure of glycemic excursion reflecting GV independently of glucose level. Calculation of the MAGE was obtained throughout a locally written SAS macro by measuring the arithmetic mean of the differences between consecutive peaks and nadirs provided that the differences are greater than one SD of the mean glucose value.[24]

As a sensitivity analysis, we performed the same explorations using the CV and MAGE derived from all available BG measurement.

2.7. DCCT population

We analyzed the datasets collected during the Diabetes and Complication Control Trial (DCCT),[1] and publicly accessible, which were stored in SAS format (available at www.gcrc.umn.edu). Briefly, 1441 T1D participants (13 to 39 years of age) were enrolled in the study designed to compare the effect of intensive versus conventional BG management on the development of microvascular complications of diabetes. We calculated GV parameters (CV and MAGE) based on 7-P SMBG measured quarterly from baseline to year 10 in intensive and conventional groups using the same methodology as in VARDIA participants.

2.8. Statistical analysis

A sample size of 55 patients per GV quintiles was needed to detect a difference of 7 of HFS-I score between extreme quintiles considering a HFS-II standard deviation of 13, a bilateral test, an 80% power at a 0.05 significance level. The study expected to have a 50% rate of responders for the questionnaire. The total rounded number of patients was planned to be 600.

Baseline quantitative variables were expressed as mean ± SD or median (25th–75th percentile) for skewed distributions; baseline

qualitative variables were presented as frequencies and percentages. Between-group comparisons were tested by Student *t*-test, unpaired Mann–Whitney *U* test, Kruskal-Wallis test or $\chi 2$-test. Spearman's correlation coefficient (R) was used to assess the relationships between FOH scores, glucose variability, and clinical characteristics. Partial correlation analysis was used to study the relationships between FOH scores and GV after adjustment for the effects of age, diabetes duration, BMI and HbA1c. Associations between FOH scores and history of recent severe hypoglycemia were illustrated by box plots and whiskers and between BG variability and numbers of hypoglycemia episodes during follow-up by regression plots.

P values <0.05 were considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Participant characteristics

A total of 570 participants were included in the study, and a total of 379 returned their questionnaires – responders - and 148 did not -non-responders - (Fig. 1). The differences in clinical characteristics of participants according to their responder status are presented in Supplementary Table 1. Responders, compared to non-responders, were significantly older, more frequently had hypertension, had significantly lower HbA1c and eGFR but were not significantly different with regard to diabetes duration, systolic blood pressure (measured during the visit) and gender.

HFS scoring was available only for 365. These participants (54% men and 46% women) had a mean age of 49 ± 16 years and mean diabetes duration of 25 ± 13 years. All characteristics of these participants, who were considered as the study population, are given in Table 1. Among these, 178 (49%) had 3 fully completed 7-point SMBG profiles, 51 (14%) strictly 2 fully completed profiles, 69 (19%) 3 incomplete profiles but 17 to 19 points and 51 (14%) had no full profile and ≤16 points and 16 (4%) had no BG data (Supplementary Fig. 1). All in all, 82% (n = 298) of these participants had available data for both the HFS questionnaire and GV calculation.

Forty-three (11.8%) participants had a history of one or more recent (in the previous 6 months) episodes of severe hypoglycemia. Clinical and biological characteristics of participants according to this medical history are detailed in Supplementary Table 2. Participants with history of recent severe hypoglycemia had longer diabetes duration compared to participants without (28 ± 13 vs. 24 ± 13 years; $P = 0.0302$). During the 2-week follow-up, 311 (87.5%) participants reported at least 1 episode of clinical hypoglycemia. Among these participants, 301 had at least one documented symptomatic hypoglycemia including 9 severe episodes. Three to eight episodes of documented symptomatic hypoglycemia per patient (median of 4) occurred during the 2-week follow-up with no difference between participants with or without recent episode of severe hypoglycemia (3(1–7) vs. 3(1–7); $P = 0.318$).

