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Nicotine dependence and the International Association for the Study of Pain neuropathic pain grade in patients with chronic low back pain and radicular pain: is there an association?

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Background: This study investigated whether current smoking and a higher nicotine dependency were associated with chronic low back pain (LBP), lumbar related leg pain (sciatica) and/or radicular neuropathic pain.
Methods: A cross-sectional study was conducted on 150 patients (mean age, 60.1 ± 13.1 yr). Demographic data, the International Association for the Study of Pain (IASP) neuropathic pain grade, STarT Back tool, and the Fagerström test were completed. A control group (n = 50) was recruited.
Results: There was a significant difference between current smokers and non-smokers in the chronic LBP group in the mean pain score (P = 0.025), total STarT Back score (P = 0.015), worst pain location (P = 0.020), most distal pain radiation (P = 0.042), and in the IASP neuropathic pain grade (P = 0.026). There was a significant difference in the mean Fagerström score between the four IASP neuropathic pain grades (P = 0.005). Current smoking yielded an odds ratio (OR) of 3.071 (P = 0.011) for developing chronic LBP and sciatica, and an OR of 4.028 (P = 0.002) for obtaining an IASP "definite/probable" neuropathic pain grade, for both cohorts. The likelihood for chronic LBP and sciatica increased by 40.9% (P = 0.007), while the likelihood for an IASP neuropathic grade of "definite/probable" increased by 50.8% (P = 0.002), for both cohorts, for every one unit increase in the Fagerström score.
Conclusions: A current smoking status and higher nicotine dependence increase the odds for chronic LBP, sciatica and radicular neuropathic pain.

Key Words: Chronic Pain; Cross-Sectional Studies; Low Back Pain; Neuralgia; Nicotine; Non-Smokers; Radiculopathy; Smoking; Tobacco Use Disorder.

INTRODUCTION

In the last three decades low back pain was globally the highest-ranking cause of disability [1]. Most patients with acute low back pain recover within six weeks. Approximately 5%-10% of patients with low back pain experience persistent symptoms lasting more than the expected recovery time [2]. Lumbar radiculopathies are the most

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frequently encountered neuropathic pain condition [3], the latter being defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" by the International Association for the Study of Pain (IASP) [4]. Lumbar radiculopathies are considered to be mainly of a neuropathic nature [5], hence their higher disability and chronification, compared to axial low back pain, which is thought to arise primarily due to nociceptive pain [6]. This is clinically evident by the refractoriness of neuropathic pain to treatment, including strong analgesics [7].

Multiple organ systems are adversely affected by cigarette smoking, including an increased risk for low back pain [8,9], sciatica [10] and development of various peripheral neuropathies [11-14]. The latter are a prerequisite for the development of neuropathic pain [3]. Smokers tend to report higher pain intensity, require more analgesics, and their pain impacts more negatively on their lives, compared to non-smokers [15]. Çelik et al. [16] evaluated nicotine dependence using the Fagerström Test for Nicotine Dependence and neuropathic pain using the Douleur Neuropathique 4 (DN4) questionnaire. They found a significant correlation between the number of packets of cigarettes smoked per year and a positive DN4 score. However, this study did not report the pathoanatomical etiology leading to neuropathic pain; hence the analysis of specific patient subgroups, which could be more susceptible to the negative impact of smoking on neuropathic pain could not be carried out.

The updated IASP neuropathic pain grading system states that the use of neuropathic pain questionnaires, like the DN4, can lead only to a "possible" neuropathic pain grade [17], but the sensory examination of the DN4 can potentially increase a "possible" neuropathic pain grade to a "probable" one. However, the DN4 includes only two sensory modalities, while IASP grading system bedside sensory testing advocates testing for at least five sensory modalities. The psychometric properties of the DN4 vary with the pain etiology, which influenced the validity of results, for example in post lumbar surgery, the DN4 obtained a sensitivity of 62% and a specificity of 44% [18] while in low back pain it obtained a sensitivity of 80% and a specificity of 92% [19]. In their study, Çelik et al. [16] did not assess for any psychological factors which have been found have a crucial role in both neuropathic pain perpetuation and smoking habits [15]. Furthermore, this study did not mention if ex-smokers were included and adjusted for in their results.

This paper aims to improve on Çelik et al. [16]. It is a cross-sectional study to investigate the association between patients with chronic low back pain with nicotine addiction and daily cigarette consumption. The patient group includes a subset of patients suffering from radicular neuropathic pain. The study's objectives were to evaluate the following null hypotheses:

1. A higher Fagerström score did not increase the risk for chronic low back pain, sciatica, or chronic radicular neuropathic pain.
2. Current smokers do not have an increased risk for chronic low back pain, sciatica, or chronic radicular neuropathic pain compared to lifetime non-smokers.
3. Current smokers do not have higher pain intensity and STarT Back scores compared to lifetime non-smokers.
4. Male smokers do not have an increased incidence of chronic low back pain, lumbar related leg pain (sciatica), or chronic radicular neuropathic pain compared to female smokers.

MATERIALS AND METHODS

1. Study design and setting

Ethical approval for this study was obtained from the research committee at a local rehabilitation hospital in Malta, Europe (04/03/2019). During their first session patients referred for chronic low back pain, sciatica, or chronic radicular neuropathic pain, were approached by a third party, independent of the study. Written informed consent was obtained from all study participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted between March and November 2019 in a Musculoskeletal Physiotherapy Outpatient Clinic. The term chronic low back pain referred to pain in the region between the lower thoracic margin and the horizontal gluteal folds extending beyond three months [20]. Pain distal to the gluteal fold was considered as pain in the lower limb. Radicular neuropathic pain referred to neuropathic pain according to the IASP in a radicular pattern [4]. Lumbar related leg pain (sciatica) referred to any pain radiation into the leg, be it of nociceptive or neuropathic origins.

