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ORIGINAL ARTICLE

# Risk factors for depression and anxiety in painful and painless diabetic polyneuropathy: A multicentre observational cross-sectional study

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## Abstract

**Background:** Despite the high prevalence of depression and anxiety in chronic pain conditions, current knowledge concerning emotional distress among painful diabetic polyneuropathy (pDSPN) and other diabetes mellitus (DM) sufferers is limited.

**Methods:** This observational multicentre cohort study employed the Hospital Anxiety and Depression Scale, the Beck Depression Inventory II and the State-Trait Anxiety Inventory to assess symptoms of depression and anxiety in several

groups with diabetes, as well as in a control group. The study cohort included 347 pDSPN patients aged 63.4 years (median), 55.9% males; 311 pain-free diabetic polyneuropathy (nDSPN) patients aged 63.7 years, 57.9% males; 50 diabetes mellitus (DM) patients without polyneuropathy aged 61.5 years, 44.0% males; and 71 healthy controls (HC) aged 63.0 years, 42.3% males. The roles played in emotional distress were explored in terms of the biological, the clinical (diabetes-, neuropathy- and pain-related), the socio-economic and the cognitive factors (catastrophizing).

**Results:** The study disclosed a significantly higher prevalence of the symptoms of depression and anxiety not only in pDSPN (46.7% and 60.7%, respectively), but also in patients with nDSPN (24.4% and 44.4%) and DM without polyneuropathy (22.0% and 30.0%) compared with HCs (7.0% and 14.1%, $p < 0.001$). Multiple regression analysis demonstrated the severity of pain and neuropathy, catastrophic thinking, type 2 DM, lower age and female sex as independent contributors to depression and anxiety.

**Conclusions:** In addition to the severity of neuropathic pain and its cognitive processing, the severity of diabetic polyneuropathy and demographic factors are key independent contributors to emotional distress in diabetic individuals.

**Significance:** In large cohorts of well-defined painless and painful diabetic polyneuropathy patients and diabetic subjects without polyneuropathy, we found a high prevalence of the symptoms of depression and anxiety, mainly in painful individuals. We have confirmed neuropathic pain, its severity and cognitive processing (pain catastrophizing) as dominant risk factors for depression and anxiety. Furthermore, some demographic factors (lower age, female sex), type 2 diabetes mellitus and severity of diabetic polyneuropathy were newly identified as important contributors to emotional distress independent of pain.

## 1 | INTRODUCTION

A large body of evidence indicates that anxiety and depression are much more frequent in patients with chronic neuropathic pain. Multiple studies performed in a variety of settings (community-based and treatment-seeking) and employing different approaches to the assessment of mood disorders in a range of chronic pain syndromes, support this (Rosemann et al., 2007; Tsai, 2005). Furthermore, among those who suffer from pain, there exists a more close association between emotional distress and the pain experienced in women than in men, in younger individuals of lower socio-economic status, people of higher body mass index (BMI) and those experiencing greater pain intensity, longer duration and greater disability status (Ohayon, 2007). Illness beliefs and pain-coping mechanisms also have significant influences on the relationship between pain and emotional distress (McCracken et al., 2004).

The psychological aspects of what has become known as 'painful diabetic distal symmetrical sensory-motor polyneuropathy' (pDSPN) have been studied extensively, but current knowledge of exactly what contributes to emotional distress in pDSPN is very limited in the context of diabetes mellitus (Selvarajah et al., 2014). To date, factors reported as associated with emotional distress include those related to diabetes itself (poor control of glycaemia, longer duration of the disorder and the presence of complications including DSPN) (Collins et al., 2009; de Groot et al., 2001; Lustman et al., 2000). A few reports have considered the relationship between the combination of diabetes and pDSPN and emotional distress. However, these have, in the main, reported on pain descriptors and the impact of pDSPN on quality of life (Aslam et al., 2014; Davies et al., 2006; Galer et al., 2000). A study of 121 pDSPN patients disclosed a high prevalence of emotional distress and highlighted a range of independent contributors to symptoms of anxiety and depression arising out of individual circumstances and experiences (Selvarajah et al., 2014). A study of 332 type 1 diabetes mellitus (T1DM) patients reported that neuropathy had the greatest association with

distress and depression independent of pain (Bai et al., 2017).

To date, studies evaluating emotional distress and other psychological disturbances in diabetic patients have focused largely upon painful diabetic polyneuropathy and the influence of chronic pain. Correct identification of the key contributors to the psychological profile of diabetic patients may play an important role in predicting disability and in planning and analysing psychological interventions that may improve the quality of life in these patients. This study was therefore performed in well-defined subgroups of diabetic patients and healthy controls, sufficiently large and varied to study the effects of these factors upon emotional distress as expressed by depression and anxiety. Several alternative indicators of emotional distress were employed to describe its prevalence, together with a comprehensive analysis that included biological (demographic), clinical (diabetes-, neuropathy- and pain-related), socio-economic (educational level, work status) and cognitive factors (pain catastrophizing) in an exploration of their contributions to psychological profiles, either independently or through their modification of neuropathic pain.

## 2 | METHODS

### 2.1 | Study design and patients

The design approach was that of a multicentre, cross-sectional observational cohort study. Patients with diabetic distal symmetrical sensory-motor polyneuropathy (DSPN) attending the out-patients' clinic of a major multidisciplinary university hospital for diabetes mellitus were recruited consecutively, together with those from a number of other collaborating centres in the Czech Republic and Slovakia. Detailed clinical assessments of them were carried out. In addition to DSPN patients, smaller control groups of diabetic patients without polyneuropathy and non-diabetic healthy volunteers were evaluated. The study was designed as a secondary analysis of data gathered in the course of a wider international grant project supported by the European Commission (602133-ncRNAPain). It was approved by the respective local health authorities: the Ethical Committees of the University Hospital Brno (No.602133), and of the Rhineland-Palatinate Medical Association (9142-F), registered with the German Clinical Trials Register; https://www.germanctr.de/ (Registration Number DRKS00008964). Some data from a portion of the patients with DSPN and healthy controls have already been included in a published study that centres upon sensory phenotypes and risk factors for painful diabetic neuropathy (Raputova et al., 2017).

Patients with diabetes mellitus type 1 or 2, over the age of 18 years, with already-diagnosed DSPN, or with symptoms and signs suggestive of DSPN, were consecutively recruited from eight diabetes centres (all providing the routine care for the general diabetic population according to the national standards) in the Czech Republic and Slovakia between January 2014 and December 2019. Logistics and methodology were co-ordinated by researchers from the University Hospital Brno, who also recruited diabetic patients without polyneuropathy and a group of non-diabetic healthy controls among employees, relatives and volunteers. Both control groups were recruited with regard to the age distribution of the neuropathy group to form the age-adjusted groups. All participants signed written informed consent before inclusion.

All neuropathy patients first underwent an evaluation to confirm or exclude a diagnosis of DSPN and therefore their eligibility for the study. Patients reported their medical history and drug prescription medication in detail. Their ages, ethnicities, levels of education, employment status, date of diabetes diagnosis, its type and treatment were also recorded. Alcohol consumption was quantified using standard units with a cut-off of 3/2 standard drinks/day in men/women (Saunders et al., 1993). Basic clinical parameters were recorded for each participant (height, weight, BMI and blood pressure). Routine blood analysis was performed to exclude other causes of polyneuropathy (vitamin B12 and folate levels, thyroid hormones, serum protein electrophoresis, blood count, serum creatinine, bilirubin and transaminases), glycosylated haemoglobin (HbA1C) and serum lipid spectrum. A structured neurological examination was conducted to assess the clinical signs and symptoms of DSPN. Nerve conduction studies (NCS) were conducted to confirm the diagnosis of DSPN. In patients with clinical symptoms and signs of neuropathy, who did not comply with NCS criteria for DSPN (19 cases), skin biopsy with an evaluation of intra-epidermal nerve fibre density and thermal quantitative sensory testing (QST) were also performed to disclose small fibre neuropathy (Rolke et al., 2006; Tesfaye et al., 2010). If confirmed (i.e. both tests were abnormal), the patients were considered as having confirmed DSPN (Tesfaye et al., 2010). All the diagnostic tests performed (structured neurological examination, QST, skin biopsy, particular questionnaires) are described in detail in the Supporting Information.

Exclusion criteria were as follows:

1. Neuropathic pain condition attributable to a cause other than pDSPN
2. Central nervous system lesions (detection based on history, clinical examination and imaging of the brain and/or spinal cord, as necessary)

3. History or presence of laboratory abnormalities indicating a disease, condition or treatment that might constitute a cause of polyneuropathy other than diabetes (including excess alcohol consumption >3/2 standard drinks/day in men/women respectively).

Included into the DSPN group were patients with a combination of symptoms (decreased sensation, positive sensory symptoms, such as burning or aching pain, mainly in the toes, feet or legs) or signs (decreased distal sensation, decreased or absent ankle reflexes) of distal symmetrical sensory-motor diabetic neuropathy and abnormalities in NCS, all otherwise complying with the criteria for definite DSPN (European Medicines Agency, 2007; Tesfaye et al., 2010).

Two control groups were included in addition to the DSPN subgroups: a group of patients with diabetes mellitus type 1 or 2 (DM group) and a group of non-diabetic healthy volunteers (HC group), both having no other known risk factors for polyneuropathy in present or past (with the exception of diabetes mellitus in DM group), exhibiting no clinical symptoms or signs of polyneuropathy and having normal NCS findings and normal cold and warm sensory thresholds in thermal QST. The diagnosis of diabetes mellitus type 1 (T1DM) or type 2 (T2DM) was based on international criteria (American Diabetes Association, 2013).

Subjects meeting study-group inclusion and exclusion criteria then underwent pain assessment and the severity of neuropathy was evaluated, while psychological scores were established and questionnaires administered. Recruitment of study participants and the criteria used to subdivide the participants into the subgroups appear in the flow diagram (Figure 1).

