



# Association between sleep disturbances, fear of hypoglycemia and psychological well-being in adults with type 1 diabetes mellitus, data from cross-sectional VARDIA study

Valentine Suteau, Pierre-Jean Saulnier, Matthieu Wargny, Linda Gonder-Frederick, Elise Gand, Lucy Chaillous, Ingrid Allix, Séverine Dubois, Fabrice Bonnet, Anne-Marie Leguerrier, et al.

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3     **Association between sleep disturbances, fear of hypoglycemia and psychological well-being in adults with type**  
4                                     **1 diabetes mellitus, data from cross-sectional VARDIA Study**

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6     **Authors and affiliations**

7     V Suteau<sup>a,b</sup>, PJ Saulnier<sup>c,d</sup>, M Wargny<sup>e</sup>, L Gonder-Frederick<sup>f</sup>, E Gand<sup>c</sup>, L Chaillous<sup>e</sup>, I Allix<sup>b</sup>, S Dubois<sup>b,g</sup>, F Bonnet<sup>h</sup>,  
8     A-M Leguerrier<sup>h</sup>, G Fradet<sup>i</sup>, I Delcourt Crespin<sup>i</sup>, V Kerlan<sup>j</sup>, D. Gouet<sup>k</sup>, C Perlemoine<sup>l</sup>, PH Ducluzeau<sup>m</sup>, M Pichelin<sup>e</sup>, S  
9     Ragot<sup>e</sup>, S Hadjadj<sup>e,d,l</sup>, B Cariou<sup>e</sup>, C Briet<sup>a,b</sup> for the VARDIA study group.

10

11     <sup>a</sup>Institut MITOVASC, UMR CNRS 6015, INSERM 1083, Université d'Angers, 3 rue Roger Amsler, 49100 Angers,  
12     France ;

13     <sup>b</sup>Diabetes department, CHU d'Angers, 4 rue Larrey, 49100 ANGERS, France ;

14     <sup>c</sup> Clinical Investigation Center CIC1402, CHU de Poitiers 2 rue de la Milettrie, 86000 Poitiers, France ;

15     <sup>d</sup>CHU Poitiers, Diabetes department, 2 rue de la Milétrie, CS 90577, 86000 Poitiers, France ;

16     <sup>e</sup> L'institut du thorax, CHU Nantes, INSERM CIC1413, Hôpital Nord Laennec Boulevard Jacques-Monod Saint-  
17     Herblain, 44093 Nantes Cedex 1, France ;

18     <sup>f</sup> University of Virginia, Charlottesville-VA, USA;

19     <sup>g</sup> INSERM U1063, Oxidative Stress and Metabolic Pathologies, Université d'Angers, CHU Angers, 4 Rue Larrey,  
20     49933 Angers Cedex 9, France;

21     <sup>h</sup>CHU Rennes, Diabetes department, 2 rue Henri Le Guilloux, 35033 Rennes cedex 9, France;

22     <sup>i</sup>CH Départementale Vendée, Boulevard Stéphane Moreau, 85000 La Roche-sur-Yon, France;

23     <sup>j</sup>CHU Brest, Diabetes department, Hôpital de La Cavale Blanche, Boulevard Tanguy Prigent, 29200 Brest, France ;

24     <sup>k</sup>CH La Rochelle, Diabetes department, Rue du docteur Schweitzer, 17019 La Rochelle Cedex, France ;

25     <sup>l</sup>CH Bretagne Sud, Diabetes department, 5 Avenue Choiseul, 56322 Lorient, France ;

26     <sup>m</sup>CHU Tours, Diabetes department, 2, boulevard Tonnellé - 37044 Tours cedex 9, France ;

27

28 <sup>1</sup> Present adress : L'institut du thorax, CHU Nantes, INSERM CIC1413, Hôpital Nord Laennec Boulevard Jacques-  
29 Monod Saint-Herblain, 44093 Nantes Cedex 1, France.

30

31 **E-mail adress**

32

33 valentine.courant@chu-angers.fr; pierrejean.saulnier@gmail.com; matthieu.wargny@chu-nantes.fr;  
34 LAG3G@hscmail.mcc.virginia.edu; elise.gand@chu-poitiers.fr; lucy.chaillous@chu-nantes.fr; In.Allix@chu-  
35 angers.fr; Se.Dubois@chu-angers.fr; fabrice.bonnet@chu-rennes.fr; anne-marie.leguerrier@chu-rennes.fr;  
36 gerard.fradet@chd-vendee.fr; ingrid.delcourt-crespin@chd-vendee.fr; veronique.kerlan@chu-brest.fr;  
37 gouet@me.com; c.perlemoine@ch-bretagne-sud.fr, ph.ducluzeau@chu-tours.fr; Matthieu.Pichelin@univ-nantes.fr;  
38 stephanie.ragot@univ-poitiers.fr; samy.hadjadj@univ-nantes.fr; bertrand.cariou@univ-nantes.fr; claire.briet@chu-  
39 angers.fr.

40

41 **Corresponding author**

42 Claire BRIET, MD, PhD, [claire.briet@chu-angers.fr](mailto:claire.briet@chu-angers.fr)

43 +33(0)241354240

44 Diabetes department, CHU d'Angers, 4 rue Larrey, 49100 ANGERS, France

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49   **STRUCTURED ABSTRACT**

50

51   Aim: To assess the relationship between sleep quality, fear of hypoglycemia, glycemic variability and psychological  
52   well-being in type 1 diabetes mellitus.

53   Methods: Our data were provided by the VARDIA Study, a multicentric cross-sectional study conducted between  
54   June and December 2015. Sleep characteristics were assessed by the Pittsburgh Sleep Quality Index (PSQI). Fear of  
55   hypoglycemia and psychological well-being were measured with the Hypoglycemia Fear Survey version II (HFS-II)  
56   and the Hospital Anxiety and Depression Scale (HADS), respectively. Glycemic variability (GV) was determined  
57   using the CV of three 7-point self-monitoring blood glucose profiles and the mean amplitude of glycemic excursion  
58   (MAGE).

59   Results: 315 patients were eligible for PSQI questionnaire analysis: 54% women, mean age  $47\pm15$ , mean diabetes  
60   duration of  $24\pm13$  years, HbA1c of  $7.6\pm0.9\%$  ( $60\pm7.5$ mmol/mol). Average PSQI score was  $6.0\pm3.3$  and 59.8% of the  
61   patients had a PSQI score  $>5$ . HFS-II score and HADS were significantly higher among “poor” sleepers ( $p<0.0001$ )  
62   and PSQI score was positively associated with HADS ( $\beta=0.22$ ; 95% CI=0.08;0.35). GV evaluated by CV or MAGE  
63   did not differ between “poor” and “good” sleepers ( $p=0.28$  and  $0.54$ , respectively).

64   Conclusions: Adult patients with type 1 diabetes have sleep disturbances which correlate with psychological well-  
65   being. This study suggests that psychological management can be a target to improve sleep quality in adults with type  
66   1 diabetes mellitus.