This study was conducted at the local rehabilitation hospital's Musculoskeletal Physiotherapy Outpatients Department. The final sample size, hereunder referred to as the "chronic pain group" was determined by the number of referrals recruited by the clinic and examined by the principal investigator (ES) during the eight-month data collection period (March to November 2019). A control group free from chronic low back pain and/or sciatica

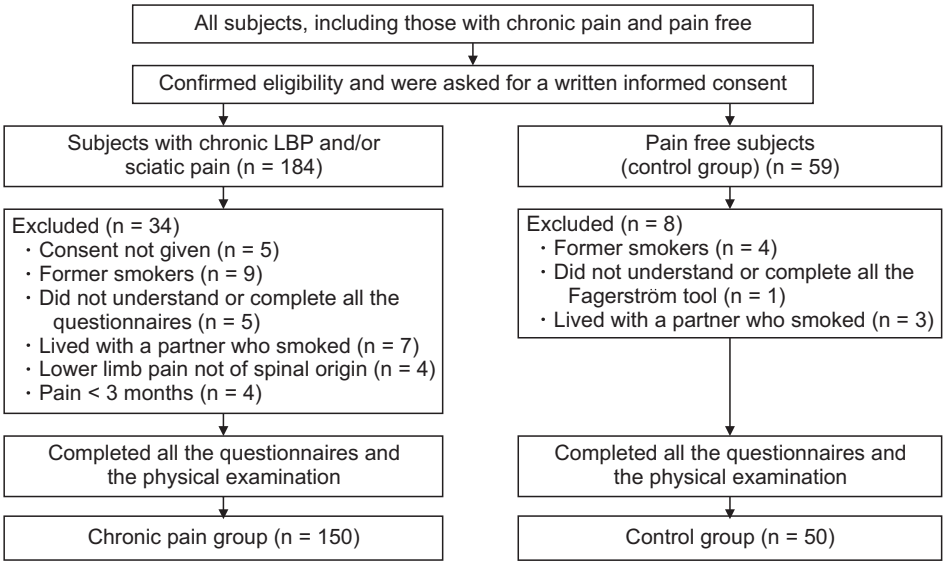

Fig. 1. Flow diagram of the participants in the study. LBP: low back pain.

for the past year was recruited (n = 50, **Fig. 1**). The control group was adequately age- and sex-matched to the chronic pain group. The patients included in this study form part of an ongoing observational study evaluating the management and outcome of patients with chronic spinal pain attending the Musculoskeletal Physiotherapy Outpatients Department at a local rehabilitation hospital in Malta. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was used throughout this paper [21].

2. Participants

Subjects of both sexes were included in the chronic pain group if they fulfilled all of the following criteria: 1) above 18 years of age; 2) referred to the Musculoskeletal Physiotherapy Outpatient's facilities for chronic low back and/or sciatica; 3) with pain duration of ≥ 3 months; 4) who were either lifetime non-smokers or current smokers.

Subjects were excluded from taking part in this study if they were unable to complete all the questionnaires, suffered from psychosis or severe depression, cognitive impairment or intellectual disability, substance abuse or severe alcoholism, known diabetic neuropathy or had been diagnosed with length-dependent polyneuropathy, had pain of unknown origin, visceral pain, complex regional pain syndrome, headaches, had severe musculoskeletal pain, other than chronic low back pain and/or sciatica, and significant comorbidities. Subjects who lived with a partner/relative who smoked were also excluded from this study due to passive smoking. Ex-smokers were excluded as the harmful effects of smoking can last for up to 30 years. Thus, smoking cessation can reduce but not eliminate the risk of the onset of low back pain [10]. Therefore, it was decided to remove participants who were former smokers. The control group needed to reach the same criteria, except they must not have complained of chronic low back pain and sciatica over the past year.

3. Patient-reported outcome measures

1) Demographics

Demographic data on sex, age, occupation (housewife/man, light work or manual work), and pain chronicity were recorded for the chronic pain group.

2) Pain assessment

Three separate numerical rating scales (NRS) for lowest, mean, and highest pain intensity were used. Each of the three individual NRS had the anchors "no pain" and "worst imaginable pain (0-10)." The expected mean age from clinical experience was expected between 50 and 60 years of age therefore the NRS was preferred over the visual analogue scale, since the latter is associated with a higher frequency of incomplete scores with an increase in the participants' age [22]. The worst pain location was classified as either in the lower limb or in the low back. The most distal pain radiation was categorized into five sections: the low back, thigh and/or knee, upper calf, lower calf and/or ankle, and in the foot [23].

The drug history was self-reported, as it is not listed in the referral form. Analgesic drugs were categorized into the five main classes: opioids, antidepressants, gabapentinoids, non-steroidal anti-inflammatory drugs, and acetaminophen. From this data, the current number of oral analgesic drug classes being used, irrespective of dosage

and frequency, was recorded. Patients using combination analgesic formulations were grouped together.

The IASP neuropathic pain grading system [17] was used to systematically grade the probability of the presence of neuropathic pain in the chronic pain group. With regards to the pain being in a neuroanatomically plausible distribution, the various dermatome charts were consulted to try to allocate the painful area to a specific spinal level. In subjects who could not be easily assigned to a specific spinal level *via* the dermatome charts (*e.g.*, pain radiated to either aspect of the calf only), this did not hinder these participants' progression in the IASP grading system, considering that dermatomes are malleable physiological constructs and can vary substantially [24].

The first author (ES) completed a bedside-derived quantitative sensory examination in the most painful area identified by the participants [17]. The examination procedure was adopted from the study by Hasvik et al. [23]. The examination included the response to static pressure, dynamic light tactile touch, pinprick, vibration, windup, warm and cold, and sensory threshold to punctate tactile stimulation. Initially, a demonstration was performed on the patients' arm, followed by testing in the most painful area. The latter was compared to a homologous contralateral reference site. Two repetitions of each test procedure were done.

Dynamic light tactile touch was assessed with two strokes over 2-3 cm using a SENSELab™ Brush-05 (Somedic SenseLab AB, Sösdala, Sweden). Static pressure was assessed using the blunt side of the brush with just enough pressure to indent the skin. Pinprick was assessed using a 5.1 g Semmes-Weinstein type monofilament (Baseline® Tactile Monofilaments™; Fabrication Enterprises Inc., White Plains, NY, USA). Wind up (temporal summation) was assessed by using the same 5.1 g Semmes-Weinstein type monofilament and applied at 2 Hz for 30 seconds. Cold and warm temperatures were assessed by using two test tubes, each one filled with water at 25°C or 40°C, which was rolled slowly with minimal pressure. Semmes-Weinstein type monofilaments ranging from 0.07 g to 300.0 g (Baseline® Tactile Monofilaments™) were used to test for the sensory detection threshold, where the value corresponding to the monofilament force was used. The lowest detected monofilament strength was recorded. The vibration detection threshold was evaluated using a Rydel-Seiffer 128 Hz graduated (8/8 scale) tuning fork (Baseline® Rydel-Seiffer; Fabrication Enterprises Inc.). The patient's instant report when the vibration sensation disappeared marked the lowest vibration threshold, with the value corresponding to the tuning fork 8/8 scale. Vibration testing was first conducted on the painful side and then on a bony prominence if the two did not coincide. The choice of the bony prominence was based on the dermatome supplied by the nerve root suspected to be causing the pain and the sensory changes (*e.g.*, the medial aspect of the hallux in the case where L5 radiculopathy is suspected). The mean value of the two repetitions was recorded [23].