3.2. Glycemic variability

In the VARDIA study, mean CV was 39.8 ± 9.7% and mean MAGE was 118.7 ± 42.2 mg/dL. CV and MAGE were positively inter-correlated ($R = 0.76$, $P < 0.0001$).

GV indices were negatively correlated with BMI and with SBP, whereas MAGE but not CV positively correlated with baseline HbA1c (Supplementary Table 3). CV and MAGE were not significantly different between men and women (39.5 ± 9.5 vs. 40.1 ± 9.9%, $P = 0.645$ and 117.6 ± 44.3 vs. 119.6 ± 40.5 mg/dL, $P = 0.691$, respectively), nor between participants treated with CSII or with MDI (39.5 ± 9.4 vs. 40.9 ± 10.1%, $P = 0.494$ and 116.8 ± 38.5 vs. 121.3 ± 46.8 mg/dL, $P = 0.374$). GV parameters were significantly positively correlated with the number of documented episodes of symptomatic hypoglycemia during follow-up ($R = 0.41$, $P < 0.0001$ and $R = 0.20$, $P = 0.0005$ for CV and MAGE, respectively), as illustrated in Fig. 2. These correlations remained statistically significant after adjustment for known hypoglycemia risk factors: diabetes duration, HbA1c, history of proliferative retinopathy, BMI, eGFR and insulin dose ($R = 0.42$, $P < 0.0001$ and $R = 0.23$, $P < 0.0001$ for CV and MAGE, respectively).

In the DCCT dataset, mean CV was 40.2 ± 7.3% and mean MAGE was 148.9 ± 32.7 mg/dL. In participants treated in the experimental group (intensive BG management, n = 711) compared to those in the

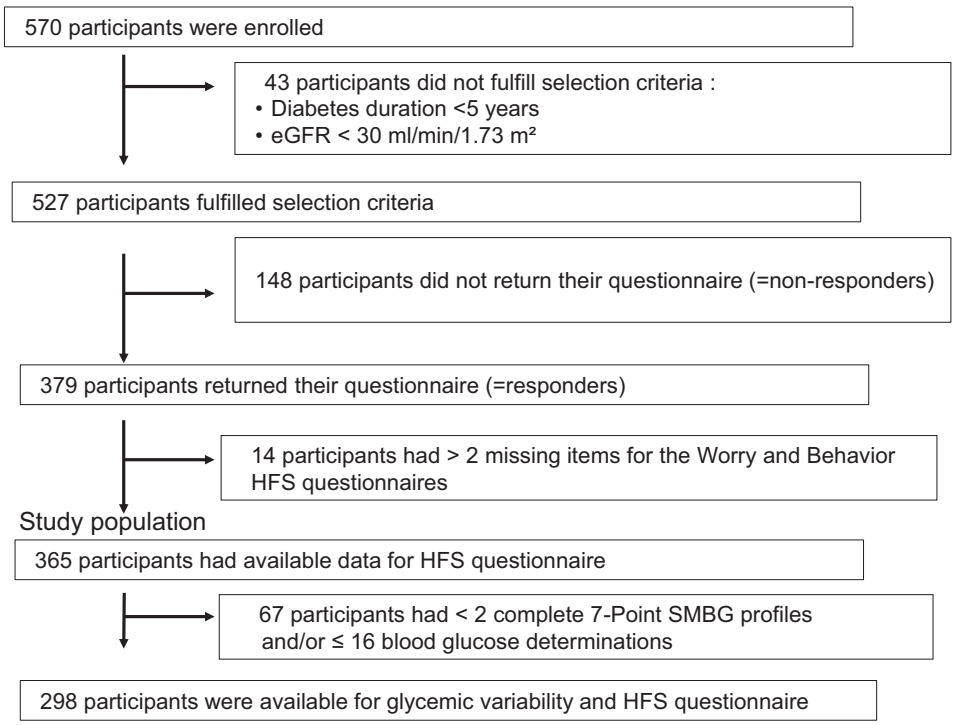

Fig. 1. Flow chart of the study population.

