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Anxiety disorders as predictors of suicidality in people with type 2 diabetes mellitus: Findings of a study in six European countries

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Summary

Aim. Anxiety disorders are significant predictors of suicidality and are proposed to be independent risk factors for suicide attempts. They are common in people with type 2 diabetes (T2DM) and are associated with longer duration of diabetes and poorer treatment outcomes. The aim was to examine associations between anxiety disorders and suicidal thoughts and behaviour in people with T2DM, to establish the prevalence of suicidality among people with T2DM in the selected European countries and to examine whether anxiety disorders were predictive of current outcomes of suicidality in this population using data from the International Prevalence and Treatment of Diabetes and Depression study.

Material and methods. The study sample comprised 1063 adults with T2DM from 6 European countries. The presence of anxiety disorders and suicidality was assessed with the MINI International Neuropsychiatric Interview. The group of participants with current suicidal risk was compared with the group of participants with no suicidal risk.

Results. The participants from Germany were more likely to report suicidality than those from other countries, whereas people from Serbia and Ukraine were less likely to report it. Depression and anxiety disorders significantly contributed to the increased presence of suicidality among people with T2DM. Agoraphobia was a significant predictor of suicidality when controlling for depression. The participants with T2DM and comorbid agoraphobia had 4.86 times higher odds to report suicidality than those without agoraphobia.

Conclusions. Agoraphobia was a significant predictor of suicidality in people with T2DM.

Key words: anxiety disorders, type 2 diabetes mellitus, suicidality

Background

Anxiety disorders (AD), considered as a whole category of disorders, are significant predictors of suicidality [1-3]. The suicidal continuum includes: suicide ideation, suicide plans, attempted suicide and completed suicide [1]. Even though the association is weak [4], most findings suggest that anxiety disorders are independent risk factors for suicide attempts and should be considered as a serious public health problem [5, 6]. The risk is even higher for people with comorbid personality disorders [7, 8] and mood disorders, although some controversy in the subject still remains [9, 10].

In a recent meta-analysis [1], the increase in the risk of suicide has been demonstrated for each subtype of anxiety, except obsessive-compulsive disorder (OCD). The results remained inconclusive for OCD, although research suggests that this disorder type may also be a risk factor [11]. There is a robust association between suicidal ideation and/or attempts and social anxiety disorder (SAD) [12]. Findings also link suicidal ideation and behaviour to generalised anxiety disorder (GAD) [1] which is the most frequently diagnosed anxiety disorder (three times higher than any other anxiety disorder [13]), panic disorder (PD) [14, 15], body dysmorphic disorder (BDD) [16], and to post-traumatic stress disorder (PTSD) [17]. However, concerning PTSD, some types of traumas [18] and the comorbidity of alcohol abuse and depression [19] make individuals especially vulnerable to suicidal ideation [20]. Overall, suicidal ideation, suicide plans and attempts are more frequent in people with anxiety disorders than in the general population. Symptom severity is associated with a higher suicidal ideation risk in PD, PTSD, and OCD, ranging from 10% to more than 50% [12].

Type 2 diabetes mellitus (T2DM) is a disease with a high prevalence in the general population, reaching 8% among middle-aged people, and is associated with a high incidence of somatic and psychological complications [21-23]. The risk of diabetes complications is related to the effectiveness of glycaemic control, with few patients able to maintain glycaemic control at normal levels [21].

Anxiety disorders are common in people with diabetes [21-23]; however, reports of the prevalence of co-occurring anxiety disorders and their impact on the course of the disease remain rare due to methodological problems related to small sample sizes. Adults with T2DM have a significantly higher rate of GAD and PD, compared to people without diabetes: 122% higher for GAD and 85% higher for PD, with a frequent co-occurrence of GAD and major depressive disorder [24]. Those findings were confirmed by the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study that showed a prevalence of anxiety disorders in T2DM persons at 18% [25]. The most common diagnosis was GAD (8.5%) and lifetime PD (5.1%). Four percent of the study participants had more than one psychiatric disorder and 2.8% more than one anxiety disorder. Anxiety disorders were more prevalent in women and were associated with longer duration of diabetes, more diabetes complications and poorer diabetes control.

1. Aim of study

The overall aim of the present study was to examine associations between anxiety disorders and suicidal thoughts and behaviour in people with T2DM using the follow-up data of the INTERPRET-DD study [25]. We aimed to establish the prevalence of suicidality among people with T2DM in selected European countries and to examine whether anxiety disorders were predictive of current (past month) outcomes of suicidality in people with T2DM.