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68   **Keywords:** Fear of hypoglycemia - Sleep disturbances– Glycemic variability- Anxiety- Depression - Type 1 diabetes  
69   mellitus

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## 72 INTRODUCTION

73

74 The most recent recommendations in diabetes management draw attention to the assessment of sleep pattern and  
75 duration [1]. However, the majority of studies have been conducted in type 2 diabetes [2,3]. Few studies have focused  
76 on sleep in people with type 1 diabetes mellitus, particularly among adults. We know that in comparison with  
77 controls, patients with type 1 diabetes seem to have shorter sleep duration and poorer sleep quality [4]. Moreover,  
78 short sleep duration and poor sleep quality are associated with increased HbA1c [4]. Conversely, altered glucose  
79 metabolism may affect sleep, suggesting that there are bidirectional relationship between sleep and diabetes [5]. Sleep  
80 disturbances have also negative implications for diabetes management including psychosocial outcomes and  
81 psychological state which also influence sleep quality [6]. While most of the studies have focused on relationships  
82 between sleep quality and glycemic control, little is known about the relationship between sleep quality and other  
83 diabetes-related outcomes [7]. Identification of factors associated with sleep disturbances, specific to patients with  
84 type 1 diabetes mellitus, is mandatory to improve diabetes management and sleep quality.

85 Hypoglycemia (blood glucose (BG) level  $< 70$  mg/dL) is the most common adverse event associated with intensive  
86 insulin therapy and a major limiting factor in the management of type 1 diabetes mellitus [8]. Despite advancements  
87 in diabetes therapies (treatment regimens and technology) over the past few decades, hypoglycemia may still result in  
88 significant anxiety and in a fear of hypoglycemia (FOH). FOH is defined as “the degree of fear associated with  
89 episodes of hypoglycemia and their negative consequences”[9]. It has clinical implications because FOH alters  
90 quality of life, diabetes self-management, and metabolic control. FOH is a major contributor to psychological burden  
91 in people with type 1 diabetes mellitus and can affect sleep quality [9,10]. Following a nocturnal hypoglycemic  
92 episode, individuals reported poor sleep quality [11]. FOH seems to be worse at night and may contribute to poor  
93 sleep quality and sleep disruption [9–11]. Although FOH is common among patients with type 1 diabetes mellitus,  
94 little is known about FOH and sleep characteristics in adults with type 1 diabetes mellitus.

95 Moreover, there also is an association between glycemic variability (GV) and diabetes-related quality of life in  
96 patients with type 1 diabetes mellitus [12,13]. GV, characterized by daily fluctuations in BG, seems to be associated  
97 with diabetes complications [14,15]. Studies indicate that GV seems to be associated with poorer sleep quality and

98 shorter sleep duration [16,17]. Therefore, current evidence suggests that GV may disrupt sleep but few studies have  
99 specifically assessed relation between GV and sleep quality in adults with T1D.  
100 The aims of this study are to assess possible links between sleep disturbances and diabetes-related factors in adults  
101 with type 1 diabetes mellitus, including FOH, GV and psychological status, in a large cross-sectional study.

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## 105 MATERIAL AND METHODS

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### 107 1. Study population

108 Our data were extracted from a multicentric observational cross-sectional study, the VARDIA Study  
109 (NCT02790060), which organization is detailed elsewhere [18]. Patients were recruited in 9 outpatient diabetes  
110 clinics in medical centers from Western France from June to December 2015. Inclusion criteria were: type 1 diabetes  
111 mellitus diagnosed for  $\geq 5$  years, stable insulin therapy (type of insulin and number of injections or continuous  
112 subcutaneous insulin infusion) for  $\geq 3$  months, age 18 to 75 years, and ability to self-monitor BG at least twice a day.  
113 Each participant provided written informed consent. The project was approved by The Poitiers University Hospital  
114 Ethics Committee (CPP Ouest III).

### 115 2. Study measurements

116 For each eligible patient, data were collected by the investigators from medical examination and medical record (see  
117 2.5 *Covariates* for more details). Patients were also asked to complete a set of questionnaires at home within a 2-week  
118 time period after the inclusion. At the same time, they were also invited to perform three 7-point blood glucose  
119 profiles. Patients were considered responders if they returned their questionnaires within 3 months with, if necessary,  
120 2 monthly phone reminders.

#### 121 2.1. Assessment of subjective sleep characteristics

122 The Pittsburgh Sleep Quality Index (PSQI) is a well-documented instrument used to measure the quality and patterns  
123 of sleep in adults. The French version of the PSQI was used to assess sleep quality during the past month [19]. The  
124 19-item self-report PSQI generate seven component scores (C1-C7), with equal weight from 0 to 3: subjective sleep  
125 quality (C1); sleep latency (C2); sleep duration (C3); habitual sleep efficiency (C4); sleep disturbances (C5); use of  
126 sleep medication (C6); and daytime dysfunction (C7). The global PSQI score, the sum of all component scores,  
127 ranges from 0 to 21, with higher scores indicating worse sleep quality. It differentiates “poor” (global score  $>5$ ) from  
128 “good” sleep quality (global score  $\leq 5$ ) [20].

## **2.2. Assessment of Fear of hypoglycemia**

FOH was measured with the Hypoglycemia Fear Survey version II (HFS-II), as previously described [21]. Addition of items for Worry subscale (HFS-W) and items for Behavior subscale (HFS-B) gives a total score for HFS-II (HFS-II Score). Higher scores indicate greater FOH. HFS-II was incomplete for 48 participants. We substituted missing values with the mean of the responder's answered questions for the specific subscale when fewer than three questions were not answered (i.e 43/48 patients).

## **2.3. Assessment of glycemic variability**

Assessment of GV was described in detail in the VARDIA study [18]. Briefly, over two weeks, three 7-point self-monitoring blood glucose (SMBG) profiles were determined by the participants at home: 3 pre-meal /3 post-prandial/1 night. GV was determined using the CV of the BG and the mean amplitude of glycemic excursion (MAGE) [22]. In order to limit impact of missing data in the 7-point profiles, we only assessed GV in patients who had three full 7-point profiles (21 points considered) or two full 7-point profiles (14 points considered). In case of 3 incomplete profiles we only considered patients with at least 80% of the BG measures i.e. with at least 17 points.

## **2.4. Assessment of psychological well-being**

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [23]. The HADS includes 14 items scoring anxiety and depression. Each item is measured on a four-point scale (0-3), with a subscale range from 0 to 21 for anxiety (HADS-A) and depression (HADS-D), and a total score range from 0 to 42. Higher scores indicate more severe anxiety or depression. If the score of a subscale was greater than or equal to 8, patients were considered to have a tendency for anxiety or depression [24].

## **2.5. Covariates**

Demographic and lifestyle factors (age, gender, education...) were assessed through patients' questionnaires. Data from clinical examination were collected and included: weight, height, waist circumference, hip circumference, blood pressure and heart rate. BMI was defined as weight in kilograms divided by height in meters squared. Waist-to-hip ratio (WHR) was calculated by dividing waist by hip circumference. Medical doctors were required to provide diabetic microvascular and macrovascular complications from medical record (last ophthalmic assessment, urinary albumin excretion, cardiovascular history...). All current medication used were also listed.



### 156 3. Statistical analysis

157 Categorical variables were presented giving frequency and percentage of each modality. Quantitative variables were  
158 expressed using mean  $\pm$  SD for normally distributed variables or median  $\pm$  interquartile range (IQR) for non-normally  
159 distributed variables.

160 Comparisons between “good” and “poor” sleepers were tested by Fisher’s exact test for categorical variables. For  
161 normally distributed variables, difference of means between groups was tested with Student’s t-test for unpaired  
162 series (Welch’s unequal variance t-test if needed). In case of skewed distribution, we used the Mann–Whitney U test.

163 Correlation between PSQI score and indexes of GV, HFS scores and HADS scores were assessed through  
164 Spearman’s coefficient.

