Diabetic polyneuropathy and pain, prevalence, and patient characteristics: a cross-sectional questionnaire study of 5,514 patients with recently diagnosed type 2 diabetes

Sandra Sif Gylfadottir,a,b Diana Hedevang Christensen,a,c,e Sia Kromann Nicolaisen,c Henning Andersen,a,d Brian Christopher Callaghan,a,e Mustapha Itani,a,f Karolina Snopek Khan,a,b,d Alexander Gramm Kristensen,a,b,g Jens Steen Nielsen,a Søren Hein Sindrup,a,f Niels Trolle Andersen,a Troels Stæhelin Jensen,a,b,d Reimar Wernich Thomsen,a Nanna Brix Finnerup,a,b,d

Abstract

Most studies of diabetic polyneuropathy (DPN) and painful DPN are conducted in persons with longstanding diabetes. This cross-sectional study aimed to estimate the prevalence of DPN and painful DPN, important risk factors, and the association with mental health in recently diagnosed type 2 diabetes. A total of 5514 (82%) patients (median diabetes duration 4.6 years) enrolled in the Danish Centre for Strategic Research in Type 2 Diabetes cohort responded to a detailed questionnaire on neuropathy and pain. A score ≥4 on the MNSI questionnaire determined possible DPN, whereas pain presence in both feet together with a score ≥3 on the DN4 questionnaire determined possible painful DPN. The prevalence of possible DPN and possible painful DPN was 18% and 10%, respectively. Female sex, age, diabetes duration, body mass index, and smoking were associated with possible DPN, whereas only smoking showed a clear association with possible painful DPN (odds ratio 1.52 [95% confidence interval: 1.20–1.93]). Possible DPN and painful DPN were independently and additively associated with lower quality of life, poorer sleep, and symptoms of depression and anxiety. Possible DPN itself had greater impact on mental health than neuropathic pain. This large study emphasizes the importance of careful screening for DPN and pain early in the course of type 2 diabetes.

Keywords: Painful diabetic polyneuropathy, Polyneuropathy, Neuropathic pain, Prevalence, Patient characteristics, Quality of life, Mental health

1. Introduction

Diabetic polyneuropathy (DPN) is a serious diabetes complication. Previous studies have reported a wide range of prevalence from 26% to 50% for DPN, and between 8% and 30% for painful DPN. This variation may be explained by different assessment methods and definitions of DPN, and differentially selected study populations. Most studies have examined patients with long duration of diabetes, ie, 8 to 17 years, whereas little is known about the prevalence of DPN and painful DPN in recently diagnosed diabetes. Accumulating evidence suggest that not only hyperglycemia, but also factors, such as increasing diabetes duration, type 2 vs type 1 diabetes, obesity, smoking, and female sex, may be linked to DPN and painful DPN, which particularly may be true in type 2 diabetes. However, existing studies are old, based on mixed population (eg, nondiabetes, type 1 diabetes, and type 2 diabetes), include patients with longstanding diabetes, are of smaller size, or only investigate painful DPN. Less evidence on factors associated with DPN and painful DPN in recently diagnosed type 2 diabetes.
recently diagnosed type 2 diabetes patients is available from large-scale studies.

In patients with diabetes, chronic neuropathic pain has been related to decreased quality of life (QoL), poor sleep, and symptoms of anxiety and depression. By contrast, the impact of DPN itself—regardless of pain—on QoL and mental health comorbidities is uncertain in type 2 diabetes. A study suggested that having DPN without painful symptoms had no effect on mental health-related measures, whereas other studies found depression to be more common both among patients with diabetes with painless and painful DPN.

To fill these knowledge gaps, we conducted a questionnaire survey on neuropathy and pain in the large Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort that enrolls patients with recently diagnosed type 2 diabetes throughout Denmark. The aims of this article are (1) to explore the prevalence of possible DPN and painful DPN in recently diagnosed type 2 diabetes patients, (2) to investigate patient characteristics and lifestyle factors associated with possible DPN and painful DPN, and (3) to examine the impact of possible DPN and painful DPN on mental health in recently diagnosed type 2 diabetes.

2. Methods

2.1. Setting and patients

This study is based on the 7011 patients with type 2 diabetes consecutively enrolled in the DD2 cohort by February 2016. Detailed information on the logistics and characteristics of this cohort has previously been reported. In brief, the DD2 cohort began enrolment in November 2010, and the project is ongoing. Enrolment of newly or recently diagnosed (median diabetes duration at time of enrolment 1.3 year, interquartile range [IQR] 0.3-2.9 years) type 2 diabetes patients takes place at the general practitioner’s office and outpatient hospital clinics (Departments of Endocrinology) in Denmark. During the DD2 enrolment period, all patients have been diagnosed with diabetes according to the WHO criteria.

2.2. Questionnaire

By June 7, 2016, a detailed questionnaire consisting of 41 questions was sent out to all patients alive and living in Denmark with a known address enrolled into DD2 (N = 6726) (Fig. 1). A complete version of the questionnaire is available in the supplementary digital content (supplementary Table 1, available...
as supplemental digital content at http://links.lww.com/PAIN/A903). In September 2016 and again in October 2016, a reminder was sent to those who had not provided a response. All patients were sent a paper version and a link to an electronic version allowing them to answer in their preferred way. All patients were asked to return a blank questionnaire including a note of the reason if they did not want to participate in the questionnaire survey. A subsample of the cohort was invited for a detailed clinical examination, and these results will be presented in a separate publication.

