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ORIGINAL ARTICLE

Multi-angles of smoking and mild cognitive impairment: is the association mediated by sleep duration?

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Abstract

Although the association between cigarette smoking and risk of mild cognitive impairment (MCI) is controversial, most recent studies have shown that this influence is negative. However, it is unknown how multiple factors of smoking affect MCI, and the mechanisms of different smoking factors are not yet clarified. This study will examine the impact of various angles of smoking on MCI and the potential mediating effects of sleep duration on smoking MCI association in the elderly. In the case group, 109 elderly people who met the inclusion criteria were selected, and 123 were selected in the control group. Participant characteristics include sleep duration and a detailed lifetime history of smoking. After adjusting the relevant covariates, higher odds of MCI occurrence were found in ex-smokers/current smokers; moderate/heavy smokers; smokers for 30–44, 45–59 and more than 60 years; smokers with cumulative smoking duration of 30–44 or more than 60 years and smokers with cumulative dose smoking intensity of 200–399 or 400–599 cigarettes monthly. Elderly subjects who had quit smoking for 21 years or longer were found to have lower odds of MCI occurrence. The indirect effects of smoking on MCI via sleep duration were statistically significant, as the ratio of indirect effect to total effect ranged from 0.14 to 0.29. Smoking affects cognitive function through multi-angles of smoking and influences the cognitive function partly via the duration of sleep.

Keywords Smoking · Mild cognitive impairment · Dementia · Sleep

Introduction

The World Alzheimer Report 2015 [1] states that there are over 9.9 million new cases of dementia each year worldwide, which implies one new case every 3.2 s. Furthermore, the World Alzheimer Report 2016 [2] explains that due to the insidious onset of cognitive function decline, only 40–50% of those living with dementia in high-income countries have received a diagnosis, a rate that is unlikely to exceed 5–10% in low- and middle-income countries. Mild cognitive impairment (MCI) is viewed as a transitional stage from normal health to dementia, with a conversion rate of 60.5~100% to dementia in 5~10 years [3, 4]. Given limitations of therapeutic methods for dementia, an understanding of risk factors and interventional therapies for MCI is crucial for the development of preventive projects and early interventions.

Cigarette smoking is a widespread lifestyle practice worldwide and independently associated with incidence of MCI [5–7]. In 2012, 31.1% of all men and 6.2% of all women were daily smokers [8], and in China, more than three hundred million adults smoke [9]. Although several very early studies have reported that smoking played a protective role in cognitive function because of the short-time beneficial effect of nicotine on cognitive performance [10, 11], recent prospective studies and meta-analyses have indicated a negative impact of smoking on cognition, and it has been increasingly recognised that smoking is a risk factor for cognitive function [6, 12]. Meanwhile, not only the smoking status but also the smoking duration links to cognitive function, as evidenced by studies

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showing that current smokers had an increased risk of Alzheimer's disease (AD) compared with former smokers, while exposure to smoking during mid-life predicted greater cognitive impairment in later life [6, 13]. Additionally, certain studies state that smoking reduction/cessation can ameliorate cognitive status [14, 15].

Individuals with sleep complaints often exhibit unhealthy lifestyles such as smoking. Some smokers may be motivated to smoke at night due to the emergence of nicotine withdrawal symptoms within a few hours of going to sleep, and waking during the night to smoke would seem to represent an intrusion to sleep [16]. An early study has suggested that cigarette smokers were significantly more likely than non-smokers to report problems in going to sleep and problems staying asleep [17]. The rates of current cigarette smokers varied according to the usual hours of sleep and were lowest among adults who suffered sleep loss or excessive sleep duration [18]. A recent study involving 9893 subjects indicated that cigarettes smoked per day and prevalence of heavy smoking were higher in the short-sleep group and lower in the excessive-sleep group [19].

Almost half of older adults have reported at least one sleep problem [20]. One of the problems is sleep deprivation, which leads to short sleep, tiredness, fatigue and ultimately cognitive decline and changes in sleep duration (decreasing from 8, 7 or 6 h to less sleep time) [21]. A previous study examined the association of sleep duration with cognitive function in a cohort of 1844 community-dwelling older women and suggested that women sleeping ≤ 5 h/night scored worse than women sleeping 7 h/night in cognitive performance [22]. However, a meta-analysis has reported a U-shaped association between sleep duration and cognitive decline, which means that either short or long sleep duration was accompanied by a higher incident risk of cognitive impairment [23].