2. Material and methods

2.1. The INTERPRET-DD study

The data set was derived from the INTERPRET-DD study, a detailed protocol being available in published articles [26, 27]. To summarise, a sample of approximately 200 people with T2DM at each of the participating diabetes clinics in the collaborating countries was invited to participate in the study. Between September 2013 and May 2015, individuals were invited to participate in the study by the practitioners in the diabetes clinic providing secondary or tertiary care. In each collaborating country, the research team included at least one psychiatrist and one endocrinologist. Written informed consent was obtained prior to participating in the research study. Ethics approval was obtained both from the Open University Research Ethics Committee and from each country's local ethics committee [26].

Individuals were included in the study if they were 18-65 years of age, had T2DM diagnosed at least 12 months earlier and attended the diabetes out-patient (second-

ary care) facilities in their respective countries. The exclusion criteria were: (1) T2DM for less than 12 months, (2) diagnosis of type 1 diabetes, (3) communication or cognitive difficulties or inability to complete the survey tools, (4) hospital stay or planning an admission for in-patient care to a hospital, (5) dementia, Parkinson's disease, epilepsy or other serious neurological condition, (6) clinical diagnosis of dependency on alcohol or other substance (not tobacco) or diagnosis of schizophrenia, (7) current/within last 3 months participation in other studies (except observational studies), (8) living outside the diabetes clinic catchment area/unlikely to be available for follow-up, (9) currently pregnant or pregnant/had a child in the last 6 months, (10) any life-threatening or unstable severe condition (e.g. cancer, stroke) in the last 6 months or not fully recovered/having more than minor effects from a stroke [26, 27]. People with: gestational diabetes, latent autoimmune diabetes in adults (LADA), maturity onset diabetes of the young (MODY), 'type 3c diabetes' and diabetes associated with rare genetic syndromes (Wolfram syndrome, Alström syndrome) were also not included in the study.

2.2. Participants

All INTERPRET-DD records of individuals with T2DM in Europe who had completed the section on anxiety disorders and suicidality in the MINI International Neuropsychiatric Interview (MINI) were included in the study. Thus, this study included data from six countries from Europe: Germany, Italy, Poland, Russia, Serbia and Ukraine. Records from other countries were excluded from the analysis. From a total of 2,783 people with T2DM across all countries included in the INTERPRET-DD study [27], the sample in the analysis comprised 1,063 people with T2DM from Europe.

Eligible study participants were adults diagnosed with T2DM, aged between 19–65 years (M = 55.6; SD = 8.6). The sample included 564 women (53.1%) and 499 men (46.9%). Table 1 provides the overall details of the participants. Data are presented for continuous variables (e.g. age, duration of diabetes, level of HbA1c) involving means, standard deviations (SDs), medians, quartiles and marginal values – minimum and maximum.

Table 1. **Socio-demographic and clinical characteristics of study participants with T2DM (N = 1063)**

Socio-demographic characteristics		**Value**
Age [years]	Mean (SD)	55.6 (8.6)
	Median	58.0
	Quartiles (Q1, Q3)	52, 62
	Min-Max	<19; 65>

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Gender	Women	564 (53.1%)	
	Men	499 (46.9%)	
Marital status*	Single	149 (14.0%)	
	Married/co-habiting	736 (69.2%)	
	Widowed	79 (7.4%)	
	Divorced	98 (9.2%)	
Place of residence	Rural areas	96 (9.0%)	
	Urban areas	967 (91.0%)	
Education	No formal education	1 (0.1%)	
	Some/completed primary school	97 (9.1%)	
	Some/completed secondary school	599 (56.4%)	
	Higher education (college, post-grad/ professional)	366 (34.4%)	
Family income status	No regular income (e.g. unemployed/student)	87 (8.2%)	
	Regular income (e.g. part/full-time work, pension)	976 (91.8%)	
Clinical characteristics		**Value**	
		[%]	[mmol/mol]
HbA1c [%; mmol/mol]	Mean (SD)	7.8 (1.8)	61.8 (20.0)
	Median	7.4	57.0
	Quartiles (Q1, Q3)	6.4, 8.8	46.5, 72.7
	Min-Max	<3.1; 17.2>	<10.5; 164.5>
Diabetes duration [years]	Mean (SD)	9.2 (7.0)	
	Median	7	
	Quartiles (Q1, Q3)	4, 13	
	Min-Max	<1; 40>	
Family history of diabetes*	No family history	359 (33.8%)	
	Diabetes in 1st degree relative (parent, sibling)	446 (42.0%)	
	Diabetes in 2nd degree relative (grandparent, aunt, uncle, cousin)	170 (16.0%)	
	Diabetes in both 1st and 2nd degree relatives	86 (8.1%)	