2.3. Patient characteristics

Patient demographics included in the questionnaire were age, sex, height, and weight. Lifestyle factors included smoking habits, alcohol consumption (>7/14 units of alcohol [women/men], which is the maximum safe amount recommended by the Danish Health Authority), and questions on physical activity level.

2.4. Diabetic polyneuropathy

There is no gold standard for identifying polyneuropathy for epidemiological research purposes, but the Michigan Neuropathy Screening Instrument questionnaire part (MNSIq) is a commonly used symptom-based screening tool for identifying DPN.2,8,43 We used the MNSIq and the validated cutoff of ≥4/13 abnormal responses to define possible DPN.15,33 This cutoff had a sensitivity of 40% and a specificity of 92% for detecting confirmed clinical neuropathy in a selected group of patients with long-standing type 1 diabetes.24

Questions on gait instability and falls, as well as frequency and severity of falls, were also included in the questionnaire.

2.5. Painful diabetic polyneuropathy and other pain

The questionnaire contained questions on general pain (any constant or recurrent pain and location of pain) and pain in both feet. Patients reporting pain in both feet were given more detailed questions about the pain. They filled out the 7-item Douleur Neuropathique en 4 Questions (DN4) that is a screening tool for neuropathic pain and with a high performance in DPN.32,35 The DN4 questionnaire comprises 7 “yes” or “no” items related to pain quality; 4 sensory descriptors (tingling, pins and needles, numbness, and itching) and 3 pain descriptors (burning, painful cold, and electric shock sensation). Only patients with pain in the feet completed the DN4, and it was specified that it concerned characteristics of the pain in their feet (Supplementary table 1, available as supplemental digital content at http://links.lww.com/PAIN/A903). A DN4 score of ≥3/7 has a sensitivity and specificity of 84% for identifying clinically confirmed painful DPN.32 Patients with pain in both feet and a DN4 score ≥3 were considered to have possible painful DPN regardless of MNSIq score (Fig. 2). Our neuropathic pain definition was in accordance with the consensus statement (NeuroPPIC) from the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) for the basic “entry level” to identify possible neuropathic pain in questionnaire studies.39 We included additional questions on pain quality, use of pain medications, and pain duration and pain intensity within the previous 24 hours and 7 days at the time of evaluation were recorded. For the latter, we used a numeric rating scale (NRS) ranging from 0 to 10, with 0 denoting no pain and 10 the worst possible pain. We used the Patient-Reported Outcome Measurement Information System (PROMIS) short form v1.0—Pain Interference 4a to assess pain interference with daily activities, household, and social activities within the previous 7 days.22

2.6. Mental health

The patients rated their QoL in the previous 7 days using an NRS ranging from 0 to 10, with 10 being the best QoL possible and 0 the worst.20 Sleep disturbance and symptoms of depression and anxiety were assessed using the PROMIS Short Forms 4a. The instruments grade symptoms experienced during the previous 7 days with a frequency or severity grading of symptoms from “never” to “always” or from “bad” to “very good” with 5 options. The scores are converted into PROMIS T-scores, which are standardized relative to an American/US reference population and are used to categorize the level of impairment/symptoms (normal, mild, moderate, and severe).22,29

2.7. Ethical considerations

All DD2 patients volunteered to participate in the DD2 study and gave written informed consent. The Danish National Committee on Health Research Ethics (record number S-20100082) has approved the DD2 project. The Danish Data Protection Agency (record number 2008-58-0035) has approved the DD2 project, and the study is registered at Aarhus University internal notification no. 62908-250.

2.8. Statistical analyses

Mean values (±SD) were used to describe normally distributed data, and medians (IQR) to describe non-normally distributed variables. Information on both DPN (defined based on MNSIq) and painful DPN (defined based on DN4 and pain location in both feet) status was available for a subpopulation of 5249 patients. Combination of MNSIq-defined possible DPN and DN4-defined possible painful DPN status yielded 4 distinct groups (Fig. 2) for
which descriptive data were provided. Finally, descriptive data on age, sex, and diabetes duration were provided for responders and nonresponders.

We calculated the prevalence of DPN and painful DPN with 95% confidence intervals (CIs) using the exact method for binomial distributions.

We used multivariable linear (age, body mass index [BMI], diabetes duration, and height) and logistic (sex, smoking status [ever (former + current) vs never], and alcohol consumption) regressions and modeled each patient characteristic as a function of possible DPN and possible painful DPN and an interaction term of DPN and painful DPN, while controlling for age, sex, and diabetes duration. If no significant interaction was observed between DPN and painful DPN, each regression was rerun without the interaction term. The significance level was chosen at <0.05. The cross-sectional study design facilitates an investigation of associations, not of temporal relationships. Therefore, possible DPN and possible painful DPN could be included as the independent variables enabling us to include both DPN and painful DPN simultaneously in the multivariable regression models used to examine associations with patient characteristics. This approach allowed us (1) to investigate the association of the evaluated patient characteristics and possible DPN defined by DN4 and pain in both feet separately from the association with possible DPN defined by MNSIq, and (2) to handle the fact that some patients had possible painful DPN but had an MNSIq score <4 (Fig. 2), including the evaluation of possible interaction between possible DPN defined by MNSIq and possible painful DPN defined by DN4.