The patient's subjective score was used in case of the loss to static or dynamic light tactile pressure and touch, pinprick, vibration, warm and cold. Scoring was done as no sensation, decreased, normal, or increased sensation. A reduced or complete loss of sensation was classified as a negative sensory sign. In cases where the pain was elicited by the test modality, a NRS (0-10) was administered to the patient. During the examination for wind up, the presence of pain escalation during the testing procedure was considered at par to hypoesthesia to the other sensory modalities. In case of an inconsistent result between the two test repetitions, the result for the specific testing modality was scored as a normal response. In the absence of negative sensory signs in the most painful area, the sensory examination was repeated in another painful area within the same neuroanatomically plausible distribution (usually within the lower limb, especially in cases where the worst pain location was the low back).

The patient interview and clinical assessment were used to classify patients according to the IASP neuropathic pain special interest group grading system into "unlikely," "possible," "probable," and "definite" neuropathic pain [17] (**Fig. 2**). A grade of "definite" neuropathic pain was based on an magnetic resonance imaging (MRI) scan showing a disc lesion or a stenotic lumbar level (including canal, foraminal, and lateral recess stenosis) corresponding to the clinical signs and symptoms. In subjects graded with "possible" neuropathic pain, and where the sensory signs were difficult to demonstrate but the MRI confirmed the nature of the lesion, the level of "probable" neuropathic pain was used, as stated in the legend of **Fig. 2** of Finnerup et al. [17]. In those patients who were not graded as having "probable" neuropathic pain by this approach, the methodology adopted by Hasvik et al. [23] was used to classify patients with chronic low back pain according to the IASP neuropathic pain grading system [17]. Henceforth, the patient data were manually reviewed by three of the authors (ES, VM, SLM) for sensory abnormalities outside of the most painful area.

Owing to the reduced probability that neuropathic pain arises from positive sensory signs [17], distinct signs from other modalities and direct evidence for radiculopathies from strictly neuroanatomically plausible distributions, *e.g.*, corresponding tendon reflex or myotomal muscle weakness, were necessary to grade the patient with "probable" NP (**Fig. 2**). This approach is justified, since spinal nerves are mixed sensory and motor nerves, and the pres-

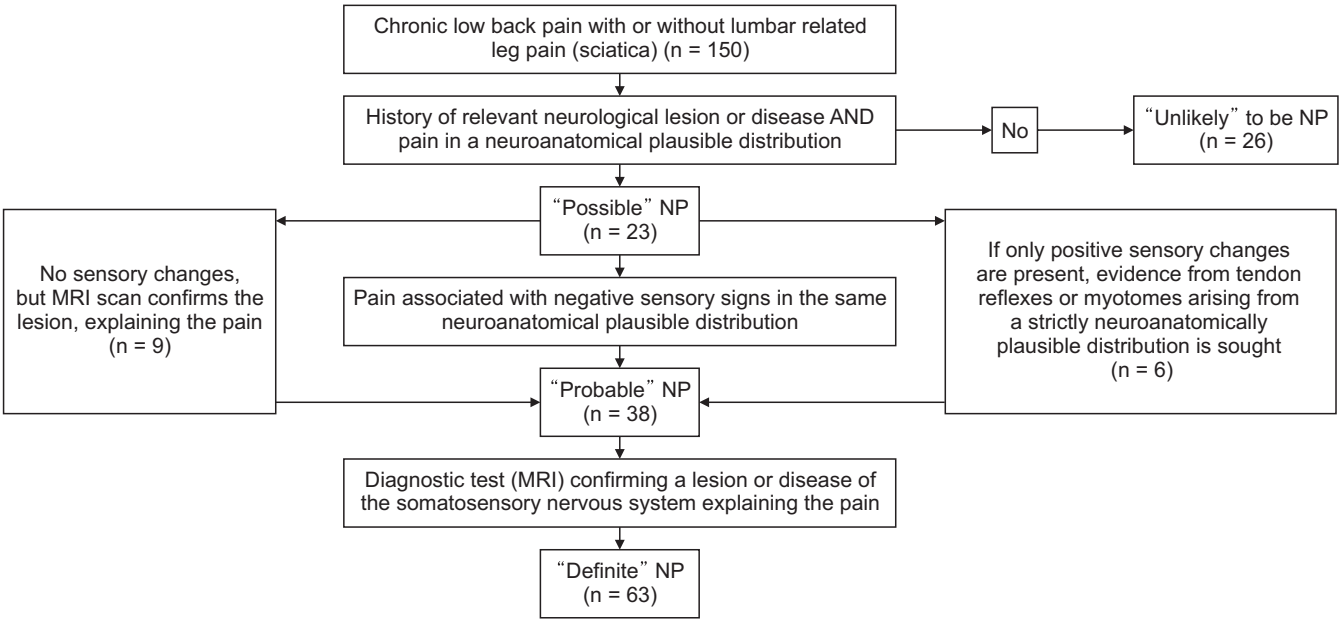

Fig. 2. Flow diagram of the chronic pain subjects' International Association for the Study of Pain neuropathic pain (NP) grading. MRI: magnetic resonance imaging.

ence of negative motor signs portray a neural conduction block, which is the prerequisite for neuropathic pain [25].

3) Smoking

The Fagerström Test for Nicotine Dependence quantifies the nicotine addiction risk [26]. This test consists of six questions with a possible total score ranging from 0-10. A score of 8-10 indicates very high dependence, 6-7 high dependency, 5 medium dependence, 3-4 low dependence, 0-2 signifies minimal nicotine dependence. Item number 4 of the Fagerström Test measures the number of cigarettes smoked daily grouped into four categories. A higher cigarette consumption on this variable contributes to a higher total score on the questionnaire. The number of cigarettes smoked daily (item number 4) and the overall Fagerström score, were included separately in the analysis.

4) Outcome predictor

The STarT Back tool measures an overview of treatment-modifiable domains, including disability, pain radiation, and psychological factors, all of which are amenable to treatment [27]. The total score ranges from 0 to 9, and it is scored by adding up the positive responses. The STarT Back distress subscale score ranges from 0 to 5, and is composed of a question each assessing fear, catastrophizing, depression, anxiety, and bothersomeness. This subscale can replace the use of multiple unidimensional psychological tools as a primary screening tool for psychological issues. The individual items in the distress subscale were related to full length unidimensional psychological questionnaires in a secondary care physiotherapy outpatient department [28]. The total STarT Back score, but even more the distress subscore, predicted pain severity [29]. A higher psychosocial score was related to a higher risk of pain. The STarT Back score had a correlation of 0.4 with disability and fear of movement [30]. The overall STarT Back scores ($\beta = 0.22$) and STarT Back psychosocial scores ($\beta = 0.25$) predicted disability at 6 months [31]. The distress subscore and the total STarT Back score were included as separate variables in the analysis.