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Other recorded diseases or diabetes complications*	Stroke or cerebrovascular incident	81 (7.6%)
	Myocardial infarction	112 (10.5%)
	Any other recorded heart disease	262 (24.6%)
	Diabetic retinopathy	269 (25.3%)
	Macular oedema	76 (7.1%)
	Diabetic neuropathy	352 (33.1%)
	Diabetic nephropathy	114 (10.7%)
	Peripheral vascular disease	164 (15.4%)
	Thyroid abnormality	296 (27.8%)
	Neurological disorders, e.g. Parkinson's disease or epilepsy	23 (2.2%)
	Any other medical conditions diagnosed and treated, incl. any mental disorders	451 (42.4%)
Other self-reported diseases or medical complaints (lifetime)	Any heart disease or other heart problems	353 (33.2%)
	Any kidney disease	147 (13.8%)
	Any problems with vision/eyes	442 (41.6%)
	Any problems with legs/feet	366 (34.4%)
	Arterial hypertension	769 (72.3%)
	Hypercholesterolaemia	592 (55.7%)
Diabetes medications*	No diabetes medications	34 (3.2%)
	Oral hypoglycaemic agents only	550 (51.7%)
	Insulin only	190 (17.9%)
	Both oral agents and insulin	287 (27.0%)
Other medications*	Blood pressure-lowering medications	761 (71.6%)
	Drugs for depression	23 (2.2%)
Smoking status*	Never	517 (48.6%)
	Past	328 (30.9%)
	Current	212 (19.9%)
Exercise frequency*	Rarely/never	494 (46.5%)
	Monthly	63 (5.9%)
	Weekly	258 (24.3%)
	Daily	237 (22.3%)

Note: * – The percentages do not sum up to 100, since the respondents could choose more than one answer or there were some missing responses. As a general rule, SPSS analysis commands that performed computations handle missing data by omitting the missing values.

2.3. Procedure

First, the investigators completed an information form for each eligible individual. This form included clinical and socio-demographic information from medical records [26, 27]. Each participant completed a set of questionnaires: the Patient Health Questionnaire (PHQ-9) [28, 29], the WHO-5 Well-being Questionnaire [30,31] and the Problem Areas in Diabetes Scale (PAID) [32].

In order to assess the presence of anxiety disorders and suicidality, the records from the MINI International Neuropsychiatric Interview version 5 or 6, depending on the current standards in psychiatric practice at the centre, were employed [33, 34]. The MINI has been widely considered as a gold diagnostic standard and used in a range of different populations – including those with serious illnesses and in community surveys and is a reliable tool indicating the diagnostic category according to DSM-IV criteria [35]. The MINI allows for information to be obtained on the presence of the following anxiety disorders: panic disorder, agoraphobia, social phobia and generalised anxiety disorder. PTSD and OCD were excluded as they are no longer classified as anxiety disorders in the most recent DSM (DSM-5) [35] and ICD (ICD-11) [36] revisions.

The MINI assessment was conducted by a trained psychiatrist or clinical psychologist and lasted between 15 and 40 minutes. Current suicidal risk was assessed with the MINI module on suicidality, which differed between MINI-5 and MINI-6. The MINI-5 module comprised five questions regarding suicidal thoughts and behaviour in the past month and one question on any previous suicide attempt in lifetime [33]. Negative answers to all the questions resulted in no current suicidal risk, whereas one or more positive answers, depending on the weight of each item, resulted in either low, moderate or high current suicidal risk in the participant.

The MINI-6 module on suicidality comprised three screening questions (not included in the final score), fourteen questions regarding suicidal thoughts and behaviour in the past month and one question on any previous suicide attempt in lifetime. Similarly to MINI 5, all negative answers resulted in no current suicidal risk. If at least one answer was positive, the total sum of points assigned to each question determined either low (1-8 points), moderate (9-16 points) or high (17 points or more) current suicidal risk [33].

