The Relationship Between Smoking and Multiple Sclerosis Severity in Saudi Arabia

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Abstract

Introduction

Multiple sclerosis (MS) is an autoimmune disease that can be disabling to patients. Smoking has been proposed to be a risk factor for MS and to increase the risk of progression of the disease and its severity. However, it is still not clear how smoking affects people with MS (PwMS) regarding disease phenotype, symptoms, relapses, course, and disability. The aim of this study is to investigate the effect of smoking on PwMS in Saudi Arabia.

Methods

This is an online questionnaire-based cross-sectional study. PwMS were randomly contacted through different MS societies and associations to participate in the study. The questionnaire inquired about demographics, MS phenotype and severity, and smoking status of the participants. Data were collected between May 30, 2021, and July 5, 2021.

Results

Four hundred twenty-nine PwMS participated in the study. The mean age was 33.7, with a mean disease duration of 8.1 years. About 61.1% of the participants were female. About 62.2% did not know the specific MS phenotype they have. About 35.7% were current or previous smokers, with a mean smoking duration of 13.9 years. Smoking was significantly associated with the presence of multiple MS symptoms (p-value = 0.009) and their number (p-value = 0.050). In addition, there was a significant positive correlation between pack-years smoking and the number of MS symptoms with a Pearson’s r value of 0.165 (p-value = 0.001). No significant associations were found between smoking and recent relapses and disease progression, disability in terms of walking, needing a cane, or needing a wheelchair.

Conclusion

Smoking was shown to have a significant effect on the number of symptoms experienced by PwMS. Higher pack-years of smoking correlates positively and significantly with a higher number of MS symptoms. Further studies to examine these relations are hence warranted.

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Introduction

Multiple sclerosis (MS) is the most common autoimmune disease affecting the central nervous system. Its worldwide prevalence has been reported to increase from 2.3 million in 2013 to 2.8 million (36/100,000) in 2020 [1]. The disease is categorized into three main phenotypes based on the clinical course and symptomatology: relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS). RRMS is the most common phenotype, approximately affecting 85% of patients [2]. MS is a major cause of non-traumatic neurological disability [3]. Several lifestyle and nutritional interventions are proposed to decrease the risk of disability associated with MS and the progression of the disease, such as vitamin D supplementation, exercise, plant-based diet, and smoking cessation [4]. A lack of control over these factors in addition to other factors is thought to be responsible for an increase in the number of MS in the Arabian Gulf region [5]. MS is also shown to be more severe in Saudi Arabia than in other countries [6], with an overall MS prevalence of 40.4/100,000 in the country [7].

Smoking is considered one of the main risk factors for multiple sclerosis [8,9]. A systematic review showed...
strong evidence of the causal role of smoking in MS, using Hill’s criteria [10]. Smoking was also associated with higher levels of MS physical pain and worse long-term disease prognosis [11]. Smoking is also hypothesized to play a role in MS progression [10,12]. In addition, smoking is shown to increase the frequency of relapses, trigger the onset of MS symptoms, and alter the activity of MS disease-modifying drugs. All of which could lead to the negative role of smoking on MS [13]. The relationship between smoking and MS severity, course, and progression in Saudi Arabia has not been investigated yet. This study aims to provide an insight into this relationship and investigate the role of smoking on the increased severity and prevalence of MS in the country.

Materials And Methods

Design and setting
This is an online questionnaire-based cross-sectional study done in Saudi Arabia. Simple random sampling technique was implemented. MS societies and associations were contacted to randomly send a link of the questionnaire to registered people with MS (PwMS) study. This study has been approved by Umm Al-Qura University (UQU) institutional review board (IRB) No. HAPO-02-K-012-2021-03-625.

The link displayed an explanation of the purpose of the study and its targeted population, IRB approval, an informed consent form ensuring the anonymity of participants, and a choice to either agree or disagree to participate in the study. Data were collected between May 30, 2021, and July 5, 2021. The targeted sample size was calculated to be 570 using “sample size for estimating a proportion” equation described by Thompson [14]. A 95% confidence interval was implanted for the calculation, with an error proportion of 5%, population proportion of 50%, and an estimated total population of 10,000.