165 For multivariate approach, we first transformed the parameters of interest using Z-score. Then, we used a classical  
166 multivariate logistic regression to study the association between poor sleep quality and assumed confounders:  
167 variables which associated with poor sleep quality in univariate analyses (gender, WHR, HADS, GV, HFS-II) and  
168 traditional confounders (i.e. age, gender) were included in the proposed model. Linear regression models were  
169 constructed with the same approach. All cases with missing values were deleted before calculating the regression  
170 models.

171 P-values<0.05 were considered statistically significant. Data analyses were performed with R software version 3.3.3  
172 (R foundation for statistical Computing, Vienna, Austria) and Graph pad PRISM 6 (Graph Pad Software, Inc., San  
173 Diego, CA).

## 174    **RESULTS**

175

### 176    **1.   Clinical characteristics**

177    Between June and December 2015, 570 patients were recruited. 379 patients (66%) returned their questionnaires and  
178    315 were eligible for PSQI questionnaire analysis (Supplemental Fig 1.). The differences in clinical characteristics  
179    between responders and non-responders (i.e participants who did not respond to the set of questionnaires and who  
180    were not eligible for the PSQI analysis) are presented in Supplemental Table 1. Overall, the two populations  
181    (responders and non-responders) were comparable.

182    The study sample (responders only) was comprised of 54% women. Patients were  $47\pm15$  years old, and had a mean  
183    type 1 diabetes duration of  $24\pm13$  years. Multiple daily insulin injections were used by 132 patients while the other  
184    165 (52%) patients used continuous subcutaneous insulin infusion. History of microvascular complications and  
185    macrovascular complications were present in 120 (46%) and 32 (10%). The participants had a BMI of  $25.3\pm4.3$  kg/m<sup>2</sup>  
186    and a mean blood pressure of 128/74 mmHg.

#### 187        **1.1.   Hypoglycemia and fear of hypoglycemia**

188    Occurrence of at least one severe hypoglycemia event in the 6 months prior to questionnaire completion was reported  
189    by 35 (11%) patients. Severe hypoglycemia was defined as events requiring assistance from others to restore normal  
190    glucose levels [25].

191    The mean global HFS-II score was  $67.3\pm18.7$ . The greatest worries were having hypoglycemia while sleeping and  
192    having hypoglycemia while doing important things. The more frequent behaviors to avoid hypoglycemia were  
193    decreasing insulin dose and checking BG more than six times a day.

#### 194        **1.2.   Glycemic control and glycemic variability**

195    The mean HbA1c was  $7.6\pm0.9\%$  ( $60\pm7.5$  mmol/mol). Mean CV was  $39.9\pm9.4\%$  and mean MAGE score was  
196     $118.6\pm39.8$ .

#### 197        **1.3.   Anxiety and depression**

198    The mean total HADS was  $12\pm6$  which would be considered to be in the non-symptomatic range. The mean score for  
199    anxiety was  $8\pm4$  which indicates mild anxiety. Mean depression subscale score was in the normal range ( $4\pm3$ ).

## 200    **2. Sleep characteristics**

201    The patients showed an average PSQI Score of  $6.0 \pm 3.3$ , and 156 (59.8%) patients had a total PSQI score  $>5$ ,  
202    indicating poor sleep quality. A subjective sleep duration  $>7$  hours per night was reported by 50.6% of patients. In the  
203    individual domains of the PSQI questionnaire, patients most often reported poor sleep quality, increased sleep latency  
204    and sleep disturbances. Additional sleep characteristics are shown in **Table 1**.

## 205    **3. Factors associated with sleep disturbances**

### 206        **3.1. Comparisons between good and poor sleepers**

207    Patients were divided in two groups: poor sleep quality (PSQI score  $>5$ ,  $n=156$ ) and good sleep quality (PSQI score  $\leq$   
208    5,  $n=159$ ). Participant characteristics according to their level of sleep disturbances are described in **Table 2**.

#### 209            **3.1.1. Baseline characteristics**

210    In comparison to participants with good sleep quality, “poor sleepers” were more likely to be women ( $p=0.042$ ), have  
211    a smaller WHR ( $p=0.049$ ), and have less coronary revascularization ( $p=0.035$ ) but with very few events. Diabetes  
212    duration, microvascular and macrovascular complications were not significantly different between the two groups.

#### 213            **3.1.2. Hypoglycemia and fear of hypoglycemia**

214    Sleep disturbances were not associated with severe hypoglycemia in the six months prior to questionnaire completion  
215    (**Table 2**). There was no difference in hypoglycemic episodes between good and poor sleepers.  
216    HFS-II score was significantly higher among patients with sleep disturbances ( $p<0.0001$ ). Similarly, HFS-B and  
217    HFS-W subscales were higher when PSQI score was  $> 5$  ( $p=0.0034$  and  $p=0.0002$  respectively). Analysis according  
218    to seven components of PSQI score revealed higher HFS-II scores mainly for the first component, referring to sleep  
219    quality (**Supplemental Fig 2**).

#### 220            **3.1.3. Anxiety and depression**

221    Poor sleep quality was significantly associated with higher HADS, HADS-A, HADS-D scores and higher  
222    antidepressant use ( $p=0.045$ ) but not anxiolytic use ( $p=0.38$ ) (**Table 2**).

#### 223            **3.1.4. Glycemic control and glycemic variability**

224    GV evaluated by CV or MAGE score did not differ between “poor” and “good” sleepers (**Table 2**). In addition, there  
225    was no difference in glycemic control assessed by HbA1c and mean glycemia computed from BG measures between

the two groups. CV was not different according in both groups for different components of PSQI score, i.e. self-reported sleep duration, sleep quality, daytime sleepiness, or the prevalence of sleep disorders (data not shown).

### 3.1.5. Multivariate analysis

In the multivariable logistic regression model including potential confounders (i.e., age, gender, WHR, GV, FOH and anxiety and depression assessments), only HAD score was significantly associated with sleep disturbances after stepwise selection (OR = 1.40; 95% CI: 1.50–1.86) (**Table 3**).

## 3.2. Correlation analysis

Although the threshold of 5 gives the global PSQI score an excellent sensitivity to distinguish good and poor sleepers, we wanted to directly assess the correlation between global PSQI score and potential factors associated with sleep disturbances.

### 3.2.1. Baseline characteristics

Neither the WHR nor the BMI were significantly correlated with the global PSQI score ( $\rho=0.09$ ,  $p=0.16$ ;  $\rho=-0.06$ ,  $p=0.28$ , respectively).

### 3.2.2. Fear of hypoglycemia

Sleep disturbances were positively correlated with HFS-II, HFS-B and HFS-W scores ( $\rho=0.25$ ,  $p<0.0001$ ;  $\rho=0.19$ ,  $p=0.0001$ ;  $\rho=0.24$ ,  $p<0.0001$  respectively) (**Figure 1a**).

### 3.2.3. Anxiety and depression

Sleep disturbances were positively correlated with total HADS, HADS-A and HADS-D ( $\rho=0.29$ ,  $p<0.0001$ ;  $\rho=0.27$ ,  $p<0.0001$ ;  $\rho=0.23$ ,  $p<0.0001$ , respectively) (**Figure 1b**). Moreover, HADS, HADS-A, HADS-D scores were significantly correlated with HFS-II score ( $\rho=0.47$ ,  $\rho=0.46$  and  $\rho=0.36$ ,  $p<0.0001$ , respectively).

