Tobacco Use in Fibromyalgia Is Associated With Cognitive Dysfunction: A Prospective Questionnaire Study

Lin Ge, MD; Ryan S. D'Souza, MD; Terry Oh, MD; Ann Vincent, MD;
Arya B. Mohabbat, MD; Jason Eldrige, MD; Li Jiang, MD; Mary O. Whipple, BA;
Samantha J. McAllister, BA; Zhen Wang, PhD; Wenchun Qu, MD, MS, PhD;
and William D. Mauck, MD

Abstract

Objective: To evaluate the association between smoking and cognitive function in patients with fibromyalgia.

Patients and Methods: We surveyed 668 patients with fibromyalgia from May 1, 2012 through November 30, 2013 at a major tertiary referral center. Patients were categorized by smoking status. Primary outcome of interest was cognitive function (MASQ questionnaire), and secondary outcomes included fibromyalgia symptom severity (FIQ-R questionnaire), quality of life (SF-36 questionnaire), fatigue (MFI-20 questionnaire), sleep (MOS-sleep scale), anxiety (GAD-7 questionnaire), and depression (PHQ-9 questionnaire). Independent Students' t-tests and χ^2 tests were performed for continuous and categorical variables, respectively. Univariate regression analysis identified variables predictive of outcomes, adjusting for age, gender, body mass index, marital status, and educational level.

Results: Ninety-four (14.07%) patients self-identified as smokers. There was an association of lower education level, unmarried status, and younger age in smokers compared with nonsmokers. In the adjusted univariate regression analysis, fibromyalgia smokers reported greater perceived total cognitive dysfunction (P=.009) and greater subscale scores of perceived difficulty in language (P=.03), verbal memory (P=.003), visual-spatial memory (P=.02), and attention (P=.04) compared with nonsmokers with fibromyalgia. For secondary outcomes, smokers with fibromyalgia reported greater severity of fibromyalgia-related symptoms (P=.006), worse quality-of-life index in the mental component scale (P=.02), greater sleep problems (P=.01), and increased anxiety (P=.001) compared with nonsmokers who had fibromyalgia.

Conclusion: In patients with fibromyalgia, smoking is a risk factor for cognitive dysfunction. Moreover, smokers with fibromyalgia were more likely to report increased severity of fibromyalgia symptoms, worse quality of life, more sleep problems, and increased anxiety compared with nonsmokers with fibromyalgia.

From the Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN (L.G., T.O., L.J., W.Q.); Department of Rheumatology, Guang An Men Hospital, China Academy of Chinese Medical Science, Beijing, China (L.G.); Department of Anesthesiology and Perioperative Medicine, Mayo Clinic,

Affiliations continued at the end of this article.

Fibromyalgia (FM) is a prevalent disorder estimated to affect 2% to 6.4% of the US adult population (more than 5 million Americans).[1-4] In addition to chronic widespread musculoskeletal pain, patients with FM also report a constellation of debilitating symptoms comprising fatigue, sleep disturbance, psychological distress, and poor quality of life.[5,6] Importantly, cognitive impairment is one of the core manifestations of FM, colloquially referred to as "fibrofog," and may be even more disabling than symptoms of pain. Studies report that 50% to 80% of patients with FM experience memory decline, mental confusion, and difficulties with concentration.[7,8] Yet there is a paucity of data describing risk factors that may explain the correlation between FM and cognitive dysfunction.[9,10]

Cigarette smoking—a pervasive high-risk behavior representing a global health concern and the leading cause of early preventable death in the developed world—is associated

with greater intensity of pain and functional impairment in patients with chronic pain, including patients with FM.[11-14] Furthermore, smoking has been linked to significant cognitive impairment in both elderly and young patients.[15,16] To the best of our knowledge, no study has investigated the association of smoking and cognitive ability in patients with FM. To this end, the objective of our prospective questionnaire study was to evaluate the association of smoking with cognitive function in patients with FM. We hypothesize that tobacco use in FM is associated with greater impairment in cognitive function compared with patients with FM who do not smoke. In addition, we sought to investigate the association of smoking with other secondary outcomes, including FM severity of symptoms, quality of life, fatigue, sleep, and mood disorders.