## 2.2 | Assessment of pain and sensory function

Assessment of any existing pain was performed in the course of neurological examination. This included its descriptors, distribution, duration, intensity, course over time, factors alleviating or exacerbating/evoking pain and any analgesic treatment. Based on clinical evaluation and the results of additional tests (NCS; QST and skin biopsy performed mainly in patients with normal NCS findings), the pain in every patient was classified as neuropathic (NeuP) or non-neuropathic using the International Association for the Study of Pain (IASP)/Neuropathic Pain Special Interest Group (NeuPSIG) definition (Treede et al., 2008). The severity of NeuP was quantified in terms of an 11-step scale (Numerical Rating Scale; NRS). The assessment included current pain intensity, as well as mean, minimum and maximum pain intensity during the preceding week and before analgesic therapy. Ongoing analgesic therapy was not withheld before the assessment. Patients with DSPN were further classified as pain-suffering group (pDSPN; mean pain intensity of ≥4 in the NRS scale in the week immediately preceding clinical examination or in pre-treatment period in the patients already receiving analgesic therapy ($N = 208$) who had the effect documented in their clinical files) or pain-free DSPN (nDSPN; mean NRS ≤3) (European Medicines Agency, 2007). To be classified as pDSPN, participants had to exhibit chronic (i.e. >3 months) peripheral NeuP at the time of the clinical assessment and to meet the criteria for probable or definite NeuP provided by the updated IASP grading system (Finnerup et al., 2016). Classification of the 208 pDSPN patients with histories of analgesic therapy into responders and non-responders proceeded after (Raputova et al., 2017). For certain analyses, the pDSPN group was further divided into moderate (NRS 4–6) and severe pain (NRS 7–10), while the nDSPN group contained patients at NRS 0 and those with mild pain (NRS 1–3). In addition, pain and its impact on everyday life were quantified and characterized using the Graded Chronic Pain Scale (GCPS; Von Korff et al., 1992). The Neuropathic Pain Symptom Inventory (NPSI; Bouhassira et al., 2004) a self-administered questionnaire, was employed to evaluate NeuP symptoms. A Czech validated version of the NPSI was used for this (Srotova et al., 2015).

## 2.3 | Neuropathy severity and disability

The modified Toronto Clinical Neuropathy Score (mTCNS) was applied to quantify severity of DSPN (Bril et al., 2009). The INCAT Overall Disability Sum Score (ODSS) was used to quantify disability in DSPN (Merkies et al., 2002). All the scales and questionnaires used to describe pain or neuropathy severity and disability are described in Supporting Information in more detail.

## 2.4 | Psychological scores and questionnaires

### 2.4.1 | Cognitive assessment: Pain catastrophizing

The Pain Catastrophizing Scale (PCS) was used to assess negative cognitions and subjective appraisals of pain. PCS assesses a patient's propensity to develop catastrophic thinking (Sullivan et al., 1995) and it is a well-known predictor of the consequences of pain including affective disorders and disability. Three domains of catastrophizing were evaluated (rumination, magnification and helplessness).

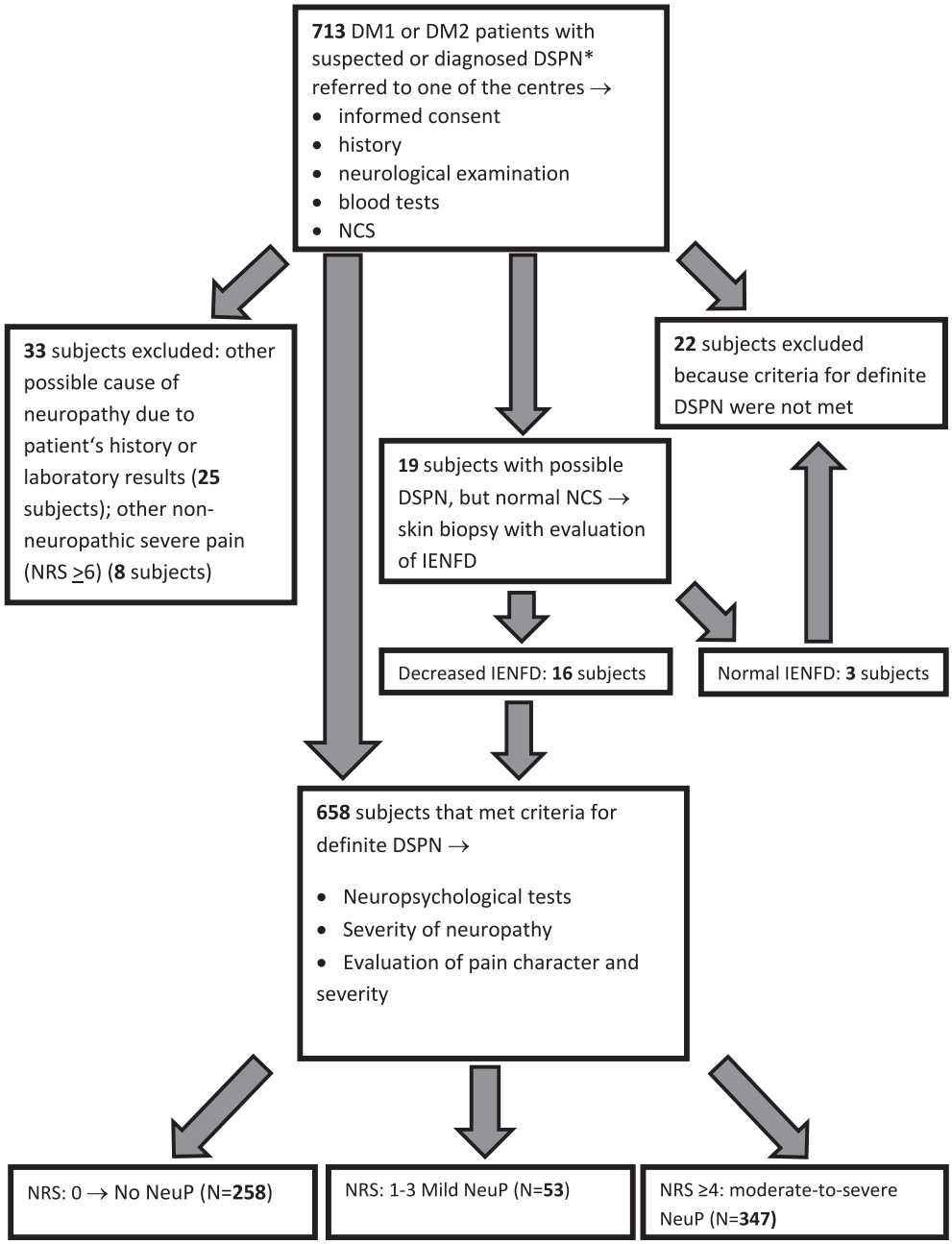


**FIGURE 1** Flow diagram of recruitment of diabetic patients with painful and painless diabetic polyneuropathy

### 2.4.2 | Symptoms of affective distress: Depression and anxiety

Symptoms of depression and anxiety were evaluated by means of the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory II (BDI II) and the State-Trait Anxiety Inventory Form Y (STAI-Y).

Hospital Anxiety and Depression Scale comprises two subscales that evaluate dimensions of anxiety (HADS-A) and depression (HADS-D, Herrmann, 1997). It focuses on the cognitive aspects of affective distress, deliberately not covering somatic symptoms in order to increase the likelihood that HADS is measuring degree of affective disorder rather than symptoms of pain, other illness or medication side effects. Scores range from 0 to 21 for each subscale.

The updated versions of the Beck Depression Inventory (BDI-II, Beck et al., 1996) has been demonstrated as an appropriate psychometric tool, capable of quantifying the severity of depression, and, to a lesser degree, discriminating between depressed and non-depressed subjects (Wang & Gorenstein, 2013). It comprises 21 questions related to the affective, cognitive, motivational and physiological symptoms of depression.

The updated version of the State-Trait Anxiety Inventory, STAI-Y 1 and 2 (Spielberger et al., 1983) comprises separate self-reported scales for measuring state

and trait anxiety. The S-Anxiety scale (STAI, Form Y-1) consists of 20 statements that investigate how respondents feel 'right now, at this moment'. The T-Anxiety scale (STAI, Form Y-2) consists of 20 statements that assess how subjects feel in general. Trait anxiety refers to relatively stable individual differences in vulnerability to anxiety, that is to differences between people in terms of their tendencies to perceive stressful situation as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety reactions.

Copyrighted Czech versions of all the psychological tests undertaken were obtained from the institutions of the authors (PCS), from Mind Garden, Inc. (STAI-Y), or from Czech translations of the original tests, (forward-backward translation methodology), approved by the authors and validated and approved by the Czech-Moravian Psychological Society (BDI II, HADS).

### 2.5 | Statistical evaluation

Standard summary statistics were applied to describe primary data: Continuous parameters were summarized as median (minimum-maximum). Categorical parameters are expressed as absolute and relative frequencies. All continuous variables were tested for normality with the Kolmogorov–Smirnov test and by visualization of N-P plots. Study questionnaires were scored by means of standard scoring conventions. Missing data for continuous/ordinal and categorical independent variables were replaced by the overall mean or nearest median for that variable respectively. Four categories of independent variables were defined: (1) biological: age, sex and BMI; (2) clinical (diabetes-, neuropathy- and pain-related), (3) socio-economical (educational level, work status) and (4) cognitive factors (catastrophic thinking, response to analgesic therapy). Spearman correlation coefficients were used to assess the relationships of dependent variables (HADS-D, HADS-A, BDI-II, STAI-Y1, 2 scores) with continuous variables. Chí square tests (for categorical variables) and Mann–Whitney or Kruskal–Wallis tests (for continuous variables) with post hoc tests were employed to examine differences between groups (HC, DM, nDSPN and pDSPN) and other categorical variables.

Statistical significance for multiple comparisons was established using Bonferroni's correction. A propensity score approach was used to form matched groups of HC, DM, nDSPN and pDSPN subjects with reduced equal numbers of participants ($4 \times 50$ subjects) with age and sex as predefined confounders. Univariate correlations of continuous variables and comparisons of categorical variables in the pooled 200 subjects in relation to psychological outcomes were performed using Spearman's correlations, Mann–Whitney or Kruskal–Wallis tests. Variables associated with symptoms of depression and anxiety at $p < 0.1$ in univariate analyses were entered into a multiple regression models to establish contributors to the development of abnormalities of outcome measures expressing degree of depression and anxiety. In the event of close inter-correlation of parameters ($r > 0.7$) the more clinically appropriate parameter was included. Backward stepwise removal of factors served to obtain a parsimonious model. Any variable with its highest $p$-value insignificant at a level of 0.05 level was excluded at each step. The variance inflation factor was calculated to ensure that the independent variables were not closely correlated with one another, with scores above 5 suggesting a problem with the regression model. An additional multiple regression model was also calculated for three diabetic subgroups (i.e. DM, nDSPN and pDSPN). All analyses were conducted using the Statistical Package for Social Sciences for Windows, version 25 or 27 (SPSS Inc.).

## 3 | RESULTS

### 3.1 | Study participants

Of 713 DM1 or DM2 patients with suspected or diagnosed DSPN, a total of 658 met the study eligibility criteria. Of the remainder, 22 did not meet the criteria for DSPN and 33 encountered exclusion criteria (Figure 1). According to the predefined cut-off for pre-treatment pain intensity (NRS ≥4) and other criteria for chronic neuropathic pain, 347 patients complied with the definition of pDSPN (177 of these exhibited severe pain, at NRS 7–10), while 311 patients were included into the nDSPN group (53 of these, however, suffered from mild pain. at NRS 1–3). In the 59 patients included into the pDSPN group on the grounds of the pre-treatment pain intensity, those who had responded to analgesic therapy, the mean NRS in the preceding week was below 4. Already included into a previous study (investigating a different matter) (Raputova et al., 2017) and included into the work herein were 158 pDSPN and 74 nDSPN patients. A smaller group of patients with diabetes without polyneuropathy (DM group, $N = 50$) and non-diabetic healthy volunteers (HC group, $N = 71$), both age-adjusted to the DSPN subgroups, were also recruited and assessed.

