The Relationship Between Smoking, Passive Smoking, and Cognitive Impairment: Results from Indonesian Public Health Center Databases

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Received: 13 November 2023

Accepted: 15 May 2024

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DOI 10.5001/omj.2024.94

Abstract

Objective: Previous studies reported that smoking increases the risk for cognitive impairment, including mild cognitive impairment and dementia, because its toxins cause neuronal cell inflammation. However, few evaluated chronic passive smoking exposure on cognitive impairment. This study aims to determine the association between smoking, passive smoking, and cognitive impairment and examines the dose-response effect.

Methods: This 2-year survey is a population-based study in four scattered Indonesian public health centers from the rural areas of Giritontro, Pracimantoro, Pedan, and Karangdowo. Each public health center covers approximately 30,000 population. We used simple random sampling and obtained 409 participants aged 30-60. Smoking and passive smoking were determined by self-assessment. Mini-Mental State Examination was used to evaluate cognitive impairment. Lifestyle, socio-demographic factors, and chronic diseases were also adjusted for the study's analyses.

Results: A relationship between cognitive impairment and smoking was found with a trend of significance in elevated risk of cognitive impairment with collective pack-years, adjustment of odds ratio (OR) 1.61 (95% confidence interval [CI], 0.98 - 2.31) for ≥20 pack-years. Participants who never smoked but were passive smoking had a slightly lower risk of cognitive impairment than those who did not smoke and never smoked (adjusted OR = 2.01; 95%CI, 1.37 - 2.70). They were comparable with OR of 10-19 pack-years total exposure of active smoking with an adjustment of 1.86 OR (95%CI, 1.24 - 2.42).

Conclusions: Overall results show a dose-response relationship between smoking and cognitive impairment with a significant effect on ≥20 pack-years of exposure. Passive smoking also indicates a significant risk of cognitive impairment equivalent to an estimated 10–19 pack-years of active smoking.

Keywords: neurodegenerative, cognitive impairment, dementia, smoking, epidemiology

Introduction

Cognition is the capability to analyze, comprehend, solve problems, memorize, and save information.[1] Cognitive impairment causes a significant burden on patients' daily activities, social life, and families and physicians who give their health care.[2] Both mild cognitive impairment (MCI) and dementia are marked by clear evidence of cognitive impairment. The major contrast between them is that dementia involves more than one cognitive domain in the latter disease course, and considerable interference with daily life is apparent.[3] Approximately 47 million people had dementia in 2015. Moreover, they also contribute to a financial burden of USD 818 billion, estimated to triple by 2050 worldwide. Meanwhile, 85% of those costs are directly associated with family and social support instead of medical care.[4] Several studies show that 16% of people will have MCI, and 14% will suffer from dementia by 70 years old.[5]

These disease burdens get worse as neurodegenerative diseases are not curable.[1] Thus, strategic public health promotion and prevention policies could significantly reduce costs.

Studies recommend active healthy lifestyle as hypertension prevention since 45 years old to reduce cognitive impairment incidence, as 35% of hypertension cases are accountable to a combination of modifiable risk factors. These include physical inactivity, smoking, and lack of social activities. These prevention strategies are believed to prevent or delay a third of cognitive impairment cases.[4] Numerous studies showed a consistent association between smoking and mild cognitive impairment to dementia. However, there is a lack of studies regarding passive smoking and cognitive impairment, as cigarette smoke exposure contributes to complex pro-inflammatory responses in neuronal cells.[6] Passive smoking, also known as second hand smoke (SHS), is inhalation of others' tobacco smoke. Cancer, heart disease, and early degenerative diseases can become more likely as a result. All passive smoking is harmful, but it poses a special risk to children.[7] As the population ages, the prevalence of cognitive impairment is believed to rise significantly over the following decades, especially in low-to-middle-income countries such as Indonesia.

Nowadays, 40.3% of Indonesia's population are active smokers. Moreover, 37.7% of Indonesian adolescents aged 13 to 15 had smoked cigarettes.[8] More than 70% of them smoke 2-3 times daily within the house among their non-smoker families.[9] Those statistics show an alarming national burden as smoking habits will deteriorate cognitive performance in the future and harm surrounding passive smoking person.[10] According to the abovementioned issues, this study aims to determine the association between smoking, passive smoking, and cognitive impairment in Indonesia.