The INTERPRET-DD study raters indicated either present current suicidal risk or its absence, accordingly. Those deemed to be at risk of suicide were immediately referred for psychiatric consultation for treatment.

For the purposes of statistical analysis in this study, the low, moderate and high-risk groups remained collapsed and were compared as a whole with a group of participants with no (all answers negative) suicidal risk.

2.4. Statistical analyses

2.4.1. The prevalence of suicidality among people with T2DM in the selected European countries

To achieve the first research goal of assessing the associations between suicidality and country of origin among adults with T2DM across the six European countries, cross tabulation analyses were performed. The prevalence of suicidality in each country was examined by intersecting the variable 'country' with the two groups established based on the MINI suicidality outcome (suicidality or no suicidality).

This procedure allowed us to verify the percentage of participants that presented the highest suicidality amongst the people with T2DM from the same country and also the distribution of suicidality within the countries enrolled. A chi-square test was performed in order to determine if there was a significant association between suicidality and country – we intended to establish which of the countries contributed the most to the chi-square statistical significance. This was obtained by the analysis of the standardised residuals. If the value of the residual was outside ±1.96 then it was significant [37].

2.4.2. Anxiety disorders as predictors of suicidality

The second objective of this study was to examine whether anxiety disorders were significant predictors of suicidality among people with T2DM across the selected countries.

In order to verify whether current anxiety disorders were significant predictors of suicidality in adults with T2DM a multiple logistic regression was performed. In the first step, the presence of depression identified as recurrent, current or past was introduced into the model as a control variable. The second step involved four current anxiety disorders as predictors of suicidality: panic disorder, agoraphobia, social phobia and generalised anxiety disorder. We employed a sequential regression method of entry with block-wise selection to explore the increment in explained variance by anxiety disorders, as compared to the model including only depression. To assess whether the estimated multiple logistic models fitted the data, the Hosmer-Lemeshow goodness-of-fit test was employed [38, 39]. For significant predictors of suicidality, odd ratios with 95% confidence intervals (CI) were calculated.

The statistical analyses were carried out using SPSS version 25 for Windows. Statistical significance for all of the conducted analyses was established at $p < 0.05$.

3. Results

3.1. Association between suicidality and country of origin among adults with T2DM

The proportion of participants who reported suicidality by country is presented in Table 2. However, a chi-square test to verify significance of the associations between country of origin and suicidality was not conducted because 8.3% of cells had expected

counts of less than 5. For that reason, we instead used Fisher's exact test with the row variable 'country' having six levels (Germany, Italy, Poland, Russia, Serbia, Ukraine) and the column variable 'suicidality' with two levels (yes, no). The results of the Fisher exact test indicated an overall significant difference in suicidality between the six countries ($p < 0.001$, two-tailed Fisher's exact test).

To identify which country's population reported the significantly higher probability of suicide, compared with the inhabitants of other countries, we conducted a series of Fisher's exact tests (see Table 2). The results indicate that subjects recruited in Germany were significantly more likely to report suicidality than people enrolled in other countries (19.66% versus 2%, respectively; $p < 0.001$, Fisher's exact test). Conversely, people from Serbia were less likely to report suicidality than those in the overall sample from other countries (0% versus 4.86%, respectively; $p < 0.001$, Fisher's exact test). Likewise, the Ukrainians were less likely to be suicidal than the participants in the overall sample from other countries (0.77% versus 4.39%, respectively; $p < 0.026$, Fisher's exact test). Among participants from Italy, Poland and Russia the difference in the numbers of suicidal and non-suicidal people was not statistically significant compared to the overall sample from other countries (although the latter was close to significance). The declared suicidality from Poland and Russia was similar (respectively 2.3% and 2.0%). Among Italians, 4.5% of participants indicated suicidality.

