

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

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### **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 5,514 (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  $\geq 4$  on the MNSI

questionnaire determined possible DPN whereas pain presence in both feet together with a score  $\geq 3$  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, BMI, and smoking were associated with possible DPN, whereas only smoking showed a clear association with possible painful DPN (OR 1.52 [95% CI: 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

## Introduction

Diabetic polyneuropathy (DPN) is a serious diabetes complication. Previous studies have reported a wide range of prevalence from 26% to 50% for DPN,[1; 25; 37; 38; 44] and between 8-30% for painful DPN.[1; 3; 7; 12; 13; 37; 43] This variation may be explained by different assessment methods and definitions of DPN, and differentially selected study populations.[28; 31; 34; 40; 42] Most studies have examined patients with long duration of diabetes i.e. 8-17 years,[3; 7; 13; 30; 31; 35; 37; 38; 44] 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 like increasing diabetes duration, type 2 versus type 1 diabetes, obesity, smoking, and female sex,[2; 3; 7; 11; 13; 23; 30; 31; 35; 37; 38; 44] may be linked to DPN and painful DPN, which particularly may be true in type 2 diabetes. However, existing studies are either

old[44], based on mixed population (e.g. non-diabetes, type 1 diabetes, and type 2 diabetes,[3; 7; 12; 13; 38; 44]) include patients with longstanding diabetes,[3; 7; 13; 30; 35; 37; 38; 44] are of smaller size,[3; 7; 12; 30; 35] or only investigate painful DPN.[1; 3; 12] Less evidence on factors associated with DPN and painful DPN in recently diagnosed type 2 diabetes patients is available from large-scale studies.

In diabetes patients, chronic neuropathic pain has been related to decreased quality of life (QoL), poor sleep, and symptoms of anxiety and depression.[4; 7; 11; 13; 18; 19; 21; 35; 38; 41] In contrast, the impact of DPN itself - regardless of pain - on quality of life 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,[38] whereas other studies found depression to be more common both among diabetes patients with painless and painful DPN.[4; 11]

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 which enrolls patients with recently diagnosed type 2 diabetes throughout Denmark. The aims of this paper 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.

## **Methods**

### **Setting and patients**

This study is based on the 7,011 type 2 diabetes patients consecutively enrolled in the DD2 cohort by February 2016. Detailed information on the logistics and characteristics of this

cohort have previously been reported.[10; 26] 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, 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.[10]

### **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=6,726) (Figure 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, these results will be presented in a separate publication.

### **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.

## DPN

There is no gold standard for identifying polyneuropathy for epidemiological research purposes, but the Michigan Neuropathy Screening Instrument questionnaire part (MNSIq[15]) is a commonly used symptom based screening tool for identifying DPN.[2; 8; 43] ***We used the MNSIq and the validated cutoff of  $\geq 4/13$  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 longstanding type 1 diabetes.[24]

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

### Painful DPN 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) which 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, 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  $\geq 3/7$  has a sensitivity and specificity of 84% for identifying clinically confirmed painful DPN.[32] ***Patients with pain in both feet and a DN4-score  $\geq 3$  were considered to have possible painful DPN [6; 17; 32; 35]***

*regardless of MNSIq-score* (Figure 2). Our neuropathic pain-definition was in accordance with the consensus statement (NeuroPPIC) from the Neuropathic 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 0-10, 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]

### **Mental health**

The patients rated their QoL in the previous 7 days using a 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 five 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, severe).[22; 29]



## 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.

## Statistical analyses

Means (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 5,249 patients. Combination of MNSIq-defined possible DPN and DN4-defined possible painful DPN status yielded four distinct groups (Figure 2) for which descriptive data were provided. Finally, descriptive data on age, sex, and diabetes duration were provided for responders and non-responders.

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

We used multivariable linear (age, body mass index [BMI], diabetes duration, height) and logistic (sex, smoking status [ever (former + current) vs. never], alcohol consumption) regressions and modelled 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 a MNSIq score < 4 (Figure 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 BMI-mental health, could be bidirectional, 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.