Table 1
Baseline characteristics of the study population.

Clinical characteristics	$n = 365$
Age (years)	49 ± 16
Men	138 (54%)
Body mass index (kg/m^2)	25.3 ± 4.3
Diabetes duration (years)	25 ± 13
Systolic blood pressure (mmHg)	128 ± 14
Diastolic blood pressure (mmHg)	74 ± 10
Diabetes complications	
Cardiovascular disease	26 (10.2%)
Peripheral arterial disease	12 (4.7%)
Coronary artery disease	16 (6.3%)
Cerebrovascular artery disease	5 (2.0%)
Retinopathy	89 (35%)
Peripheral neuropathy	30 (11.8)
Hypertension	114 (44.7%)
Normo/micro/macro-albuminuria	232/15/2 (93.2/6.0/0.8)
eGFR (mL/min/1.7$_{3m^2}$)	97.3 ± 17.7
Insulin regimen	
CSII/MDI (% of CSII)	148 / 107 (58%)
1 injection	7 (6.6)
2 injections	2 (1.9)
≥3 injections	97 (91.5)
Insulin daily dose (UI/day)	40 (26–53)
Hypoglycemia	
Experienced severe hypoglycemia (previous 6 months) n (%)	20 (11.8%)
Frequency hypoglycemia per week (physician)	3 (1–5)
Experienced clinical hypoglycemia during follow up (diary) n (%)	230 (90.2%)
Experienced documented hypoglycemia during follow up (diary) n(%) (diary) n(%)	223 (87.5%)
Frequency of documented hypoglycemia per week (diary)	4 (3–8)
Experienced severe hypoglycemia during follow up (diary) n (%)	9 (2.4%)
Frequency severe hypoglycemia per week (diary)	1 (1–1)
Glycemic variability*	
Blood glucose CV (%)	39.8 ± 9.7
MAGE (mg/dL)	118.7 ± 42.2
Glycemic control	
HbA1c (%)	7.5 ± 0.8
HbA1c (mmol/mol)	58 ± 9

Data are presented as mean ± standard deviation, median (25th–75th percentiles), or number (%).
CSII, continuous subcutaneous insulin infusion; MDI, multiple-daily injection regimen; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursions; eGFR, estimated glomerular filtration rate, HbA1c, glycated hemoglobin.
*available in 298 participants.

standard group (conventional BG management n = 730), CV was significantly higher (43.4 ± 5.7 vs. 37.1 ± 7.3% $P < 0.0001$) and MAGE significantly lower (136.7 ± 28.7 vs. 160.8 ± 31.9 mg/dL, $P < 0.0001$, respectively). CV and MAGE were correlated to each other (R = 0.55, $P < 0.0001$ and R = 0.39, $P < 0.0001$ in the experimental group and in the standard group, respectively).

3.3. Fear of hypoglycemia

Mean HFS-II Total, Behavior subscale, and Worry subscale scores were 67 ± 18, HFS-B 30 ± 8 and HFS-W 37 ± 13. HFS-II, HFS-B and HFS-W scores were not different in men compared to women (66 ± 18 vs. 69 ± 19, $P = 0.262$; 30 ± 8 vs. 30 ± 8, $P = 0.592$ and 36 ± 13 vs. 38 ± 17, $P = 0.0840$, respectively). HFS-II, HFS-B and HFS-W scores were not different in patients treated with CSII or with MDI (67 ± 18 vs. 67 ± 19, $P = 0.919$; 30 ± 8 vs. 30 ± 8, $P = 0.483$ and 37 ± 13 vs. 37 ± 14, $P = 0.777$, respectively). HFS-II, HFS-B and HFS-W scores were not different in patients with ≥2 full 7-P SMBG profiles or ≥ 17-point SMBG profiles compared to those with <17 SMBG points (67 ± 18 vs. 69 ± 19, $P = 0.295$; 30 ± 8 vs. 30 ± 9, $P = 0.819$ and 37 ± 13 vs. 39 ± 14, $P = 0.113$).