PATIENTS AND METHODS

Patients

This was a prospective questionnaire study that included 668 patients with FM who were seen in the Fibromyalgia Clinic at a major tertiary referral center (Mayo Clinic, Rochester, Minnesota), between May 2012 and November 2013. At the time of enrollment, a clinician confirmed the diagnosis of FM as stated by the American College of Rheumatology 1990 criteria[17] and/or 2010 criteria.[18] Informed consent was obtained from all participants, and our study was approved by our hospital's Institutional Review Board. Smoking status was abstracted from the electronic medical record. Patients were divided into 2 groups: nonsmoker (lifetime abstinent or previous user) and smoker (current user).

Outcome Measures

Primary Outcome. The Multiple Ability Self-Report Questionnaire (MASQ) was used to assess cognitive dysfunction. It is a 38-item measure that assesses 5 domains of perceived cognitive difficulties: language, visual perception, verbal memory, visual spatial function, and attention/concentration. Scores on each cognitive domain ranges from 0 to 30 or 0 to 40. The maximum total score is 190. Higher scores indicate greater perceived difficulties in cognitive function.[19]

Secondary Outcomes. The Revised Fibromyalgia Impact Questionnaire (FIQ-R) has 21 items designed to assess severity of FM symptoms, functional status, and overall impact of FM. Weighted summary score ranges from 0 to 100. Higher scores indicate more severe symptoms, with scores of 0 to <39, ≥39 to <59, and ≥59 to 100, indicating mild, moderate, and severe symptoms, respectively.[20]

The 36-item Short Form Health Survey (SF-36) is a health-related quality-of-life (QOL) measure. The SF-36 yields 8 subscales: vitality, physical function, bodily pain, general health perceptions, physical-role functioning, emotional-role functioning, social-role functioning, and mental health. The 8 subscales are combined into 2 domains: physical component summary and mental component summary. Each scale is transformed into a 0 to 100 scale with lower scores indicating poorer health and quality-of-life measure.[21]

The Multidimensional Fatigue Inventory (MFI-20) is a 20-item measure that assesses multiple aspects of fatigue in 5 domains including general fatigue, physical fatigue, reduced activities, reduced motivation, and mental fatigue. Subscale scores range from 4 to 20, with higher scores indicating greater fatigue.[22]

The 9-item Patient Health Questionnaire Depression Scale (PHQ-9) assesses for symptoms of depression.[23] Scores range between 0 and 27. A total score greater than or equal to 10 indicates the presence of major depressive symptoms. Symptoms of anxiety were assessed with the 7-item Generalized Anxiety Scale (GAD-7).[24] GAD-7 score ranges from 0 to 21 with scores of 5, 10, and 15 representing mild, moderate, and severe anxiety symptoms, respectively.

The Medical Outcomes Study Sleep Scale (MOS-Sleep) scale is a 12-item measure to assess sleep, described in 6 dimensions: sleep disturbance, sleep adequacy, sleep quantity, somnolence, snoring, and awakening with shortness of breath or headache. Summary scores range from 0 to 100, with higher scores indicating poorer sleep.[25]

Statistical Analysis

Demographic characteristics and primary and secondary outcomes were summarized by

TABLE 1. Demographic and Social Characteristics of Patients With Fibromyalgia Based on Smoking Status

Characteristic	Smoking status		P value
	Nonsmokers (n=574)	Smokers (n=94)	
Age (years)	47.92±13.08	43.00±11.73	.001
Gender			.92
Female	521 (90.77%)	85 (90.43%)	
BMI	30.30±7.90	29.50±6.24	.64
Race			.68
Caucasian	511 (89.02%)	85 (90.43%)	
Alcohol			.58
Current alcoholic	299 (54.46%)	49 (57.65%)	
Marital status			<.001
Married	405 (70.93%)	48 (51.06%)	
Employment			.49
Employed	266 (46.34%)	43 (45.74%)	
Unemployed	180 (31.36%)	36 (38.30%)	
Retired	70 (12.20%)	7 (7.45%)	
Homemaker	43 (7.49%)	5 (5.32%)	
Other	15 (2.61%)	3 (3.19%)	
Education level			<.001
Grade ≤12 y	95 (17.43%)	36 (41.86%)	
Opioid			.39
Endorses opioid use	170 (29.62%)	32 (34.04%)	

Note that sample N value does not reflect sample size for all categories, as there were missing data for various categories.

mean and standard deviations for continuous variables and frequency (%) for categorical variables. Students' t-tests and Pearson's χ^2 tests were used to compare the continuous and categorical outcome measures, respectively, between smokers and nonsmokers. We also constructed multiple linear regression models on outcomes after adjusting for age, gender, body mass index (BMI), marital status, and education level. Although P values less than .05 are generally considered statistically significant, the issue of multiple comparisons in our study design increases the probability of false positive results by chance alone. Thus, we adjusted significant threshold values for each outcome association based on the Benjamini–Hochberg false discovery control procedure with a false discovery rate of 5%.[26,27] This adjustment in significance threshold values was performed separately for our prespecified primary and secondary outcomes of interest. All analyses were performed using SPSS (SPSS Statistics

for Windows, Version 21.0, IBM, Armonk, NY).