To minimize bias by the principal investigator, the STarT Back tool and the Fagerström Test were administered at the end of the clinical assessment. To obtain single blinding, the participants were briefed about the aims of the study but not about the content of the data collection. The participants were instructed to fill up the questionnaires independently on paper. If they encountered any difficulties, the assessor was able to help them.

5) Control group

All participants within the control group had to self-report the above measures except those related to pain.

4. Statistical methods

All questionnaires were entered into the SPSS ver. 25.0 statistics package (IBM Co., Armonk, NY, USA), with which

Table 1. Mean Patient Characteristics Scores Grouped by Smoking Status

Patient characteristic	Smoker (n = 50)	Non-smoker (n = 100)	*P* value
Age (yr)	57.2 ± 11.9	61.6 ± 13.6	0.055
Lowest pain score (NRS) (range 0-10)	2.2 ± 2.2	2.1 ± 2.2	0.678
Average pain score (NRS) (range 0-10)	5.9 ± 2.3	4.9 ± 2.6	0.025
Highest pain score (NRS) (range 0-10)	8.8 ± 1.6	8.4 ± 1.6	0.178
Pain chronicity (yr)	4.5 ± 5.8	5.5 ± 8.1	0.415
Current number of analgesic drug classes consumed	1.2 ± 1.1	1.1 ± 1.0	0.528
Fagerström score (range 0-10)	4.2 ± 2.2	0.0 ± 0.0	< 0.001
STarT Back distress score (range 0-5)	2.7 ± 1.3	2.3 ± 1.5	0.068
STarT Back total score (range 0-9)	5.3 ± 1.9	4.4 ± 2.1	0.015

Values are presented as mean ± standard deviation.
NRS: numerical rating scale.

Table 2. Association Between Worst Pain Location and the Current Smoking Status

Variable	Smoking status		Total
	Yes	No	
Worst pain location			
Lower back	16 (32.0)	52 (52.0)	68 (45.3)
Lower limb	34 (68.0)	48 (48.0)	82 (54.7)
Total	50 (100.0)	100 (100.0)	150 (100.0)

Values are presented as number (%).
$X^2(1) = 5.380$, $P = 0.020$.

statistical analysis was also carried out. Questionnaires with missing data were excluded from the analysis. The participants demographic and physiological characteristics were presented descriptively using mean and ranges. Testing for normal distribution were carried out on continuous data using the Shapiro–Wilk test. If data was not normally distributed, the non-parametric equivalent were used. Statistical analysis was carried out with significance being considered at a 0.05 level. An independent sample *t*-test was used to compare differences in mean score for continuous variables (age, chronicity, lowest NRS, average NRS, highest NRS, current number of analgesic drugs consumed, Fagerström score, STarT Back distress subscore, and total STarT Back score). Difference in mean were checked by sex (male, female), smoking status (smoker, non-smoker), and frequency of cigarettes smoked (10 or less, more than 20).

The One-Way ANOVA test will be used to compare the mean Fagerström scores, ranging from 0 to 10, between the four neuropathic pain grades. The chi-square test will be used to test for association between two categorical variables. This included smoking status (yes, no), sex (male, female), worst pain location (lower back, lower limb), most distal pain radiation (lower back, knee, upper calf, lower calf/ankle, foot).

The difference in the two proportion z-test was used to compare the percentage of patients whose worst pain was located in the lower limb between males and females, and between smokers of 10 cigarettes or less and smokers of more than 20 cigarettes.

Multinomial logistic regression analysis was used to relate a categorical dependent variable (IASP "definite/probable" grade) to all possible predictors if an initial statistical correlation was found. Odds ratios (OR) with 95% confidence interval (CI) will be computed.

RESULTS

1. Sample description

Fig. 1 and **2** provide a flow diagram of the participants enrolled in this study. **Tables 1**-**4** show the baseline demographic and descriptive data of the subjects within the chronic pain group. **Table 4** clearly shows a larger percentage of smokers (56.0%) than lifetime non-smokers (35.0%) who have an IASP "definite" neuropathic pain grade. Conversely, there is a more significant percentage ($P = 0.026$) of lifetime non-smokers (23.0%) than smokers (6.0%) who have an IASP "unlikely" neuropathic pain grade. There was a significant association between smoking status and occupation ($P = 0.048$), however occupation was not significantly associated with the IASP neuropathic pain grading ($P = 0.095$). The control group was adequately age ($P = 0.874$) and sex ($P = 0.934$) matched. However, there was a statistically significant difference ($P = 0.009$) in the number of current smokers between the chronic pain group (33.3%) and the control group (14.0%) (**Appendix**).

2. Comparison of current smokers and lifetime non-smokers within the chronic pain group

There was a significant difference in the mean pain score ($P = 0.025$), mean Fagerström score ($P < 0.001$) and mean total

Table 3. Association Between Most Distal Pain Radiation in the Lower Limb and Smoking Status

Variable	Smoking status		Total
	Yes	No	
Most distal pain radiation			
Lower back	5 (10.0)	31 (31.0)	36 (24.0)
Thigh and knee	6 (12.0)	16 (16.0)	22 (14.7)
Upper calf	4 (8.0)	6 (6.0)	10 (6.7)
Lower calf and ankle	10 (20.0)	14 (14.0)	24 (16.0)
Foot	25 (50.0)	33 (33.0)	58 (38.7)
Total	50 (100.0)	100 (100.0)	150 (100.0)

Values are presented as number (%).
$X^2(4) = 9.930$, $P = 0.042$.

Table 4. Association Between IASP Neuropathic Pain Grades and Smoking Status

Variable	Smoking status		Total
	Yes	No	
IASP neuropathic pain grade			
Definite	28 (56.0)	35 (35.0)	63 (42.0)
Probable	12 (24.0)	26 (26.0)	38 (25.3)
Possible	7 (14.0)	16 (16.0)	23 (15.3)
Unlikely	3 (6.0)	23 (23.0)	26 (17.3)
Total	50 (100.0)	100 (100.0)	150 (100.0)

Values are presented as number (%).
$X^2(3) = 9.197$, $P = 0.026$.
IASP: International Association for the Study of Pain.