Questionnaire and variables
We utilized Google Forms (Google, Mountain View, California, United States) to design and distribute our questionnaire. It consisted of three sections. The first section included different demographics of the participants. The second section included questions asking about MS severity: disease phenotype, year of diagnosis, relapses in the last year and any new MRI findings, the ability to walk for different distances in a flat terrain, any walking aids or wheelchair use, and inquired about current symptoms (e.g., dysarthria, weakness, ataxia). Self-reported disability status scale (SRDSS) was used to estimate the Expanded Disability Status Scale (EDSS) score categories (<5.5, 4-6.5, ≥7) [15]. The third section asked about smoking status (smokers, previous smokers, or non-smokers). It also inquired about duration of smoking (few months, less than five years, five to 10 years, more than 10 years), year of smoking cessation for previous smokers, age when smoking started, how many cigarettes a participant smokes daily, and about the regularity of smoking. Pack-years of smoking was calculated for each participant, and heaviness of smoking was classified as light smokers (>0-20 pack-years), moderate smokers (>20-40 pack-years), and heavy smokers (>40 pack-years). The questionnaire was distributed in Arabic, and the results were later translated to English for analysis and publication purposes.

Data analysis
Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM, Chicago, Illinois, United States). Descriptive analyses were used to present participants’ demographics, disease phenotype, and smoking status. The association between categorical variables was examined using chi square test. Correlation between continuous variables was examined using Pearson’s r. A 95% confidence interval and a significance level of 5% were utilized.

Results
Demographics
A total of 429 participants completed the questionnaire. Two hundred sixty-two (61.1%) of the sample were females. The mean age was 33.7 ± 9.6 years. Non-smoker participants were 276 (64.3%) of the total sample, while current smokers were 99 (23.1%), and previous smokers were 54 (12.6%). The mean duration of smoking was 13.9 ± 8.9 years, and the mean pack-years of smoking was 15.0 ± 15.3 (Table 1).
Categorical variables

| Category               | n   | %    |
|------------------------|-----|------|
| Gender                 |     |      |
| Male                   | 167 | 38.9 |
| Female                 | 262 | 61.1 |
| Nationality            |     |      |
| Saudi                  | 387 | 90.2 |
| Non-Saudi              | 89  | 19.8 |
| Education              |     |      |
| Less than high school  | 15  | 3.5  |
| High school            | 115 | 26.8 |
| Bachelor               | 260 | 60.6 |
| Master                 | 36  | 8.4  |
| PhD or higher          | 3   | 0.7  |
| Income                 |     |      |
| Less than 5,000 SR     | 221 | 51.5 |
| 5,000-10,000 SR        | 114 | 26.6 |
| 10,000-15,000 SR       | 56  | 13.1 |
| More than 15,000 SR    | 38  | 8.9  |
| Smoking status         |     |      |
| Non-smoker             | 275 | 64.1 |
| Ever smoker            | 153 | 35.7 |
| Previous smoker        | 54  | 12.6 |
| Current smoker         | 99  | 23.1 |
| Smoking heaviness      |     |      |
| Non-smoker             | 275 | 64.1 |
| Light smoker           | 82  | 19.1 |
| Moderate smoker        | 17  | 4.0  |
| Heavy smoker           | 6   | 1.4  |
| Unknown                | 49  | 11.4 |
| Total                  | 429 | 100.0|

**TABLE 1: Demographics and descriptive statistics**

Light smoker: >0-20 pack-years, moderate smoker: >20-40 pack-years, and heavy smoker: >40 pack-years. SD: standard deviation, SR: Saudi riyal.
### Continuous variables

|                      | Mean | SD  |
|----------------------|------|-----|
| Disease duration     | 8.1  | 6.7 |
| Relapses in last year| 1.0  | 2.0 |
| Number of current symptoms | 2.3  | 1.6 |