RESULTS

A total of 668 patients were surveyed with a mean age of 47.2±13.0 years (range 18 to 83 years); 606 (90.71%) patients were female. There were 574 (85.93%) nonsmokers and 94 (14.07%) smokers. The sociodemographic characteristics of participants are displayed in Table 1. Internal consistency was assessed for questionnaires with multiple-item measures including the MASQ scale (Cronbach's α= 0.91), FIQ-R scale (Cronbach's α= 0.82), SF-36 scale (Cronbach's α= 0.91), and the MFI-20 scale (Cronbach's α= 0.80).

Primary Outcome

Table 2 demonstrates primary and secondary outcome measures. Univariate analysis adjusting for covariates of age, gender, BMI, marital status, and education level revealed an association between smoking and higher perceived cognitive dysfunction (P=.009) and higher MASQ subscale scores in perceived difficulty in language (P=.03), verbal memory (P=.003), visual-spatial memory (P=.02), and attention (P=.04).

Secondary Outcomes
Fibromyalgia Symptom Severity
(FIQ-R). After adjusting for age, gender, BMI, marital status, and education level, a correlation was identified between smoking and greater FIQ-R total score (P=.003) and subscale measures of symptoms (P=.006), overall (P=.002), and function scores (P=.005).

Quality of Life (SF-36). Adjusted analysis identified a correlation between smoking and worse mental component score (P=.02), physical functioning (P=.01), and vitality (P=.006) but not bodily pain (P=.03 was higher than significance threshold of .0239).

Fatigue (MFI-20). Adjusted analysis identified a correlation between smoking and worse motivation scores (P=.02).

Sleep (MOS-sleep scale). Adjusted analysis identified a correlation between smoking and worse sleep scores (P=.01).

TABLE 2. Comparison of Primary and Secondary Outcomes Based on Smoking Status

Characteristic	Nonsmoker n=574 Mean±SD	Smoker n=94 Mean±SD	β (95% CI)	P value Not adjusted*	P value Adjusted†	Adjusted Significance Threshold
MASQ total	94.88±22.73	103.52±21.39	7.15 (1.77-12.52)	.001	.009‡	.0167
Language	19.53±5.37	21.20±5.67	1.42 (0.12-2.72)	.006	.03‡	.0333
Visual-perceptual ability	14.20±4.61	15.04±4.49	0.76 (−0.35-1.86)	.10	.18	.0500
Verbal memory	21.80±5.78	24.42±5.78	2.11 (0.74-3.48)	<.001	.003‡	.0083
Visual-spatial memory	17.96±5.19	19.58±4.71	1.47 (0.26-2.69)	.005	.02‡	.0250
Attention/Concentration	21.45±5.59	23.27±4.85	1.36 (0.06-2.67)	.003	.04‡	.0417
FIQ-R Total score	57.72±17.93	65.44±17.80	6.60 (2.29-10.91)	<.001	.003‡	.0065
Symptoms	30.98±7.84	34.22±7.94	2.67 (0.77-4.56)	<.001	.006‡	.0109
Overall	12.16±5.53	14.48±5.15	2.01 (0.72-3.30)	<.001	.002‡	.0043
Function	14.53±7.33	17.18±7.16	2.49 (0.76-4.22)	.001	.005‡	.0087
SF -36						
PF (physical functioning)	31.91±21.12	25.62±15.87	-6.35 (−11.18 to −1.53)	.001	.01‡	.0152
RP (role physical)	20.34±19.26	16.95±15.75	-3.92 (−8.42-0.58)	.11	.09	.0370
BP (bodily pain)	16.65±16.60	13.09±13.33	-4.41 (−8.28 to −0.54)	.02	.03§	.0239
GH (general health)	25.55±19.45	23.52±17.98	-1.85 (−6.39-2.70)	.35	.42	.0478
VT (vitality)	16.51±14.16	13.31±10.63	-4.57 (−7.83 to −1.31)	.01	.006‡	.0130
SF (social functioning)	23.00±26.20	18.78±23.30	-4.59 (−10.82-1.64)	.15	.15	.0435
RE (role emotional)	36.53±32.46	29.73±26.00	-7.04 (−14.77-0.70)	.03	.07	.0326
MH (mental health)	39.25±25.91	33.28±21.91	-6.00 (−12.13-0.13)	.02	.06	.0283
PCS (physical component scale)	29.94±8.40	28.35±7.37	-1.82 (−3.86-0.21)	.10	.08	.0348
MCS (mental component Scale)	38.76±12.34	35.02±12.20	-3.63 (−6.71-0.54)	.01	.02‡	.0217
MFI-20 total	75.39±13.79	78.71±13.78	2.96 (−0.46-6.38)	.04	.09	.0391
General	18.08±2.41	18.65±2.19	0.54 (−0.02-1.11)	.03	.06	.0304
Physical	16.37±3.59	16.72±3.21	0.59 (−0.26-1.45)	.38	.17	.0457
Mental	13.98±4.38	14.60±4.17	0.39 (−0.66-1.44)	.21	.46	.0500
Motivation	12.13±3.94	13.45±4.23	1.13 (0.18-2.09)	.003	.02‡	.020
Activity	14.88±4.33	15.67±3.96	0.78 (−0.24-1.81)	.10	.13	.0413
MOS sleep scale	56.80±18.79	65.66±17.66	5.51 (1.21-9.82)	<.001	.01‡	.0174
GAD 7 total	8.11±5.85	10.93±5.63	2.32 (0.91-3.73)	<.001	.001‡	.0022
PHQ 9 total	11.94±5.71	13.84±5.69	1.49 (0.09-2.89)	.004	.04§	.0261