STarT Back score ($P = 0.015$) between current smokers and lifetime non-smokers. There were no significant differences between the two groups in the other variables (**Table 1**). The difference between the two groups in the mean age (yr) nearly achieved statistical significance ($P = 0.055$). There was no statistically significant difference ($P = 0.102$) between male smokers (45.6%) and female smokers (54.4%) (**Appendix - Sex**).

1) Worst pain location and radiation

A significantly larger percentage of the current smokers (68.0%) reported the lower limb as their worst pain location, compared to non-smokers (48.0%) ($P = 0.020$) (**Table 2**). There was a significantly ($P = 0.042$) larger proportion of lifetime non-smokers (31.0%) which reported pain localized to the low back, while a more significant percentage of current smokers (50.0%) reported pain radiation into the foot (**Table 3**).

2) Relationship between IASP neuropathic pain grade and patient characteristics

The multinomial logistic regression model (**Appendix - Multinomial logistic model**) which relates the IASP neuropathic pain grade to eleven predictors, adjusted for age, sex, average pain intensity, and psychological distress, identifies four significant predictors, where the most distal pain radiation is the best predictor of neuropathic pain ($P < 0.001$), followed by the STarT Back score ($P < 0.001$), sex ($P = 0.001$), and worst pain location ($P = 0.035$). These four predictors (sex, worst pain location, most distal pain radiation, total STarT Back score) explain 67.7% of the total variation in the IASP neuropathic pain grades (Nagelkerke Pseudo R square value = 0.677).

3) Current smoking and sex

More male smokers (61.5%) were graded with a "definite" neuropathic pain grade compared to females (50.0%). However, this difference is not significant ($P = 0.728$). The mean patient characteristic scores between male and female smokers were not significant (**Appendix - Sex**).

4) Dose-response effect

Fig. 3 shows that the mean Fagerström score increases significantly with a correspondingly higher IASP neuropathic pain grade ($P < 0.005$). The mean Fagerström score increases from 0.42 ± 1.50 for subjects with an "unlikely" neuropathic pain grade to 2.17 ± 2.82 in subjects graded having a "definite" neuropathic pain grade (**Appendix - Dose-response effect**). The mean patient characteristic scores between heavy smokers (≥ 21 cigarettes daily) and light smokers (0-10 cigarettes daily) were compared (**Table 5**). There was a statistically significant difference between the two groups in the mean Fagerström score ($P < 0.001$), STarT Back distress subscore ($P = 0.001$), the total STarT Back score ($P < 0.001$), and in the percentage of subjects classified as having "definite" neuropathic pain between light smokers (35.7%) and heavy smokers (81.3%) ($P = 0.011$).

3. Risk factors for the presence of chronic low back pain and radicular neuropathic pain

1) Sex

The male sex was not significantly associated with having chronic low back pain, including lumbar related leg pain (sciatica) ($P = 0.934$; 95% CI, 0.537-1.965) or with having chronic radicular neuropathic pain (IASP "definite/probable" grade) ($P = 0.227$; 95% CI, 0.769-3.022), rather than being pain-free (**Appendix - Risk factors**).

2) Age

An increase in age was not significantly associated with having chronic low back pain, including lumbar related leg pain (sciatica) (P = 0.873; 95% CI, 0.977-1.027) or with having chronic radicular neuropathic pain (IASP "definite/probable" grade) (P = 0.824; 95% CI, 0.977-1.030), rather than being pain-free (**Appendix - Risk factors**).

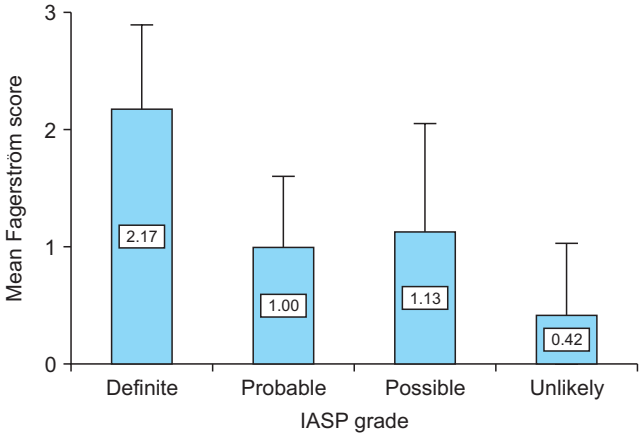

Fig. 3. The 95% confidence intervals for the mean Fagerström score by International Association for the Study of Pain (IASP) neuropathic pain grade category.

3) Current smoker status

Compared to a lifetime non-smoker, a current smoking status yielded an OR of 3.071 (P = 0.011; 95% CI, 1.289-7.316) for the presence of chronic low back pain, including lumbar related leg pain (sciatica), rather than being pain-free. The OR that a current smoker has chronic radicular neuropathic pain (IASP "definite/probable" grade) rather than being pain-free, is 4.028 times that of a lifetime non-smoker (P = 0.002; 95% CI, 1.650-9.837) (**Appendix - Risk factors**).

4) Nicotine dependence - Fagerström score

Every 1 unit increase in the Fagerström score increases the odds that a patient has chronic low back pain, including lumbar related leg pain (sciatica) by 40.9% (P = 0.007; 95% CI, 1.096-1.812), rather than being pain-free. Every 1 unit increase in the Fagerström score increases the odds that a patient has chronic radicular neuropathic pain (IASP "definite/probable" grade) by 50.8% (P = 0.002; 95% CI, 1.160-1.961), rather than being pain-free (**Appendix - Risk factors**).