### Categorical variables

|                      | n   | %   |
|----------------------|-----|-----|
| **MS phenotype**     |     |     |
| RRMS                 | 106 | 24.7|
| PPMS                 | 33  | 7.7 |
| SPMS                 | 23  | 5.4 |
| Don't know           | 267 | 62.2|
| **Relapse in the last year** |     |     |
| Yes                  | 157 | 36.6|
| No                   | 210 | 49.0|
| Don't know           | 62  | 14.5|
| **New MRI lesion in the last year** |     |     |
| Yes                  | 152 | 35.4|
| No                   | 149 | 34.7|
| Don't know           | 128 | 29.8|
| **Progression in the last year** |     |     |
| Yes                  | 138 | 32.2|
| No                   | 235 | 54.8|
| Don't know           | 56  | 13.1|
| **Ability to walk on a flat terrain** |     |     |
| More than 500 m      | 175 | 40.8|
| 10-500 m             | 141 | 32.9|
| Less than 10 m       | 113 | 26.3|
| **Need a cane to walk** |     |     |
| Yes                  | 90  | 21.0|
| No                   | 339 | 79.0|
| **Need a wheelchair to mobilize** |     |     |
| Yes                  | 50  | 11.7|
| No                   | 379 | 88.2|
| **SRDSS**            |     |     |
| 3.5 or less          | 168 | 39.2|
| 4-6.5                | 148 | 34.5|
| 7 or more            | 113 | 26.3|
| **Presence of at least one current symptom** |     |     |
| Yes                  | 361 | 84.1|
| No                   | 68  | 15.9|
Presence of multiple current symptoms

|                   | Non-smoker | Ever-smoker | Total | p-value |
|-------------------|------------|-------------|-------|---------|
| Three or less symptoms | 318        | 74.1        |       |         |
| More than three symptoms | 111        | 25.9        |       |         |
| Total              | 429        | 100.0       |       |         |

### TABLE 2: Multiple sclerosis outcomes

Light smoker: >0-20 pack-years, moderate smoker: >20-40 pack-years, and heavy smoker: >40 pack-years. SD: standard deviation, MS: multiple sclerosis, RRMS: relapsing-remitting MS, PPMS: primary progressive MS, SPMS: secondary progressive MS, SRDSS: self-reported disability status scale.

#### Relation between smoking and MS

**Phenotype**

The statistical analysis showed a significant difference between ever-smokers (current smokers and previous smokers) and non-smokers in terms of their MS phenotype (p-value = 0.003) (Table 3). This difference persisted when tested between smokers, previous smokers, and non-smokers (p-value = 0.008). In addition, there was a significant difference between light smokers, moderate smokers, and heavy smokers in terms of disease phenotype (p-value = 0.01) (Table 4). However, there was no significant difference between different smoking durations and disease phenotype (p-value = 0.31) (Table 4).
| Phenotype | Total | p-value |
|-----------|-------|---------|
| RRMS      |       |         |
| Non-smoker| 105   | 24.8%   |
| Few months| 16    | 7.6%    |
| Less than five years | 6 | 24.0% |
| Five to 10 years | 31 | 34.4% |
| More than 10 years | 155 | 36.6% |
| PPMS      |       |         |
| Non-smoker| 126   | 48.9%   |
| Few months| 14    | 5.0%    |
| Less than five years | 11 | 55.0% |
| Five to 10 years | 12 | 48.0% |
| More than 10 years | 207 | 57.8% |
| SPMS      |       |         |
| Non-smoker| 80    | 29.6%   |
| Few months| 30.8% |         |
| Less than five years | 3 | 15.0% |
| Five to 10 years | 4 | 16.0% |
| More than 10 years | 125 | 35.5% |
| Don't know | 189 | 62.6% |
| Relapses in last year |       |         |
| Yes | 108 | 39.3% |
| No | 126 | 45.8% |
| Don't know | 41 | 14.9% |
| New MRI lesions in last year |       |         |
| Yes | 95 | 34.5% |
| No | 100 | 36.4% |
| Don't know | 80 | 29.1% |
| Progression in last year |       |         |
| Yes | 89 | 32.4% |
| No | 157 | 57.1% |
| Don't know | 29 | 10.5% |