To evaluate the impact of DPN and painful DPN on mental health, we used the same approach as described above, a multivariable linear regression to model QoL and T-scores for sleep, depression, and anxiety as functions of DPN and painful DPN and adjusted for age, sex, diabetes duration, and BMI (model 1). To control for possible confounding by pain other than neuropathic pain in the feet, the regressions were rerun including a variable of the number of pain locations other than extremities (model 2). Because obesity is strongly associated with mental health outcomes, we adjusted for BMI. However, the direction of the association of BMI-mental health could be bidirectional, and thus, we performed a sensitivity analysis in which we left out BMI in the regressions. All regressions were first run including an interaction term between DPN and painful DPN, and if no interaction was observed, the regressions were rerun without the interaction term. We used a Wald test to compare the sizes of the associations of DPN and painful DPN with mental health outcomes in the regression models without interaction term.

Finally, the correlation between mental health and pain intensity in the feet was estimated using Spearman’s rho.

There were few missing data, and all analyses were performed as complete case analyses.

Data were analyzed using STATA version 14.

3. Results
3.1. Patient population
As seen in Figure 1, the number of patients responding to the questionnaire was 5755 (85.6%). Of these, 225 (3.3%) returned a blank questionnaire (136 [60.4%] patients provided a reason for nonparticipation), and 16 (0.2%) patients were excluded because they answered the questionnaire multiple times. Of the remaining 5514 patients (82% of those who initially received a questionnaire), 42.7% were women, mean (±SD) age was 64.1 (10.9) years, and median duration of diabetes (IQR) was 4.6 (3.5-5.7) years. Further patient characteristics are provided in Table 1. Diabetes duration and sex distribution were similar among responders and nonresponders (supplementary Table 2, available as supplemental digital content at http://links.lww.com/PAIN/A903), but nonresponders were slightly younger than responders (mean age [±SD] 59.6 [12.8] vs 64.1 [10.9]).

| Table 1: Characteristics of the 5514 patients who returned a fully or partly completed questionnaire. |
|--------------------------|
| Variables               |
| Demographics            |
| Female, n (%), N = 5514  |
| Age, years, mean (SD), N = 5514 |
| Diabetes duration, years, median (IQR), N = 5512 |
| Lifestyle and anthropometric factors |
| Height, cm, mean (SD), N = 5455 |
| Weight, kg, mean (SD), N = 5457 |
| BMI, kg/m², median (IQR), N = 5412 |
| Smoking, n (%), N = 5493 |
| Active smoker, n (%)     |
| Daily smoker, n (%)      |
| Occasionally smoker, n (%) |
| Previous smoker, n (%)   |
| Never smoker, n (%)      |
| Alcohol consumption*, n (%), N = 5426 |
| Physical activity†, days, median (IQR), N = 5434 |
| Quality of life, sleep, depression, and anxiety |
| Quality of life, NRS 0-10, median (IQR), N = 5394 |
| Sleep, PROMIS-29, T-score, mean (SD), N = 4739 |
| Anxiety, PROMIS-29, T-score, mean (SD), N = 5274 |
| Depression, PROMIS-29, T-score, mean (SD), N = 5348 |
| PROMIS-29, T-score categories |
| Sleep, n (%) |
| Mild impairment, n (%)   |
| Moderate impairment, n (%) |
| Severe impairment, n (%)  |
| Anxiety, n (%) |
| Mild impairment, n (%)   |
| Moderate impairment, n (%) |
| Severe impairment, n (%)  |
| Depression, n (%)        |
| Mild impairment, n (%)   |
| Moderate impairment, n (%) |
| Severe impairment, n (%)  |
| General pain |
| Pain (constant or recurrent), n (%), N = 5439 |
| Pain location (in the last 3 months), n (%), N = 5439 |
| Head or face, n (%)      |
| Lower and upper back, n (%) |
| Shoulders, n (%)         |
| Hands or arms, n (%)     |
| Stomach, n (%)           |
| Legs, n (%)              |
| Other, n (%)             |
| Gait instability and falls |
| Gait instability, n (%), N = 5394 |
| Falls (during last year), n (%), N = 5455 |

Mean values (SD) were used to describe normally distributed data, and medians (IQR) to describe non-normally distributed variables.  
* Alcohol units per week.  
† Number of days per week with minimum 30 minutes of physical activity.  
BMI: body mass index; DN4, Douleur Neuropathique en 4 Questions; IQR, interquartile range; MNSIq, Michigan neuropathy screening questionnaire; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System.
3.2. Prevalence

Of the 5359 patients with valid answers on the MNSIq, 962 had a score ≥4, suggesting a prevalence of possible DPN of 18.0% (95% CI: 16.9%-19.0%) (Fig. 1; supplementary Table 3, available as supplemental digital content at http://links.lww.com/PAIN/A903).