HFS-II Total score positively correlated with HbA1c while HFS-B weakly positively correlated with diabetes duration, HbA1c and SBP. HFS-B negatively correlated with daily insulin dose and HFS-W with SBP, as illustrated in Supplementary Table 3.

3.4. Fear of hypoglycemia and glycemic variability

MAGE weakly correlated positively with HFS-II score (R = 0.13, $P = 0.03$) and HFS-W (R = 0.15, $P = 0.011$) but not HFS-B (R = 0.09, $P = 0.15$). CV did not correlate with any HFS score (Table 2). After adjustment for age, diabetes duration, HbA1c and BMI, neither CV nor MAGE were significantly associated with any HFS score (Table 2). Further adjustment for history of severe hypoglycemia did not modify these findings. However participants with a history of severe hypoglycemia had higher HFS-II Total score (73 ± 21 vs. 66 ± 18, $P = 0.026$) and HFS-W subscale scores (42 ± 16 vs. 37 ± 13, $P = 0.020$) but did not have significantly different HFS-B subscale scores (32 ± 8 vs. 30 ± 8; $P = 0.211$) compared to those without (Fig. 3).

3.5. Sensitivity analysis

As a sensitivity analysis, we performed the same analyses using the CV and MAGE derived from all available BG instead of our strict selection (≥2 full 7-P SMBG profiles or ≥17-point SMBG profiles). This led to a numerical increase of analyzed participants (n = 349). Median CV and MAGE increased to 40.3 (33.6–47.0) and 114.1 (90.2–143.8) mg/dL. CV and MAGE remained not significantly associated with any HFS score after adjustment (data not shown) and significantly positively correlated with the number of documented episodes of symptomatic hypoglycemia during follow-up (R = 0.39, $P < 0.0001$ and R = 0.25, $P = 0.0005$ for CV and MAGE, respectively).

4. Discussion

We investigated the relationship between GV and fear of hypoglycemia in T1D participants and found that GV was not significantly associated with HFS scores in models that controlled for age, diabetes duration, HbA1c and BMI. Higher CVs were associated with more frequent documented symptomatic hypoglycemia during follow-up. In addition, participants with a positive history of severe hypoglycemia in the 6 months prior to study participation had higher HFS scores, indicating a higher fear of hypoglycemia. Interestingly, these participants had significantly higher Worry subscale score but not higher Behavior subscale scores.

One of the key questions in our study is to address the generalizability of our results. We encountered a possible selection bias in our population, because our recruitment was hospital-based. Of note, participants with T1D are mainly followed by specialists.[25] In the western part of France, where recruitment took place, most of the specialists are located in participating hospitals, leading to a possible though unlikely selection bias. Thus, it is reassuring to observe that the French participants of the VARDIA study, recruited in 2015 from Diabetic clinics, were very similar with regard to CV, MAGE and HbA1c magnitude to the participants of the intensive group of the DCCT trial who were specifically recruited for clinical research purposes. We consequently strongly believe that our conclusions are of interest and probably can be generalized to participants with T1D in westernized countries.

The main objective in our study was to assess the relationship between glucose variability and FOH. We found no significant association, after adjustment for confounding factors, between glucose variability indexes, such as CV or MAGE and FOH indexes whether considering Worry or Behavior subset scores. To the best of our knowledge, this question has been examined only once, in a very recent study by Martyn-Nemeth et al.[26] These authors performed a CGM study on a small group of 35