**TABLE 3: Smoking status association with other variables**

p-values < 0.05 are given in bold. RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, SRDSS: self-reported disability status scale.
Ability to walk different distances on a flat terrain

| Distance          | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|-------------------|------------|--------------|----------------|--------------|-------|
| More than 500 m   | 104 (37.8%) | 4 (15.0%)    | 15 (60.0%)     | 41 (45.6%)   | 172 (40.7%) |
| 10-500 m          | 93 (33.8%)  | 7 (25.9%)    | 7 (28.0%)      | 28 (31.1%)   | 140 (33.1%) |
| Less than 10 m    | 78 (26.4%)  | 2 (7.7%)     | 7 (28.0%)      | 21 (23.3%)   | 111 (26.2%) |

Need a cane to walk

| Requirement | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|-------------|------------|--------------|----------------|--------------|-------|
| Yes         | 53 (19.3%) | 1 (3.8%)     | 2 (8.0%)       | 26 (28.9%)   | 89 (21.0%) |
| No          | 222 (80.7%)| 12 (36.3%)   | 23 (72.0%)     | 64 (71.1%)   | 334 (73.0%) |

Need a wheelchair to mobilize

| Requirement | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|-------------|------------|--------------|----------------|--------------|-------|
| Yes         | 34 (12.4%) | 4 (13.8%)    | 1 (4.0%)       | 9 (10.0%)    | 49 (11.6%) |
| No          | 241 (87.6%)| 12 (35.3%)   | 24 (66.0%)     | 81 (90.0%)   | 374 (88.4%) |

SRDSS

| Score     | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|-----------|------------|--------------|----------------|--------------|-------|
| 3.5 or less | 100 (36.4%) | 4 (13.8%)    | 15 (60.0%)     | 38 (42.2%)   | 165 (39.0%) |
| 4-6.5     | 97 (35.3%)  | 7 (25.9%)    | 7 (28.0%)      | 31 (34.4%)   | 147 (34.8%) |
| 7 or more | 78 (28.4%)  | 2 (6.1%)     | 3 (12.0%)      | 21 (23.3%)   | 111 (26.2%) |

Presence of at least one current symptoms

| Requirement   | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|---------------|------------|--------------|----------------|--------------|-------|
| Yes           | 232 (84.4%)| 13 (40.6%)   | 23 (92.0%)     | 73 (81.1%)   | 359 (84.9%) |
| No            | 43 (15.6%) | 0 (0.0%)     | 2 (8.0%)       | 17 (18.9%)   | 64 (15.1%) |

Presence of multiple current symptoms

| Symptoms       | Non-smoker | Light smoker | Moderate smoker | Heavy smoker | Total |
|----------------|------------|--------------|----------------|--------------|-------|
| Three or less symptoms | 215 (78.2%) | 6 (18.8%) | 10 (50.0%) | 22 (88.0%) | 314 (74.2%)   |
| More than three symptoms | 60 (21.8%) | 7 (23.3%) | 10 (50.0%) | 3 (12.0%) | 109 (25.8%)   |

### TABLE 4: Smoking duration association with other variables

p-values < 0.05 are given in bold. RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, SRDSS: self-reported disability status scale.

Presence of MS Symptoms

There was no significant association between smoking status and the current presence of symptoms (p-value = 0.98) (Table 3). Similarly, there was no significant association between smoking duration and the current presence of symptoms (p-value = 0.31) (Table 4). Nor was there a significant association between heaviness of smoking and the current presence of symptoms (p-value = 0.34) (Table 5).
## TABLE 5: Smoking heaviness association with other variables

p-values < 0.05 are given in bold. Light smoker: >0-20 pack-years, moderate smoker: >20-40 pack-years, and heavy smoker: >40 pack-years. RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, SRDSS: self-reported disability status scale.