Table 2. **Cross tabulation for observed and expected number of people with T2DM with suicidality presence by country (N = 1063)**

	Suicidality							
	No				Yes			
Country	N_e	N_{ob}	% from country	standardised residuals	N_e	N_{ob}	% from country	standardised residuals
Germany	112.4	94	80.3%	-1.7	4.6	23	19.7%	8.5
% from suicidality			9.2%				54.8%	
Italy	193.1	192	95.5%	-0.1	7.9	9	4.5%	0.4
% from suicidality			18.8%				21.4%	
Poland	208.4	212	97.7%	0.2	8.6	5	2.3%	-1.2
% from suicidality			20.8%				11.9%	
Russia	191.1	195	98.0%	0.3	7.9	4	2.0%	-1.4
% from suicidality			19.1%				9.5%	
Serbia	191.1	199	100.0%	0.6	7.9	0	0.0%	-2.8
% from suicidality			19.5%				0.0%	
Ukraine	124.9	129	99.2%	0.4	5.1	1	0.8%	-1.8
% from suicidality			12.6%				2.4%	

Note: N_e – expected number of individuals with suicidality; N_{ob} – observed number of individuals with suicidality.

Chi-square test to verify significance of the associations between country of origins and suicidality was not conducted because 8.3% of cells had expected counts of less than 5.

3.2. Anxiety disorders as predictors of current suicidality among people with T2DM

The prevalence of anxiety disorders in the sample and by country is reported in Table 3. The socio-demographic variables: age, sex, marital status and family income were controlled and did not influence the results of the analysis.

Multiple logistic regression analysis was used to determine which of the anxiety disorders predicted suicidality when past, recurrent and/or current depression in records were included into the model as a control variable. The initial stage of this analysis included only depression in the model, and determined that this model was significantly different from the model with only the constant, $\chi 2 = 26.982$, $p < 0.001$, $df = 1$. This model explained about 9% of suicidality among people with T2DM (Nagelkerke $R^2 = 0.089$).

Subsequent stages of the analysis considered the contribution of the anxiety disorders as predictor variables to the overall model while controlling for depression. The chi-square value of 14.24 ($df = 4$, $p = 0.007$) indicated that adding the set of anxiety disorders to the model significantly increased presence of suicidality among people with T2DM. The results revealed that depression (current, recurrent and/or past) and anxiety disorders significantly contributed to the explanatory power of the model, $\chi 2(5) = 41.226$, $p < 0.001$ (Table 4).

Importantly, only one type of anxiety disorder – agoraphobia – was a significant predictor of suicidality when controlling for depression. The other current anxiety disorders: panic disorder, social phobia and generalised anxiety disorder did not significantly predict suicidality.

Depression and agoraphobia jointly explained approximately 14% of the variability in respondents' suicidality (Nagelkerke $R^2 = 0.135$). The Hosmer–Lemeshow test indicated goodness-of-fit of the final model (H-L $\chi^2(3) = 0.749$; $p = 0.862$). The results of the logistic regression analysis are presented in Table 4.

Current, recurrent and/or past depression was significantly related to suicidality, Wald(1) = 18.37, $p < 0.001$. The results showed that the odds of presence of suicidality are 4.27 times greater for participants with T2DM and comorbid depression (current, recurrent or past) as opposed to those with no history of depression. In addition, the participants with T2DM and comorbid agoraphobia had 4.86 times higher odds to present suicidality than those without this anxiety disorder, Wald(1) = 13.01, $p < 0.001$.

Table 3. **The prevalence of anxiety disorders in the study population of patients with T2DM by country (N = 1063)**

	Country					
	Germany	Italy	Poland	Russia	Serbia	Ukraine
	N = 117	N = 201	N = 217	N = 199	N = 199	N = 130
Panic disorder	1 (0.9%)[a]	2 (1.0%)[a]	9 (4.1%)	20 (10.1%)	0 (0.0%)	30 (23.1%)

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Agoraphobia	13 (11.1%)	4 (2.0%)	8 (3.7%)	28 (14.1%)	3 (1.5%)	6 (4.6%)
Social phobia	0 (0.0%)	0 (0.0%)	10 (4.6%)	21 (10.6%)	0 (0.0%)	11 (8.5%)
Generalised anxiety disorder	1 (0.9%)	2 (1.0%)	9 (4.1%)	20 (10.1%)	0 (0.0%)	30 (23.1%)

Table 4. **Summary of multiple logistic regression analysis for suicidality as the dependent variable (DV) with depression and anxiety disorders as predictors**