Of the 5372 patients with valid data to assess painful DPN, 536 reported pain in both feet and had a DN4 score ≥3, corresponding to a prevalence of possible painful DPN of 10.0% (95% CI: 9.2%-10.8%) (Fig. 1; supplementary Table 3, available as supplemental digital content at http://links.lww.com/PAIN/A903). Of those with painful DPN, 130 (28.0%) did not fulfill the MNSIq criteria for DPN (Table 2).

Prevalence was stable across questionnaire intervals (supplementary Table 4, available as supplemental digital content at http://links.lww.com/PAIN/A903).

3.3. Pain: painful diabetic polyneuropathy

As shown in Table 3, more than 80% of the patients with painful DPN had pain in the feet for more than 1 year. Pain often interfered with daily activities, including household chores and social activities (79.2%), and 60.1% reported concomitant drug treatment for their pain. The average (±SD) pain intensity in the feet was 5.3 (2.1) the last 7 days on an NRS (0-10), and 76.2% had moderate to severe pain intensity (NRS ≥4). The most common pain description from the DN4

| Variables | MNSIq <4 and either no pain or DN4 <3, n = 4181 | MNSIq <4 and pain with DN4 ≥3, n = 130† | MNSIq ≥4 and either no pain or DN4 <3, n = 552* | MNSIq ≥4 and pain with DN4 ≥3, n = 386*† |
|-----------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Female, n (%) | 1712 (41.0) | 58 (44.6) | 258 (46.7) | 188 (48.7) |
| Age, years, mean (SD), N = 5249 | 64.3 (10.8) | 64.1 (10.6) | 62.3 (10.8) | 63.1 (10.9) |
| Duration of diabetes, years, median (IQR), N = 5247 | 4.5 (3.4; 5.6) | 4.8 (3.4; 5.9) | 4.7 (3.6; 5.9) | 4.9 (3.8; 6.1) |
| Height, cm, mean (SD), N = 5197 | 172.7 (9.3) | 172.0 (10.1) | 172.6 (10.0) | 172.7 (10.0) |
| BMI, kg/m², median (IQR), N = 5159 | 29.4 (26.2; 33.1) | 29.6 (27.3; 34.8) | 31.2 (27.8; 35.5) | 31.5 (27.5; 35.7) |
| Ever smoker, n (%), N = 5231 | 29.4 (26.2; 33.1) | 29.6 (27.3; 34.8) | 31.2 (27.8; 35.5) | 31.5 (27.5; 35.7) |
| Alcohol consumption, >7/14 (female/male)‡, n (%), N = 5176 | 685 (16.1) | 19 (14.7) | 74 (13.8) | 60 (15.8) |
| Quality of life, NRS 0-10, median (IQR), N = 5177 | 8.0 (7.0; 9.0) | 7.0 (5.0; 8.0) | 7.0 (5.0; 8.0) | 6.0 (4.0; 7.0) |
| PROMIS-29, T-score, mean (SD) | | | | |
| Sleep, N = 4591 | 47.0 (7.0) | 49.9 (7.2) | 52.2 (7.7) | 54.0 (7.5) |
| Depression, N = 5147 | 47.5 (7.8) | 51.1 (8.8) | 52.3 (9.0) | 55.5 (8.9) |
| Anxiety, N = 5080 | 49.0 (8.0) | 52.2 (8.8) | 53.6 (8.7) | 56.1 (8.5) |
| PROMIS-29, T-score, categories: | | | | |
| Sleep impairment (mild—severe), n (%) | 418 (11.4) | 30 (23.9) | 157 (33.1) | 139 (41.4) |
| Symptoms of anxiety (mild—severe), n (%) | 1090 (26.9) | 48 (37.2) | 253 (48.3) | 216 (57.9) |
| Symptoms of depression (mild—severe), n (%) | 843 (20.5) | 50 (38.8) | 238 (44.3) | 208 (55.2) |
| No. of other pain locations§, N = 5235 | | | | |
| 0 | 2371 (56.9) | 30 (23.1) | 160 (29.1) | 55 (14.3) |
| 1 | 735 (17.6) | 28 (21.5) | 99 (18.0) | 69 (17.9) |
| 2 | 588 (14.1) | 32 (24.6) | 129 (23.5) | 94 (24.4) |
| 3 | 343 (8.2) | 27 (20.8) | 92 (16.7) | 92 (23.9) |
| 4 | 121 (2.9) | 11 (8.5) | 61 (11.1) | 57 (14.8) |
| 5 | 12 (0.3) | 2 (1.5) | 9 (1.6) | 18 (4.7) |

Mean values (SDs) were used to describe normally distributed data, and medians (IQR) to describe non-normally distributed variables. Missing data <3.2% except for sleep impairment (missing data 12.5%, no difference between neuropathy groups).