## **Results**

### **Patient population**

As seen in Figure 1 the number of patients responding to the questionnaire was 5,755 (85.6%). Of these, 225 (3.3%) returned a blank questionnaire (136 (60.4%) patients provided a reason for non-participating) and 16 (0.2%) patients were excluded because they answered the questionnaire multiple times. Of the remaining 5,514 patients (82% of those who initially received a questionnaire), 42.7% were women, mean ( $\pm$ 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 non-responders (supplementary Table 2, available as supplemental digital content at <http://links.lww.com/PAIN/A903>), but non-responders were slightly younger than responders (mean age ( $\pm$ SD) 59.6 (12.8) vs. 64.1 (10.9)).

### **Prevalence**

Of the 5,359 patients with valid answers on the MNSIq, 962 had a score  $\geq 4$ , suggesting a prevalence of possible DPN of 18.0% (95% CI: 16.9%; 19.0%) (Figure 1; supplementary Table 3, available as supplemental digital content at <http://links.lww.com/PAIN/A903>).

Of the 5,372 patients with valid data to assess painful DPN, 536 reported pain in both feet and had a DN4 score  $\geq 3$ , corresponding to a prevalence of possible painful DPN of 10.0% (95% CI 9.2%; 10.8%) (Figure 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 were stable across questionnaire intervals (supplementary Table 4, available as supplemental digital content at <http://links.lww.com/PAIN/A903>).

### **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 ( $\pm$ SD) pain intensity in the feet was 5.3 (2.1) the last 7 days on a NRS (0 – 10) and 76.2 % had moderate to severe pain intensity ( $\text{NRS} \geq 4$ ). The most common pain description from the DN4 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 ( $\pm$ 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 in both groups prickling feeling, burning pain, and leg pain (supplementary Figure 1A, available as supplemental digital content at <http://links.lww.com/PAIN/A903>).

### **Pain: pain other than painful DPN**

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).

### **Association between DPN and painful DPN 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 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 which was statistically significant associated with painful DPN (OR: 1.52 [1.20; 1.93]) (Table 4).

### **Association between DPN, painful DPN 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; -1.01], painful DPN: -0.85 [-1.04; -0.667]) 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: 3.987 [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 were in general higher than that of painful DPN (Supplementary Table 5, supplementary Figure 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, e.g. 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 e.g. QoL score ( $-0.85 + -0.57 = -1.42$ ) was of the same order of magnitude as having pain in three other areas/locations (-1.29) e.g. 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>).

## 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 which was only statistically significant associated with smoking. In

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 (18%) and painful DPN (10%) found in this study are similar to the prevalence reported in two survey studies using the MNSIq for the diagnosis of DPN and the MNSI in combination with Brief Pain Inventory (BPI) to diagnose painful DPN.[2; 43] In the ADDITION Denmark cohort study consisting of 1445 screenings-detected type 2 diabetes patients the prevalence of DPN at time of diabetes diagnosis was of 13.1%, [2] whereas in a French nationwide cohort study consisting of 1023 type 1 and 2 diabetes patients with a mean duration of diabetes of 15 years, the prevalence of painful DPN was 8% using a MNSIq cutoff of 7 as compared to 4 in our study.[43] In a large UK study of diabetes patients in a community health care setting the duration of diabetes was similar to our study (median 5 years), but the prevalence estimate of painful DPN twice as high or 21%. [1] This difference may be related to painful DPN being defined based on a clinical evaluation in the UK study. Other studies of more longstanding diabetes have likewise reported higher prevalence of both DPN and painful DPN than our study.[1; 3; 25; 31; 37; 38] These differences may be partly explained by the longer diabetes duration, but also by the different diagnostic criteria used for DPN and painful DPN. Thus, our use of questionnaire-based tools to determine DPN and painful DPN in the absence of clinical examination and confirmatory tests reduces the level of certainty of the DPN diagnoses. [14; 17; 33] Moreover, the sensitivity of a MNSIq score  $\geq 4$  was 40% compared to clinically defined DPN in a study of younger patients with longstanding type 1 diabetes, thus,

we likely also underestimate DPN prevalence in our cohort. We do not know whether this sensitivity can be applied to our type 2 diabetes cohort, but it is likely that the MNSIq also underestimate DPN prevalence in our cohort.