Groups did not differ in age ($p = 0.680$; Kruskal–Wallis test), but healthy controls and DM patients had a lower proportion of males (42% and 44% respectively) compared to nDSPN and pDSPN groups (58% and 56% respectively; $p = 0.022$, $Chi^2$ test). In response to the disproportion of the sexes and the sizes of the groups evaluated, only differences in demographic, socio-economic and clinical

parameters between the two largest and age- and sex-adjusted subgroups of patients with DSPN were initially calculated; results appear in Table 1. Furthermore, corrected age- and sex-matched subgroups of HC, DM, nDSPN and pDSPN subjects were defined for additional analyses, each with a reduced and equal number of subjects ($n = 50$) in all groups.

## 3.2 | Characteristics of pain-suffering and pain-free diabetic polyneuropathy groups

Comparison of variables between the nDSPN and pDSPN subgroups showed that they differed in the proportions of subjects with a tertiary university education, regularly working participants, together with those with a 'standard' pathway of employment (in regular work or retired), all of these being lower in pDSPN patients than in those with nDSPN. The proportion of participants who had retired in response to pain conditions was higher in the pDSPN group. Furthermore, pDSPN patients exhibited a higher BMIs, a lower proportion of type 1 DM, a higher prevalence of arterial hypertension and more severe degrees of polyneuropathy and disability (expressed as subscores and summed scores of mTCNS and ODSS tests) in pDSPN compared with nDSPN patients (Table 1).

## 3.3 | Pain severity and response to analgesic therapy

Comparison of DSPN patients with any neuropathic pain related to polyneuropathy graded according to severity as mild (NRS 1–3), moderate (NRS 4–6) and severe (NRS 7–10) revealed that they did not differ in terms of basic demographics and diabetes-related characteristics, with the exception of age (significantly lower age in the severe pain group than in the moderate pain groups; Table S1). Not surprisingly, these groups also differed in pain-related characteristics and disability graded with NPSI and GCPS with the highest values appearing in the severe pain group (Table S1).

There was a higher prevalence of catastrophic thinking in the pDSPN group compared with the nDSPN group: mean score 16.6 vs. 11.7, $p < 0.001$; percentage of abnormal score 31.4% versus 8.3% (Table 1). Similarly, the scores in all three PCS domains were significantly higher in pDSPN than in nDSPN.

No differences in basic demographic and diabetes-related characteristics were disclosed between those who responded to analgesic therapy and those who did not (Table S2).

## 3.4 | Depression and anxiety

The scores of all questionnaires reflecting symptoms of depression and anxiety and proportions of abnormal scores in all the groups assessed are summarized in Tables 2 and 3. The proportions of abnormal values were calculated using both 90th and 95th percentiles of the values found in the HC group as cut-offs for determination of abnormality (these were in accord with generally recommended cut-offs; Beck et al., 1996; Herrmann, 1997; Spielberger et al., 1983; Sullivan et al., 1995; Wang & Gorenstein, 2013).

In uncorrected groups, the percentages of abnormal scores in pDSPN deploying the 90th percentile cut-off exceeded 30% using all questionnaires were as follows: 37.5% (STAI-Y2), 37.2% (HADS-A), 36.3% (HADS-D), 35.7% (BDI-II) and 31.7% (STAI-Y1) (Table 2). Abnormal HADS-D and/or HADS-A scores were present in 52.7% of pDSPN patients. Abnormal HADS-D and/or BDI-II scores reflecting symptoms of depression were presented in 46.7% of pDSPN patients. Abnormal scores in any of the questionnaires reflecting symptoms of anxiety (STAI-Y1, Y2 and HADS-A) were present in 60.5% of pDSPN patients. Abnormal scores in any of questionnaires (STAI-Y1, Y2, HADS-A, HADS-D, BDI-II) were present in 64.8% of pDSPN patients. In response to both the disproportionate numbers of participants and the proportion of the sexes in HC and DM compared to the nDSPN and pDSPN groups, statistical comparisons were first made between the nDSPN and pDSPN subgroups without significant difference in age and sex (Table 2). The scores and proportions of abnormal findings from all the questionnaires administered and their combinations were significantly higher in pDSPN than in nDSPN ($p < 0.001$; Table 2). In nDSPN patients, the prevalence of depression (24.4%) and anxiety (44.4%) was lower compared with pDSPN ($p < 0.001$), but still higher compared with HC (7.0% and 14.1%; $p = 0.012$ and $p < 0.001$). Similarly, in DM patients, the prevalence of depression and anxiety was lower than in pDSPN patients ($p = 0.001$ and $p < 0.001$), but still higher than to HC ($p = 0.017$ and $p = 0.033$).

The results of the additional analysis of psychological tests in corrected age- and sex-matched subgroups with reduced and equal number of participants are summarized in Table 3 and expressed in Figure 2. The median values of all depression and anxiety tests were significantly higher in pDSPN compared with all other groups (with the exception of STAI-Y1 and HADS-D values, which were significantly higher than in DM and HC, but not in the nDSPN group) and further increased with the pain severity being significantly higher in patients with severe pain comparing to mild and moderate pain subgroups in all the tests with the exception of

**TABLE 1** Characteristics of the study population

| Variables expressed as median (min–max.) or *n* (%) | Study populations | | | | Comparison of nDSPN and pDSPN groups (*p*)[a] |
|---|---|---|---|---|---|
| | HC group (*n* =71) | DM group (*n* = 50) | nDSPN (*n* = 311) | pDSPN (*n* = 347) | |
| Biological | | | | | |
| Age (years) | 63.0 (24.0; 6.1) | 61.5 (22.4; 85.9) | 63.7 (17.3; 86.8) | 63.4 (23.9; 86.2) | 0.959 |
| Sex (male) | 30 (42.3) | 22 (44.0) | 176 (57.9) | 194 (55.9) | 0.610 |
| Ethnicity (Caucasian) | 71 (100.0) | 50 (100.0) | 311 (100.0) | 347 (100.0) | 1.000 |
| BMI (kg/m$^2$) | 25.4 (17.2; 41.1) | 28.1 (17.7; 42.0) | 29.0 (17.9; 46.9) | 30.2 (16.9; 49.9) | **0.002** |
| Socio-economic | | | | | |
| Education | | | | | |
| Primary | 1 (1.4) | 0 (0.0) | 5 (1.5) | 10 (3.0) | **0.001** |
| Lower secondary | 16 (22.5) | 10 (20.0) | 72 (24.1) | 98 (27.8) | |
| Higher secondary | 36 (50.7) | 28 (56.0) | 152 (48.5) | 190 (56.3) | |
| Tertiary—University | 18 (25.3) | 12 (24.0) | 82 (25.9)[b] | 49 (12.9)[b] | |
| Employment | | | | | |
| In regular work | 37 (52.1) | 38 (76.0) | 119 (38.3)[b] | 92 (26.5)[b] | **0.001** |
| Sick-leave | 2 (2.8) | 0 (0.0) | 1 (0.3) | 5 (1.4) | |
| Sick-leave for pain condition | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.9) | |
| Retired | 32 (45.1) | 12 (24.0) | 187 (60.1) | 228 (65.7) | |
| Retired for pain condition | 0 (0.0) | 0 (0.0) | 0 (0.0)[b] | 17 (4.9)[b] | |
| Home-care, student | | | 2 (0.6) | 0 (0.0) | |
| Unemployed | | | 2 (0.6) | 2 (0.6) | |
| In regular work or retired | 69 (97.2) | 50 (100.0) | 302 (97.1) | 320 (92.2) | **0.006** |
| Clinical | | | | | |
| Diabetes type I | NA | 14 (28.0) | 87 (28.0) | 56 (16.1) | **<0.001** |
| HbA1c (%) | NA | 7.0 (5.3; 10.8) | 7.3 (5.1; 13.0) | 7.3 (5.0; 13.2) | 0.200 |
| Diabetes duration (years) | NA | 9.1 (0.9; 33.3) | 14.0 (0.5; 58.3) | 12.4 (0.6; 62.4) | 0.662 |
| Uncontrolled diabetes (HbA1c ≥7) | NA | 26 (52.0) | 180 (57.9) | 197 (56.8) | 0.775 |
| Complications, microvascular | | | | | |
| Nephropathy | NA | 4 (8.0) | 44 (14.2) | 59 (17.0) | 0.314 |
| Retinopathy | NA | 2 (4.0) | 39 (12.5) | 39 (11.2) | 0.606 |
| Any microvascular complication | NA | 6 (12.0) | 70 (22.5) | 82 (23.6) | 0.732 |

TABLE 1 (Continued)

| Variables expressed as median (min–max.) or *n* (%) | Study populations | | | | Comparison of nDSPN and pDSPN groups (*p*)[a] |
|---|---|---|---|---|---|
| | HC group (*n* =71) | DM group (*n* = 50) | nDSPN (*n* = 311) | pDSPN (*n* = 347) | |
| Complications, macrovascular | | | | | |
| Peripheral vascular disease | NA | 2 (4.0) | 19 (6.1) | 24 (6.9) | 0.676 |
| Ischemic heart disease | NA | 6 (12.0) | 69 (22.2) | 86 (24.8) | 0.433 |
| Cerebrovascular disease | NA | 2 (4.0) | 16 (5.1) | 22 (6.3) | 0.512 |
| Any macrovascular complication | NA | 10 (20.0) | 91 (29.3) | 118 (34.0) | 0.192 |
| Comorbidities | | | | | |
| Arterial hypertension | NA | 16 (32.0) | 219 (70.4) | 294 (84.7) | **<0.001** |
| Dyslipidemia | NA | 20 (40.0) | 197 (63.3) | 229 (66.0) | 0.477 |
| mTCNS | | | | | |
| Symptom score | NA | NA | 0.0 (0.0; 9.0) | 6.0 (0.0; 18.0) | **<<0.001** |
| Sensory test score | NA | NA | 3.0 (0.0; 15.0) | 7.0 (0.0; 15.0) | **<<0.001** |
| Sum mTCNS score | NA | NA | 4.0 (0.0; 21.0) | 14.0 (1.0; 33.0) | **<<0.001** |
| ODSS | | | | | |
| Arm disability scale | NA | NA | 0.0 (0.0; 3.0) | 0.0 (0.0; 3.0) | **<<0.001** |
| Leg disability scale | NA | NA | 0.0 (0.0; 7.0) | 1.0 (0.0; 6.0) | **<<0.001** |
| Overall disability sum score | NA | NA | 0.0 (0.0; 7.0) | 1.0 (0.0; 8.0) | **<<0.001** |
| Any paresis (MRC ≤4 in any muscle group) | 0 (0.0) | 0 (0.0) | 20 (6.4) | 74 (21.3) | **<0.001** |
| Moderate to severe paresis (MRC≤3 in ≥2 muscle groups) | 0 (0.0) | 0 (0.0) | 2 (0.6) | 16 (4.6) | **0.002** |
| NPSI (previous 24 h) | | | | | |
| Burning score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 3.0) | 3.0 (0.0; 10.0) | **<<0.001** |
| Deep pain score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 2.0) | 2.0 (0.0; 10.0) | **<<0.001** |
| Paroxysmal pain score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 3.0) | 1.0 (0.0; 10.0) | **<<0.001** |
| Evoked pain score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 2.0) | 0.0 (0.0; 10.0) | **<<0.001** |
| Paresthesia/dysesthesia | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 3.0) | 4.0 (0.0; 10.0) | **<<0.001** |
| Total score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 16.0) | 20.0 (4.0; 80.0) | **<<0.001** |
| GCPS (previous 6 months) | | | | | |
| Characteristic pain intensity | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 36.0) | 49.0 (25.0; 96.7) | **<<0.001** |
| GCPS disability score | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 26.7) | 10.0 (0.0; 100.0) | **<<0.001** |
| GCPS classification (0–4) | NA | 0.0 (0.0; 0.0) | 0.0 (0.0; 1.0) | 1.0 (0.0; 4.0) | **<<0.001** |