DISCUSSION

The results of this cross-sectional study support the hy-

Table 5. Dose-response Effect of Daily Cigarette Consumption

Patient characteristic	0-10 cigarettes daily (n = 14)	≥ 21 cigarettes daily (n = 16)	P value
Fagerström score (range 0-10)	1.71 ± 1.14	6.25 ± 1.48	< 0.001
Age (yr)	55.0 ± 14.35	58.5 ± 9.48	0.432
Chronicity (yr)	3.15 ± 2.92	6.61 ± 8.44	0.156
Lowest pain score (NRS) (range 0-10)	2.6 ± 2.6	2.5 ± 2.3	0.938
Average pain score (NRS) (range 0-10)	6.3 ± 2.6	6.3 ± 2.6	0.984
Highest pain score (NRS) (range 0-10)	8.9 ± 1.8	9.1 ± 1.4	0.652
STarT Back distress subscore (range 0-5)	2.21 ± 0.89	3.56 ± 1.15	0.001
STarT Back total score (range 0-9)	4.14 ± 1.66	6.65 ± 1.36	< 0.001
Lower limb as worst pain location	9 (64.3)	12 (75.0)	0.522
IASP neuropathic pain grade			
Unlikely	1 (7.1)	0 (0.0)	0.276
Possible	2 (14.3)	1 (6.3)	0.465
Probable	6 (42.9)	2 (12.5)	0.060
Definite	5 (35.7)	13 (81.3)	0.011
Most distal pain radiation			
Low back only	1 (7.1)	2 (12.5)	0.624
Till knee level	2 (14.3)	0 (0.0)	0.119
Upper calf	1 (7.1)	1 (6.3)	0.920
Lower calf or ankle	1 (7.1)	4 (25.0)	0.190
Foot	9 (64.3)	9 (56.3)	0.653

Values are presented as mean ± standard deviation or number (%).
NRS: numerical rating scale, IASP: International Association for the Study of Pain.

pothesis that a higher Fagerström score and a current smoking status, both independently increase the risk for chronic low back pain and radicular neuropathic pain. Current smokers have higher mean pain intensity and higher total STarT Back scores compared to lifetime non-smokers. However, this study failed to identify sex differences in the outcomes. A recent study by Khan et al. [15] found that, compared to non-smokers, current smokers had a higher pain intensity while certain domains of the STarT Back tool (pain interference, physical functioning, depression, and anxiety; all $P < 0.001$) were also more significantly prevalent in this population when assessed using a respective full length questionnaire.

1. Smoking prevalence in subjects with chronic low back pain

The prevalence of tobacco smokers in the European Region population is 28% while in the US it stands at 17% [32]. In chronic pain sufferers the percentage of smokers is higher, ranging from 28.3%-82.2% [33-36]. Our study found a smoking prevalence of 33.3% amongst subjects with chronic pain, this being slightly higher than the European Region standard. In the control group (pain free) only 14% were smokers. This reflects the association between chronic pain and smoking, especially patients suffering from chronic neuropathic pain, who are more prone to be dependent on nicotine and hence consume more cigarettes daily.

2. Nicotine addiction

To the authors' best knowledge, there is, as yet, no paper evaluating nicotine dependence in chronic low back pain subjects utilizing the IASP neuropathic pain grading system, so direct comparison with other studies is limited. Probably the study by Çelik et al. [16] is the most similar to ours, since it used the DN4 and the Fagerström score. Their study concluded that patients with neuropathic pain (positive DN4 score) consumed more packets of cigarettes per year compared to those who obtained a negative DN4 score ($P < 0.05$).

Similarly, we found that current smokers who had a higher Fagerström score ($P = 0.005$) or consumed a higher number of cigarettes ($P = 0.011$) had a higher chance of being diagnosed with chronic neuropathic pain. In Çelik et al. [16], each standard deviation increase in the Fagerström score (2.7) yielded an OR of 1.29 (95% CI, 1.14-1.46). However, our study obtained an OR of 1.409 (95% CI, 1.096-1.812) for chronic low back pain and sciatica and an OR of 1.508 (95% CI, 1.160-1.961) for chronic radicular neuropathic pain for every 1 unit increase in the Fagerström score. Therefore, our study portrays a much higher OR, primarily due to the way results are presented (standard deviation increase *vs.* 1 unit increase in Fagerström score) and possibly due to the differences in the populations being investigated. Çelik et al. [16] did not analyze their OR in comparison to a smoking-free control group, but their OR were compared to subjects having a negative score on the DN4. These participants could still be experiencing nociceptive pain which is captured with the IASP neuropathic pain grading system, but not by the methodology adopted by Çelik et al. [16].

Other studies [37-39] examined nicotine dependence and low back pain. However their results could not be compared directly to ours since they used different methods to examine nicotine dependence, namely, the Diagnostic Interview Schedule (DIS-III-R) in Shaw et al. [38] and the World Health Organization's Composite International Diagnostic Interview (WHO-CIDI) in Zvolensky et al. [39]. Shemory et al. [37] failed to mention which method was used to asses nicotine dependency. Furthermore, none of these studies examined the neuropathic pain component of low back pain, but rather two papers [38,39] looked explicitly at chronic low back pain, while Shemory et al. [37] did not mention if their paper was evaluating either acute or chronic low back pain. These four papers [37-40] concluded that nicotine dependence provided higher ORs (range, 1.95-4.49) compared to this study (1.508). However, the different diagnostic criteria for nicotine dependence and the potentially diverse populations of subjects with low back pain can significantly alter the ORs.

3. Smoking status

Various systematic reviews [8-10,40-43] have explored the relationship between low back pain, sciatica, and smoking. However, these studies do not adhere to the same concept underlying sciatica and hence differ in their definitions of it. Furthermore, these studies do not mention if neuropathic pain was assessed. A systematic review by Cook et al. [10] found "inconsistent operational definitions" underlying sciatica, raging from referred pain below the knee, or a definitive or non-definitive area in the lower limb, to a medical diagnosis during hospital admission. Such a spectrum of definitions will impact the inclusion and exclusion criteria of the respective studies making interpretation of results more difficult. A limitation of the studies mentioned above is that they evaluated smoking status only, and therefore, did not asses for nicotine dependency. This can have stronger implications within a biopsychosocial context. Furthermore, some of these reviews [10,40,42] did not asses the relationship between smoking and chronic sciatica, hence such discrepancies between these studies

and the current one must be considered.

A systematic review by Ferreira et al. [8] (Assessing the Methodological Quality of Systematic Reviews [AMSTAR] grade 6, n = 1,960), assessing twin subjects with chronic low back pain, was identified by an umbrella review [9]. The previous review found an OR of 3.0 (95% CI, 2.8-3.3), which is comparable to this study. However, this review did not differentiate between chronic and acute back pain, and it provided a pooled OR for the most persistent low back pain occurrence. The same umbrella review identified a systematic review by Cook et al. [10] (AMSTAR grade 7, n = 7,701) looking for the risk factors underlying first-time incidence sciatica, which was limited by the lack of diagnostic criteria underlying sciatica. Cook et al. [10] found an OR ranging from 1.5 (95% CI, 1.1-2.1) to 9.6 (95% CI, 1.7-53.0). Our OR for low back and lumbar related leg pain, in which the latter could be interpreted as sciatica, was 3.071 and, while for radicular neuropathic pain, which can also be interpreted as sciatica, was 4.028. Both of our ORs fit within the range of ORs provided [10], but our systematic approach in defining the neuropathic pain grades of sciatica could provide more reproducible and reliable results.