Our associations of female sex, smoking, higher BMI and longer duration of diabetes with DPN in recently diagnosed type 2 diabetes corroborate previous studies of patients with longstanding diabetes.[23; 27; 44] However, in contrast to some previous studies, we only observed an association of painful DPN with smoking status and not with e.g. sex, age, and BMI.[1; 23; 31; 38] An explanation may be our analytical approach which – in comparison with most previous studies - allowed us to disentangle the effect of the risk factor on pain occurrence in DPN independent from that on DPN risk itself.[23; 27; 44] Moreover, power was reduced for painful DPN due to the lower prevalence, however, the estimates were smaller for painful DPN than DPN. We did not observe an association between body height and DPN, although it has been proposed that tall stature is a risk factor for peripheral neuropathy due to increased nerve length and nerve surface area.[9] Surprisingly, we observed that DPN was negatively associated with age. Increasing age is generally a marker of longer diabetes duration, however, the DD2 enrolls type 2 diabetes patients around time of diabetes diagnosis. A younger age at time of diagnosis is a marker of a worse phenotype,[5] which may explain our observation of a negative association of age and DPN. Moreover, non-responders were in general younger and we cannot exclude that part of the age-association may be explained by a responder bias if non-responder have DPN to a lesser extent than responders.

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.[7; 35; 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[4; 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 were weak. The effect of DPN and painful DPN on mental health measures was additive, thus, those fulfilling both the DPN and painful DPN criteria had the most severe symptoms, which is in accordance with an Italian study showing more severe depressive symptoms among those with painful DPN as compared to those with non-painful using Beck depression inventory II.[11] In concert with other studies, many of the patients in all three neuropathy groups had complaints of general pain (e.g. back and neck pain, headache and stomachache).[21; 35] The effect size of general pain in 2 bodily localizations on QoL, depression, anxiety and sleep scores was of a similar order of magnitude as that of DPN and painful DPN. Patients with possible DPN and painful DPN more often had pain at other locations than the group without any DPN, also suggesting that positive answers to the MNSIq and pain in the feet could be due to other causes than DPN.

A large proportion (3/4) of the patients with painful DPN reported neuropathic pain of moderate to severe intensity ( $NRS \geq 4$ ) and 60.1% reported use of pain medication. This is similar to results published before.[7; 21] Pain intensity was positively correlated to symptoms of anxiety, depression, and sleep disturbance. The fact that many of the patients had moderate to severe pain intensity despite taking drugs for their pain may indicate either inappropriate treatment or a lack of effective neuropathic drug treatments.[16]

The main strength of this questionnaire study is the large sample size, the high response rate (85.6%) and the low level of missing data. Reassuringly, similar estimates of the prevalence were observed across questionnaire intervals.

The DD2 cohort enrolls patients from primary care and hospital outpatient clinics. Since around half of the patients have been enrolled from hospital outpatient clinics, the DD2 cohort may hold patients with more severe diabetes than the average type 2 diabetes population in Denmark. However, baseline data from the DD2 cohort are similar to data from a cohort of type 2 patients receiving their first glucose-lowering drug indicating that the DD2 cohort is representative of recently diagnosed type 2 diabetes patients in Denmark.[10; 36] The cross-sectional design of this study has some innate limitations including the inability to determine temporal relationships. Lastly, we lack information on other diabetes complications and comorbidity, which can affect QoL related outcome measures.

In conclusion, in this largest questionnaire study of possible DPN in recently diagnosed type 2 diabetes patients, a significant proportion of patients had possible DPN and possible painful DPN. The presence of possible DPN was associated with female sex, longer diabetes duration, higher BMI, and smoking, whereas smoking was the only factor clearly associated with painful DPN. Patients with possible DPN and painful DPN reported lower QoL and more symptoms of anxiety, depression, and poor sleep. Since DPN in recently diagnosed diabetes patients is associated with modifiable risk factors and has major impact on quality of life, it is important to carefully screen for this early complication in type 2 diabetes.

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Christensen collected the data, designed the study, performed the statistical analyses, drafted the manuscript, contributed to the discussion, and approved the final manuscript. S.K.

Nicolaisen designed the study, researched the data, revised the manuscript critically, contributed to the discussion, and approved the final manuscript. N.T. Andersen, R.W.

Thomsen, N.B. Finnerup, B.C. Callaghan, J.S. Nielsen, S.H. Sindrup, H. Andersen, M. Itani, K.S. Khan, A.G. Kristensen, and T.S. Jensen designed the study, revised the manuscript critically, contributed to the discussion, and approved the final manuscript.