*vNine hundred thirty-eight (552 + 386) patients with MNSIq-defined DPN.
†Five hundred sixteen (130 + 386) patients with DN4-defined painful DPN.
‡Alcohol units per week.
§Possible pain locations: head/face, lower or upper back, shoulders, stomach, or “other location” (category capturing locations not listed here). Arms and legs excepted because pain in these locations could be due to diabetic polyneuropathy.
BMI: body mass index; DN4, douleur neuropathique en questions; DPN, diabetic polyneuropathy; IQR, interquartile range; MNSIq, Michigan neuropathy screening questionnaire; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System.
was burning pain (71.8%), 36.4% reported cold pain, and 38.2% had electric shock like pain (data not shown). There was a negative correlation between reported QoL and the intensity of pain (Spearman’s rho –0.24, P < 0.001) and a positive but weak correlation between reported symptoms of anxiety, depression, and poor sleep and pain in the feet within the last 7 days (Spearman’s rho 0.25, 0.23, and 0.26, P < 0.001) (data not shown).

The small group of patients with painful DPN that did not fulfill the MNSIq criteria for DPN (N = 130) did not differ from those with painful DPN fulfilling the MNSIq criteria (N = 386) regarding age, sex, duration of diabetes, and use of pain medications (Table 2). However, they reported lower mean (± SD) pain intensity (average 7 days: 4.3 [2.1] vs 5.6 [2.1] [data not shown]). The most common pain descriptors on the MNSIq were prickling feeling, burning pain, and leg pain in both groups (supplementary Fig. 1A, available as supplemental digital content at http://links.lww.com/PAIN/A903).

3.4. Pain: pain other than painful diabetic neuropathy

A higher proportion of patients with possible DPN and possible painful DPN had complaints of pain in various body sites compared to those with no DPN (Table 2). The proportion of patients reporting pain at 2 or more locations other than the extremities was 24.5% in those without DPN, 55.4% in those with painful DPN not fulfilling the MNSIq criteria for DPN, 52.7% in those with DPN not fulfilling the criteria for painful DPN, and 67.6% in those with painful DPN fulfilling the MNSIq criteria for DPN (Table 2).

3.5. Association between diabetic polyneuropathy and painful diabetic neuropathy and patient characteristics

We found no statistically significant interaction between possible DPN defined by MNSIq and possible painful DPN defined by DN4 and pain in both feet, suggesting that the estimates of association between possible DPN and patient characteristics were independent of the presence of possible painful DPN, and vice versa.

After correction for age, sex, diabetes duration, and painful DPN, DPN was statistically significantly associated with younger age, longer duration of diabetes, higher BMI, female sex, and presence of ever tobacco smoking (Table 4). Associations were generally weaker for painful DPN except for ever tobacco smoking that was statistically significant associated with painful DPN (odds ratio: 1.52 [1.20-1.93]) (Table 4).

3.6. Association between diabetic polyneuropathy, painful diabetic polyneuropathy, and mental health

Again, we found no statistically significant interaction between possible DPN defined by MNSIq and possible painful DPN defined by DN4 and pain in both feet, suggesting that the estimates of association between possible DPN and mental health outcomes were independent of the estimates of association of possible painful DPN, and vice versa.

Both DPN and painful DPN were independently and additively associated with lower QoL (DPN: –1.16 [–1.31 to –1.01], painful DPN: –0.85 [–1.04 to –0.67]), and higher T-scores of depression (DPN: 4.18 [3.53-4.84], painful DPN: 3.35 [2.51-4.18]), poor sleep (DPN: 4.65 [4.04-5.27], painful DPN: 2.22 [1.44-3.00]), and anxiety (DPN: 3.97 [3.31-4.64], painful DPN: 2.73 [1.89-3.58]) after controlling for age, sex, diabetes duration, BMI, and DPN or painful DPN status (Table 5). The size of the effect of DPN on mental health outcomes was in general higher than that of painful DPN (Supplementary Table 5, supplementary Fig. 2, available as supplemental digital content at http://links.lww.com/PAIN/A903).

Further controlling for pain in other bodily localizations reduced the effect size of the associations, eg, for depression (DPN: 2.95 [2.30-3.59], painful DPN: 2.12 [1.30-2.93]). The total effect of fulfilling both the criteria for DPN and painful DPN on eg, QoL score (–0.85 + –0.57 = –1.42) was of the same order of magnitude as having pain in 3 other areas/locations (–1.29), eg, headache, back pain, and stomach pain (Table 5).

Leaving BMI out of the models resulted in slightly higher DPN and painful DPN estimates for all mental health outcomes, thus not changing any conclusions (supplementary Table 6, available as supplemental digital content at http://links.lww.com/PAIN/A903).

4. Discussion

In this large study of a nationwide cohort with recently diagnosed type 2 diabetes patients, the prevalence of possible DPN was 18% and the prevalence of possible painful DPN was 10%. We found an association between possible DPN and female sex, smoking, longer diabetes duration, lower age, and higher BMI, whereas most relations were weaker for possible painful DPN that was only statistically significant associated with smoking. By contrast, both possible DPN and painful DPN were independently and additively associated with decreased QoL and increased symptoms of depression, anxiety, and poor sleep. Moreover, possible DPN had greater impact on mental health than possible neuropathic pain.