DV: Suicidality											
Model 1											
	B	SE	Wald	df	p	Exp(B)	95% CI		Nagelkerke R^2	χ^2(df)	p
							lower	upper			
(constant)	-3.815	0.238	256.365	1	0.000	0.022			0.089	$\chi^2(1) = 6.982$	< 0.001
Depression	1.690	0.322	27.617	1	0.000	5.420	2.886	10.179			
Model 2											
(constant)	-3.929	0.247	253.546	1	0.000	0.020			0.135	$\chi^2(4) = 14.244$	= 0.007
Depression	1.451	0.338	18.375	1	0.000	4.267	2.198	8.285			
Panic disorder	-0.289	0.608	0.227	1	0.634	0.749	0.228	2.464			
Agoraphobia	1.581	0.438	13.010	1	0.000	4.860	2.058	11.475			
Social phobia	-0.948	0.830	1.305	1	0.253	0.388	0.076	1.971			
GAD	0.546	0.473	1.331	1	0.249	1.726	0.683	4.363			

Note: Overall final model: χ^2 (5) = 41.226; $p < 0.001$. The data shown under 'B' represent the estimated regression coefficients that predicted suicidality for each variable included in the model, the Wald statistic provides a test of each of these coefficients, and the Exp(B) coefficient provides information related to the estimated odds ratio of suicidality presence resulting from the presence of the predictor variable.

4. Discussion

The results of our study are consistent with previous reports of increased risk of suicidality in people diagnosed with diabetes [40]. In this sample of 1,063 participants with T2DM from six countries included in the INTERPRET-DD study a total of 2.4% declared suicidality; however, the results showed great differences between countries.

One type of anxiety disorder – agoraphobia – was a significant predictor of suicidality when depression was controlled for. Other anxiety disorders: panic disorder, social phobia and generalised anxiety disorder did not significantly predict suicidality. The odds of presence of suicidality were about 4 times greater for people with T2DM and

depression (current, recurrent or past), compared to those with no history of depression. In addition, those with agoraphobia had almost 5 times higher odds to present suicidality than those without this anxiety disorder.

Historically, there remains significant differences in suicide rates between different European countries, with suicide rates particularly high in the societies of Eastern Europe and generally lower in Mediterranean countries [41]. The World Health Organisation (WHO) reported that in 2016 the age-standardised suicide rates per 100,000 people reached: 5.5 in Italy, 9.1 in Germany, 10.9 in Serbia, 13.4 in Poland, 18.5 in Ukraine and 26.5 in Russia [42]. According to the most recent Eurostat data, the number of deaths due to suicide per 100,000 inhabitants in European Union member countries ranges from 5 (in Cyprus) to 32 (in Lithuania), with an average of 11 [43]. Among the countries included in our analysis, 6, 12 and 16 deaths due to suicide per 100,000 people were reported in Italy, Germany and Poland, respectively [43]. It should be noted that people with T2DM from countries with lower suicide rates in the general population (Germany and Italy) were characterised by a higher prevalence of suicidality compared with the participants from countries with higher suicide rates in the general population (Poland, Serbia, Ukraine and Russia). It may be hypothesised that the burden of a chronic and potentially disabling disease such as T2DM has a different impact on suicidality in different societies. Germany and Italy are characterised by longer life expectancy compared to the other countries. A diagnosis of a chronic disease may result in a greater discrepancy between one's expectations towards length and quality of life before and after the diagnosis.

A multi-national study on suicidality showed the lifetime prevalence of suicidal ideation, plans, and attempts worldwide was 9.2%, 3.1%, and 2.7%, respectively [44]. A study by Pompili et al. [45] reported that Italian outpatients with T1DM and T2DM showed greater hopelessness and suicide ideation than outpatients admitted to departments of cardiology, gastroenterology, and pneumology [45]. A recent study from Italy showed the lifetime prevalence of suicide ideation, plans, and attempts was 3.0%, 0.7% and 0.5%, respectively [41]. In the Italian population with T2DM included in our study, the overall prevalence of suicidality was higher, at 4.5%, compared with all the subgroups in the Italian study. In Germany the prevalence of suicidal ideation in the general population reached 8.0% [46], whereas in our study the overall occurrence of suicidality in the German population with T2DM reached 19.7%. The results of the EZOP Poland study conducted on a Polish population aged 18-64 showed the lifetime prevalence of 'any event that could be qualified as suicide attempt' at 0.7% [47], while 1.7% of the population 'thought about committing suicide' [48]. In this study, the prevalence of suicidality in Polish subjects with T2DM was higher and reached 2.3%. It was lower, however, than the prevalence measured in a group of Polish outpatients with a diagnosis of epilepsy, in 10% of whom the suicidal ideations were revealed [49].