(Continues)

TABLE 1 (Continued)

| Variables expressed as median (min–max.) or *n* (%) | Study populations | | | | Comparison of nDSPN and pDSPN groups (*p*)[a] |
|---|---|---|---|---|---|
| | HC group (*n* =71) | DM group (*n* = 50) | nDSPN (*n* = 311) | pDSPN (*n* = 347) | |
| QST: Raw data[c] | | | | | |
| CDT (°C) | −3.7 (−9.3;−1.0) | −3.1 (−9.9; −1.0) | −6.3 (−32.0;−1.2) | −9.6 (−32.0;−1.3) | **<0.001** |
| WDT (°C) | 8.7 (2.0; 16.5) | 6.5 (1.7; 13.0) | 10.2 (2.0; 18.9) | 13.6 (2.6; 18.5) | **<<0.001** |
| QST: *Z*-scores[c] | | | | | |
| CDT (*Z*-score) | −0.4 (−1.9; 1.9) | −0.1 (−2.0; 1.5) | −1.1 (−3.9; 1.4) | −1.6 (−4.3; 1.2) | **<0.001** |
| WDT (*Z*-score) | −0.6 (−2.5; 1.5) | −0.5 (−1.9; 1.8) | −1.2 (−2.9; 1.5) | −1.7 (−2.8; 1.6) | **<<0.001** |
| PCS | 7.0 (0.0; 31.0) | 7.0 (0.0; 32.0) | 11.0 (0.0; 41.0) | 16.0 (0.0; 51.0) | **<0.001** |
| PCS Rumination | 2.0 (0.0; 10.0) | 2.0 (0.0;10.0) | 4.0 (0.0; 16.0) | 5.0 (0.0; 16.0) | **<0.001** |
| PCS Magnification | 2.0 (0.0; 7.0) | 2.0 (0.0; 7.0) | 3.0 (0.0; 8.0) | 3.0 (0.0; 12.0) | **0.002** |
| PCS Helplessness | 2.0 (0.0; 14.0) | 3.0 (0.0; 16.0) | 5.0 (0.0; 19.0) | 7.0 (0.0; 23.0) | **<0.001** |

*Note:* Descriptive statistics: median (minimum; maximum values) for continuous variables, absolute and relative frequencies for categorical variables.

Abbreviations: BMI, body mass index; DM, patients with diabetes without polyneuropathy; GCPS, Graded Chronic Pain Scale; HbA1c, Glycosylated haemoglobin; HC, non-diabetic healthy controls; MRC, Medical Research Council scale (range 0–5 in every muscle group tested); mTCNS, modified Toronto Clinical Neuropathy Score; NA, not attributable; nDSPN, Pain-free Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS 0–3); NPSI, Neuropathic Pain Symptom Inventory; ODSS, Overall Disability Sum Score; PCS, Pain Catastrophizing Scale; pDSPN, Painful Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS ≥4); QST, Quantitative Sensory Testing of thermal modalities performed on the dorsum of the foot.

[a]*p*-value of non-parametric Mann–Whitney test for continuous variables, *p*-value of Chi-square test for categorical variables (only nDSPN and pDSPN are compared in both cases); significant *p*-values appear in bold type.

[b]Significant difference in post hoc tests after Bonferroni's correction for multiple comparisons <<0.001 = $<10^{-6}$.

[c]QST testing for thermal thresholds is available from 66.5% of individuals included in this study. Besides basic threshold values (in °C), the QST data are also expressed as the *Z*-scores showing how many standard deviations below or above the population mean a raw score is, when using the normal values published by Magerl et al. (2010).

**TABLE 2** Summary statistics of psychological tests for symptoms of depression and anxiety

| Psychological tests | Study populations | | | | Comparison of nDSPN and pDSPN groups ($p$)[a] |
|---|---|---|---|---|---|
| | HC ($n = 71$) | DM ($n = 50$) | nDSPN ($n = 311$) | pDSPN ($n = 347$) | |
| BDI II: median (min–max); 5th; 90th; 95th percentiles | 5.0 (0.0–24.0); 0.0; 14.0; 17.0 | 8.0 (0.0–20.0); 1.0; 15.0; 20.0 | 8.0 (0.0–36.0); 0.0; 17.0; 21.0 | 11.0 (0.0–42–0); 2.0; 25.0; 30.0 | **<<0.001** |
| Abnormality (>14): $n$ (%) | 5 (7.0) | 6 (12.0) | 49 (15.7) | 124 (35.7) | **<<0.001** |
| Abnormality (>17): $n$ (%) | 2 (2.8) | 4 (8.0) | 27 (8.7) | 90 (25.9) | **<<0.001** |
| STAI-Y1: median (min–max); 5th; 90th; 95th percentiles | 35.0 (20.0–54.0); 23.0; 43.0; 46.0 | 35.0 (24.0–54.0); 26.0; 47.0; 50.0 | 35.0 (20.0–66.0); 22.0; 48.0; 53.0 | 39.0 (20.0–72.0); 23.0; 52.0; 58.0 | **<0.001** |
| Abnormality (>43): (%) | 7 (9.9) | 7 (1.0) | 63 (20.3) | 110 (31.7) | **<0.001** |
| Abnormality (>46): (%) | 2 (2.8) | 5 (10.0) | 46 (14.8) | 73 (21.0) | **0.038** |
| STAI-Y2: median (min–max); 5th; 90th; 95th percentiles | 33.0 (20.0–50.0); 23.0; 42.0; 46.0 | 35.0 (25.0–60.0); 26.0; 47.0; 53.0 | 36.0 (20.0–66.0); 22.0; 50.0; 55.0 | 40.0 (20.0–70.0); 23.0; 55.0; 58.0 | **<0.001** |
| Abnormality (>43): (%) | 7 (9.9) | 9 (18.0) | 75 (24.1) | 110 (37.5) | **0.031** |
| Abnormality (>46): (%) | 2 (2.8) | 5 (10.0) | 52 (16.7) | 96 (27.7) | **<0.001** |
| HADS-A: median (min–max); 5th; 90th; 95th percentiles | 2.0 (0.0–9.0); 0.0; 7.0; 7.0 | 4.0 (1.0–10.0); 1.0; 8.5; 9.0 | 5.0 (0.0–16.0); 0.0; 12.0; 14.0 | 6.05 (0.0–16.0); 0.0; 12.5; 14.0 | **0.009** |
| Abnormality (>7): $n$ (%) | 1 (1.4) | 7 (14.0) | 78 (25.1) | 129 (37.2) | **<0.001** |
| Abnormality (>8): $n$ (%) | 1 (1.4) | 5 (10.0) | 55 (17.7) | 107 (30.8) | **<0.001** |
| HADS–D: median (min.–max.); 5th; 90th; 95th percentiles | 1.0 (0.0–9.0); 0.0; 7.0; 7.0 | 2.0 (1.0–10.0); 1.0; 8.0; 8.0 | 4.0 (0.0–16.0); 0.0; 9.0; 14.0 | 6.0 (0.0–17.0); 1.0; 11.5; 15.0 | **0.004** |
| Abnormality (>7): $n$ (%) | 1 (1.4) | 7 (14.0) | 53 (17.0) | 126 (36.3) | **<<0.001** |
| Abnormality (>8): $n$ (%) | 1 (1.4) | 2 (4.0) | 33 (10.6) | 98 (28.2) | **<<0.001** |
| Abnormal[b] HADS-A/HADS-D: $n$ (%): | | | | | |
| Either/or: | 1 (1.4) | 10 (20.0) | 98 (31.5) | 183 (52.7) | **<<0.001** |
| Both: | 0 (0.0) | 4 (8.0) | 33 (10.6) | 73 (21.0) | **<<<0.001** |
| Abnormal[b] BDI II/ HADS-D: $n$ (%): | | | | | |
| Either/or: | 5 (7.0) | 11 (22.0) | 76 (24.4) | 162 (46.7) | **<<<0.001** |
| Both: | 0 (0.0) | 2 (4.0) | 25 (8.0) | 73 (21.0) | **<<<0.001** |
| Abnormal[b] STAI-Y1/ Y2/HADS-A: $n$ (%): | | | | | |
| Any: | 10 (14.1) | 15 (30.0) | 138 (44.4) | 210 (60.5) | **<0.001** |
| All: | 0 (0.0) | 0 (0.0) | 31 (10.0) | 63 (18.2) | **0.003** |
| Abnormal[b] STAIY1/Y2/HADS-D/HADS–A/BDI–II: $n$ (%): | | | | | |
| Any: | 11 (15.5) | 17 (34.0) | 170 (54.7) | 225 (64.8) | **0.008** |
| All: | 0 (0.0) | 0 (0.0) | 29 (9.3) | 55 (15.9) | **0.01** |

*Note:* Abbreviation: BDI-II, Beck Depression Inventory—II; DM, patients with diabetes without polyneuropathy; HADS-A, Hospital Anxiety and Depression Scale—Anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; HC, non-diabetic healthy controls; nDSPN, Pain-free Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS 0–3); pDSPN, Painful Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS ≥4); STAI-Y1, State-Trait Anxiety Inventory—State; STAI-Y2, State-Trait Anxiety Inventory—Trait.

[a]$p$-value of non-parametric Mann–Whitney test for continuous variables, $p$-value of Chi-square test for categorical variables (only nDSPN and pDSPN are compared in both cases); significant $p$-values appear in bold type.