This is the largest questionnaire study to date that examines the prevalence and clinical characteristics of possible DPN and painful DPN in a cohort of recently diagnosed type 2 diabetes patients using validated screening tools. The prevalence of DPN...
Table 4

The estimates of the association between neuropathy and clinical characteristics among the 5249 patients with information on status of both possible DPN (defined by MNSIq) and possible painful DPN (defined by DN4 and pain location in both feet).

| Characteristic | Female | Smoking† | Alcohol overconsumption‡ | Age, year | BMI, kg/m² | Diabetes duration, year | Height, cm |
|----------------|--------|----------|--------------------------|-----------|------------|------------------------|------------|
|                | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Possible DPN   | 1.24 (1.05-1.46)* | 1.36 (1.04-1.57) | 0.94 (0.74-1.19) | -1.90 (2.78 to -0.02) | 1.67 (1.19 to 2.14)* | 0.25 (0.06 to 0.44)* | 0.43 (-0.11 to 0.98) |
| Possible painful DPN | 1.11 (0.90-1.37) | 1.52 (1.20-1.93)* | 1.09 (0.81-1.46) | 0.45 (-0.69 to 1.57) | 0.35 (-0.26 to 0.95) | 0.21 (-0.78 to 0.47) | 0.00 (-0.00 to 0.00) |

BMI: body mass index; CI, confidence interval; DN4, Douleur Neuropathique en 4; DPN, diabetic polyneuropathy; MNSIq, Michigan neuropathy screening questionnaire; OR, odds ratio; β, beta coefficient.

*P-value, 0.05, **P-value, 0.001.

† Smoking: Ever smoking (current or former) vs never smoking.
‡ Alcohol overconsumption: 7/14 units per week (women/men).
§ Multivariable logistic (sex, smoking, and alcohol) and linear (age, BMI, diabetes duration, and height) regressions adjusted for age, sex, diabetes duration, and possible painful DPN.
‖ Multivariable logistic (sex, smoking, and alcohol) and linear (age, BMI, diabetes duration, and height) regressions adjusted for age, sex, diabetes duration, and possible DPN.

Our observation that painful DPN was associated with lower QoL and symptoms of depression, anxiety, and poor sleep is consistent with previous studies of diabetes.3,25,31,37,38 However, we also observed a tendency towards that DPN itself was associated with worse mental health independent of neuropathic pain, which has been observed in some studies3,11 but not all studies.38 and we even observed that DPN itself (MNSIq-defined) had a stronger association with worse mental health outcomes than neuropathic pain. In accordance, the correlation between pain intensity and mental health outcomes was weak. The effect of DPN and painful DPN on mental health measures was additive, and thus, those with both conditions reported the worst mental health outcomes.
Table 5

The estimates of the association between neuropathy and quality of life, depression, sleep, and anxiety among the 5249 patients with sufficient information to determine status of both possible DPN (defined by MNSIq) and possible painful DPN (defined by DN4 and pain location in both feet).

| Quality of life (NRS 0-10) | Depression T-scores | Sleep disturbance T-scores | Anxiety T-scores |
|---------------------------|---------------------|---------------------------|-----------------|
|                            | b (95% CI)          | b (95% CI)                | b (95% CI)      |
| Possible DPN              | 1.16 (-1.31 to -0.10)** | 0.85 (1.04 to 0.67)** | 0.85 (1.00 to 0.67)** |
| Possible painful DPN      | 2.95 (2.30-3.59)**   | 0.57 (0.39 to 0.76)**      | 0.67 (0.46 to 0.97)** |

Possible painful DPN

| No. of other pain locations | Model 1† | Model 2‡ |
|-----------------------------|----------|----------|
|                             | b (95% CI) | b (95% CI) |
| 1                           | -0.60 (-1.07 to -0.13) | -0.57 (-0.76 to -0.38) |
| 2                           | 2.85 (2.24-3.89) | 1.21 (1.03-1.39) |
| 3                           | 5.57 (4.83-6.31) | 1.82 (1.50-2.13) |
| 4                           | 7.67 (6.62-8.72) | 3.47 (2.86-4.09) |
| 5                           | 10.22 (8.31-12.06) | 3.76 (3.24-4.36) |

CI, confidence interval; DN4, Douleur Neuropathique en 4 questions; DPN, diabetic polyneuropathy; MNSIq, Michigan neuropathy screening questionnaire; OR, odds ratio.

*P-value < 0.05, **P-value < 0.001.
† Model 1: Adjusted for age, sex, diabetes duration, BMI, and DPN or painful DPN, respectively.
‡ Model 2: Adjusted for age, sex, diabetes duration, BMI, number of pain locations other than extremities (head/face, lower or upper back, shoulders, stomach, or “other location” [category capturing locations not listed here]), and DPN or painful DPN, respectively.

Conflict of interest statement

The authors have no conflicts of interest to declare.
The Danish Centre for Strategic Research in Type 2 Diabetes Project (DD2) is supported by the Danish Agency for Science [grant number 09-067009, 09-075724], the Danish Health and Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners are listed on the website (www.dd2.nu). The International Diabetic Neuropathy Consortium (IDNC) research programme is supported by a Novo Nordisk Foundation Challenge Programme grant (Grant number NNF14OC0011633). None of the study funders were involved in the design of the study; the collection, analysis, and interpretation of data; writing the manuscript; or the decision to submit the manuscript for publication. T.S. Jensen and N.B. Finnerup are members of the DOLORisk consortium funded by the European Commission Horizon 2020 (ID633491). Data availability: More information about the DD2 cohort can be found at the Danish DD2 website www.dd2.nu. The DD2 national cohort study is supported by unrestricted donation from Novo Nordisk A/S. Project partners included: the Danish Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners were listed on the website (www.dd2.nu). The IDNC research programme is supported by unrestricted donation from Novo Nordisk A/S. Project partners included: the Danish Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners were listed on the website (www.dd2.nu).