*Unadjusted analysis was performed with independent Students' t-tests.

†Adjusted analysis was performed with linear regression adjusting for age, gender, body mass index, marital status, and education level.

‡Adjusted P value achieves significance from adjusted significance threshold per the Benjamini−Hochberg false discovery control procedure.

§Adjusted P value was below P=.05 but failed to achieve significance from adjusted significance threshold per the Benjamini−Hochberg false discovery control procedure.

Data on cognitive symptoms, symptom severity of fibromyalgia, quality of life, fatigue, sleep, anxiety, and depression are presented based on smoking status. Unadjusted and adjusted analyses (adjusted for age, gender, body mass index, marital status, and level of education) are presented.

β = beta coefficient; CI = confidence interval; ªFIQ-R = the Revised Fibromyalgia Impact Questionnaire; GAD 7 = 7-item Generalized Anxiety Scale; MASQ = Multiple Ability Self-Report Questionnaire; MCS = Mental Component Summary; MFI = Multidimensional Fatigue Inventory; MOS-sleep scale = Medical Outcomes Study Sleep Scale; PCS = Physical Component Summary; PHQ9 = 9-item Patient Health Questionnaire-Depression Scale; SF-36 = 36-item Short Form Health Survey.

Mood (GAD7 and PHQ9). Adjusted analysis identified a correlation between smoking and increased anxiety (P=.001) but not increased depressive symptoms (P=.04 was higher than significance threshold of .0261).

DISCUSSION

We demonstrate a significant association between active smoking in patients with FM and worse overall cognitive function. Furthermore, a greater perceived difficulty in language, verbal memory, visual-spatial memory, and attention was also noted in smokers with FM. This is crucial because cognitive impairment can be debilitating and is associated with higher severity of pain, depression, anxiety, negative affect, low self-esteem, and pain catastrophizing in patients with FM.[28] The impairment in domains of

working, episodic, and sematic memory can be so severe that it mimics approximately 20 years of aging.[29]