### 3.2.4. Glycemic variability

CV was slightly negatively correlated with PSQI score ( $\rho=-0.14$ ,  $p=0.026$ ) whereas MAGE score was not correlated with PSQI score (**Figure 1c and d**).

### 3.2.5. Multivariate analysis

Potential factors correlated with sleep quality were analyzed in a multiple linear regression model, which included the potential confounding factors (i.e., age, gender, WHR, glycemic variability, fear of hypoglycemia and anxiety and depression assessments) (**Table 4**). The analysis revealed that HAD score was significantly positively associated with sleep quality ( $\beta_{(+1 \text{ SD})} = 0.22$ , 95% CI [0.08 to 0.35],  $p = 0.0014$ ). In contrast, the CV of BG was significantly negatively associated with sleep disturbances ( $\beta_{(+1 \text{ SD})} = 0.16$ , 95% CI [0.28 to -0.04],  $p = 0.010$ ). FOH was not significantly associated with PSQI score, neither before nor after stepwise selection (**Table 4**).

## 259 DISCUSSION

260

261 In this cross-sectional study of a large cohort of adults with type 1 diabetes mellitus, we found that more than half of  
262 the patients appeared to have poor sleep quality. There was a significant association between poor sleep quality and  
263 psychological status with a positive association between PSQI and HAD scores in multivariate analyses.

264 Poor sleep quality is a complaint among patients with type 1 diabetes mellitus. Our findings were consistent with  
265 previous studies indicating that persons with type 1 diabetes mellitus suffer from sleep disturbances [16,27].  
266 However, some previous studies in adults with type 1 diabetes mellitus found a lower proportion of sleep  
267 disturbances than here, though assessed with the same questionnaire. Except for two recent studies reporting about  
268 50% of patient with poor sleep quality [11,17], the other reported approximately one-third of patients with type 1  
269 diabetes mellitus with PSQI score  $>5$  [7,27,28]. Several methodological factors can contribute to differences in the  
270 prevalence of sleep disturbances. For example, in the study by Adler et al., patients were younger (21.96 versus 47.2  
271 years old). Moreover, psychiatric disorders and use of psychotropic medication were exclusion criteria in two of these  
272 three studies [7,28]. In addition to poor sleep quality, the 315 type 1 diabetes patients in our study reported, and a  
273 short sleep duration, with half reporting sleep duration below the recommended 7h /night. This high prevalence of  
274 sleep disturbances and decreased sleep duration may have clinical implications such as negative effects on glucose  
275 metabolism.

276 Altered glucose metabolism may impact sleep quality and GV is suspected to interact with sleep parameters [5,7,16].  
277 To our knowledge, this is the largest study to specifically investigate the link between sleep quality and GV in type 1  
278 diabetes mellitus. Surprisingly, GV assessed by CV or MAGE score was not significantly different between “good”  
279 and “poor” sleeper. Moreover, an unexpected negative correlation was found between CV values and PSQI score,  
280 even when data were adjusted for potential confounding factors. However, due to a large number of subjects in our  
281 study, very small correlations can be statistically significant but this correlation was quite small ( $\rho=-0.16$ ) and  
282 further research will be needed to confirm this relationship. Moreover, this correlation was not found with MAGE  
283 showing the difficulty of interpretation of GV in absence of gold standard. Another explanation could be that  
284 glycemic variability was high in all patients in our population (i.e.  $CV>36\%$ ), making the visualization of difference  
285 between groups difficult. Smaller studies have found no correlation between GV and sleep quality [11,16,17]. The

286 differences may be due to the methodology used (Continuous Glucose Monitoring (CGM) vs SMBG,  
287 polysomnography vs self-report questionnaire) or some other factors.

288 We aimed to evaluate if FOH could impact sleep in patients with type 1 diabetes. In our study, patients with poorer  
289 sleep quality had higher levels of FOH (higher HFS-II scores). However, this association was no longer significant in  
290 multivariate model. Although this question may seem quite intuitive, only one other study has assessed in only 63  
291 adult participants [11]. As in our study, comparisons of subject characteristics according to sleep quality group  
292 showed a significant association between poor sleepers and FOH but the regression model was not adjusted for  
293 psychological status. Studies of the relationship between FOH and sleep have also been conducted in pediatric T1D  
294 populations and analyzed parents' FOH [29,30]. One study found that children of parents with more FOH had worse  
295 sleep quality than children of parents with less FOH, and parents with the highest levels of FOH had poorer sleep  
296 quality [29]. Another found that the greatest worries of parents of children with T1D were related to hypoglycemia  
297 during sleep [30]. Consistent with studies in children, many patients in our study were worried about having  
298 hypoglycemia while sleeping. Similar findings were reported in previous studies in adult patients with type 1 diabetes  
299 mellitus [31,32]. Therefore, it appears that FOH specifically concerning episodes occurring during sleep has a  
300 significant negative influence on sleep quality.

301 High FOH is also a critical factor to psychological well-being and quality of life in patients with type 1 diabetes  
302 mellitus [10,31]. Therefore, we considered anxiety and depression as variables with a possible link with sleep  
303 disturbances. In our study, the HADS, HADS-A and HADS-D scores were significantly associated with sleep quality  
304 in univariate analysis and in the multivariate model. A previous study found that HADS scores were risk factors for  
305 impaired sleep quality in 99 patients with type 1 diabetes mellitus [7]. The relationship between sleep quality and  
306 psychological status is likely to be bidirectional. In this way, poor sleep quality has a negative impact on emotions  
307 and psychological factors. Anxiety symptoms are more common in people with diabetes than in a non-diabetic  
308 population [33]. Similarly, elevated depressive symptoms and depressive disorders more often affect patients with  
309 type 1 diabetes mellitus than their non-diabetic counterparts [34]. In patients with diabetes, these comorbidities are  
310 associated with poorer adherence and glycemic control [35,36]. Moreover, the positive association between diabetes  
311 and anxiety symptoms can be explained by many factors including specific phobias such as FOH [37]. In our study,  
312 we found that HADS scores were significantly correlated with HFS-II score.

313 Due to its cross-sectional design, our study could not propose any causal relationship between sleep quality and  
314 psychological well-being. A hypothesis is to consider that patients with poor sleep quality were more prone to worry  
315 in different aspects of their personal lives, including fear of hypoglycemia. In other words, poor sleep quality could  
316 make you more sensitive to worry and lower your psychological resilience. Thus, psychological conditions must be  
317 considered in diabetes management [1].

318 The strengths of this study included use of a validated questionnaire to assess sleep disturbances. The PSQI score has  
319 a diagnosis sensitivity of 89,6% and a specificity of 86,5% with a cut-off of 5 to identify poor sleep quality [20].  
320 Furthermore, the number of participants was important. Other studies previously published in type 1 diabetes have  
321 been limited to youth and/or small samples [11,17,27–29]. Finally, this study evaluated sleep habits in a real-world  
322 setting rather than a clinical sleep laboratory.

323 Methodological limitations of this study included the use of BG measurements made using SMBG and not  
324 Continuous Glucose Monitoring (CGM). The number of BG measurements was also limited. Certain BG peaks or  
325 nadirs could be missed in assessing GV. However, glucose variability do not appear to be influenced by measurement  
326 method [38]. Moreover, the response rate to the questionnaires was 34%, which could induce a non-response bias.  
327 However, there was no substantial difference observed between the characteristics of responders and non-responders.  
328 In addition, this was a secondary data analysis and may not have been fully powered to address the aims of the  
329 current study. Finally, because this was a cross-sectional study, no causal relationship can be established.