Method

Study design and participants and groups

A standardised case-control study of MCI was established in the First Affiliated Hospital of Jilin University. According to the existing formula for calculating sample size and incidence of MCI among Chinese people [24], the result showed that at least 97 older people should be included in each group. All participants who enrolled in this study met the enrolment criteria and provided written consent to participate in study. The eligibility criteria for all participants were ages of 60 or older. The participants in the group complied with Petersen's MCI criteria [3] ((1) subjective cognitive complaint; (2) objective cognitive impairment, defined as scoring below 1.5 standard deviation from the mean (according to age- and education-specific norms) on the Mini-Mental State Examination Scale; (3) essentially preserved daily functioning, defined as scoring ≤ 26 on the Activity Daily Living Scale; (4) not demented, defined as scoring 0.5 on the Clinical Dementia Rating Scale and > 7 on the Hachinski Ischemic Scale). The exclusion criteria were history of stroke and other related history of mental diseases such as neurological disorders, brain trauma or head injury resulting in loss of consciousness or depression/anxiety, as diagnosed by physician.

Independent variables (multi-angles of smoking)

Information regarding smoking metrics is in reference to the guidelines for smoking from the World Health Organization (WHO) [25]. Participants who had smoked at least 100 cigarettes in their life were defined as smokers, otherwise, as non-smokers. With regard to smoking status, smokers were classified as light smokers who smoked 10 or less cigarettes per day and moderate smokers who smoked over 10 but less than 20 cigarettes daily, as well as heavy smokers who smoked 20 or more cigarettes daily. Smoking duration indicates the period since initiation of smoking. Smoking cessation duration indicates the sum of duration of quitting smoking. Cumulative smoking duration indicates the smoking duration minus the smoking cessation duration, while cumulative dose of smoking intensity was calculated by dividing the cumulative smoking duration by the smoking duration and then multiplying the quantities of cigarettes per month. Passive smoking indicates that the never smokers were exposed to the cigarette smoke that smokers produced more than 1 day in 1 week and for at least 15 min each time. The Fagerstrom test for nicotine dependence (FTND) [26] is considered to be a self-reporting tool that conceptualises dependence through physiological and behavioural symptoms. A total score for nicotine dependence (FTND) was obtained, and ≥ 6 indicated severe dependence. There were no other types of smoking such as pipe or water-pipe smoking Table 1.

Other potentially relevant variables

Sociodemographic factors

Sociodemographic variables included age, sex, school education and marriage status. Age was used as a continuous variable, and sex (male and female), school education (illiterate, primary school, junior middle school, high school and college/university) and marriage status (married, unmarried and divorced/widowed) were used as categorical variables.

Anthropometric and lifestyle factors

The body mass index (BMI) was calculated as weight in kilogrammes divided by square of the height in metres (kg/m^2) and was defined as a continuous variable. Sleep duration

Table 1 Information regarding multi-angles of smoking

Information regarding multi-angles of smoking (unit)	Classification
Smoking	Smokers, never smokers
Smoking status	Never smokers, ex-smokers, current smokers
Smoking intensity	Light smoker, moderate smokers, heavy smokers
Smoking duration (year)	0~30, 30~39, 40~49, 50–59, 60~
Smoking cessation duration (year)	0~10, 10~20, 21~
Cumulative smoking duration (year)	0~15, 15~29, 30~44, 45~59, 60~
Cumulative dose of smoking intensity (in cigarettes per month)	0–199, 200–399, 400–599, 600~
Passive smoking	Yes, no
Nicotine dependence (severe dependence)	Yes, no

was assessed with the question 'how many hours including the daytime sleep do you have usually?' Physical activity duration was also collected as a continuous variable. Drinking was categorised as non-drinker and drinker.

Physical conditions

Historical or current heart diseases, hypertension, hyperlipaemia and diabetes were included as binary variables (yes/no). A diagnosis was made if the participants fulfilled any of the available criteria, and the presence of all these diseases were testified by medical records or physician reports. Other relevant diseases, family history and medication use were also recorded to avoid omitting important content.