A scoping review by Green et al. [43] identified two systematic reviews [40,41]. Shiri et al. [41] found that current smoking yields an OR of 1.79 (95% CI, 1.27-2.50; n = 31,811) for developing chronic low back pain, while Shiri et al. [40] conducted a systematic review which studied the association of smoking with lumbar radicular pain. However, it did not conduct a meta-analysis of the selected papers, and hence it failed to provide an OR.

A meta-analysis [42] examined the risk of smoking in regards to sciatica. Current smokers had an OR of 1.64 (95% CI, 1.24-2.16; n = 10,853) for lumbar radicular pain, and an OR of 1.35 (95% CI, 1.09-1.68; n = 110,374) for clinically verified sciatica. However, this review did not provide any information on what constituted "clinically verified sciatica" with only brief mentions of nerve root irritation. Yet these can vary in nature, with negative sensory and motor signs carrying a higher diagnostic value towards neuropathic pain [17].

In the current study, both smoking status and the Fagerström score were found to be significantly related to the IASP neuropathic pain grade when analyzed individually. However, in the logistic regression model, these two predictors were not found to be significant when analyzed collectively with other predictors. It is well known that a lone predictor could be rendered a very important contributor in explaining variations in the IASP neuropathic pain grade, but could be rendered unimportant in the presence of other predictors, for example worst pain location, distal pain radiation, and total STarT Back score. The suitability of a predictor in a fitted model often depends on what the other predictors are included with it.

4. Sex

Possibly due to the relatively small sample size, our study could not find a statistically significant association between sex and smoking status (P = 0.102) and a sex subgroup analysis evaluating exclusively current smokers could not establish a significant difference across all the variables being studied. This is similar to most previous studies, yet one study [44] found that only males who were current smokers had a significant prevalence of lumbosacral radicular pain. Likewise, in a 28-year longitudinal study [45] found that male smokers had a hazard ratio (HR) of 2.0 (95% CI, 1.1-3.6) for developing sciatica, while females had an HR of 1.8 (95% CI, 0.8-3.9).

5. Strengths and limitations of the study

The exclusion of former smokers is one of the strengths of this study, since it avoids the introduction of any confounding factors, for example, the length of time participants had stopped smoking and any on-and-off smoking periods. Furthermore, previous smoking can substantially outlast the smoking-free interval [10], thus possibly influencing the results of a study. Hence, a limitation of the current study is its cross-sectional nature and the small sample size.

This study assessed nicotine dependency rather than just exclusively evaluating the smoking status and daily cigarette consumption. Exploration of this potentially treatment-modifiable construct could further unravel the complexity of the biopsychosocial model of chronic spinal pain. There was a high enrollment and completion rate, while the control group and the chronic pain group were sex- and age-matched, therefore the basic demographic differences should not affect the results.

Diagnosing neuropathic pain is essential, as it tends to lower the quality of life to a higher degree compared to nociceptive pain. A strength of the current study was the use of the IASP neuropathic pain grading system to grade the presence of neuropathic pain in chronic low back pain subjects with or without lumbar related leg pain (sciatica). Most of the papers cited [10,11,40,42,43] did not quantify the neuropathic pain component of sciatica, while neuropathic pain questionnaires, such as DN4, yield variable sensitivities and specificities [18,19]. The use of the IASP neuropathic pain grading system is considered a strength of the current study since it offers a valid and reliable tool, making comparison of results between subjects and any future studies possible.

The population of the study was very specific: subjects with chronic low back and/or leg pain. This makes the participants more homogenous, but limits generalization to other back pain presentations *e.g.*, acute or subacute and to other neuropathic pain conditions. This study did not assess how long current smokers have engaged in this activity, which might have been hindered by a significant element of recall bias. A large proportion of subjects (about 75%) in both groups recounted a history of at least 15 years of smoking but fluctuated in the daily consumption of cigarettes. Despite the dose-response analysis carried out in this paper, the temporal aspects of daily cigarette consumption could influence the symptomatology and possibly affect the conclusion of this study. The study group was a consecutive sample of patients referred from the state acute hospital. Subjects who were not keen to engage in physiotherapy could have been missed by this study. This might have introduced selection bias. However, the study group is representative of the clinic caseload.

This study concluded that a higher nicotine dependence, measured by the Fagerström score, increases the risk for chronic low back pain, sciatica and radicular neuropathic pain. Future research, possibly using longitudinal studies, could further investigate this association and possible causation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix

Control group matching

Group		Sex		Total
		Male	Female	
Chronic pain	Count	64	86	150
	Percentage	75.3	74.8	75.0
Pain free	Count	21	29	50
	Percentage	24.7	25.2	25.0
Total	Count	85	115	200
	Percentage	100.0	100.0	100.0

$X^2(1) = 0.007$, $P = 0.934$.

Group	Sample size	Mean age	Standard deviation	Standard error
Chronic pain	150	60.13	13.179	1.076
Pain free	50	59.8	11.622	1.644

$t(198) = 0.159$, $P = 0.874$.

Group		Smoking status		Total
		Yes	No	
Chronic pain	Count	50	100	150
	Percentage	87.7	69.9	75.0
Pain free	Count	7	43	50
	Percentage	12.3	30.1	25.0
Total	Count	57	143	200
	Percentage	100.0	100.0	100.0

$X^2(1) = 6.879$, $P = 0.009$.

Occupation

The association between occupation and smoking status

Occupation		Smoking status		Total
		Yes	No	
Housewife/man	Count	8	30	38
	Percentage	16.0	30.0	25.3
Light work	Count	14	34	48
	Percentage	28.0	34.0	32.0
Manual work	Count	28	36	64
	Percentage	56.0	36.0	42.7
Total	Count	50	100	150
	Percentage	100.0	100.0	100.0

$X^2(2) = 6.0789$, $P = 0.048$.

The association between occupation and IASP neuropathic pain grade

Occupation		IASP neuropathic pain grade				Total
		Unlikely	Possible	Probable	Definite	
Housewife/man	Count	9	8	9	12	38
	Percentage	34.6	34.8	23.7	19.0	25.3
Light work	Count	8	11	12	17	48
	Percentage	30.8	47.8	31.6	27.0	32.0
Manual work	Count	9	4	17	34	64
	Percentage	34.6	17.4	44.7	54.0	42.7
Total	Count	26	23	38	63	150
	Percentage	100.0	100.0	100.0	100.0	100.0

IASP: International Association for the Study of Pain.
$X^2(6) = 10.8$, $P = 0.095$.