330

331



## 332 CONCLUSION

333 In conclusion, many adults with type 1 diabetes mellitus in this study reported sleep disturbances. Clinical care should  
334 consistently include assessment of sleep duration and sleep quality. Various aspects of diabetes could be linked to  
335 disturbed sleep and have implications for management of type 1 diabetes mellitus. In this study, people with type 1  
336 diabetes mellitus with poor sleep quality had greater anxiety and depression symptoms than those who reported good  
337 sleep quality. This suggests that psychological well-being is a target for intervention to improve sleep quality in  
338 adults with type 1 diabetes mellitus.

339 Further research is needed regarding the influence of new diabetes-related technology, particularly low suspend pump  
340 treatment, closed-loop system and CGM, to reduce fear of hypoglycemia and anxiety improve sleep quality and  
341 glucose control. Another challenge would be to characterize sleep disturbances and GV with a multi-method  
342 approach, including objective measures of sleep such as actigraphy or polysomnography along with CGM data. This  
343 would allow for a better understanding of the relationship between sleep and type 1 diabetes mellitus.

344

345

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366

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485 **Table I. Subjective sleep disturbances in patients with type 1 diabetes in VARDIA study**

Pittsburgh Sleep Quality Index (PSQI)	n = 315
Global score	5 (4, 8)
Poor sleep quality (PSQI score > 5) n (%)	156 (59.8 %)
Component scores (0–3 points)	
C1: Overall sleep quality	1 (1, 2)
C2: Sleep latency	1 (0, 2)
C3: Subjective duration	1 (0, 1)
C4: Sleep efficiency	0 (0, 1)
C5: Sleep disturbance	1 (1, 2)
C6: Need medications to sleep	0 (0, 0)
C7: Daytime dysfunction	1 (0, 1)

486 Abbreviations: PSQI = Pittsburgh Sleep Quality Index. Data are reported as number (%), or median (25<sup>th</sup> – 75<sup>th</sup>  
487 percentiles)  
488

**Table II. Clinical characteristics of patients with type 1 diabetes according to PSQI score in VARDIA study (n=315)**

	Good sleepers (PSQI score ≤ 5) N = 159	Poor sleepers (PSQI score > 5) N = 156	p-value
<b>Demographic factors</b>			
Age (years)	47 (35-58.5)	47 (37-61)	0.27
Women n (%)	77 (48.4 %)	94 (60.3 %)	<b>0.042</b>
Education			0.29
<i>Primary education</i>	9 (5.8 %)	14 (9.2 %)	
<i>Secondary education</i>	82 (52.6 %)	86 (56.6 %)	
<i>Tertiary education</i>	65 (41.7 %)	52 (34.2 %)	
<b>Clinical characteristics</b>			
BMI (kg/m <sup>2</sup> )	25.6 ± 4.1	25.0 ± 4.5	0.24
Obesity (IMC ≥ 30)	23 (14.5 %)	22 (14.1 %)	1
Hypertension	55 (34.6 %)	47 (30.1 %)	0.40
Waist-to-hip ratio	0.89 ± 0.10	0.86 ± 0.09	<b>0.049</b>
SBP (mmHg)	128.6 ± 14	126.6 ± 13.7	0.22
DBP (mmHg)	73.9 ± 10	73.7 ± 10.1	0.83
Diabetes duration (years)	21 (12-33)	22.5 (13-34.2)	0.32
<b>Insulin</b>			
Insulin regimen: CSII	83 (52.2 %)	82 (52.6 %)	0.56
Mean insulin dose (U/kg.d)	0.64 ± 0.27	0.64 ± 0.42	0.93
<b>Diabetes complications</b>			
<i>Microvascular</i>			
Retinopathy			0.19
Absent	114 (71.7 %)	100 (64.1 %)	
non-proliferative retinopathy	30 (18.9 %)	43 (27.6 %)	

proliferative retinopathy	15 (9.4 %)	13 (8.3 %)	
Pan retinal photocoagulation	23 (14.9 %)	21 (13.6 %)	0.87
Macular edema	8 (5.2 %)	10 (6.5 %)	0.64
<b>Nephropathy</b>			
Urinary albumin excretion (mg/g)	61 (20-222)	50 (10.8-145.2)	0.15
Albuminuria (n=45/48)			0.47
<i>Normo-albuminuria</i>	14 (31.1 %)	20 (41.7 %)	
<i>Microalbuminuria</i>	22 (48.9 %)	22 (45.8 %)	
<i>Microalbuminuria</i>	9 (20 %)	6 (12.5 %)	
eGFR (mL/min/1.73m <sup>2</sup> )	99.4 ± 18.1	98.3 ± 16.8	0.56
<b>Neuropathy</b>			
Peripheral neuropathy	14 (8 %)	21 (13.0 %)	0.15
Erectile dysfunction	11 (9.6 %)	12 (15.0 %)	0.27
Orthostatic hypotension	5 (4.5 %)	5 (5.4 %)	1
<b>Macrovascular</b>			
Cardiovascular disease	17 (10.7 %)	15 (9.6 %)	0.85
Myocardial infarction	6 (3.8 %)	4 (2.6 %)	0.75
Coronary revascularization	10 (6.3 %)	2 (1.3 %)	<b>0.035</b>
Cerebrovascular disease	3 (1.9 %)	3 (1.9 %)	1
Peripheral arterial disease	8 (5 %)	6 (3.8 %)	0.79
<b>Hypoglycemia</b>			
Frequency of confirmed hypoglycemia per week	3 (1-5)	3 (1-4)	0.47
Experienced severe hypoglycemia (previous 6 months)	19 (12.2 %)	16 (10.5 %)	0.72
<b>Fear of hypoglycemia</b>			
HFS-II total	60 (52-72.9)	68.5 (56-85)	<b>&lt;0.0001</b>
HFS-II B	27 (23-33.1)	31 (25-36)	<b>0.0034</b>
HFS-II W	33 (25-39.8)	37.5 (30-48.8)	<b>0.0002</b>
<b>Glycemic control</b>			
Mean glycemia	149.1 ± 20.7	154.2 ± 26.3	0.085
HbA1c (%)	7.6 ± 0.9	7.7 ± 1.0	0.60
HbA1c (mmol/mol)	60.0±7.5	61±8.6	0,60
HbA1c ≥ 7.5 % (≥58 mmol/mol)	30 (47.6 %)	23 (47.9 %)	1
<b>Glycemic variability</b>			
Blood glucose CV (%)	40.5 ± 9.2	39.3 ± 9.5	0.28
MAGE (mg/dL)	117.1 ± 40.1	120.1 ± 39.6	0.54
<b>Hospital Anxiety and Depression Scale</b>			
Total score	10 (6-14)	13 (8-18)	<b>&lt;0.0001</b>
Anxiety score	6 (4-9)	8 (5-11.5)	<b>&lt;0.0001</b>
Depression score	3 (1-5)	4 (2-7)	<b>0.0027</b>
<b>Medications</b>			
Antidepressant	5 (3.1 %)	14 (9.0 %)	<b>0.045</b>
Anxiolytic	4 (2.5 %)	7 (4.5 %)	0.69
Antihypertensive	55 (34.6 %)	47 (30.1 %)	0.70