Our findings of associations between smoking and cognitive problems are concordant with several previous studies[15,16] but extend to a FM patient population and describe dissociable domains tapped by well-validated translational cognitive questionnaires. Although our questionnaires did not assess the specific subdomains of language ability, other studies have demonstrated that current smokers do perform more poorly in receptive and expressive vocabulary[30] and demonstrate poorer verbal fluency and verbal knowledge.[31] Similarly, other studies reveal that tobacco smoking is detrimental to other cognitive domains of verbal memory, visual-spatial memory, and inattention.[32] However, controversy exists on this subject, as some studies even propose that nicotine may be neuroprotective and may have positive effects on certain cognitive domains including memory, attention, fine motor skills, and executive function.[33,34] A meta-analysis by Heishman and colleagues investigating the acute effects of nicotine or smoking on human performance reported positive effects on 6 domains including fine motor, alerting attention, orienting attention, episodic memory, and working memory.[35] However, most studies report increased risk of negative cognitive outcomes with smoking and propose potential mechanisms for tobacco smoke's harmful effects comprising oxidative stress, inflammation, and atherosclerotic processes.[33,36]

Based on findings from our study, it is unclear whether smoking results in cognitive impairment or whether people with cognitive impairment use nicotine to cope with perceived cognitive dysfunction. For instance, a study by Weingarten et al revealed that most smokers who had FM used smoking to cope with pain symptoms via distraction and relaxation, to lessen emotional distress resulting from pain-induced frustration or sadness, and as justification for resting during smoking breaks.[37] Thus, it would be useful for future studies to explore the utility of medications that help patients quit smoking to assess whether cognitive deficits improve after cessation of smoking.

Furthermore, our analysis revealed that active smoking in patients with FM was associated with worse secondary outcomes of severity FM symptoms, quality-of-life measures, fatigue, sleep problems, and anxiety than in nonsmokers. These findings are also consistent with previous studies; for instance, a comparable study on patients with FM found that tobacco users reported worse physical impairment, work interference, pain, unrefreshed awakening, and stiffness.[38] Smokers with FM also experienced more tender points and bodily pain.[39] Similarly, worse quality-of-life measures,[39,40] greater fatigue,[41] and increased rates of mood disorders[39] are reported in smokers with FM.

Our study identified 14.07% of the total patient cohort as smokers, which is a lower than expected proportion of reported smokers with FM, based on previous reports ranging from approximately 22% to 25%.[42,43] However, our reported rates are comparable with those previously reported in large series of patients with chronic pain, particularly a 15.3% rate of smoking in 25,417 patients with rheumatic diseases from the National Data Bank for Rheumatic Disease.[44] Furthermore, our rate is concordant with a previous study occurring in the same institution as our study, with a reported smoking rate of 14.7% in a chronic-pain population.[13] Despite this, our study similarly demonstrated that smokers had lower levels of education, higher rates of unmarried status, and younger age compared with nonsmokers. The proportion of alcohol consumption and the use of opioids were not significantly different between the 2 groups.

Strengths of our study included an objective and robust methodology. Unlike previous case-control studies, our prospective questionnaire study, using logistic regression to control for potential confounding factors (age, gender, BMI, marital status, educational level), is less likely to have generated information bias. A comprehensive assessment of variables was also described, including our primary outcome measure of cognitive dysfunction, but also diverse secondary outcome measures of severity of FM symptoms, quality-of-life metrics, fatigue, sleep, anxiety, and depression. All Cronbach's α values for multiple-item questionnaires in our study were greater than or equal to .80, indicating good internal consistency.[45] These high internal consistency

reliability values are consistent with previous validation studies.[46-49]

Our analyses must be interpreted in the context of several notable limitations. We defined smoking as a binary variable: current user or nonsmoker. The latter category comprised both lifetime abstinent patients and previous smokers, which may complicate the interpretation of our results. A more appropriate method would be to categorize never smokers, former smokers, and current smokers separately in our statistical analyses. It may be plausible that the effects of smoking on cognition may not be evident in former smokers who have recovered from the detrimental effects of smoking, similar to how cessation of smoking is associated with reduced risk of lung cancer[50] and cardiovascular disease.[51] Another limitation was the lack of data on quantity of tobacco use (ie, pack-years) and exposure to second-hand smoke. A dose-related association between smoking pack-years and worse cognitive impairment has been reported.[52,53] Moreover, as smoking status and cognition were both assessed by self-report, we may be limited by recall and reporting bias. Although we adjusted our significance threshold for multiple comparisons in our statistical methods, this introduces the risk for Type II error.

CONCLUSION
In the FM patient population, smokers reported increased cognitive dysfunction than nonsmokers. Although the cause-effect relationship between smoking and cognition is unclear, clinicians who care for patients with FM should be aware of this association. Future studies should extend these results longitudinally to assess causality and investigate the effects of nicotine-containing agents as well as antismoking medications on cognition.