Mental conditions

The Hamilton Depression Rating Scale and Hamilton Anxiety Scale were used to assess the mental status of the participants.

Statistical analysis

Descriptive analyses were conducted to characterise study samples. These analyses included unweighted frequencies, weighted proportions, means and standard deviation ($\bar{\chi} \pm$ SD). Significance tests for differences in ($\bar{\chi} \pm$ SD) and proportions were conducted using the *t* test and chi-squared test, if data followed the standard normal distribution; otherwise, the Wilcoxon rank sum test (*z*-test) was performed for non-normal data.

To explore the correlation between multi-angles of smoking and MCI, first risk factors of MCI were identified by using non-conditional logistic regression analysis. Subsequent adjusted models included all the aforementioned risk factors simultaneously to estimate the association between multi-angles of smoking and MCI; the results were expressed as odds ratio (OR) and 95% confidence intervals (CIs). The Hosmer-Lemeshow test was performed for goodness-of-fit.

Mediation analysis was conducted by the PROCESS procedure for SPSS 23.0. Data on multi-angles of smoking were selected as continuous variables. All of these analyses were adjusted for covariates included in the non-conditional logistic regression analysis above. Unstandardised coefficients (β) with their standard errors (SE) were reported for each model. Bias-corrected (BC) 95% CIs for the indirect effects were generated from 1000 bootstrap samples, and statistical significance was indicated when the CI values did not cross zero. Bootstrapping is recommended for testing of indirect effects because it does not assume normality in sampling distribution. All statistical analyses were conducted using IBM SPSS 23.0, and all tests were two sided with the significance level set at $p < 0.05$. Zhao et al. [27] have described the procedure that can be used to investigate the mediating effect of this study (Fig. 1).

Results

Baseline characteristics

The characteristics of study participants are presented in Table 2, and there were statistically significant differences between the two groups in terms of age, sex, BMI, sleep duration, physical activity duration, diabetes, smoking, drinking, depression and anxiety. The number of participants who were smokers with MCI was twice the number of those who were never smokers. After adjusting for the pertinent variables above, the risk factors of MCI included age, sex, sleep duration, drinking and smoking.

Multi-angles of smoking (Smoking metrics)

The smoking metrics for multi-angles of smoking are shown in Table 3. There were significant differences in the two groups with respect to smoking, smoking status,

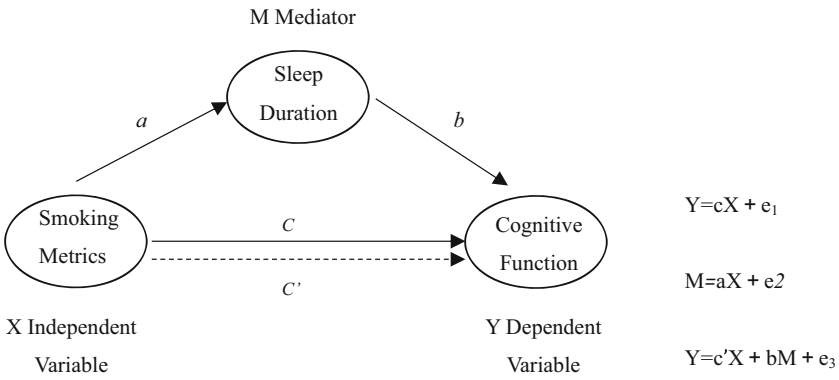

Fig. 1 Mediating role of smoking in smoking MCI association

smoking intensity, smoking duration, smoking cessation duration (year), smoking cessation duration (year), cumulative smoking duration (year) and cumulative dose of smoking intensity (in cigarettes per month), whereas the differences were not significant with regard to nicotine dependence and passive smoking.

The effects of multi-angles of smoking on MCI

Smoking status and MCI

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.485$). After adjusting age, sex, sleep duration and drinking, compared with the elderly who were never smokers and the elderly who were ex-smokers, current smokers were found to exhibit 3.042 and 2.628 times higher odds of MCI occurrence (OR = 3.042, 95% CI = 1.456–6.356 and OR = 2.628, 95% CI = 1.106–6.245), respectively (Supplementary 1).