Sex

The association between sex and smoking status

Sex		Smoking status		Total
		Yes	No	
Male	Count	26	38	64
	Percentage	52.0	38.0	42.7
Female	Count	24	62	86
	Percentage	48.0	62.0	57.3
Total	Count	50	100	150
	Percentage	100.0	100.0	100.0

$X^2(1) = 2.671$, $P = 0.102$.

IASP neuropathic pain grade in male and female current smokers

IASP neuropathic pain grade		Sex (current smokers)		Total
		Male	Female	
Definite	Count	16	12	28
	Percentage	61.5	50.0	56.0
Probable	Count	5	7	12
	Percentage	19.2	29.2	24.0
Possible	Count	4	3	7
	Percentage	15.4	12.5	14.0
Unlikely	Count	1	2	3
	Percentage	3.8	8.3	6.0
Total	Count	26	24	50
	Percentage	100.0	100.0	100.0

IASP: International Association for the Study of Pain.
$X^2(3) = 1.303$, $P = 0.728$.

Mean patient characteristics scores grouped by male and female smokers

Patient characteristic	Sex (current smokers)				*P* value
	Male (n = 26)		Female (n = 24)		
	Mean	Standard deviation	Mean	Standard deviation	
Fagerström score	4.62	2.43	3.83	1.93	0.212
Age (yr)	55.77	9.56	58.79	14.01	0.375
Chronicity (yr)	4.75	7.02	4.18	4.37	0.734
Current analgesic drug classes consumed	1.00	1.06	1.33	1.09	0.283
Lowest pain score (NRS)	1.96	2.11	2.54	2.30	0.357
Average pain score (NRS)	5.42	2.42	6.46	2.13	0.115
Highest pain score (NRS)	8.42	1.84	9.21	1.22	0.083
STarT Back distress subscore	2.69	1.35	2.75	1.22	0.087
STarT Back total score	5.31	2.22	5.29	1.63	0.971

NRS: numerical rating scale.

Patient characteristic	Sex (current smokers)				*P* value
	Male (n = 26)		Female (n = 24)		
	Frequency	Percentage	Frequency	Percentage	
Worst pain location					
Low back	11	42.3	5	20.8	0.103
Lower limb	15	57.7	19	79.2	0.103
Most distal pain radiation					
Low back	3	11.5	2	8.3	0.704
Till knee level	5	19.2	1	4.2	0.101
Upper calf	3	11.5	1	4.2	0.337
Lower calf/ankle	5	19.2	5	20.8	0.889
Foot	10	38.5	15	62.5	0.089

Multinomial logistic model

Likelihood ratio tests

Effect	Model fitting criteria	Likelihood ratio tests	df	*P* value
	-2 Log Likelihood	Chi-square		
Average pain score (NRS)	223.946	1.174	3	0.759
Pain chronicity (yr)	224.633	1.861	3	0.602
Age (yr)	225.299	2.527	3	0.470
Fagerström score	223.632	0.860	3	0.835
STarT Back distress subscore	229.826	7.054	3	0.070
STarT Back total score	229.881	7.109	3	0.068
Current number of analgesic drug classes consumed	225.638	2.866	3	0.413
Sex	238.343	15.571	3	0.001
Cigarettes per day	225.156	2.384	9	0.984
Worst pain location	233.374	10.602	3	0.014
Most distal pain radiation	282.982	60.210	12	0.000

NRS: numerical rating scale.

Dose-response effect

Mean Fagerström score grouped by IASP neuropathic pain grade category

IASP neuropathic pain grade	Sample size	Mean Fagerström score	Standard deviation	*P* value
Definite	63	2.17	2.820	0.005
Probable	38	1.00	1.816	
Possible	23	1.13	2.117	
Unlikely	26	0.42	1.501	

IASP: International Association for the Study of Pain.

The relationship between daily cigarette consumption and the total Fagerström score

Cigarettes/day	Total Fagerström score									Grand total
	0	1	2	3	4	5	6	7	8	
0-10	2	4	5	2	1					14
11-20			3	2	3	9	2	1		20
21-30			1			2	6	3	1	13
31 or more								1	2	3
Grand total	2	4	9	4	4	11	8	5	3	50

Risk factors for the presence of chronic low back pain and radicular neuropathic pain

Sex

Chronic low back pain	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	1.087	0.215	25.627	1	< 0.001			
Male	0.027	0.331	0.007	1	0.934	1.028	0.537	1.965
Female	0	.	.	0	.	.	.	.

The reference category is: Control group.
CI: confidence interval.

IASP (definite/probable)	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.504	0.235	4.590	1	0.032			
Male	0.422	0.349	1.461	1	0.227	1.525	0.769	3.022
Female	0	.	.	0	.	.	.	.

The reference category is: Control group.
IASP: International Association for the Study of Pain, CI: confidence interval.

Age

Chronic low back pain	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.976	0.782	1.559	1	0.212			
Age	0.002	0.013	0.026	1	0.873	1.002	0.977	1.027

The reference category is: Control group.
CI: confidence interval.

IASP (definite/ probable)	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.521	0.835	0.389	1	0.533			
Age	0.003	0.014	0.050	1	0.824	1.003	0.977	1.030

The reference category is: Control group.
IASP: International Association for the Study of Pain, CI: confidence interval.

Current smoker status

Chronic low back pain	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.844	0.182	21.418	1	< 0.001			
Smoker	1.122	0.443	6.421	1	0.011	3.071	1.289	7.316
Non-smoker	0	.	.	0	.	.	.	.

The reference category is: Control group.
CI: confidence interval.

IASP (definite/ probable)	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.350	0.199	3.084	1	0.079			
Smoker	1.393	0.456	9.355	1	0.002	4.028	1.650	9.837
Non-smoker	0	.	.	0	.	.	.	.

The reference category is: Control group.
IASP: International Association for the Study of Pain, CI: confidence interval.

Nicotine addiction - Fagerström score

Chronic low back pain	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.836	0.177	22.361	1	< 0.001			
Fagerström score	0.343	0.128	7.168	1	0.007	1.409	1.096	1.812

The reference category is: Control group.
CI: confidence interval.

IASP (definite/ probable)	B	Standard error	Wald	df	*P* value	Odds ratio	95% CI for odds ratio	
							Lower bound	Upper bound
Intercept	0.345	0.193	3.211	1	0.073			
Fagerström score	0.411	0.134	9.400	1	0.002	1.508	1.160	1.961

The reference category is: Control group.
IASP: International Association for the Study of Pain, CI: confidence interval.