490 Abbreviations: PSQI = Pittsburgh Sleep Quality Index, CSII = Continuous subcutaneous insulin infusion,

491 SAP = Systolic Arterial Pressure, DAP =Diastolic Arterial Pressure, MAGE = Mean Amplitude of Glycemic  
 492 Excursions, HFS-II, hypoglycemia fear survey total score; HFS-B, hypoglycemia fear survey Behavior subset score;  
 493 HFS-W, hypoglycemia fear survey Worry subset score.  
 494 Data are reported as number (%) for categorical variables, as mean  $\pm$  SD or as median with interquartile ranges  
 495 (IQR), if appropriate for continuous data.  
 496 p values <0.05 are shown in boldface.  
 497

498

499 **Table III.** Factors associated with impaired sleep quality (PSQI score >5) in adults with type 1 diabetes, assessed  
 500 using univariate and multivariate logistic regression. VARDIA study with full available data  
 501

Poor sleep quality: PSQI score > 5 (n=212)				502
(/+1 SD)*	Univariate models	Multivariate models		503
		Without selection	After stepwise selection	504
		OR (95% CI)	OR (95% CI)	505
Age	1.17 [0.89; 1.54]	1.29 [0.96; 1.74]	-	506
Female sex	1.35 [0.78; 2.35]	0.96 [0.48; 1.93]	-	507
Waist-to-hip ratio	0.78 [0.59; 1.02]	<b>0.69 [0.48; 0.99]</b>	-	508
Blood glucose CV	0.91 [0.70; 1.17]	0.87 [0.66; 1.14]	-	509
HFS-II total	<b>1.38 [1.05; 1.83]</b>	1.23 [0.90; 1.69]	-	510
HFS-II B	1.23 [0.93; 1.61]	-	-	511
HFS-II W	<b>1.40 [1.05; 1.87]</b>	-	-	512
HAD score	<b>1.40 [1.05; 1.86]</b>	1.27 [0.92; 1.75]	<b>1.40 [1.50; 1.86]</b>	513
HADS-A	1.39 [1.05; 1.84]	-	-	514
HADS-B	1.25 [0.95; 1.64]	-	-	515
				516
				517

518 Abbreviations: PSQI = Pittsburgh Sleep Quality Index, HFS-II, hypoglycemia fear survey total score; HFS-B,  
 519 hypoglycemia fear survey Behavior subset score; HFS-W, hypoglycemia fear survey Worry subset score, HADS =  
 520 Hospital Anxiety Depression Score, HADS-A = Hospital Anxiety Depression Score, Anxiety subscale, HADS-B =  
 521 Hospital Anxiety Depression Score, Depression subscale.

522 \*Values are OR [95% CI] assessed for an increase of 1 standard-deviation of the parameter (except for Sex), in bold  
 523 when associated p-value<0.05.

524 For multivariate logistic regression models, we present the results before and after stepwise selection (both  
 525 descending and ascending, considering a *p-value* threshold = 0.05) on the following independent parameters: age, sex,  
 526 waist-to-hip ratio, blood glucose CV, HFS-II total and HADS score. Analyzes made with observations without  
 527 missing data for all potential confounding factors (n=212).  
 528



529 **Table IV.** Factors associated with sleep quality (PSQI total score) in adult with type 1 diabetes, assessed using  
530 univariate and multivariate linear regression. VARDIA study with full available data  
531

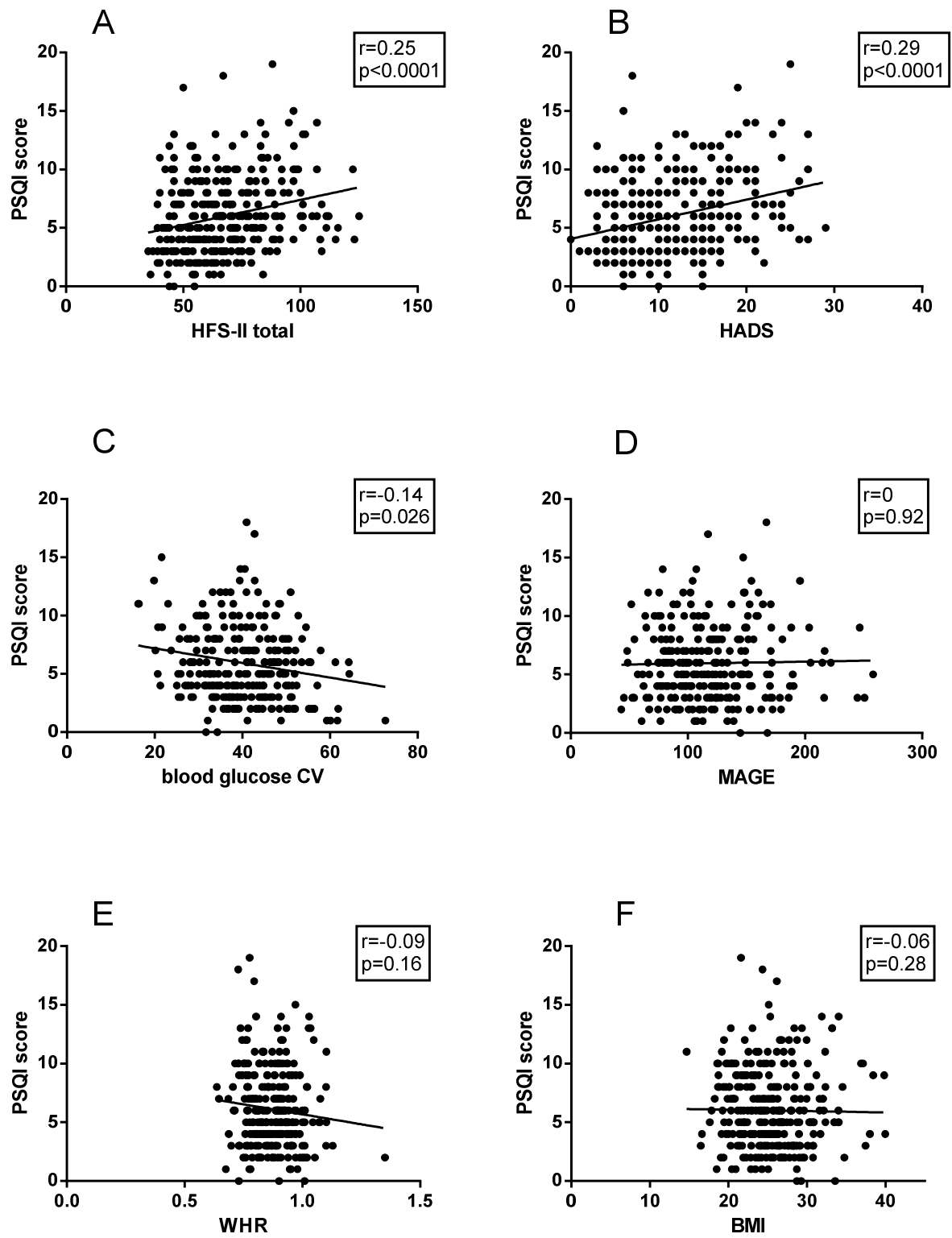
(/+1 SD)*	Sleep quality assessed by PSQI total score (n=212)		
	Univariate Models	Multivariate models	
		Without selection	After stepwise selection
	$\beta$ (95%)CI	$\beta$ (95%)CI	$\beta$ (95%)CI
Age	0.07 [-0.07; 0.20]	0.11 [-0.03; 0.24]	-
Female Sex	0.19 [-0.09; 0.46]	0.05 [-0.27; 0.36]	-
Waist-to-hip ratio	-0.11 [-0.25; 0.03]	-0.13 [-0.28; 0.03]	-
Blood glucose CV	<b>-0.18 [-0.31; -0.05]</b>	<b>-0.18 [-0.30; -0.06]</b>	<b>-0.16 [-0.28; -0.04]</b>
HFS-II total	<b>0.20 [0.07; 0.33]</b>	<b>0.10 [-0.04; 0.24]</b>	-
HFS-II B	<b>0.15 [0.02; 0.29]</b>	-	-
HFS-II W	<b>0.19 [0.06; 0.32]</b>	-	-
HAD score	<b>0.15 [0.01; 0.30]</b>	0.16 [0.02; 0.31]	<b>0.22 [0.08; 0.35]</b>
HADS-A	0.13 [-0.01; 0.26]	-	-
HADS-D	0.13 [-0.01; 0.28]	-	-