Smoking intensity and MCI

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.869$). After adjusting the age, sex, sleep duration and drinking, compared with the elderly who were never smokers and the elderly who were moderate smokers, heavy smokers were found to exhibit 4.200 and 3.116 times higher odds of MCI occurrence (OR = 4.200, 95% CI = 1.856–9.505 and OR = 3.116, 95% CI = 1.203–8.070), respectively (Supplementary 2).

Smoking duration

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.348$). After adjusting the age, sex, sleep duration and drinking, compared with the elderly who were never smokers, the elderly who had been smokers for 30–44, 45–59 and more than 60 years were found to exhibit 2.727, 2.870 and 3.775 times higher odds of MCI occurrence (OR = 2.727, 95% CI = 1.042–7.140, $p = 0.041$; OR = 2.870, 95% CI = 1.133–7.271, $p = 0.026$ and OR = 3.775, 95% CI = 1.328–10.731, $p = 0.013$), respectively (Supplementary 3).

Smoking cessation duration

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.103$). After adjusting the age, sex, sleep duration and drinking, compared with the elderly who had quit smoking for less than 10 years, the elderly who had quit smoking for 21 years were found to exhibit 0.236 times lower odds of MCI occurrence (OR = 0.236, 95% CI = 0.079–0.707, $p = 0.010$) (Supplementary 4).

Cumulative smoking duration

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.898$). After adjusting the age, sex, sleep duration and drinking, compared with the elderly who were never smokers, the elderly who had a cumulative smoking duration for 30–44 years or more than 60 years were found to exhibit 3.838 and 15.637 times higher odds of MCI occurrence (OR = 3.838, 95% CI = 1.595–9.233, $p = 0.003$), (OR = 15.637, 95% CI = 1.604–152.424, $p = 0.018$), respectively (Supplementary 5).

Cumulative dose of smoking intensity

The multivariable model showed no evidence of lack of fit based on the Hosmer-Lemeshow statistic ($p = 0.823$). After adjusting the age, sex, sleep duration and drinking, compared with the elderly who were never smokers, the elderly who had a cumulative dose smoking intensity of 200–399 and 400–599 cigarettes monthly were found to exhibit 3.883 and 5.622 times higher odds of MCI occurrence (OR = 3.883, 95%

Table 2 Characteristics of the study participants

Characteristics	MCI (109)	Controls (123)	$t/\chi^2/z$	p value
Age	79.57 ± 8.50	76.50 ± 9.00	2.657*	0.008
Sex, *n* (%)				
Male	50 (45.87)	74 (60.16)	4.744*	0.029
Female	59 (54.13)	49 (39.84)		
Education, *n* (%)				
Illiterate	41 (37.61)	31 (25.20)	7.556△	0.109
Primary	22 (20.18)	24 (19.51)		
Junior high school	16 (14.68)	17 (13.82)		
Senior high school	16 (14.68)	20 (16.26)		
College/university	14 (12.84)	31 (25.20)		
Marriage, *n* (%)				
Married	63 (57.80)	77 (62.60)	1.572△	0.456
Unmarried	1 (0.92)	0 (0.00)		
Divorced/widowed	45 (41.28)	46 (37.40)		
BMI (kg/m^2)	22.12 ± 3.51	23.15 ± 4.08	2.041*	0.042
Sleep duration (h/per day)	5.21 ± 1.62	6.60 ± 2.44	5.071*	0.000
Physical activity duration (h/per day)	3.32 ± 3.12	5.07 ± 5.67	2.191▲	0.028
Chronic diseases				
Hypertension, *n* (%)				
Yes	76 (66.97)	67 (54.47)	5.686△	0.017
No	33 (33.03)	56 (45.53)		
Hyperlipaemia, *n* (%)				
Yes	43 (39.45)	39 (31.71)	1.516△	0.218
No	66 (60.55)	84 (68.29)		
Diabetes, *n* (%)				
Yes	56 (51.38)	45 (36.59)	5.143*	0.023
No	53 (48.62)	78 (63.41)		
Heart diseases, *n* (%)				
Yes	75 (68.81)	79 (64.23)	0.543△	0.461
No	34 (31.19)	44 (35.77)		
COPD, *n* (%)				
Yes	24	16	3.288	0.07
No	86	107		
Smoking, *n* (%)				
Yes	72 (66.06)	51 (41.46)	14.03△	0.000
No	37 (33.94)	72 (58.54)		
Drinking, *n* (%)				
Yes	64 (58.72)	56 (45.53)	4.025△	0.045
No	45 (41.28)	67 (54.46)		
Depression	3.46 ± 2.06	2.59 ± 2.16	−3.110*	0.02
Anxiety	3.45 ± 1.94	2.84 ± 1.99	−2.371*	0.019