ACKNOWLEDGMENTS
We are grateful to Dr Phillip Schulte and Dr Darrell Schroeder for reviewing our statistical methodology. Permission has been obtained from those acknowledged.

Affiliations (Continued from the first page of this article.): Rochester, MN (R.S.D.); Department of Medicine, Mayo Clinic, Rochester, MN (A.V., A.B.M., S.J.M.); Department of Anesthesiology, Pain Division, Mayo Clinic, Rochester, MN (J.E., W.Q., W.D.M.); and Department of Nursing, Mayo Clinic, Rochester, MN (M.O.W., Z.W.).

L.G. and R.S.D. are first authors of this paper.

Correspondence: Address to Wenchun Qu, MD, MS, PhD, 200 First St SW, Rochester, MN 55905 (qu.wenchun@mayo.edu).

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38(1):19-28.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis Rheum*. 2008;58(1): 26-35.
3. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. *Arthritis Care Res (Hoboken)*. 2013;65(5):786-792.
4. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004;292(19):2388-2395.
5. Smith HS, Harris R, Clauw D. Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. *Pain Physician*. 2011;14(2):e217-e245.
6. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. *Pharmacoeconomics*. 2014; 32(5):457-466.
7. Katz RS, Heard AR, Mills M, Leavitt F. The prevalence and clinical impact of reported cognitive difficulties (fibrofog) in patients with rheumatic disease with and without fibromyalgia. *J Clin Rheumatol*. 2004;10(2):53-58.
8. Bertolucci PH, de Oliveira FF. Cognitive impairment in fibromyalgia. *Curr Pain Headache Rep*. 2013;17(7):344.
9. Fava A, Plastino M, Cristiano D, et al. Insulin resistance possible risk factor for cognitive impairment in fibromialgic patients. *Metab Brain Dis*. 2013;28(4):619-627.

10. Low LA, Schweinhardt P. Early life adversity as a risk factor for fibromyalgia in later life. *Pain Res Treat*. 2012;2012: 140832.

11. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther*. 2008;83(4):531-541.

12. Weingarten TN, Iverson BC, Shi Y, Schroeder DR, Warner DO, Reid KI. Impact of tobacco use on the symptoms of painful temporomandibular joint disorders. *Pain*. 2009;147(1-3):67-71.

13. Weingarten TN, Moeschler SM, Ptaszynski AE, Hooten WM, Beebe TJ, Warner DO. An assessment of the association between smoking status, pain intensity, and functional interference in patients with chronic pain. *Pain Physician*. 2008;11(5):643-653.

14. Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: pathophysiology and clinical implications. *Anesthesiology*. 2010;113(4):977-992.

15. Chamberlain SR, Odlaug BL, Schreiber LR, Grant JE. Association between tobacco smoking and cognitive functioning in young adults. *Am J Addict*. 2012;21(suppl 1):S14-S19.

16. Razani J, Boone K, Lesser I, Weiss D. Effects of cigarette smoking history on cognitive functioning in healthy older adults. *Am J Geriatr Psychiatry*. 2004;12(4):404-411.

17. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia; report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33(2):160-172.

18. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62(5):600-610.

19. Seidenberg M, Haltiner A, Taylor MA, Hermann BB, Wyler A. Development and validation of a Multiple Ability Self-Report Questionnaire. *J Clin Exp Neuropsychol*. 1994; 16(1):93-104.

20. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. 2009;11(4): R120.

21. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000;25(24):3130-3139.

22. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manage*. 2004;27(1):14-23.

23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16(9):606-613.

24. Antony MM, Orsillo SM, Roemer L; Association for Advancement of Behavior Therapy. *Practitioner's Guide to Empirically Based Measures of Anxiety*. New York, NY: Kluwer Academic/ Plenum Publishers; 2001.

25. Allen RP, Kosinski M, Hill-Zabala CE, Calloway MO. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). *Sleep Med*. 2009;10(5): 531-539.

26. Feser WJ, Fingerlin TE, Strand MJ, Glueck DH. Calculating average power for the Benjamini-Hochberg procedure. *J Stat Theory Appl*. 2009;8(3):325-352.

27. Glueck DH, Mandel J, Karimpour-Fard A, Hunter L, Muller KE. Exact calculations of average power for the Benjamini-Hochberg procedure. *Int J Biostat*. 2008;4(1). article 11.