532 Abbreviations: PSQI = Pittsburgh Sleep Quality Index, HFS-II, hypoglycemia fear survey total score; HFS-B,  
533 hypoglycemia fear survey Behavior subset score; HFS-W, hypoglycemia fear survey Worry subset score, HADS =  
534 Hospital Anxiety Depression Score, HADS-A = Hospital Anxiety Depression Score, Anxiety subscale, HADS-D =  
535 Hospital Anxiety Depression Score, Depression subscale.

536 \*Values are  $\beta$  [95% CI] for an increase of 1 standard-deviation of the parameter (except for Sex), in bold when  
537 associated p-value<0.05.

538 For multivariate linear regression models, we present the results before and after stepwise selection (both descending  
539 and ascending, considering a *p-value* threshold = 0.05) on the following independent parameters: age, sex, waist-to-  
540 hip ratio, blood glucose CV, HFS-II total and HAD score. Analyzes made with observations without missing data for  
541 all potential confounding factors (n=212).  
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**Figure 1**

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547 **FIGURE CAPTIONS**

548 **Figure 1. Correlation between total PSQI score and possible risk factors for impaired sleep quality**

549 Association between total PSQI score and fear of hypoglycemia assessed by HFS-II total (A), psychological well-  
550 being assessed by total HADS (B), glucose variability assessed by blood glucose CV (C) and MAGE (D), WHR (E),  
551 and BMI (F).

552 Abbreviations: PSQI = Pittsburgh Sleep Quality Index, HFS-II, hypoglycemia fear survey total score, CV =  
553 coefficient of variation, MAGE = Mean Amplitude of Glycemic Excursions, BMI=Body Mass Index, WHR=waist  
554 hip ratio.

555 Relationships between PSQI score and possible risk factors were assessed through spearman's coefficient in 310  
556 patients for fear of hypoglycemia, in 301 patients for Anxiety and Depression, in 261 patients for glucose variability,  
557 in 268 patients for WHR and 315 patients for BMI. Spearman's coefficients (r) and associated p-values are indicated  
558 in the boxes.

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562    **Supplemental Table I.** Clinical characteristics of patients with type I diabetes according to their response status  
563    (n=527)

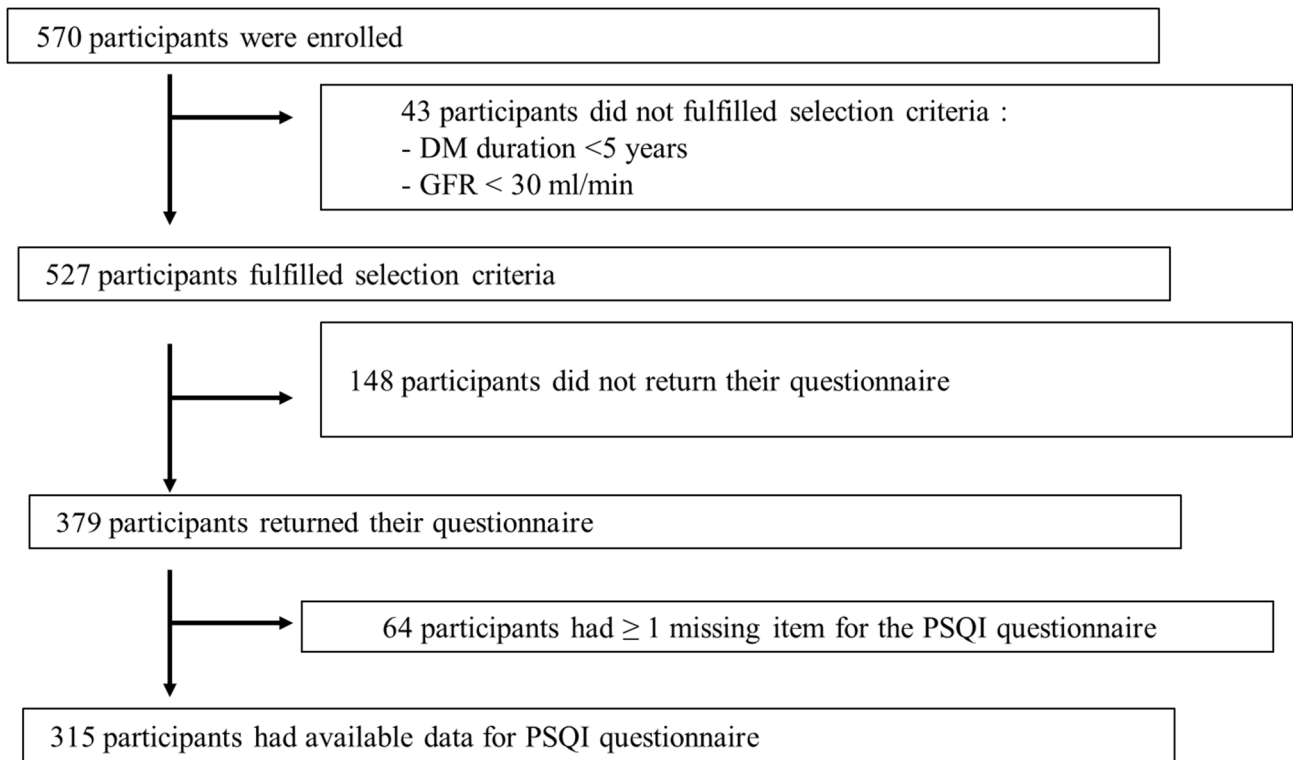
	<b>Responders n<sub>1</sub> = 315</b>	<b>Non- responders n<sub>2</sub> = 212</b>	<b>n<sub>1</sub>/n<sub>2</sub></b>
<b>Demographic factors</b>			
Age (years)	47.0 (36-60)	45.5 (33-61)	(315/212)
Women	171 (54.3 %)	107 (50.5 %)	(315/212)
Education			(308/61)
<i>Primary education</i>	23 (7.5 %)	6 (9.8 %)	
<i>Secondary education</i>	168 (54.5 %)	42 (68.9 %)	
<i>Tertiary education</i>	117 (38 %)	13 (21.3 %)	
<b>Clinical characteristics</b>			
BMI (kg/m <sup>2</sup> )	25.3 ± 4.3	25.1 ± 4.3	(315/212)
Obesity (IMC ≥ 30 kg/m <sup>2</sup> )	45 (14.3 %)	29 (13.7 %)	(315/212)
Waist-to-hip ratio	0.87 ± 0.10	0.88 ± 0.11	(268/181)
SBP (mmHg)	127.6 ± 13.9	128.1 ± 14.2	(314/211)
DBP (mmHg)	73.8 ± 10.0	73.4 ± 9.8	(313/211)
Diabetes duration (years)	22 (13-34)	21 (13-34)	(315/212)
<b>Insulin</b>			
Insulin regimen: CSII	165 (52.4 %)	29 (13.7 %)	(315/212)
Mean insulin dose (IU/kg.d)	0.64 +/- 0.35	0.64 +/- 0.56	(216/107)
<b>Diabetes complications</b>			
<i>Microvascular</i>			
Retinopathy			(315/211)
Absent	214 (67.9 %)	142 (67.3 %)	
non-proliferative retinopathy	73 (23.2 %)	41 (19.4 %)	
proliferative retinopathy	28 (8.9 %)	28 (13.3 %)	
Pan retinal photocoagulation	44 (14 %)	40 (18.9 %)	(315/212)
Macular edema	18 (5.7 %)	21 (9.9 %)	(315/212)
<b>Nephropathy</b>			
Urinary albumin excretion (mg/g)	59 (14-222)	60 (15-310)	(93/69)
Albuminuria			(93/69)
<i>Normo-albuminuria</i>	34 (36.6 %)	22 (31.9 %)	
<i>Microalbuminuria</i>	44 (47.3 %)	28 (40.6 %)	
<i>Macroalbuminuria</i>	15 (16.1 %)	19 (27.5 %)	
eGFR (mL/min)	98.9 +/- 17.5	100.7 +/- 20.3	(315/212)
<b>Neuropathy</b>			
Peripheral neuropathy	35 (11.1 %)	33 (15.6 %)	(315/212)
Erectile dysfunction	23 (7.3 %)	20 (9.4 %)	(315/212)
Orthostatic hypotension	10 (3.2 %)	7 (3.3 %)	(315/212)
<i>Macrovascular</i>			
Cardiovascular disease	32 (10.2 %)	15 (7.1 %)	(315/212)
Myocardial infarction	10 (3.2 %)	11 (5.2 %)	(315/212)
Coronary artery revascularization	12 (3.8 %)	15 (7.1 %)	(315/212)
Cerebrovascular disease	6 (1.9 %)	7 (3.3 %)	(315/212)
Peripheral arterial disease	14 (4.4 %)	18 (8.5 %)	(315/212)