The associations between diabetes and anxiety disorders are multi-dimensional. Chronic stress increases the risk of anxiety and depressive disorders [50]. Chronic stress-related hypercortisolaemia has been proposed to be a risk factor for the development of insulin resistance and T2DM [51]. A diagnosis of T2DM may also induce increased stress, which can intensify the psychological burden of life events [52]. In

people with a diagnosis of T2DM, persistent stress may further reduce motivation to take care of their health and to adhere to medical recommendations, resulting in, inter alia, less physical activity, poor diet or irregular use of medication, which may lead to poorer glycaemic control and a higher risk of developing diabetes complications [53]. This phenomenon is particularly observed in some people with type 1 diabetes, who may develop a fear of experiencing hypoglycaemia and consequently develop a tendency to reduce insulin dosing, below recommended levels [54]. In contrast, studies indicate that the use of effective anti-anxiety treatment may lead to a reduction in glycated haemoglobin levels in the long term [55].

4.1. Limitations of the study

Suicidal risk is associated with socio-cultural factors [50] and the INTERPRET-DD study participants come from a wide range of cultural backgrounds. Therefore, in order to understand the impact of anxiety disorders on suicidality in people with T2DM, we decided to narrow our analysis down to those living in European countries only. It limited the number of countries and the total number of subjects included in the study; however, it also allowed us to reduce the influence of potential confounders associated with cultural, societal or geographic contexts.

The suicide rates tend to be lower in less developed countries, with a particularly low age-standardised suicide rate per 100,000 in 2016 in Pakistan (3.1) [42], among all the countries included in the INTERPRET-DD study. In high-income economies, including European countries, the risk of suicide is higher among unskilled manual workers than in general working age population [51]. The distributions of employment by economic sector vary between the countries from different regions and the employment in the primary sector tends to be higher in some of the non-European countries [52]. However, the higher rate of employment in the primary sector in non-European countries does not necessarily contribute to higher risk of suicide in international comparisons, considering the generally lower suicide rates in these countries.

The unemployment rate in 2020 in non-European countries was more heterogenous than in the countries included in the analysis [52]. There was also a difference between the European and non-European countries with regard to gross national income per capita. The European countries in our study were classified by the World Bank as either high-income or upper-middle-income countries, with only Ukraine classified as a lower-middle-income country. Non-European countries participating in the INTERPRET-DD study were classified more diversely, as either low-income, lower-middle-income or upper-middle-income countries, with Saudi Arabia being the only country classified as a high-income economy [52].

Bangladesh and China are among only five countries in the world to have a higher suicide rate for women than for men [42], while there are no European countries with such characteristics. The suicide rates in China are also much higher in rural areas compared to urban areas [53]. Therefore, including only European countries in our analysis allowed us to mitigate the impact of the heterogeneity of the socio-economic factors on suicidality outcomes.

It should be noted that the study results concern the declared suicidality by the participants in various countries. In some countries participants may not disclose suicidal plans or ideations because of social, religious or legal reasons. A potential discrepancy between the divulged and actual suicidality may be considered a limitation of the study; however, we expect that narrowing the analysis down to only European countries may have reduced its effect due to generally smaller socio-cultural differences between them.

Another limitation is the use of different versions of the MINI questionnaire due to current psychiatric practice at the study sites or unavailability of a local translation of either of the MINI versions. The study in Germany, Italy, Serbia and Ukraine was conducted using MINI-6. In Russia, the study was conducted with MINI-6, with the exception for the diagnosis of dysthymia, which was set by MINI-5. The study in Poland was conducted with MINI-5. The module on suicidality in the MINI-6 comprises more items and may provide a considerably more detailed assessment of suicidal risk, even though the participants were eventually distributed into two analogous groups: with or without suicidal risk. Considering the vast differences of the prevalence of suicidality in the sites using MINI-6, the particularly high prevalence of suicidality in the German INTERPRET-DD sample cannot be explained only by the use of a more detailed instrument.

The PHQ-9 questionnaire also includes a self-reported item on suicidal thoughts or intentions; however, we decided not to include it in the analysis due to a different time scope of the question (2 weeks) in comparison with the MINI.

3. Conclusions

Our results illustrate the importance of taking a careful psychiatric history regarding current and lifetime anxiety disorders in individuals with T2DM, especially agoraphobia, which was a significant predictor of suicidality in this population.

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