| Variable                                         | Yes                  | No                  | Don't know          | p-value |
|--------------------------------------------------|----------------------|---------------------|---------------------|---------|
| New MRI lesions in last year                     |                      |                     |                     |         |
| Yes                                              | 95 (34.3%)           | 102 (36.8%)         | 80 (28.9%)          | 0.08    |
| No                                               | 14.8%                | 11.0%               | 29.5%               |         |
| Don't know                                       | 3 (17.6%)            | 4 (6.7%)            | 4 (6.7%)            |         |
| Progression in last year                         |                      |                     |                     |         |
| Yes                                              | 89 (32.1%)           | 159 (57.4%)         | 29 (10.5%)          | 0.19    |
| No                                               | 34.3%                | 37.8%               | 11.0%               |         |
| Don't know                                       | 35.3%                | 30.5%               | 66.7%               |         |
| Ability to walk different distances on a flat terrain |                  |                     |                     |         |
| More than 500 m                                  | 106 (38.3%)          | 93 (33.6%)          | 78 (28.2%)          | 0.10    |
| 10-500 m                                         | 51.2%                | 30.5%               | 18.3%               |         |
| Less than 10 m                                   | 29.4%                | 23.5%               | 47.1%               |         |
| Need a cane to walk                              |                      |                     |                     | 0.08    |
| Yes                                              | 53 (19.7%)           | 22 (8.9%)           | 84 (22.0%)          |         |
| No                                               | 26.8%                | 73.2%               | 78.0%               |         |
| Need a wheelchair to mobilize                    |                      |                     |                     | 0.87    |
| Yes                                              | 34 (12.3%)           | 14 (11.0%)          | 14 (17.6%)          |         |
| No                                               | 87.7%                | 89.0%               | 82.4%               |         |
| SRDSS                                            |                      |                     |                     |         |
| 3.5 or less                                      | 102 (36.8%)          | 97 (35.0%)          | 78 (28.2%)          | 0.18    |
| 4-6.5                                            | 48.8%                | 32.9%               | 18.3%               |         |
| 7 or more                                        | 29.4%                | 23.5%               | 47.1%               |         |
| Presence of at least one current symptoms        |                      |                     |                     | 0.34    |
| Yes                                              | 234 (84.5%)          | 68 (82.9%)          | 17 (100.0%)         |         |
| No                                               | 15.5%                | 14 (17.1%)          | 0 (0.0%)            |         |
| Presence of multiple current symptoms            |                      |                     |                     | 0.012   |
| Three or less symptoms                           | 216 (78.0%)          | 56 (68.3%)          | 10 (58.8%)          |         |
| More than three symptoms                         | 22.0%                | 31.7%               | 4 (66.7%)           |         |

There was a significant positive correlation between the number of pack-years smoked and the number of current MS symptoms (r = 0.165, p-value = 0.001). Smoking duration was also significantly correlated with
number of current symptoms (r = 0.107, p-value = 0.02). However, the duration since smoking cessation did 
not correlate significantly with the number of symptoms (r = 0.152, p-value = 0.31). Finally, the number of 
cigarettes smoked per day correlated significantly with the number of current MS symptoms (r = 0.128, p-
value = 0.01).

Relapses and Progression

There was no significant association between smoking status and relapse in the last year (p-value = 0.23). 
Neither was there an association with new MRI lesions (p-value = 0.66) nor progression in the last year (p-
value = 0.09) (Table 3). Similarly, there was no significant association between smoking duration and 
relapses in the last year (p-value = 0.74), new MRI lesion (p-value = 0.11), and progression in the last year 
(p-value = 0.056) (Table 4). Also, there was no significant association between heaviness of smoking in 
terms of relapses in the last year (p-value = 0.23), new MRI lesion (p-value = 0.08), and progression in the 
last year (p-value = 0.19) (Table 5). Similarly, correlation analysis showed no significant correlation between 
smoking duration and relapses in the past year (r = 0.03, p-value = 0.47), number of cigarettes smoked per 
day and relapses (r = 0.02, p-value = 0.59), or pack-years smoked and relapses (r = -0.05, p-value = 0.50).

Walking

There was no significant association between smoking status and ability to walk on flat ground for different 
distances (p-value = 0.18) (Table 3). Similarly, there was no significant association between smoking 
duration and ability to walk different distances (p-value = 0.26) (Table 4). There was no significant 
association between heaviness of smoking and ability to walk different distances either (p-value = 0.10) 
(Table 5).