[b]Abnormal values were defined using the 90th percentile established in healthy individuals as cut-off values <<0.001 = $<10^{-6}$; <<<0.001 = $<10^{-30}$

**TABLE 3** Demographics and summary statistics of psychological tests for symptoms of depression and anxiety in age- and sex-matched groups

| Demographics | Study populations | | | | Comparison of all groups ($p$)[†] |
|---|---|---|---|---|---|
| | HC ($n = 50$) | DM ($n = 50$) | nDSPN ($n = 50$) | pDSPN ($n = 50$) | |
| Age (years): median (min–max) | 60.8 (26.3–86.0) | 61.5 (22.4–85.9) | 61.9 (21.4–86.7) | 61.0 (23.9–85.6) | 0.7578 |
| Sex (male): *n* (%) | 22 (44.0) | 22 (44.0) | 22 (44.0) | 22 (44.0) | 1.000 |
| BMI: median (min–max) | 24.7 (17.5–36.5)[a] | 28.1 (17.7–42.0)[b] | 28.7 (20.6–46.1)[b] | 29.3 (18.6–49.9)[b] | **<0.001** |
| **Psychological tests** | | | | | |
| BDI II: median (min–max); 5th; 90th; 95th percentiles | 5.0 (0.0–24.0); 0.0; 14.0; 17.0[a] | 8.0 (0.0–20.0); 1.0; 15.0; 20.0[a] | 8.0 (0.0–36.0); 0.0; 15.0; 21.0[a] | 12.0 (2.0–33.0); 4.0; 24.0; 27.0[b] | **<0.001** |
| Abnormality (>14): *n* (%) | 3 (6.0)[a] | 6 (12.0)[a] | 6 (12.0)[a] | 16 (32.0)[b] | **0.002** |
| Abnormality (>17): *n* (%) | 2 (4.0)[a] | 4 (8.0)[a] | 4 (8.0)[a] | 12 (24.0)[b] | **0.007** |
| STAI-Y1: median (min–max); 5th; 90th; 95th percentiles | 36.0 (20.0–54.0); 23.0; 44.0; 46.0[a] | 35.0 (24.0–54.0); 26.0; 47.0; 50.0[a] | 36.0 (22.0–63.0); 24.0; 49.5; 53.0[ab] | 41.0 (23.0–60.0); 27.0; 50.5; 57.0[b] | **0.006** |
| Abnormality (>43): (%) | 5 (10.0)[a] | 7 (14.0)[a] | 11 (22.0)[a] | 20 (40.0)[b] | **0.001** |
| Abnormality (>46): (%) | 1 (2.0)[a] | 5 (10.0)[b] | 8 (16.0)[b] | 14 (28.0)[c] | **0.002** |
| STAI-Y2: median (min–max); 5th; 90th; 95th percentiles | 33.0 (23.0–53.0); 24.0; 41.0; 46.0[a] | 35.0 (25.0–60.0); 26.0; 47.0; 53.0[a] | 37.5 (23.0–63.0); 25.0; 50.0; 51.0[a] | 43.0 (27.0–61.0); 28.0; 54.5; 58.0[b] | **<0.001** |
| Abnormality (>43): (%) | 4 (8.0)[a] | 9 (18.0)[b] | 13 (26.0)[b] | 23 (46.0)[c] | **<0.001** |
| Abnormality (>46): (%) | 2 (4.0)[a] | 5 (10.0)[a] | 7 (14.0)[a] | 15 (30.0)[b] | **0.002** |
| HADS-A: median (min–max); 5th; 90th; 95th percentiles | 2.0 (0.0–7.0); 1.0; 7.0; 7.0[a] | 4.0 (1.0–10.0); 1.0; 8.5; 9.0[b] | 4.0 (0.0–14.0); 0.0; 8.0; 13.0[ab] | 6.5 (0.0–16.0); 0.0; 13.0; 14.0[c] | **<0.001** |
| Abnormality (>7): n (%) | 0 (0.0)[a] | 7 (14.0)[b] | 6 (12.0)[b] | 19 (38.0)[c] | **<0.001** |
| Abnormality (>8): n (%) | 0 (0.0)[a] | 5 (10.0)[b] | 4 (8.0)[b] | 18 (36.0)[c] | **<0.001** |
| HADS-D: median (min–max); 5th; 90th; 95th percentiles | 1.0 (0.0–7.0); 0.0; 7.0; 7.0[a] | 2.0 (1.0–10.0); 1.0; 8.0; 8.0[b] | 4.0 (0.0–14.0); 1.0; 8.0; 8.0[bc] | 6.0 (0.0–17.0); 0.0; 14.0; 17.0[c] | **<0.001** |
| Abnormality (>7): *n* (%) | 0 (0.0)[a] | 7 (14.0)[b] | 7 (14.0)[b] | 20 (40.0)[c] | **<0.001** |
| Abnormality (>8): *n* (%) | 0 (0.0)[a] | 2 (4.0)[b] | 2 (4.0)[b] | 16 (32.0)[c] | **<<0.001** |
| Abnormal HADS-A (>7)/HADS-D (>7): *n* (%): | | | | | |
| Either/or: | 0 (0.0)[a] | 10 (20.0)[b] | 10 (20.0)[b] | 27 (54.0)[c] | **<<0.001** |
| Both: | 0 (0.0)[a] | 4 (8.0)[a] | 3 (6.0)[a] | 12 (24.0)[b] | **<0.001** |
| Abnormal HADS-A (>8)/HADS-D (>8): *n* (%): | | | | | |
| Either/or: | 0 (0.0)[a] | 7 (14.0)[b] | 5 (10.0)[b] | 23 (46.0)[c] | **<<0.001** |
| Both: | 0 (0.0)[a] | 0 (0.0)[a] | 1 (2.0)[a] | 11 (22.0)[b] | **<0.001** |
| Abnormal BDI-II (>14)/HADS-D (>7): *n* (%): | | | | | |
| Either/or: | 3 (6.0)[a] | 11 (22.0)[b] | 10 (20.0)[b] | 25 (50.0)[c] | **<0.001** |
| Both: | 0 (0.0)[a] | 2 (4.0)[a] | 3 (6.0)[a] | 11 (22.0)[b] | **<0.001** |
| Abnormal BDI-II (>17) HADS-D (>8): *n* (%): | | | | | |
| Either/or: | 2 (4.0)[a] | 6 (12.0)[a] | 6 (12.0)[a] | 20 (40.0)[b] | **<0.001** |
| Both: | 0 (0.0)[a] | 0 (0.0)[a] | 0 (0.0)[a] | 8 (16.0)[b] | **<0.001** |
| Abnormal STAI-Y1 (>43)/Y2 (>43)/HADS-A (>7): *n* (%): | | | | | |
| Any: | 7 (14.0)[a] | 15 (30.0)[b] | 21 (42.0)[b] | 33 (66.0)[c] | **<0.001** |
| All: | 0 (0.0)[a] | 0 (0.0)[a] | 2 (4.0)[a] | 11 (22.0)[b] | **<0.001** |
| Abnormal STAI-Y1 (>46)/Y2 (>46)/HADS-A (>8): *n* (%): | | | | | |

TABLE 3 (Continued)

| Demographics | Study populations | | | | Comparison of all groups ($p$)† |
|---|---|---|---|---|---|
| | HC ($n = 50$) | DM ($n = 50$) | nDSPN ($n = 50$) | pDSPN ($n = 50$) | |
| Any: | 2 (4.0)[a] | 11 (22.0)[b] | 13 (26.0)[b] | 23 (46.0)[c] | **<0.001** |
| All: | 0 (0.0)[a] | 0 (0.0)[a] | 1 (2.0)[a] | 9 (18.0)[b] | **<0.001** |
| Abnormal STAI-Y1 (>43)/Y2 (>43)/HADS-D (>7)/HADS-A (>7)/BDI-II (>14): *n* (%): | | | | | |
| Any: | 8 (16.0)[a] | 17 (34.0)[b] | 24 (48.0)[b] | 38 (76.0)[c] | **<<0.001** |
| All: | 0 (0.0)[a] | 0 (0.0)[a] | 2 (4.0)[a] | 5 (10.0)[a] | **0.02** |
| Abnormal STAI-Y1 (>46)/ 2 (>46)/HADS-D (>8)/HADS-A (>8)/BDI-II (>17): *n* (%): | | | | | |
| Any: | 3 (6.0)[a] | 11 (22.0)[b] | 14 (28.0)[b] | 27 (54.0)[c] | **<0.001** |
| All: | 0 (0.0)[a] | 0 (0.0)[a] | 0 (0.0)[a] | 4 (8.0)[b] | **0.007** |

*Note:* Post hoc tests: a, b, c; (the same letters mark values of categories within a given row denoting groups that do not differ significantly) <<0.001 = $<10^{-6}$.

Abbreviations: BDI-II, Beck Depression Inventory-II; BMI, BMI, body mass index; DM group, Patients with diabetes without polyneuropathy; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; HC group, non-diabetic healthy controls; nDSPN, Pain-free Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS = 0); pDSPN, Painful Diabetic distal Symmetrical sensory-motor Polyneuropathy (NRS ≥4); STAI-Y1, State-Trait Anxiety Inventory—State; STAI-Y2, State-Trait Anxiety Inventory—Trait.

†*p*-value represents the comparison of all groups (Kruskal–Wallis test for continuous variables and chí-square test for categorical variables); significant *p*-values appear in bold type.

STAI-Y2 (Table S1). The values of HADS-D in nDSPN and HADS-A in DM were significantly higher than those for HC (Table 3; Figure 2).

In terms of the proportion of any abnormality in any test reflecting symptoms of depression (HADS-D or BDI-II), anxiety symptoms (STAI-Y1 or STAI-Y2 or HADS-A), or any symptoms of depression or anxiety, a significantly higher proportion of abnormal values appeared in pDSPN than in all other groups. Similarly, the nDSPN and DM group exhibited a significantly higher proportion of abnormal values than HC (Table 3) when combinations of any anxiety, any depression or any anxiety/depression tests were undertaken.

## 3.5 | Relationships between symptoms of anxiety and depression (as outcomes) and independent variables in pDSPN patients

The results obtained in the uncorrected pDSPN group ($n = 347$) are summarized in Table S3a (for continuous variables) and 3b (for categorical variables). HADS-D, BDI-II, HADS-A and STAI-Y2 correlated negatively with age at a significant level (Table S3a). Higher values from all the psychological tests were significantly associated with female sex. STAI-Y2 values were weakly associated with education level, with higher values for the secondary education level and lower at the primary education level ($p = 0.04$; Table S3b). Several other parameters reflecting neuropathy severity and disability, pain intensity and its characteristics correlated significantly with at least some of scores reflecting depressive and anxiety symptoms (Table S3a,b). Most of these correlations, however, were only were only weak, although significant.

## 3.6 | Multiple regression analysis

Multiple regression analyses were subsequently performed to examine the functional relationships between emotional distress and independent variables based on the data from corrected age- and sex-adjusted groups. Variables associated with symptoms of depression and anxiety at $p < 0.1$ were obtained by univariate analyses in the pDSPN group (Table S3a,b) and in the pooled 200 subjects made up of 50 age- and sex-adjusted individuals from each study subgroup (summarized results of univariate analyses in pooled 200 subjects appear in Table S4a,b) were included into multiple regression statistical models for anxiety (HADS-A, STAI-Y1 and Y2) and depression (BDI-II and HADS-D) (Tables 4–6).