Author contributions: S.S. Gylfadottir designed the study, performed the statistical analyses, drafted the manuscript, contributed to the discussion, and approved the final manuscript. H. Andersen, M. Itani, K.S. Khan, A.G. Kristensen, and N.B. Finnerup approved the final manuscript. N.T. Andersen, R.W. Thomsen, J. Nielsen, S.H. Sindrup, D.H. Christensen collected the data, designed the study, performed the statistical analyses, drafted the manuscript, contributed to the discussion, and approved the final manuscript. B.C. Callaghan, J.S. Nielsen, S.H. Sindrup, J. Sorensen, H. Hansen, K. Skov, J. Andersen, P. Friborg, J. Fenger, and S. Henriksen performed the final manuscript decision to submit the manuscript for publication. T.S. Jensen and N.B. Finnerup are members of the DOLORisk consortium funded by the European Commission Horizon 2020 (ID633491). Data availability: More information about the DD2 cohort can be found at the Danish DD2 website www.dd2.nu. The DD2 national cohort study is supported by unrestricted donation from Novo Nordisk A/S. Project partners included: the Danish Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners were listed on the website (www.dd2.nu). The IDNC research programme is supported by unrestricted donation from Novo Nordisk A/S. Project partners included: the Danish Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners were listed on the website (www.dd2.nu).

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A903.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A903.

References

[1] Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes care 2011;34:2220–4.
[2] Andersen ST, Witte DR, Dalgaard EM, Andersen H, Nævrot P, Fleming T, Jensen TM, Finnerup NB, Jensen TS, Lauritzen T, Feldman EL, Callaghan BC, Charles M. Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. Diabetes care 2018;41:1068–73.
[3] Aslam A, Singh J, Rajbahadari S. Prevalence of painful diabetic neuropathy using the self-completed Leeds assessment of neuropathic symptoms and signs questionnaire in a population with diabetes. Can J Diabetes 2015;39:285–95.
[4] Bai JW, Lovblom LE, Cardínez M, Weisman A, Farooq MA, Halpern EM, Boulet G, Eldelekli D, Lovsivn JA, Lythyn Y, Keenan HA, Brent MH, Paul N, Bril V, Cherney DZ, Perkins BA. Neuropathy and presence of emotional distress and depression in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. J Diabetes Complications 2017;31:1318–24.
[5] Bl A, Thomsen RW, Nielsen JS, Nicolaisen SK, Beck-Nielsen H, Rungby J, Sorensen HT, Hansen TK, Sondergaard J, Friborg S, Lauritzen T, Maidal HT. Early-onset type 2 diabetes: age gradient in clinical and behavioural risk factors in 5115 persons with newly diagnosed type 2 diabetes-results from the DD2 study. Diabetes Metab Res Rev 2018;34:e2968.
[6] Bouhassira D, Letanouë M, Hartemann A. Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study. PLoS One 2013;8:e74195.
[7] Cardínez N, Lovblom LE, Bai JW, Lewis E, Abraham A, Scarr D, Lovsivn JA, Lythyn Y, Boulet G, Farooq MA, Orszag A, Weisman A, Keenan HA, Brent MH, Paul N, Bril V, Cherney DZ, Perkins BA. Neuropathy and presence of emotional distress and depression in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. J Diabetes Complications 2018;32:660–4.
[8] Cheng YJ, Gregg EW, Kahn HS, Williams DE, Re Rekeire N, Narayan KM. Peripheral insensate neuropathy—a tall problem for US adults? Am J Epidemiol 2006;164:873–80.
[9] Christensen DH, Nicolaisen SK, Berenci K, Beck-Nielsen H, Rungby J, Friborg S, Brandslund I, Christiansen JS, Vaag A, Sorensen HT, Nielsen JS, Thomsen RW. Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: a cohort profile. BMJ Open 2018;8:e017273.
[10] D’Amato C, Morganti R, Greco C, Di Gennaro F, Cacciotti L, Longo S, Matulani G, Lauro D, Marfia GA, Spallone V. Diabetic peripheral neuropathic pain is a stronger predictor of depression than other diabetes complications and comorbidities. Diabetes Vasc Dis Res 2016;13:418–28.
[11] Daousi C, MacFarlane IA, Woodward A, Nurminko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabetic Med 2004;21:976–82.
[12] Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes care 2006;29:1518–22.
[13] England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, Cohen JA, Fisher MA, Howard JF, Kinsella LJ, Latov N, Lewis RA, Low PA, Sumner AJ. Distal symmetrical polyneuropathy: a definition for clinical research. A report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil 2005;86:167–74.
[14] Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes care 1994;17:1281–9.
[15] Finnerup NB, Attal N, Haroutounian S, Mcnicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.
[16] Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DL, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurminko T, Raja SN, Rice AS, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. PAIN 2016;157:1599–606.
[17] Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract 2000;47:123–8.
[18] Geelen CC, Smeets R, Schmitz S, van den Bergh JP, Goossens M, Verbunt JA. Anxiety affects disability and quality of life in patients with painful diabetic neuropathy. Eur J Pain 2017;21:1632–41.
[19] Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurement. JAMA 1994;272:619–26.
[20] Gore M, Brandenburg NA, Hoffman DL, Tai KS, Stacey B. Burden of illness in painful diabetic peripheral neuropathy: the patients’ perspectives. J Pain 2006;7:892–900.
[22] HealthMeasures. PROMIS health measures. Available at: http://www. healthmeasures.net/explore-measurement-systems/promis. Accessed May 1, 2019.