Unweighted frequencies (*n*), weighted mean and proportions and the mean ± deviation are displayed. *n*, number (frequencies); *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease.

*t, t test; △ χ^2, chi-squared tests; △ z, Wilcoxon rank sum test

CI = 1.531–9.852, $p = 0.0034$ and OR = 5.622, 95% CI = 1.902–16.616, $p = 0.002$), respectively (Supplementary 6).

The mediating role of sleep duration in smoking MCI association

Smoking intensity

After adjusting for age, sex and drinking, the direct effects of smoking intensity on cognitive function remained significant ($p = 0.0096$). Sleep duration appeared to partially mediate the smoking MCI association, as the corresponding 95% CIs do not include zero (boot 95% CI = 0.1316–0.0184). The ratio of the indirect effect to the total effect (ab/c) was 0.25.

Smoking duration

After adjusting for age, sex and drinking, the direct effects of smoking intensity on cognitive function remained significant ($p = 0.0000$). Sleep duration appeared to partially mediate the smoking MCI association, as the corresponding 95% CIs do not include zero (boot 95% CI = 0.0175–0.0020). The ratio of the indirect effect to the total effect (ab/c) was 0.14.

Cumulative smoking duration

After adjusting for age, sex and drinking, the direct effects of smoking intensity on cognitive function remained

Table 3 Detailed information regarding multi-angles of smoking

Multi-angles of smoking	MCI group (109)	Control group (123)	χ^2/z	*p* value
Smoking				
Yes	72 (66.06)	51 (41.46)	14.030△	0.000
No	37 (33.94)	72 (58.54)		
Smoking status				
Never smokers	37 (33.94)	72 (58.54)	14.056△	0.001
Ex-smokers	49 (44.95)	34 (28.46)		
Current smokers	23 (17.83)	17 (13.83)		
Smoking intensity				
Never smokers	37 (33.94)	72 (58.54)	−4.135▲	0.000
Light smokers	15 (47.70)	19 (15.45)		
Moderate smokers	34 (31.19)	20 (16.26)		
Heavy smokers	23 (21.10)	12 (9.80)		
Smoking duration (year)				
Never smokers	37 (33.94)	72 (59.34)	−3.731▲	0.000
< 30	8 (7.34)	6 (4.88)		
30–39	8 (7.34)	5 (4.07)		
40–49	17 (16.00)	14 (11.38)		
50–59	19 (17.43)	16 (13.01)		
60-	20 (18.34)	10 (8.13)		
Smoking cessation duration (year)				
0–10	24 (52.17)	50 (64.94)	−2.847▲	0.004
11–20	12 (26.09)	8 (10.39)		
> 21	10 (21.74)	19 (24.68)		
Cumulative smoking duration (year)				
Never smokers	37 (33.94)	72 (58.54)	−4.056▲	0.000
<15	6 (5.50)	2 (1.62)		
15–29	13 (11.93)	18 (14.63)		
30–44	26 (23.85)	17 (13.82)		
45–59	17 (39.45)	13 (10.57)		
60-	10 (9.20)	1 (0.81)+		
Cumulative dose of smoking intensity (in cigarettes per month)				
0–199	18 (25.00)	23 (45.10)	−1.972▲	0.049
200–399	24 (33.33)	13 (25.49)		
400–599	18 (25.00)	8 (15.69)		
600-	12 (16.67)	7 (13.73)		
Nicotine dependence (severe dependence)				
Yes	16 (22.22)	9 (17.65)	0.386△	0.543
No	56 (77.78)	42 (82.35)		
Passive smoking				
Yes	20 (20.18)	29 (23.58)	0.948△	0.310
No	89 (79.82)	94 (76.42)		

△ χ^2 test, ▲ *z* test

significant ($p = 0.0001$). Sleep duration appeared to partially mediate the smoking MCI association, as the corresponding 95% CIs do not include zero (boot 95% CI = 0.0242–0.0042). The ratio of the indirect effect to the total effect (ab/c) was 0.17.