In the depression models, the final regression revealed that 30.4% ($R^2$) of the variance in HADS-D score could be accounted for by mean pain intensity ($\beta = 0.145$; $p = 0.032$), diabetes type 2 ($\beta = 0.294$; $p < 0.001$) and PCS magnification score ($\beta = 0.282$; $p < 0.001$). Similarly, 27.9% of the variance in BDI-II could be accounted for by mean pain intensity ($\beta = 0.287$; $p < 0.001$), female sex ($\beta = 0.191$; $p = 0.009$), age ($\beta = -0.144$; $p = 0.046$) and PCS magnification score ($\beta = 0.291$; $p < 0.001$; Table 4). Alternative models for both depression tests could be created with mean pain intensity replaced by mTCNS summed score, resulting in similar $R^2$ values for HADS-D (0.304) and BDI-II (0.289; Table 5).

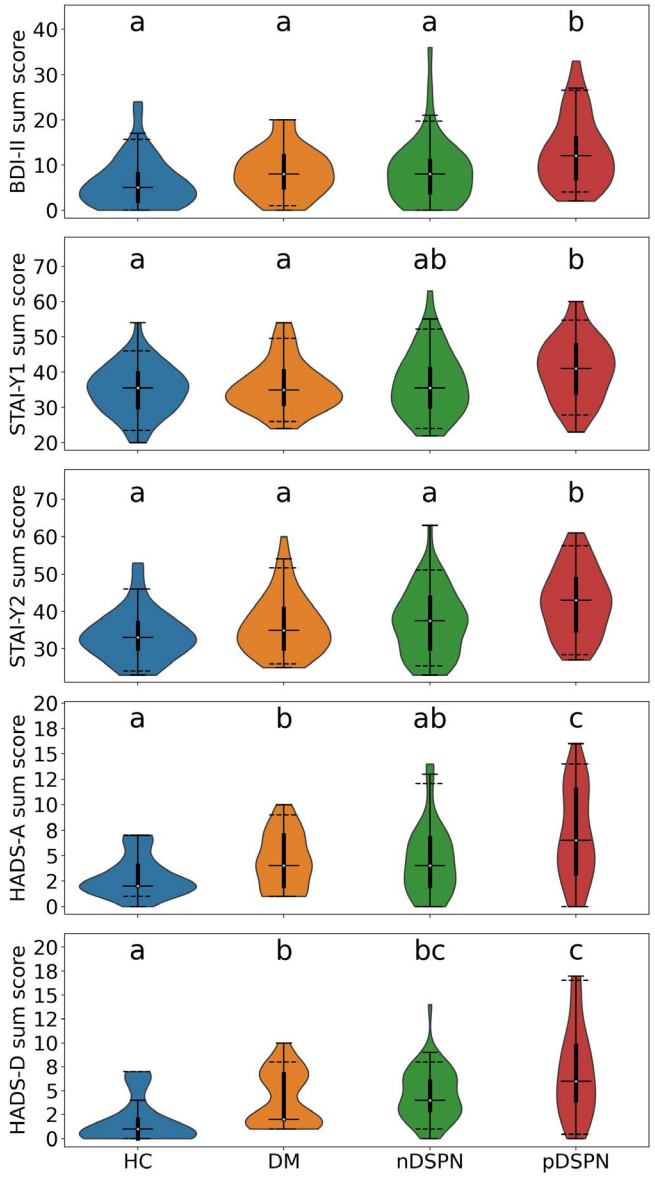


**FIGURE 2** Violin plots of scores for symptoms of depression and anxiety in the groups of healthy volunteers and diabetic patients. Violin plots of scores for symptoms of depression and anxiety with internal boxplots expressing median, quartiles, 5th and 95th percentiles and minimum-maximum values in groups of healthy volunteers and diabetic patients. The *p*-value of the comparison between all the groups (Kruskal–Wallis test) reached <0.001 for all tests with the exception of STAI-Y1 ($p = 0.006$). Differences between individual groups were calculated using post hoc tests and are expressed as the letters a, b, c; the same letters mark values of categories within a given row, denoting groups that are not mutually statistically different. HC group, Non-diabetic healthy controls; DM group, Patients with diabetes without PNP; nDSPN, Pain-free diabetic distal symmetrical polyneuropathy; pDSPN, Painful diabetic distal symmetrical polyneuropathy; BDI-II, Beck Depression Inventory - II; HADS-A, Hospital Anxiety and Depression Scale - Anxiety; HADS-D, Hospital Anxiety and Depression Scale - Depression; STAI-Y1, State-Trait Anxiety Inventory - State; STAI-Y2, State-Trait Anxiety Inventory - Trait

The final regression for anxiety models revealed that 20% of the variance in the HADS-A score could be accounted for by mean pain intensity ($\beta = 0.243$; $p = 0.001$), T2DM ($\beta = 0.160$; $p = 0.021$) and PCS magnification score ($\beta = 0.197$; $p = 0.005$). Similarly, 12.2% of the variance in STAI-Y1 could be accounted for by mean pain intensity ($\beta = 0.168$; $p = 0.029$), female sex ($\beta = 0.129$; $p = 0.057$) and any clinical sensory disturbance ($\beta = 0.216$; $p = 0.006$). Finally, 21% of the variance in STAI-Y2 could be accounted for by mean pain intensity ($\beta = 0.249$; $p < 0.001$), female sex ($\beta = 0.182$; $p = 0.005$), PCS magnification score ($\beta = 0.185$; $p = 0.008$) and BMI ($\beta = 0.165$; $p = 0.013$; Table 6).

The same multiple regression analyses based on data from uncorrected groups of study subjects showed similar, but less significant and conclusive results (not shown).

Furthermore, we performed the same multiple regression analysis in three age- and sex-adjusted diabetic subgroups (50 patients each), that is without non-diabetic controls (two alternative models for depression—Tables S5a,b, and one for anxiety—Table S5c). The results were very similar to those obtained with non-diabetic controls included, with some minor differences. In contrast to the original multiple regression analysis, in this alternative model, both microvascular complications and mMRC had a significant impact on HADS-D, while age no longer contributed significantly to the depression.

## 4 | DISCUSSION

In contrast to most previous studies, which included only pain-suffering DSPN patients, largely with moderate-to severe pain, this study evaluated the prevalence and risk factors for depression and anxiety in a large and well-defined group of pDSPN patients, including those with mild pain and in direct comparison with diabetic patients with nDSPN, without DSPN and healthy controls. The study disclosed a high prevalence of the symptoms of depression and anxiety in diabetic patients, predominantly in those with painful polyneuropathy. Severity of pain and its cognitive processing (catastrophic thinking), together with lower age, female sex, the presence of T2DM and the severity of polyneuropathy were demonstrated herein as the most important factors contributing to emotional distress in diabetic patients and non-diabetic healthy controls.

### 4.1 | Prevalence of depression and anxiety

The prevalence of affective distress estimated in neuropathic pain conditions by previous studies stands at around

**TABLE 4** Multiple regression analysis of depression tests[a]

| | HADS-D | | | BDI II | | |
|---|---|---|---|---|---|---|
| *R* square ($R^2$) | 0.288 (0.537) | | | 0.279 (0.528) | | |
| ANOVA (whole model significance) | <0.001 | | | <0.001 | | |
| *F* | 26.2 | | | 13.6 | | |
| | **Beta** | ***p*** | **VIF** | **Beta** | ***p*** | **VIF** |
| Constant (intercept) | 0.905 | 0.052 | | 4.965 | 0.041 | |
| Age | | | | –0.144 | 0.046 | 1.009 |
| Female sex | | | | 0.191 | 0.009 | 1.008 |
| Diabetes type II | 0.294 | <0.001 | 1.154 | | | |
| Mean pain intensity (previous week) | 0.145 | 0.032 | 1.230 | 0.287 | <0.001 | 1.146 |
| PCS magnification | 0.282 | <0.001 | 1.174 | 0.291 | <0.001 | 1.148 |

*Note:* Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory—II; beta, standardized beta coefficients (regression weights); *F*, overall significance of the regression model; HADS-D, Hospital Anxiety and Depression Scale—Depression; mTCNS, modified Toronto Clinical Neuropathy Score; PCS, Pain Catastrophizing Scale; R squared, coefficient of determination (the proportion of the variance in the dependent variable that is predictable from independent variable(s); VIF, variance inflation factor.

[a]Multiple regression analysis of particular tests reflecting depression or anxiety (dependent variables) and selected categorical and continuous independent variables in age- and sex-matched groups of patients/controls (50 individuals each).

**TABLE 5** Multiple regression analysis of depression tests—alternative model[a]

| | HADS–D | | | BDI II | | |
|---|---|---|---|---|---|---|
| *R* square ($R^2$) | 0.304 (0.551) | | | 0.289 (0.538) | | |
| ANOVA (whole model significance) | <0.001 | | | <0.001 | | |
| *F* | 28.4 | | | 14.4 | | |
| | **Beta** | ***p*** | **VIF** | **Beta** | ***p*** | **VIF** |
| Constant (intercept) | 1.015 | 0.029 | | 5.331 | 0.027 | |
| Age | | | | –0.147 | 0.042 | 1.009 |
| Female sex | | | | 0.200 | 0.006 | 1.009 |
| Diabetes type II | 0.287 | <0.001 | 1.132 | | | |
| mTCNS symptoms (sum score) | 0.205 | 0.003 | 1.270 | 0.316 | <0.001 | 1.209 |
| PCS magnification | 0.252 | <0.001 | 1.232 | 0.263 | 0.001 | 1.208 |

*Note:* Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory—II; beta, standardized beta coefficients (regression weights); *F*, overall significance of the regression model; HADS-D, Hospital Anxiety and Depression Scale—Depression; mTCNS, modified Toronto Clinical Neuropathy Score; PCS, Pain Catastrophizing Scale; R squared, coefficient of determination (the proportion of the variance in the dependent variable that is predictable from independent variable(s); VIF, variance inflation factor.

[a]Multiple regression analysis of particular tests reflecting depression or anxiety (dependent variables) and selected categorical and continuous independent variables in age- and sex-matched groups of patients/controls (50 individuals each).