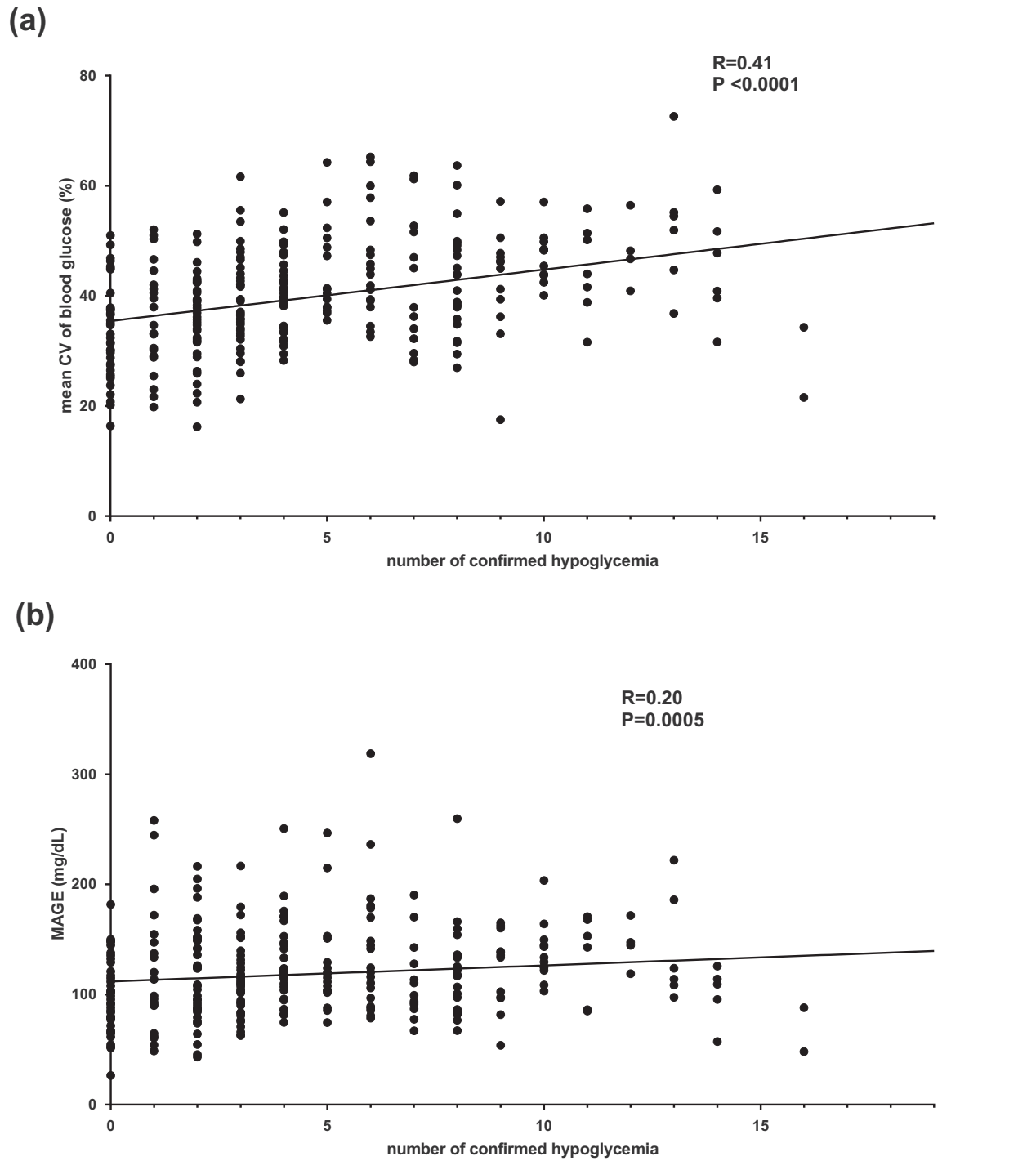

Fig. 2. Scatterplot presents the unadjusted association between numbers of symptomatic documented hypoglycemia during follow-up and blood glucose coefficient of variation (in panel a) and mean amplitude of glycemic excursions (in panel b).