Data availability: More information about the DD2 cohort can be found at the Danish DD2 website [www.dd2.nu](http://www.dd2.nu). The DD2 national advisory forum strongly encourages national and international collaboration and application form can be found via this link

[https://dd2.nu/media/1264/standard-dd2-protocol\\_final.doc](https://dd2.nu/media/1264/standard-dd2-protocol_final.doc). Interested researchers can contact DD2 via assistant professor Jens Steen Nielsen at: [jsn@rsyd.dk](mailto:jsn@rsyd.dk).

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## Tables

**Table 1:** Characteristics of the 5,514 patients who returned a fully or partly completed questionnaire

Variables	
<i>Demographics</i>	
Female, n (%), N = 5,514	2,355 (42.7)
Age, years, mean (SD), N = 5,514	64.1 (10.9)
Diabetes duration, years, median (IQR), N = 5,512	4.6 (3.5; 5.7)
<i>Lifestyle and anthropometric factors</i>	
Height, cm, mean (SD), N = 5,455	172.6 (9.4)
Weight, kg, mean (SD), N = 5,457	91.0 (20.1)
BMI, kg/m <sup>2</sup> , median (IQR), N = 5,412	29.7 (26.4; 33.5)
Smoking, n (%), N = 5,493	
Active smoker	1,078 (19.6)
Daily	849 (15.5)
Occasionally	229 (4.2)
Previous smoker	2,453 (44.7)
Never smoker	1,962 (35.7)
Alcohol consumption <sup>a</sup> , >7/14 (female/male), n (%), N = 5,426	856 (15.8)
Physical activity <sup>b</sup> , days, median (IQR), N = 5,434	4.0 (2.0;6.0)
<i>Quality of life, sleep, depression and anxiety</i>	
Quality of life, NRS 0-10, median (IQR), N = 5,394	8.0 (6.0; 9.0)
Sleep, PROMIS-29, T-score, mean (SD), N = 4,739	48.2 (7.5)

Anxiety, PROMIS-29, T-score, mean (SD), N = 5,274	50.2 (8.5)
Depression, PROMIS-29, T-score, mean (SD), N = 5,348	48.7 (8.4)
PROMIS-29, T-score categories	
Sleep, n (%)	
Mild impairment	542 (11.4)
Moderate impairment	212 (4.5)
Severe impairment	25 (0.5)
Anxiety, n (%)	
Mild impairment	1,088 (20.6)
Moderate impairment	559 (10.6)
Severe impairment	49 (0.9)
Depression, n (%)	
Mild impairment	806 (15.1)
Moderate impairment	562 (10.5)
Severe impairment	47 (0.9)
<b>General pain</b>	
Pain (Constant or recurrent), n (%), N = 5,439	2,995 (55.1)
Pain location (in the last 3 months), n (%), N = 5,439	
Head or face	1,041 (19.1)
Lower and upper back	2,138 (39.3)
Shoulders	1,376 (25.3)
Hands or arms	1,023 (18.8)
Stomach	590 (10.8)

Legs	1,447 (26.6)
Other	599 (11.0)
<i>Gait instability and falls</i>	
Gait instability, n (%), N = 5,394	1,193 (22.1)
Falls (during last year), n (%), N = 5,455	977 (17.9)

Abbreviations: SD, standard deviation; IQR, interquartile range; MNSIq, Michigan neuropathy screening questionnaire; DN4, Douleur Neuropathique en 4 Questions, BMI: body mass index; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System.

Means (SD) were used to describe normally distributed data, and medians (IQR) to describe non-normally distributed variables.

<sup>a</sup>Alcohol units per week. <sup>b</sup>Number of days per week with minimum 30 minutes of physical activity.

**Table 2:** Characteristics of the 5,249 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).

<b>Variables</b>	<b>MNSIq&lt;4 and either no pain or DN4&lt;3, n=4,181</b>	<b>MNSIq&lt;4 and pain with DN4≥3, n= 130<sup>b</sup></b>	<b>MNSIq≥4 and either no pain or DN4&lt;3, n=552</b>	<b>MNSIq≥4 and pain with DN4≥3, n=386<sup>b</sup></b>
Female, n (%), N = 5,249	1,712 (41.0)	58 (44.6)	258 (46.7)	188 (48.7)
Age, years, mean (SD), N = 5,249	64.3 (10.8)	64.1 (10.6)	62.3 (10.8)	63.1 (10.9)
Duration of diabetes, years, median (IQR), N = 5,247	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 = 5,197	172.7 (9.3)	172.0 (10.1)	172.6 (10.0)	172.7 (10.0)
BMI, kg/m <sup>2</sup> , 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 = 5,231	2,616 (62.8)	93 (72.1)	378 (68.5)	294 (76.2)
Alcohol consumption, >7/14 (female/male) <sup>c</sup> , n (%), N = 5,176	665 (16.1)	19 (14.7)	74 (13.8)	60 (15.8)
Quality of life, NRS 0-10, median (IQR), N =	8.0 (7.0; 9.0)	7.0 (5.0; 8.0)	7.0 (5.0; 8.0)	6.0 (4.0; 7.0)