Cumulative dose of smoking intensity

After adjusting for age, sex and drinking, the direct effects of smoking intensity on cognitive function remained significant ($p = 0.0339$). Sleep duration appeared to partially mediate the smoking MCI association, as the corresponding 95% CIs do not include zero (boot 95% CI = 0.0018–0.0002). The ratio of the indirect effect to the total effect (ab/c) was 0.29.

Discussion

The effect of smoking on MCI

In this study, the smoking status, smoking intensity, smoking duration, smoking cessation duration, cumulative smoking duration and cumulative dose of smoking intensity were assessed in relation to the incidence of MCI. Moreover, the effect of smoking affected MCI partially via sleep duration.

Regarding smoking status, being ex-smokers and current smokers were significantly associated with increased risk of MCI compared to never smokers in this study. It has been reported that chronic smoking contributes to the development of cardiovascular disease and coronary heart disease by elevating the level of inflammatory factors such as C reactive protein, which affects cognitive function in

the long term [28, 29]. Interestingly, the risk in ex-smokers (3.042) was higher than that in current smokers (2.628). This result is inconsistent with previous studies that reported that compared with ex-smokers; current smokers had a worse cognitive status, with current smokers exhibiting lower scores in cognitive assessment and an increased risk of incidence of AD [6, 13]. Moreover, a study showed that after adjusting for certain demographic covariates, current smokers exhibited worse cognitive function than ex-smokers in bipolar disorder and schizophrenia patients [7]. A reason for this discrepancy might be that there is a dose-response relationship between the amount smoked and disease risk for MCI, regardless of the smoking status, which means that ex-smokers might reflect a dose effect [30]. A study has reported that an association was found between greater smoking duration and poorer cognitive function in men and between smoking cessation and better cognitive function in women [15]. Another potential cause might be impaired cognitive function with respect to performance of complex information-processing tasks and memory performance in elderly ex-smokers [31, 32].

Regarding smoking intensity, the substantial increase in the risk of MCI among moderate and heavy smokers (both OR > 3) that we observed in our study is consistent with those previous reports [5, 6, 13]. According to a meta-analysis, which aimed to determine the effect of smoking intensity for women and men, and a study that presented gender differences regarding the effect of smoking intensity, the most important conclusion was that smoking intensity was a risk factor for disease in both women and men [5]. It is a fact that smokers, especially those who are heavy smokers, have worse memory and executive function; these might be due to structural deficits in smokers' brains in regions of the frontal lobe and the thalamus that are critical for such cognitive abilities, and such structural deficits become more serious with increasing level of smoking [14, 33, 34].

Regarding smoking duration and smoking cessation duration, an almost constant rise in the risk of MCI was found with rise in the level of smoking duration, while those who had quit smoking for more than 20 years exhibited a lower risk of developing MCI; however, participants who had quit smoking for 11–20 years did not have a significantly positive influence on MCI. It is easy to understand the positive effect of longer smoking cessation on MCI, because quitting smoking over 20 years might reverse the impaired structural integrity of the cerebral white matter [35]. In terms of smoking duration, for equal pack years, smoking fewer cigarettes per day for a longer duration was more deleterious than smoking more cigarettes per day for shorter duration [36]. This result was consistent with that observed in a study conducted in four different areas of the USA, in terms of the effect of smoking on heart disease [37]. However, the underlying mechanism still needs to be further explored.

Regarding cumulative smoking duration and cumulative dose of smoking intensity, the study aimed to explore the impact of cumulative quantities of cigarettes on cognitive function; regardless of the influence of smoking cessation, a dramatic increase in the risk of MCI (OR 15.637) was observed in smokers who consumed cigarettes over 60 years. During the whole lifetime, a higher risk of MCI was observed in the elderly who had 400–599 cigarettes intake per month compared with those who smoked more than 600 cigarettes monthly. The reason for this result might be population bias, which results in insufficient number of smokers in the group smoking more than 600 cigarettes monthly. Smoking has an effect on MCI, according to the cumulative scales. One study revealed that after adjusting the age and cardiovascular factors, greater cumulative smoking duration is yet a causal risk factor for reduced prior cognitive performance [15]. The underlying mechanism behind this process might be that cumulative tobacco intake over time has chronic and cumulative influence on the haemostatic system, with constantly increased levels of fibrinogen and plasma viscosity, which in turn have been associated with cognitive decline and changes in reaction time [38–40].