28. Galvez-Sánchez CM, Reyes Del Paso GA, Duschek S. Cognitive impairments in fibromyalgia syndrome: associations with positive and negative affect, alexithymia, pain catastrophizing and self-esteem. *Front Psychol*. 2018;9:377.

29. Glass JM. Fibromyalgia and cognition. *J Clin Psychiatry*. 2008; 69(suppl 2):20-24.

30. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of cigarette smoking in young adults: a comparison with pre-drug performance. *Neurotoxicol Teratol*. 2006;28(4): 517-525.

31. Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis Rheum*. 2001;44(9):2125-2133.

32. Bryant VE, Kahler CW, Devlin KN, Monti PM, Cohen RA. The effects of cigarette smoking on learning and memory performance among people living with HIV/AIDS. *AIDS Care*. 2013; 25(10):1308-1316.

33. Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev*. 2007;17(3):259-273.

34. Valentine G, Sofuoglu M. Cognitive effects of nicotine: recent progress. *Curr Neuropharmacol*. 2018;16(4):403-414.

35. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl)*. 2010;210(4):453-469.

36. Solak ZA, Kabaroğlu C, Cok G, et al. Effect of different levels of cigarette smoking on lipid peroxidation, glutathione enzymes and paraoxonase 1 activity in healthy people. *Clin Exp Med*. 2005;5(3):99-105.

37. Weingarten TN, Vincent A, Luedtke CA, et al. The perception of female smokers with fibromyalgia on the effects of smoking on fibromyalgia symptoms. *Pain Pract*. 2015;16(8): 1054-1063.

38. Weingarten TN, Podduturu VR, Hooten WM, Thompson JM, Luedtke CA, Oh TH. Impact of tobacco use in patients presenting to a multidisciplinary outpatient treatment program for fibromyalgia. *Clin J Pain*. 2009;25(1):39-43.

39. Lee SS, Kim SH, Nah SS, et al. Smoking habits influence pain and functional and psychiatric features in fibromyalgia. *Joint Bone Spine*. 2011;78(3):259-265.

40. Goesling J, Brummett CM, Meraj TS, Moser SE, Hassett AL, Ditre JW. Associations between pain, current tobacco smoking, depression, and fibromyalgia status among treatment-seeking chronic pain patients. *Pain Med*. 2015;16(7):1433-1442.

41. Rusu C, Gee ME, Lagacé C, Parlor M. Chronic fatigue syndrome and fibromyalgia in Canada: prevalence and associations with six health status indicators. *Health Promot Chronic Dis Prev Can*. 2015;35(1):3-11.

42. Orhurhu VJ, Pittelkow TP, Hooten WM. Prevalence of smoking in adults with chronic pain. *Tob Induc Dis*. 2015;13(1):17.

43. Yunus MB, Arslan S, Aldag JC. Relationship between fibromyalgia features and smoking. *Scand J Rheumatol*. 2002;31(5):301-305.

44. Wolfe F, Rasker JJ. The Symptom Intensity Scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. *J Rheumatol*. 2006;33(11):2291-2299.

45. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *Int J Med Educ*. 2011;2:53-55.

46. Kratz AL, Schilling SG, Goesling J, Williams DA. Development and initial validation of a brief self-report measure of cognitive dysfunction in fibromyalgia. *J Pain*. 2015;16(6): 527-536.

47. Costa C, Pinto AM, Pereira AT, Marques M, Macedo A, Pereira da Silva JA. Psychometric properties of the Revised Fibromyalgia Impact Questionnaire (FIQR): a contribution to the Portuguese validation of the scale. *Acta Reumatol Port*. 2016;41(3): 240-250.

48. Lin JM, Brimmer DJ, Maloney EM, Nyarko E, Belue R, Reeves WC. Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Popul Health Metr*. 2009;7:18.

49. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164.

50. Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. *JAMA*. 2005;294(12):1505-1510.
51. Serrano M, Madoz E, Ezpeleta I, et al. Smoking cessation and risk of myocardial reinfarction in coronary patients: a nested case-control study. *Rev Esp Cardiol*. 2003;56(5): 445-451.
52. Ozcan ME, Ince B, Bingöl A, et al. Association between smoking and cognitive impairment in multiple sclerosis. *Neuropsychiatr Dis Treat*. 2014;10:1715-1719.
53. Ott A, Andersen K, Dewey ME, et al. Effect of smoking on global cognitive function in nondemented elderly. *Neurology*. 2004;62(6):920-924.