5,177				
PROMIS-29, T-score, mean (SD)				
Sleep, N = 4,591	47.0 (7.0)	49.9 (7.2)	52.2 (7.7)	54.0 (7.5)
Depression, N = 5,147	47.5 (7.8)	51.1 (8.8)	52.3 (9.0)	55.5 (8.9)
Anxiety, N = 5,080	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 (25.9)	157 (33.1)	139 (41.4)
Symptoms of Anxiety (mild – severe), n (%)	1,090 (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)
Number of other pain locations <sup>d</sup> , N=5,235				
0	2,371 (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)

Abbreviations: MNSIq, Michigan neuropathy screening questionnaire; DN4, Douleur Neuropathique en questions; SD, standard deviation; IQR, interquartile range; BMI: body mass index; NRS, numeric rating scale; PROMIS, Patient-Reported Outcomes Measurement Information System.

Means (SD) were used to describe normally distributed data, and medians (IQR) to describe non-normally distributed variables

<sup>a</sup>938 patients with MNSIq-defined DPN. <sup>b</sup>516 (130+386) patients with DN4-defined painful DPN. <sup>c</sup>Alcohol units per week. <sup>d</sup>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.

Missing data < 3.2% except for sleep impairment (missing data 12.5%, no difference between neuropathy groups).



**Table 3:** Pain-related characteristics among the 536 patients with possible painful DPN

(defined by DN4 and pain location in both feet)

Variables	
Pain in the feet spreads upwards in legs, n (%), N = 529	331 (62.6)
Similar pain in hands or fingers, n (%), N = 527	228 (43.3)
Waking up at night because of pain, n (%), N = 526	264 (50.2)
Pain in the feet, duration, n (%), N = 534	
Less than a month	6 (1.1)
1-3 months	10 (1.9)
3-12 months	71 (13.3)
1-5 years	298 (55.8)
more than 5 years	149 (27.9)
Pain intensity within last 24 hours, NRS (0-10), mean (SD), N = 530	5.2 (2.1)
Pain intensity within last 7 days, NRS (0-10), mean (SD), N = 530	5.3 (2.1)
Drug treatment for pain in the feet, n (%), N = 531	319 (60.1)
Pain interference with daily activities, PROMIS-29, T – score, mean (SD), N = 525	59.1 (7.9)
PROMIS-29, T-score categories	
Mild interference with daily activities	155 (29.5)
Moderate interference with daily activities	232 (44.2)
Severe interference with daily activities	29 (5.5)

Abbreviations: DN4, Douleur Neuropathique en 4 questions, NRS, numeric rating scale; SD, standard deviation, PROMIS, Patient-Reported Outcomes Measurement Information System.

**Table 4:** The estimates of the association between neuropathy and clinical characteristics among the 5,249 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).

	Female	Smoking <sup>a</sup>	Alcohol overconsumption <sup>b</sup>	Age, year	BMI, kg/m <sup>2</sup>	Diabetes duration, year	Height, cm
	OR (95% CI)	OR (95% CI)	OR (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)
<b>Possible DPN<sup>c</sup></b>	1.24 (1.05; 1.46)*	1.36 (1.14; 1.63)*	0.94 (0.74; 1.18)	-1.90 (-2.78; -1.02)**	1.67 (1.19; 2.14)**	0.25 (0.06; 0.44)*	0.43 (-0.11; 0.96)
<b>Possible painful DPN<sup>d</sup></b>	1.11 (0.90; 1.37)	1.52 (1.20; 1.93)*	1.09 (0.81; 1.46)	0.45 (-0.68; 1.57)	0.35 (-0.26; 0.95)	0.06 (-0.18; 0.31)	0.21 (-0.47; 0.90)

Abbreviations: MNSIq, Michigan neuropathy screening questionnaire; DPN, diabetic polyneuropathy; DN4, Douleur Neuropathique en 4; BMI:

body mass index; OR, odds ratio; CI, confidence interval;  $\beta$ , beta-coefficient. <sup>a</sup>Smoking: Ever smoking (current or former) vs. never smoking.