40%–50% for depression (Gureje et al., 1998) and 25%–29% for anxiety (Turk et al., 2010). Selvarajah et al., (2014) in a cohort of 142 patients with pDSPN disclosed significantly higher prevalence of affective distress (51.4%, Selvarajah et al., 2014) than the contemporaneous reported prevalence of mood disorders and affective distress in patients with diabetes including painful neuropathy individuals (32.0% for anxiety; 22.4% for depression; Collins et al., 2009) and reported a frequent coexistence of symptoms of depression and anxiety (Selvarajah et al., 2014). The results herein are quite closely comparable with both these studies. The use of a wider battery of questionnaires in the

**TABLE 6** Multiple regression analysis of anxiety tests[a]

| | HADS-A | | | STAI-Y1 | | | STAI-Y2 | | |
|---|---|---|---|---|---|---|---|---|---|
| *R* square ($R^2$) | 0.200 (0.447) | | | 0.122 (0.349) | | | 0.210 (0.458) | | |
| ANOVA (whole model significance) | <0.001 | | | <0.001 | | | <0.001 | | |
| *F* | 16.2 | | | 9.0 | | | 12.9 | | |
| | **Beta** | ***p*** | **VIF** | **Beta** | ***p*** | **VIF** | **Beta** | ***p*** | **VIF** |
| Constant (intercept) | 2.406 | <0.001 | | 37.839 | <0.001 | | 31.7 | <0.001 | |
| Female sex | | | | 0.129 | 0.057 | 1.005 | 0.182 | 0.005 | 1.006 |
| Diabetes type II | 0.160 | 0.021 | 1.154 | | | | | | |
| Mean pain intensity (previous week) | 0.243 | 0.001 | 1.230 | 0.168 | 0.029 | 1.309 | 0.249 | <0.001 | 1.151 |
| PCS magnification | 0.197 | 0.005 | 1.174 | | | | 0.185 | 0.008 | 1.172 |
| BMI | | | | | | | 0.165 | 0.013 | 1.047 |
| Any clinical sensory disturbance | | | | 0.216 | 0.006 | 1.314 | | | |

*Note:* Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory—II; beta, standardized beta coefficients (regression weights); BMI, body mass index; *F*, overall significance of the regression model; HADS-A, Hospital Anxiety and Depression Scale—Anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; mTCNS, modified Toronto Clinical Neuropathy Score; PCS, Pain Catastrophizing Scale; R squared, coefficient of determination (the proportion of the variance in the dependent variable that is predictable from independent variable(s)); STAI-Y1, State-Trait Anxiety Inventory—State; STAI-Y2, State-Trait Anxiety Inventory—Trait; VIF, variance inflation factor.

[a]Multiple regression analysis of particular tests reflecting depression or anxiety (dependent variables) and selected categorical and continuous independent variables in age- and sex-matched groups of patients/controls (50 individuals each).

study herein even increased the proportion of pDSPN patients with signs of depression (to 46.7%) and anxiety (to 60.5%) and signs of any emotional distress to 64.8%. The proportion of nDSPN and DM patients with symptoms of anxiety reported herein (44.4% and 30.0%) or depression (24.4% and 22.0%) was significantly lower than those of pDSPN patients, but higher compared with healthy controls (14.1% and 7.0%). The presence of symptoms of anxiety or depression even in some healthy controls is not surprising considering the inclusion/exclusion criteria: for our study the controls and patients from all study groups were recruited regardless their previous contacts with psychiatry or psychology and/or current or previous presence of some depressive or anxiety symptoms. The prevalence of patients reporting some depression or anxiety symptoms in our settings is fully in line with previously reported positivity of particular questionnaires observed in general population (Ptáček et al., 2016; Stein et al., 2017).

## 4.2 | Risk factors for anxiety and depression

Previous studies of chronic pain have reported an association between emotional distress and several risk factors such as female sex, lower age, pre-existing mood disorders, lower socio-economic status, fewer social contacts, longer duration of pain, greater pain intensity and disability status, the influence of illness beliefs and pain-coping mechanisms (McCracken et al., 2004; Ohayon & Schatzberg, 2010). Unfortunately, some of these factors have also been described as risk factors for anxiety and depression beyond any chronic neuropathic pain context, so interpretation of causality is difficult (Raputova et al., 2017; Spallone & Greco, 2013). Current published knowledge of what contributes to emotional distress in pDSPN thus remains very limited (Selvarajah et al., 2014). To date, diabetes factors reported to be associated with emotional distress include the following: poor glycaemia control, duration of diabetes and the presence of diabetes complications (de Groot et al., 2001). Only few reports have considered the combined influence of both diabetes and pDSPN on emotional distress (Davies et al., 2006; Galer et al., 2000) as appears herein. This contribution confirms the importance of certain previously reported risk factors in emotional distress—female sex, lower age, severity of pain, severity of neuropathy and disability, catastrophic thinking and level of education. Some of these factors, however, contribute more to pain than to depression and anxiety; the exact mechanism of emotional distress is probably complex and certainly not fully understood. Chronic neuropathic pain in diabetic patients proved to be the predominant factor contributing to emotional distress.

Socioeconomic factors have been reported as contributing significantly to emotional distress in pain-suffering diabetic neuropathy patients (Selvarajah et al., 2014),

but the current study revealed only a weak association between education and anxiety in this subset of diabetic patients. This discrepancy may reflect the low transferability of these effects among different socioeconomic backgrounds.

Also confirmed herein is the influence of diabetes upon emotional distress in diabetic patients independent of pain, in the form of the presence of type 2 DM, but the mechanism remains unclear. The presence of diabetes mellitus irrespective of type in the analysis that included age- and sex-adjusted non-diabetic controls has not been found as an independent significant contributor to depression or anxiety. This study was unable to confirm any association between certain factors related to diabetes (such as duration, degree of control, presence of micro- and macrovascular complications, comorbidities) and emotional distress, either in pain-suffering polyneuropathy patients or diabetic patients in general, which have been reported in some previous studies (with the only exception of microvascular complications related to HADS-D score—Table S5a).

Severity of neuropathy has recently been described as closely associated with the presence and severity of pain in pDSPN (Raputova et al., 2017; Themistocleous et al., 2016), but the current study showed that it may contribute especially to symptoms of depression independent of pain in DSPN patients.

## 4.3 | Depression versus anxiety

Despite a wide overlap in the symptoms of depression and anxiety in painful diabetic neuropathy and in diabetic patients in general, partly different mechanisms and risk factors have been subject of speculation. Selvarajah et al. found that being single, unemployed or early retired, with shorter duration of diabetes and fewer diabetic microvascular complications were associated with greater anxiety symptom scores but not scores quantifying symptoms of depression. Furthermore, greater self-reported pain intensity was more strongly associated with anxiety symptoms than with scores for symptom of depression. Conversely, more severe greater quality-of-life impairment was associated with higher scores for symptoms of depression. The design of Selvarajah's study, performed only in pain-suffering DSPN patients, however, has not enabled determination of whether these factors contribute directly to emotional distress or primarily to neuropathic pain (Selvarajah et al., 2014). In the current study, some differences emerged between the proportion of abnormalities reflecting symptoms of depression and anxiety (with a higher proportion for anxiety (60.5% vs. 46.7%), but with a wide overlap. There were also differences between the presence and degree of correlation between contributing factors and the depression and anxiety scores assessed, but it is not possible to come to any conclusion regarding different mechanisms of development for anxiety and depression in painful diabetic neuropathy in the light of the findings herein.

## 4.4 | Affective state versus cognitive-interpretative process

The reciprocal relationship between affective state and cognitive–interpretive processes resulting in respondent conditioning is widely described in the chronic pain literature (Vlaeyen et al., 1995). Pain catastrophizing is generally viewed as an important cognitive factor that develops with chronic pain (Muris et al., 2007), and pain catastrophizing and emotional distress may act as prognostic indicators for pain and disability (Bergbom et al., 2011). Research into how these variables interact within individuals and over time is at an early stage (Bergbom et al., 2011). There are reports that an inverse relationship exists between positive personality traits and protection against pain perception and pain catastrophizing (Pulvers & Hood, 2013), while other authors differentiate between personality and temperament correlates of pain catastrophizing (Muris et al., 2007), or distinguish state and trait characteristics of PCS (Dumenci et al., 2020) in similar fashion to STAI-Y focused on anxiety. It is confirmed herein that catastrophic thinking as evaluated by PCS, is a powerful contributor to emotional distress not only in pain-suffering diabetic patients, but at least partly independently of the presence and severity of pain in diabetic patients as well. It may be posited that the trait or personality components of catastrophic thinking play a role in development of symptoms of depression and anxiety in individuals with non-pain conditions or vice versa, but this requires further research.

## 4.5 | Responses to treatment

According to the literature, treating pain aggressively is a possible means of alleviating mood disorders in patients with pDSPN (Fishbain et al., 2010). This contradicts other findings that suggest that this simple approach is complicated by other factors that contribute independently to emotional distress in pDSPN (Selvarajah et al., 2014). Restricting the focus to pharmacological treatments that are often ineffective can prove harmful, especially when this approach occludes other potential goals. The current study was unable to confirm, that patients, responding well to analgesic therapy displayed any different frequency or severity of emotional distress from those with inadequate response to therapy. Such findings favour the hypothesis

that at least some factors contributing to the development and severity of anxiety and depression could have independent influence upon emotional distress in patients with painful diabetic polyneuropathy.

## 5 | LIMITATIONS

Limitations of this study include the inadequate sample size of the DM group, which did not allow us to examine in detail the independent influence upon emotional distress of different aspects of diabetes mellitus.

The comparability of studies based on psychological questionnaires is debateable, since these tests are prone to several biases. The results are dependent on the method of administration and/or the criteria that define 'abnormality' (Fried, 2017). We are aware that using more tests to reflect symptoms of depression and anxiety increases the sensitivity of this battery but decreases specificity for the detection of emotional distress.

## 6 | CONCLUSION

This study draws attention to a very high prevalence of symptoms of depression and anxiety symptoms not only in patients with painful diabetic polyneuropathy, but also in diabetic patients without pain. In addition to the severity of neuropathic pain and its cognitive processing, it disclosed demographic factors (lower age, female sex), the presence of type 2 diabetes mellitus and the severity of diabetic polyneuropathy as contributors to emotional distress independent of pain in diabetic patients and age- and sex-adjusted non-diabetic healthy controls.

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### CONFLICT OF INTEREST

None of the authors has any conflict of interest to declare.

### AUTHORS' CONTRIBUTIONS

D.K. and A.R. contributed equally to the paper; they researched data and reviewed/edited the manuscripts. J.R., B.A., I.S., J.Bel., J.O., P.W., G.H., M.K., R.M., VP., E.E. and M.F. researched data, discussed the results and commented on the manuscript. E.K.N. and R.N.M. contributed to the design of the study and interpretation of the psychological questionnaires and reviewed/edited the manuscript. M.H. planned the statistical evaluation and carried out part of the statistical analysis, discussed the results and commented on the manuscript, C.S., N.U. and F.B. researched data and reviewed/edited the manuscript. J.B. and E.V. contributed to the design of the study and wrote the original manuscript, E.V. also contributed to the statistical analysis. E.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### REFERENCES

American Diabetes Association. ( 2013). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, *36*, 67–74. https://doi.org/10.2337/dc13-S067

Aslam, A., Singh, J., & Rajbhandari, S. M. (2014). The impact of painful diabetic neuropathy on quality of life: An observational study. *Diabetes & Primary Care*, *16*, 212–219.