[23] Hebert HL, Veluchamy A, Torrance N, Smith BH. Risk factors for neuropathic pain in diabetes mellitus. PAIN 2017;158:560–8.

[24] Herman WH, Pop-Busui R, Braflett BH, Martin CL, Cleary PA, Albers JW, Feldman EL. Use of the Michigan neuropathy screening instrument as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the diabetes control and complications trial/epidemiology of diabetes interventions and complications. Diabetic Med 2012;29:937–44.

[25] Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, Lim J, Malik RA, Alaim U. Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin Ther 2018;40:828–49.

[26] Nielsen JS, Thomsen RW, Steffensen C, Christiansen JS. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) study: implementation of a nationwide patient enrollment system. Clin Epidemiol 2012;4(suppl 1):27–36.

[27] Papanas N, Ziegler D. Risk factors and comorbidities in diabetic neuropathy: an update 2015. Rev Diabet Stud 2015;12:48–62.

[28] Peltier A, Goutman SA, Callaghan BC. Painful diabetic neuropathy, BMJ 2014;348:g1799.

[29] Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. Assessment 2011;18:263–83.

[30] Raputova J, Srotova I, Vlckova E, Sommer C, Uceyler N, Birklein F, Rittner HL, Reibhorn C, Adimova B, Kovalova I, Kralickova Nekvapilova E, Forer L, Belobradkova J, Oslovsky J, Weber P, Dusek L, Jarkovsky J, Bednark J. Sensory phenotype and risk factors for painful diabetic neuropathy: a cross-sectional observational study. PAIN 2017;158:2340–53.

[31] Spallone V, Greco C, Paintal and painless diabetic neuropathy: one disease or two? Curr Diabetes Rep 2013;13:533–49.

[32] Spallone V, Morganti R, D’Amato C, Greco C, Cacciotti L, Marfia GA. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. Diabetic Med 2012;29:578–85.

[33] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Laura G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285–93.

[34] Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28(suppl 1):8–14.

[35] Themistocleous AC, Ramirez JD, Shilo PR, Lees JG, Selvarajah D, Orengo C, Tesfaye S, Rice AS, Bennett DL. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. PAIN 2016;157:1132–45.

[36] Thomsen RW, Baggesen LM, Svensson E, Pedersen L, Nonreuland H, Buht ES, Haase CL, Johnsen SP. Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. Diabetes Obes Metab 2015;17:771–80.

[37] Truini A, Spallone V, Morganti R, Tamburin S, Zanette G, Schenone A, De Michielis C, Tugnoli V, Simioni V, Manganelli F, Dubbioso R, Lauria G, Lombardi R, Jann S, De Toni Franceschini L, Tesfaye S, Fiorelli M, Spagnoli A, Cruccu G. A cross sectional study investigating frequency and features of definitely diagnosed diabetic painful polyneuropathy. PAIN 2018;159:2658–66.

[38] Van Acker K, Bouhassira D, De Bacquier D, Weiss S, Matthys K, Raemen H, Mathieu C, Colin IM. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. Diabetes Metab 2009;35:206–13.

[39] van Hecke O, Kamerman PR, Attal N, Baron R, Bjornadottir G, Bennett DL, Bennett MI, Bouhassira D, Diatchenko L, Freeman R, Freynhagen R, Haanpaa M, Jensen TS, Raja SN, Rice AS, Seltzer Z, Thorgeirsson TE, Yarnitsky D, Smith BH. Neuropathic pain phenotyping by international consensus (NeuPPIC) for genetic studies: a NeuPSIG systematic review, Delphi survey, and expert panel recommendations. PAIN 2015;156:2337–53.

[40] Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. Pain Med 2002;3:660–74.

[41] Vileikyte L, Peyrot M, Gonzalez JS, Rubin RR, Garrow AP, Stickings D, Waterman C, Ulbrecht JS, Cavanagh PR, Boulton AJ. Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: a longitudinal study. Diabetologia 2009;52:1265–73.

[42] Vinik AI, Neovrot ML, Casellini C, Parson H. Diabetic neuropathy. Endocr Rev Clin North Am 2013;42:747–87.

[43] Wu EQ, Borton J, Said G, Le TK, Monz B, Rosilio M, Avoinet S. Estimated prevalence of peripheral neuropathy and associated pain in adults with diabetes in France. Curr Med Res Opin 2007;23:2035–42.

[44] Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–4.