<sup>b</sup>Alcohol overconsumption: > 7/14 units per week (women/men). <sup>c</sup>Multivariable logistic (sex, smoking, alcohol) and linear (age, BMI, diabetes duration, height) regressions adjusted for age, sex, diabetes duration, and possible painful DPN. <sup>d</sup>Multivariable logistic (sex, smoking, alcohol) and linear (age, BMI, diabetes duration, height) regressions adjusted for age, sex, diabetes duration, and possible DPN.

\*P-value<0.05, \*\*P-value<0.001

**Table 5.** The estimates of the association between neuropathy and quality of life, depression, sleep and anxiety among the 5,249 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	
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)
<b>Possible DPN</b>	-1.16 (-1.31 ; -1.01)**	-0.85 (-1.00; -0.71)**	4.18 (3.53; 4.84)**	2.95 (2.30; 3.59)**	4.65 (4.04 ; 5.27)**	3.46 (2.86; 4.06)**	3.97 (3.31 ; 4.64)**	2.82 (2.17; 3.48)**
<b>Possible painful DPN</b>	-0.85 (-1.04; -0.67)**	-0.57 (-0.76; -0.39)**	3.35 (2.51; 4.18)**	2.12 (1.30; 2.93)**	2.22 (1.44 ; 3.00)**	1.05 (0.30; 1.81)**	2.73 (1.89; 3.58)**	1.61 (0.78; 2.44)**
<b>Number of other pain locations</b>								

<b>1</b>	-	-0.60 (-0.73; -0.46)	-	1.30 (0.71; 1.89)	-	1.95 (1.40; 2.50)	-	1.28 (0.68; 1.88)
<b>2</b>	-	-0.97 (-1.11; -0.83)	-	3.47 (2.86; 4.09)	-	3.95 (3.37; 4.52)	-	3.37 (2.74; 3.99)
<b>3</b>	-	-1.29 (-1.46; -1.13)	-	5.57 (4.83; 6.31)	-	5.26 (4.57; 5.95)	-	5.20 (4.45; 5.96)
<b>4</b>	-	-1.82 (-2.05; -1.58)	-	7.67 (6.62; 8.72)	-	6.45 (5.49; 7.41)	-	6.86 (5.80; 7.93)
<b>5</b>	-	-1.58 (-2.13; -1.02)	-	8.22 (5.81; 10.62)	-	7.04 (4.78; 9.30)	-	7.42 (4.89; 9.94)

Abbreviations: MNSIq, Michigan neuropathy screening questionnaire; DPN, diabetic polyneuropathy; DN4, Douleur Neuropathique en 4

questions; OR, odds ratio; CI, confidence interval. <sup>a</sup>Model 1: Adjusted for age, sex, diabetes duration, BMI, and DPN or painful DPN,

respectively. <sup>b</sup>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.

\*P-value < 0.05, \*\*P-value<0.001

## Figure legends

**Figure 1:** Flowchart of study population.

Abbreviations: DD2, Danish Centre for strategic research in type 2 diabetes; MNSIq:

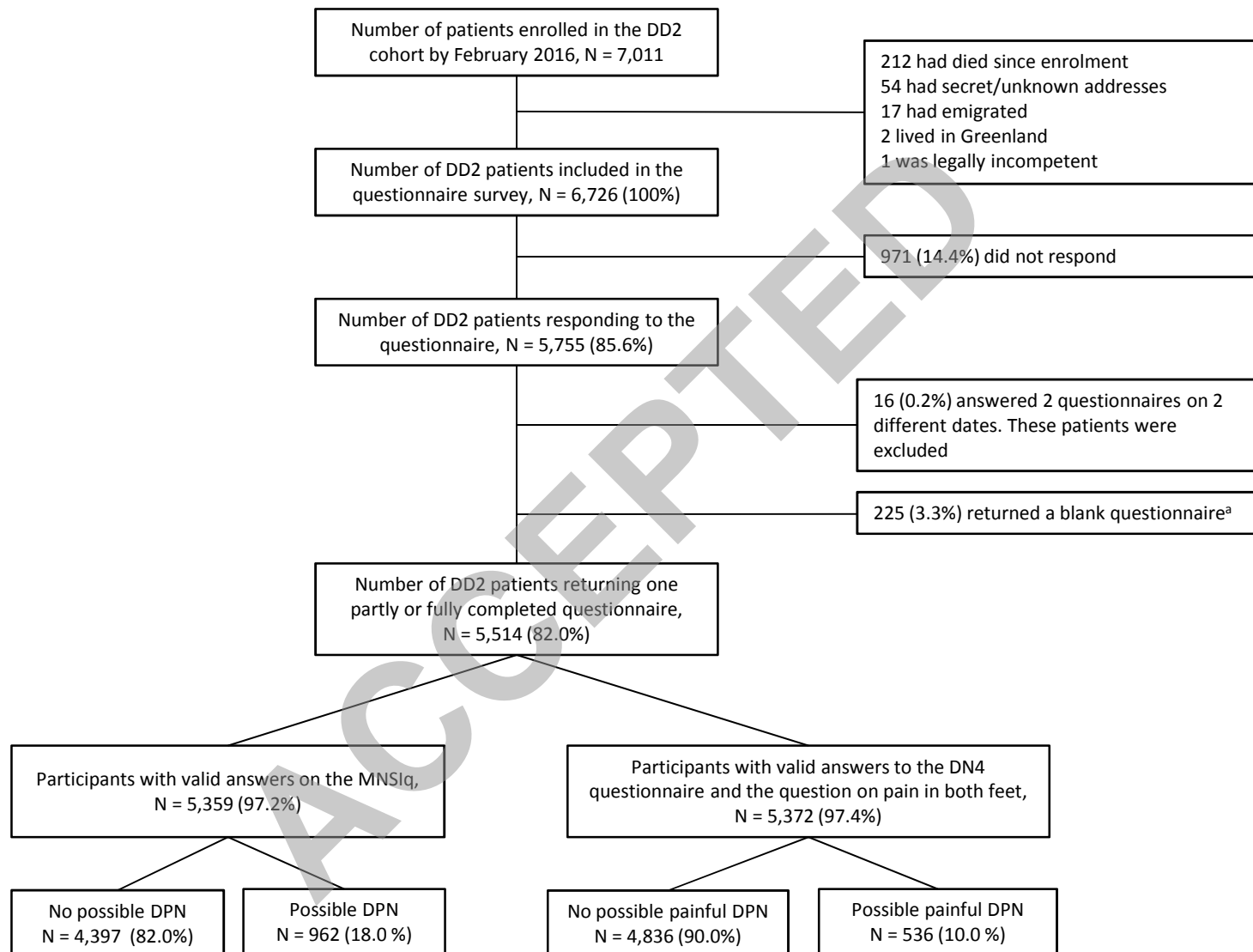
Michigan Neuropathy Screening Instrument questionnaire, DN4: Douleur Neuropathique en 4 questions.

<sup>a</sup>Reason for non-participation: No reason provided: 89 (39.6%), No surplus energy because of other comorbidity: 18 (8.0%), No surplus energy because of death/illness among near relative: 3 (1.3%), Dementia and other conditions hindering adequate answers to the questionnaire: 21 (9.3%), Too busy/no free time: 4 (1.8%), Well-regulated/solely diet-treated thus feeling the questionnaire is not relevant: 25 (11.1%), Mail delivery not possible (invalid address, full or locked mailbox): 31 (13.8%), Died in the time period February to end of questionnaire survey: 9 (4.0%), Other single reasons: 25 (11.1%).

**Figure 2:** Possible DPN and possible painful DPN definitions.

Abbreviations: MNSIq: Michigan Neuropathy Screening Instrument questionnaire, DN4: Douleur Neuropathique en 4 questions.

The numbers in the figure corresponds to the distribution of patients in the cohort of patients with available data on the criteria for both possible DPN and painful DPN (N=5,249). The numbers are evident from Table 2.



**MNSIq  $\geq 4$**

		$\div$	+	Total
Pain in both feet + DN4 $\geq 3$	$\div$	4181	552	4733
	+	130	386	516 Painful DPN
Total		4311	938 DPN	5249