Bai, J.-W., Lovblom, L. E., Cardinez, M., Weisman, A., Farooqi, M. A., Halpern, E. M., Boulet, G., Eldelekli, D., Lovshin, J. A., Lytvyn, Y., Keenan, H. A., Brent, M. H., Paul, N., Bril, V., Cherney, D. Z. I., & Perkins, B. A. (2017). Neuropathy and presence of emotional distress and depression in longstanding diabetes: Results from the Canadian study of longevity in type 1 diabetes. *Journal of Diabetes and Its Complications*, *31*, 1318–1324. https://doi.org/10.1016/j.jdiacomp.2017.05.002

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *BDI-II: Manual for the beck depression inventory* (2nd ed.). Psychological Corporation.

Bergbom, S., Boersma, K., Overmeer, T., & Linton, S. J. (2011). Relationship among pain catastrophizing, depressed mood, and outcomes across physical therapy treatments. *Physical Therapy*, *91*, 754–764. https://doi.org/10.2522/ptj.20100136

Bouhassira, D., Attal, N., Fermanian, J., Alchaar, H., Gautron, M., Masquelier, E., Rostaing, S., Lanteri-Minet, M., Collin, E., Grisart, J., & Boureau, F. (2004). Development and validation of the neuropathic pain symptom inventory. *Pain*, *108*, 248–257. https://doi.org/10.1016/j.pain.2003.12.024

Bril, V., Tomioka, S., Buchanan, R. A., Perkins, B. A., & mTCNS Study Group. (2009). Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. *Diabetic Medicine*, *26*, 240–246. https://doi.org/10.1111/j.1464-5491.2009.02667.x

Collins, M. M., Corcoran, P., & Perry, I. J. (2009). Anxiety and depression symptoms in patients with diabetes. *Diabetic Medicine*, *26*, 153–161. https://doi.org/10.1111/j.1464-5491.2008.02648.x

Davies, M., Brophy, S., Williams, R., & Taylor, A. (2006). The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*, *29*, 1518–1522. https://doi.org/10.2337/dc05-2228

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of depression and diabetes complications: A meta-analysis. *Psychosomatic Medicine*, *63*, 619–630. https://doi.org/10.1097/00006842-200107000-00015

Dumenci, L., Kroenke, K., Keefe, F. J., Ang, D. C., Slover, J., Perera, R. A., & Riddle, D. L. (2020). Disentangling trait versus state characteristics of the Pain Catastrophizing Scale and the PHQ-8 Depression Scale. *European Journal of Pain*, *24*, 1624–1634. https://doi.org/10.1002/ejp.1619

European Medicines Agency. (2007). *Guideline on clinical medicinal products intended for the treatment of neuropathic pain*. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-medicinalproducts-intended-treatment-neuropathic-pain_en.pdf

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D., Cruccu, G., Freeman, R., Hansson, P., Nurmikko, T., Raja, S. N., Rice, A. S. C., Serra, J., Smith, B. H., Treede, R.-D., & Jensen, T. S. (2016). Neuropathic pain: An updated grading system for research and clinical practice. *Pain*, *157*, 1599–1606. https://doi.org/10.1097/j.pain.0000000000000492

Fishbain, D. A., Cole, B., Lewis, J. E., & Gao, J. (2010). What is the evidence for chronic pain being etiologically associated with the DSM-IV category of sleep disorder due to a general medical condition? A structured evidence-based review. *Pain Medicine*, *11*, 158–179. https://doi.org/10.1111/j.1526-4637.2009.00706.x

Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of Affective Disorders*, *208*, 191–197. https://doi.org/10.1016/j.jad.2016.10.019

Galer, B. S., Gianas, A., & Jensen, M. P. (2000). Painful diabetic polyneuropathy: Epidemiology, pain description, and quality of life. *Diabetes Research and Clinical Practice*, *47*, 123–128. https://doi.org/10.1016/S0168-8227(99)00112-6

Gureje, O., Von Korff, M., Simon, G. E., & Gater, R. (1998). Persistent pain and well-being: A World Health Organization Study in Primary Care. *JAMA*, *280*(2), 147–151. https://doi.org/10.1001/jama.280.2.147

Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale–A review of validation data and clinical results. *Journal of Psychosomatic Research*, *42*, 17–41. https://doi.org/10.1016/s0022-3999(96)00216-4

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care*, *23*, 934–942. https://doi.org/10.2337/diacare.23.7.934

Magerl, W., Krumova, E. K., Baron, R., Tolle, T., Treede, R. D., & Maier, C. (2010). Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. *Pain*, *151*, 598–605. https://doi.org/10.1016/j.pain.2010.07.026

McCracken, L. M., Vowles, K. E., & Eccleston, C. (2004). Acceptance of chronic pain: Component analysis and a revised assessment method. *Pain*, *107*, 159–166. https://doi.org/10.1016/j.pain.2003.10.012

Merkies, I., Schmitz, P., van der Meche, F., Samijn, J., van Doorn, P., & Inflammatory Neuropathy Cause and Treatment (INCAT) Group. (2002). Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *Journal of Neurology Neurosurgery and Psychiatry*, *72*, 596–601. https://doi.org/10.1136/jnnp.72.5.596

Muris, P., Meesters, C., van den Hout, A., Wessels, S., Franken, I., & Rassin, E. (2007). Personality and temperament correlates of pain catastrophizing in young adolescents. *Child Psychiatry and Human Development*, *38*, 171–181. https://doi.org/10.1007/s10578-007-0054-9

Ohayon, M. M. (2007). Epidemiology of depression and its treatment in the general population. *Journal of Psychiatric Research*, *41*, 207–213. https://doi.org/10.1016/j.jpsychires.2006.10.006

Ohayon, M. M., & Schatzberg, A. F. (2010). Chronic pain and major depressive disorder in the general population. *Journal of Psychiatric Research*, *44*, 454–461. https://doi.org/10.1016/j.jpsychires.2009.10.013

Ptáček, R., Raboch, J., Vňuková, M., Hlinka, J., & Anders, M. (2016). Depression inventory BDI-II - standardization and its use in practice. *Česká a Slovenská Psychiatrie*, *112*(6), 270–274.

Pulvers, K., & Hood, A. (2013). The role of positive traits and pain catastrophizing in pain perception. *Current Pain and Headache Reports*, *17*, 330. https://doi.org/10.1007/s11916-013-0330-2

Raputova, J., Srotova, I., Vlckova, E., Sommer, C., Üçeyler, N., Birklein, F., Rittner, H. L., Rebhorn, C., Adamova, B., Kovalova, I., Kralickova Nekvapilova, E., Forer, L., Belobradkova, J., Olsovsky, J., Weber, P., Dusek, L., Jarkovsky, J., & Bednarik, J. (2017). Sensory phenotype and risk factors for painful diabetic neuropathy: A cross-sectional observational study. *Pain*, *158*, 2340–2353. https://doi.org/10.1097/j.pain.0000000000001034

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, D.- R., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Rolko, C., Schaub, C., ... Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*, *123*(3), 231–243. https://doi.org/10.1016/j.pain.2006.01.041

Rosemann, T., Backenstrass, M., Joest, K., Rosemann, A., Szecsenyi, J., & Laux, G. (2007). Predictors of depression in a sample of 1,021 primary care patients with osteoarthritis. *Arthritis & Rheumatism-Arthritis Care & Research*, *57*, 415–422. https://doi.org/10.1002/art.22624

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative

Project on Early Detection of Persons with Harmful Alcohol Consumption–II. *Addiction*, *88*, 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Selvarajah, D., Cash, T., Sankar, A., Thomas, L., Davies, J., Cachia, E., Gandhi, R., Wilkinson, I. D., Wilkinson, N., Emery, C. J., & Tesfaye, S. (2014). The contributors of emotional distress in painful diabetic neuropathy. *Diabetes and Vascular Disease Research*, *11*, 218–225. https://doi.org/10.1177/1479164114522135

Spallone, V., & Greco, C. (2013). Painful and painless diabetic neuropathy: One disease or two? *Current Diabetes Reports*, *13*, 533–549. https://doi.org/10.1007/s11892-013-0387-7

Spielberger, C., Gorsuch, R., Lushene, R., Vagg, P., & Jacobs, G. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y1–Y2)*. Consulting Psychologists Press.

Srotova, I., Vlckova, E., Strakova, J., Kincova, S., Ryba, L., Dusek, L., Adamova, B., & Bednarik, J. (2015). Validation of the Czech Version of the Neuropathic Pain Symptom Inventory (NPSIcz). *Czech and Slovak Neurology and Neurosurgery*, *78*, 45–56. https://doi.org/10.14735/amcsnn201545

Stein, D. J., Scott, K. M., de Jonge, P., & Kessler, R. C. (2017). Epidemiology of anxiety disorders: From surveys to nosology and back. *Dialogues in Clinical Neuroscience*, *19*, 127–136. https://doi.org/10.31887/DCNS.2017.19.2/dstein

Sullivan, M. J. L., Bishop, S., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7*, 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Tesfaye, S., Boulton, A. J. M., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., Lauria, G., Malik, R. A., Spallone, V., Vinik, A., Bernardi, L., & Valensi, P. (2010). Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*, *33*, 2285–2293. https://doi.org/10.2337/dc10-1303

Themistocleous, A. C., Ramirez, J. D., Shillo, P. R., Lees, J. G., Selvarajah, D., Orengo, C., Tesfaye, S., Rice, A. S. C., & Bennett, D. L. H. (2016). The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain*, *157*, 1132–1145. https://doi.org/10.1097/j.pain.0000000000000491

Treede, R., Jensen, T., Campbell, J., Cruccu, G., Dostrovsky, J., Griffin, J., Hansson, P., Hughes, R., Nurmikko, T., & Serra, J. (2008). Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology*, *70*, 1630–1635. https://doi.org/10.1212/01.wnl.0000282763.29778.59

Tsai, P. (2005). Predictors of distress and depression in elders with arthritic pain. *Journal of Advanced Nursing*, *51*, 158–165. https://doi.org/10.1111/j.1365-2648.2005.03481.x

Turk, D. C., Audette, J., Levy, R. M., Mackey, S. C., & Stanos, S. (2010). Assessment and treatment of psychosocial comorbidities in patients with neuropathic pain. *Mayo Clinic Proceedings*, *85*, 42–50. https://doi.org/10.4065/mcp.2009.0648

Vlaeyen, J. W. S., Kole-Snijders, A. M. J., Boeren, R. G. B., & van Eek, H. (1995). Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain*, *62*, 363–372. https://doi.org/10.1016/0304-3959(94)00279-N

Von Korff, M., Ormel, J., Keefe, F., & Dworkin, S. (1992). Grading the severity of chronic pain. *Pain*, *50*, 133–149. https://doi.org/10.1016/0304-3959(92)90154-4

Wang, Y.-P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Brazilian Journal of Psychiatry*, *35*, 416–431. https://doi.org/10.1590/1516-4446-2012-1048

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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