The mediating role of sleep duration

The present study revealed that sleep duration plays a significant mediating role in the smoking MCI association. The effect on MCI incidence with respect to being heavy smokers, long-time smokers and those smokers who had a longer cumulative smoking duration and massive cumulative dose of smoking intensity may be due partly to an indirect effect through sleep duration. There are several biologically plausible mechanisms such as oxidative stress and the removal of amyloid β protein that may explain how the speculated smoking-sleep-duration-MCI causal pathway might work.

It is widely known that chronic cigarette smoking is associated with elevated cerebral oxidative stress (OxS) such as F_2-isoprostane, which plays a significant role in decreased sleep duration [41, 42]. Moreover, shortened sleep duration or sleep deprivation has been shown to induce oxidative stress, which causes cognitive impairment. However, since the severity of obstructive sleep apnea (OSA) is independently associated with oxidative stress, it is necessary to take OSA into consideration in regard to the role of sleep in cognitive deficiency [43]. Furthermore, factors including total sleep time, rapid eyes movements (REM) duration, time spent awake during sleep and wake after sleep onset (WASO) time related to OSA patients should be considered as well [44]. Additionally, a constant decrease in melatonin, which is a chief secretory product of the pineal gland and a potent antioxidant that prevents sleep deprivation, as a result of smoking-induced oxidative stress can continuously damage the cognitive function in either animals or human beings [42, 45].

The smoking MCI association might also be caused by inefficient removal of Aβ as a result of smoking, as well shortened sleep duration. It is also a commonly accepted fact that a major pathological change associated with AD is the deposition of Aβ in the brain, which can be caused by lower efficiency of Aβ clearance [46]. The Aβ clearance from AD brains was approximately 30% lower than in controls; however, Aβ production in the brains of AD patients was reported to be similar to that of normal subjects [47]. Smoking is a factor that affects Aβ removal; a recent experiment that investigated a therapeutic strategy for AD by removing blood amyloid presented that the removal efficiencies for Aβ in smokers significantly decreased, whereas the efficiencies for non-smokers showed a tendency to increase [48]. Meanwhile, sleep deprivation resulted in chronic accumulation of Aβ and, in turn, increased the level of Aβ, which may be caused by this process, and smoking affected cognitive function [49]. Overall, the mediating role of sleep duration suggested that sleep or sleep disturbance is involved in the smoking MCI association. A previous meta-analysis has shown that compared with HE, MCI patients showed less total sleep time, which also indicated insomnia, sleep efficiency, more sleep latency and a cyclic alternating pattern [50]. Therefore, in future studies, it is necessary to investigate the history of insomnia, the use of insomnia treatments (during lifetime and current) and other possible primary sleep disturbances.

Limitation

Our study has several limitations. First, the detailed classification of the smoking metrics may result in insufficient number of smokers at certain levels such as the group with a cumulative dose of intensity of more than 600 cigarettes monthly. Moreover, no other types of smoking, such as pipe or water pipe smoking, were included. However, we believed that it can represent the general trend regarding the effect of smoking on cognitive function. Second, because the elderly in the case group exhibited MCI and their information was self-reported, it can cause some bias due to memory deficiency in MCI. However, all information was confirmed by their relatives or spouses who attended to them. Third, we were unable to utilise scales such as the Pittsburgh Sleep Quality Index for measuring objective sleep. Additionally, sleep duration only presented the average total sleep duration in 24 h, and it was not divided into night and daytime sleep; it is too subjective, and it could result in some bias. Nevertheless, such results are fundamental for further studies. Finally, the ratio of the indirect effect to total effect (ab/c) was under 1, which indicates that there are other undetected mediators; therefore, further tasks need to be undertaken to elucidate other potential mediators to offer evidence-based information for the public.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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