Cane

There was no significant association between smoking status and the need of a cane (p-value = 0.23) (Table 
3). In contrast, there was a significant difference between different smoking durations in terms of the need 
to use a cane (p-value = 0.05) (Table 4). However, there was no significant association between heaviness 
of smoking and the need to use a cane (p-value = 0.08) (Table 5).

Wheelchair

There was no significant association between smoking status and the need of a wheelchair (p-value = 0.55) 
(Table 3). Similarly, there was no significant association between smoking duration and the need of a 
wheelchair (p-value = 0.49) (Table 4). Also, there was no significant association between heaviness of 
smoking and the need to use a wheelchair (p-value = 0.87) (Table 4).

Self-Reported Disability Status Scale

There was no significant association between smoking status and SREDSS (p-value = 0.20) (Table 3). 
Similarly, there was no significant association between smoking duration and SREDSS (p-value = 0.27) 
(Table 5). Also, there was no significant association between heaviness of smoking and SREDSS (p-value = 
0.18) (Table 5).

Discussion

Our study showed that most PwMS do not know their disease phenotype, which is similar to what another 
study done in Jeddah reported [16]. This could reflect a lack of patient awareness of their disease or a lack 
of effective communication and education by physicians. In a study investigating patients’ awareness of MS in 
Saudi Arabia, it was reported that only 37% knew the correct definition of RRMS. Our study also showed that 
the proportion of PwMS who currently smoke (23.1%) is higher than the proportion of current smokers in 
the general Saudi population (19.8%) [17]. A study investigating awareness of smoking risk among PwMS in 
Jeddah also showed a high prevalence of active smokers (34.6%). It was also shown that most patients did 
not know whether smoking is a risk factor for MS or disagreed to this [16]. All of this shows that, indeed, 
smoking is prevalent among PwMS and can be a strong risk factor for the disease in Saudi Arabia. A previous 
case-control study investigating MS risk factors in Saudi Arabia also found smoking to be a strong risk factor 
[18].

In this study, our aim was to investigate the specific effects smoking has on MS severity and progression. We 
found that smoking is significantly associated with the presence of multiple MS symptoms. This association 
was evident in all statistical tests we performed. In addition, there was a significant difference between 
smoking duration and the need to use a cane to walk. This is consistent with what was reported in a 
previous review, which showed smoking to be associated with higher rates of disease activity, greater 
disability burden, more relapses, and faster rates of brain atrophy [19,20].

Although smoking status was significantly associated with MS phenotype, the huge proportion of people not
knowing their specific phenotype prompts a cautious interpretation of this association. It is important, however, that this association does not go unnoticed, as it could indicate that smoking has a role in the type of MS at onset or the later progression of RRMS to SPMS. This was found in a study done on over 1,400 PwMS, which showed smokers to be more likely to have PPMS and to progress from RRMS to SPMS [21].

Other variables, such as relapses in the last year, new MRI lesions, and SRDSS, were not associated with smoking on any statistical test we performed. The limited effects of smoking only on the presence of multiple symptoms, but not on disease progression or the number of MRI lesions, can be attributed to the high percentages of patients who do not know their clinical status accurately. It was shown in another study that only 42.6% of patients reported that they were well informed about their disease [22].

Multiple MS symptoms could significantly decrease patients’ quality of life. They can lead to more fatigue, more depressed mood, and more physical disability. These three clinical domains were constantly correlated to low health-related quality of life [23-25]. This study had several limitations. The cross-sectional design could lead to recall bias, and the online nature of the study could not allow the surveyor to help with any difficulty the participants face when answering the questionnaire. These effects could be responsible for many patients answering "don’t know" to several questions, which could have resulted in decreased power of the study.

Conclusions
Smoking status, heaviness, and duration were all significantly associated with the presence of multiple MS symptoms. The number of pack-years smoked was significantly correlated with the higher number of current symptoms. Smoking duration was also significantly associated with the need to use a cane to walk. Although smoking was not shown to be associated with other variables (such as relapses, new MRI lesions, and SRDSS), further studies are needed to confirm the absence of association. Also, more studies are needed to further investigate the specific symptoms associated with smoking.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Umm Al-Qura University (UQU) institutional review board issued approval HAPO-02-K-012-2021-03-625. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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