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	<b>Responders n<sub>1</sub> = 315</b>	<b>Non-responders n<sub>2</sub> = 212</b>	<b>n<sub>1</sub>/n<sub>2</sub></b>
<b>Hypoglycemia</b>			
<b>Frequency of confirmed hypoglycemia per week</b>	3 (1-4)	3 (1-4)	(306/202)
<b>Experienced severe hypoglycemia (previous 6 months)</b>	35 (11.1 %)	36 (17 %)	(315/212)
<b>Fear of hypoglycemia</b>			
<b>HFS-II total</b>	64 (54-79)	63 (54.5-79)	(310/55)
<b>HFS-II B</b>	29 (24-35)	28.5 (25.3-33)	(311/56)
<b>HFS-II W</b>	34 (27-44)	35.5 (27-44)	(312/58)
<b>Glycemic control</b>			
<b>Mean glycemia (mg/dL)</b>	151.6 ± 23.7	150.7 ± 26.4	(261/48)
<b>HbA1c (%)</b>	7.6 ± 0.9	7.8 ± 1.1	(262/182)
<b>HbA1c (mmol/mol)</b>	59.8 ± 10.4	61.4 ± 12.1	(262/182)
<b>HbA1c ≥ 7.5 % (≥58 mmol/mol)</b>	136 (43.2 %)	102 (48.1 %)	(315/212)
<b>Glycemic variability</b>			
<b>Blood glucose CV (%)</b>	39.9 ± 9.4	39.4 ± 11.2	(261/48)
<b>MAGE (mg/dL)</b>	118.6 ± 39.8	121.6 ± 53.4	(261/48)
<b>Hospital Anxiety and Depression Scale</b>			
<b>Total score</b>	11 (7-16)	10 (7-14)	(307/57)
<b>Anxiety score</b>	7 (5-10)	7 (4.5-9)	(310/59)
<b>Depression score</b>	4 (2-6)	3 (2-6)	(309/57)
<b>Medications</b>			
<b>Antidepressant</b>	19 (6 %)	19 (9 %)	(315/212)
<b>Anxiolytic</b>	11 (3.5 %)	12 (5.7 %)	(315/212)
<b>Antihypertensive</b>	102 (32.4 %)	70 (33 %)	(315/212)

566 Abbreviations: PSQI = Pittsburgh Sleep Quality Index, CSII = Continuous subcutaneous insulin infusion,  
567 SAP = Systolic Arterial Pressure, DAP =Diastolic Arterial Pressure, MAGE = Mean Amplitude of Glycemic  
568 Excursions, HFS-II, hypoglycemia fear survey total score; HFS-B, hypoglycemia fear survey Behavior subset score;  
569 HFS-W, hypoglycemia fear survey Worry subset score.  
570 Data are reported as number (%) for categorical variables, as mean ± SD or as median with interquartile ranges  
571 (IQR), if appropriate for continuous data.



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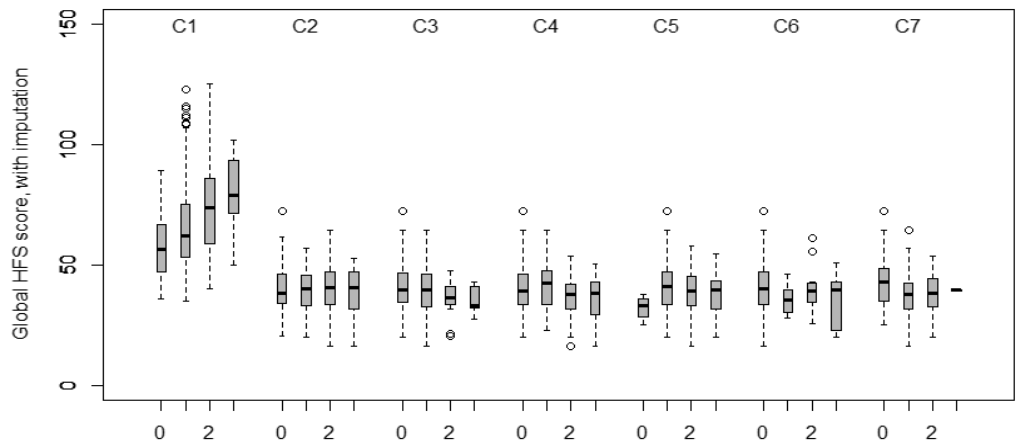
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574 **Supplemental Figure 1.** Flow chart of the study

575 Abbreviations: DM=Diabetes mellitus; GFR=Glomerular Filtration Rate; PSQI = Pittsburgh Sleep Quality Index;

576 SMBG=self-monitoring blood glucose.

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**Supplemental Figure 2.** Association between different components of PSQI score and total HFS-II.

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Abbreviations of different components of PSQI score: subjective sleep quality (C1); sleep latency (C2); sleep

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duration (C3); habitual sleep efficiency (C4); sleep disturbances (C5); use of sleep medication (C6); and daytime

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dysfunction (C7). Data are expressed as box plots (25th percentile, median, and 75th percentile) and whisker (25th

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percentile – 1.5 interquartile range, 75th percentile + 1.5 interquartile range). Components of PSQI score vary from 0

586

to 3.