T1D participants aged 18–35 years. They used daily measures of the HFS-II questionnaire allowing for possible comparison between our two studies. They found a significant association between FOH and GV, considering continuous overall net glycemic action and SD, but unfortunately, no data on MAGE or CV were available. The number of participants considered in our current study is much higher than in this study. In addition, our study was multicentered, although the precision of BG measurement in the Martyn-Nemeth et al. study was excellent with the use of CGM, which is likely to provide an accurate estimate of GV.[26]

Other determinants have been shown in different publications to be associated with FOH such as food intake,[16] quality of life or anxiety/depression[21] but exploration of these associations in our study was beyond the scope of the present work.

Another important finding in our study was the relationship between glucose variability and hypoglycemia even after adjustment for hypoglycemia risk factors.[22] This clearly sounds very intuitive, but we could confirm that the higher the glucose variability the greater the hypoglycemia incidence during a 2-week follow-up, in very good accordance with several other studies.[27,28] Furthermore, the HFS-II score was greater in participants with a positive history of severe hypoglycemia occurring in the last six months compared to those without, with a significant difference for the Worry subscale score, but not the Behavior

Table 2
Spearman's correlations of Hypoglycemia Fear Survey scores with glycemic variability indexes.

		Univariate		Partialled*	
		R	(*P* value)	R	(*P* value)
FHS-II total	CV	0.0001	(0.94)	−0.05	(0.457)
	MAGE	**0.13**	**(0.03)**	0.08	(0.17)
FHS-II B	CV	−0.03	(0.63)	−0.06	(0.313)
	MAGE	0.08	(0.17)	0.05	(0.430)
FHS-II W	CV	0.01	(0.804)	−0.03	(0.652)
	MAGE	**0.15**	**(0.011)**	0.10	(0.097)

HFS-II, hypoglycemia fear survey total score; HFS-B, hypoglycemia fear survey Behavior subset score HFS-W, hypoglycemia fear survey Worry subset score
*Correlations are adjusted for age, diabetes duration, glycated hemoglobin, and body mass index.
P values <0.05 are shown in boldface.

subscale score. This result is in good accordance with two studies performed in Germany[29] and Sweden[30] on participants with T1D on multiple daily injections. In these studies of 149 and 764 participants, respectively, the authors indeed found a significant association between severe hypoglycemia and FOH. Our findings extend these conclusions to an additional large and multi-center population. However, we found that these differences were associated with higher Worry scores but not Behavior items. We can speculate that the psychological impact of severe hypoglycemia was rather long. However, we have to highlight that this part of the study did not correspond to our primary objective. We might also have limited statistical power and the analysis of worryness and behavior changes in response to severe hypoglycemia deserves further dedicated research.

The main limitation in our study is that we could not use continuous glucose monitoring to assess glucose variability. This point is clearly a caveat even though our result compares well with the data from other studies including those from the DCCT. In addition, it is questionable whether the selected indexes for glucose variability (CV and MAGE) were different when considering either CGM or SMBG. The data from the literature indicate that while CGM helps to precisely assess time in normal glucose range, glucose variability is not largely influenced by the method of measurement. Another study limitation is that rather than being based on memory glucose meter measures, the 7-P SMBG reports were paper-based, potentially leading to bias in self-report of capillary glucose levels. Additionally, the 7P-SMBG results were not blinded and may consequently have induced a limitation of glucose variability. With extra BG measurements, patients may have attempted to limit glycemic excursion as a means of preventing hypoglycemia, but this does fit in with current care recommendations. Finally, the number of non-responders in this study was high, but since participants did not receive any monetary reward, this was to be expected and indeed corresponds to real-life motivation.

In conclusion, we found no significant association between FOH and glucose variability indexes even though GV was associated with increased frequency of hypoglycemia. The question of reducing glucose variability is important more as regards a patient's quality of life and comfort than as regards reduction of FOH in the context of intensive glucose treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.003.

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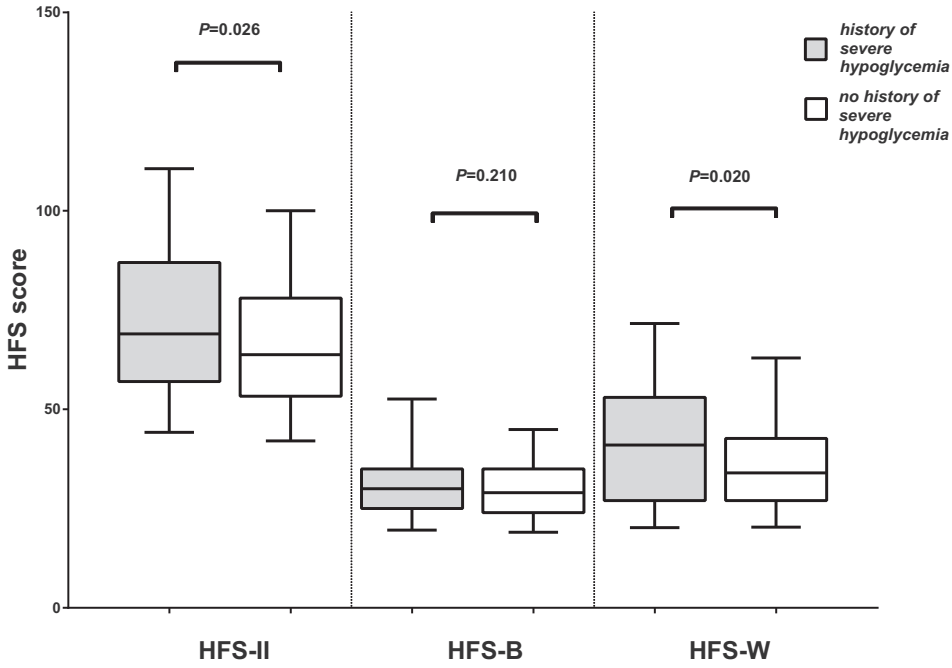

Fig. 3. Box plots present the association between history of recent severe hypoglycemia and fear of hypoglycemia survey scores in T1D population. Data are expressed as box plots (25th percentile, median, and 75th percentile) and whisker (5th and 95th percentiles).Participants with history of recent severe hypoglycemia are represented by grey boxes, participants without history of recent severe are represented by white boxes. HFS-II, hypoglycemia fear survey total score; HFS-B, hypoglycemia fear survey Behavior subset score; HFS-W, hypoglycemia fear survey Worry subset score.

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Declaration of Competing Interest

The HFS-II is copyrighted and licensed through the University of Virginia. Licensing fees are used to support Dr. Gonder-Frederick's research on fear of hypoglycemia and related topics. All other contributing authors declared no potential conflicts of interest related to this article.

Appendix A. VARDIA study group

The members of the VARDIA study group include Pierre Jean Saulnier, Samy Hadjadj, Richard Marechaud, Xavier Piguel, Florence Torremocha, Mathilde Fraty, Pauline Barbieux at CHU de Poitiers; Séverine Dubois, Valentine Courant, Claire Briet, Patrice Rodien at CHU de Angers; Veronique Kerlan, Vianney Demeocq, Emmanuel Sonnet at CHU de Brest; Caroline Perlemoine, Céline Leyer, Diana Le Penher from CH Lorient, Didier Gouet, Frédérique Duengler at CH La Rochelle; Bertrand Cariou, Lucy Chaillous, Marie Perrocheau-Guillouche, Pascal Mahot-Moreau, Anne-Laure Fournier, Matthieu Pichelin at CHU Nantes; Fabrice Bonnet, Anne-Marie Leguerrier at CHU Rennes; Ingrid Delcourt Crespin, Claire Hawken, Gérard Fradet, Isabelle Benoit-Tricaud, Amélie Ducet-Boiffard, Bernadette Lucas-Pouliquen, Barbara Feigel-Guiller at CH La Roche sur Yon, and Pierre-Henri Ducluzeau, Peggy Pierre, Lise Criniere at CHU Tours.

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