Methods

This population-based epidemiologic study was performed from 2021 to 2023 in a densely populated rural area in Central Java province, such as Giritontro, Pracimantoro, Pedan, and Karangdowo, with a total of 180,000 adult population. Their medical records were retrieved from the Sistem Informasi Manajemen Puskesmas. In the first attempt at participant recruitment, we obtained 17,526 family units, defined as at least one active smoking person with at least one passive smoking adult family member within the same house. Following the first recruitment step and informed consent participation, 3,179 participants aged 30 or older were obtained by simple random sampling method. The cognitive impairment symptoms, lifestyle, psychosocial, anthropometrics, and comorbidities were obtained from participants' self-answered questionnaires to report questions about their cognitive disturbances. Instead of cognitive impairment due to degenerative process, several metabolic disturbances such as Thyroid diseases, Cushing syndrome, pernicious anemia, drug or substance abuse, alcohol consumption or abuse, and depressive disorder were excluded from this study as they are treatable dementia.[11]

Cognitive impairment was assessed using Mini-Mental State Examination (MMSE), a validated and self-reported global assessment of cognitive status.[12] MMSE assesses orientation to place and time (10 points), short-term memory or retention (3 points), concentration (5 points), short-term memory or recall (3 points), language (fluency, comprehension, repetition), and visuospatial abilities (9 points). MMSE assessment takes 7 minutes and usually asks the same questions regarding who performed the test.[13] The normal cognitive score of MMSE ranges between 30 and 24. The severity of cognitive impairment is classified into three categories as MCI (MMSE score ranges between 23-20), moderate dementia (19-10), and severe dementia (9-0).[12] The MMSE was performed by two qualified physicians (Indonesian Medical Council Registry Number: IT00000428532427 and PZ00000428528889).

The status of active smoking was obtained by self-report with the baseline assessment of whether the participants were smoking currently and if they had smoked at least 100 tobacco cigarettes in their lifetime. Its status was classified into never (<100 and currently not smoking), former (>100 and currently not smoking), and current smoker (>100 and currently smoking). This retrospective self-reporting information on smoking behavior applies to prevalence rates with retrospective data sources adjusted to current levels.[14] The average number of cigarettes smoked per day and the number of years smoked that both former and current smokers reported much. The pack-years of the smoking parameter are calculated by multiplying 20 cigarettes or one pack per day and the number of years of smoking. It is classified as ≥20, 19-10, and <10 pack-years. This retrospective categorization has been shown to reduce the incidence of misclassification bias.[15] Passive smoking or SHS is interpreted as a non-smoking person living with active smokers at home daily. Cigarette smoke exposure to passive smoking at home was evaluated by self-report. The variables of smoking status, years of smoking, and exposure to SHS were combined into five groups of variables to avoid the effects of passive and active smoking and evaluate dose-response patterns. They consist of never smoking, no exposure to SHS, active smokers without exposure to SHS, current or former smokers with ≥20, 19-10, and <10 pack-years.

The categorical variables included: age, 30-39, 40-49, 50-59, ≥60; sex, male or female; education, illiterate, primary, secondary, higher; body mass index (BMI), <25, 25-30, ≥30 kg/m2; physical activity according to Physical Activity Scale for the Elderly (PASE) questionnaire, <100, 100–249, ≥250 with more score showing more physical activities[16]; comorbidities such as cardiovascular disease (CVD), hypertension, and diabetes mellitus (DM).

A continuous variable used means and standard deviation (SD). Simple proportions of descriptive statistics used categorical variables sample analyses. The association between cognitive impairment and both smoking and passive smoking was determined by linear regression. Multiple linear regression models adjusted the possible confounding

outcome of covariates. We also reported the MMSE scores' adjusted mean and regression coefficients. The analyses were reperformed with cognitive impairment interpreted as a dichotomous variable applying MMSE cutoff score of <24 (MCI, moderate dementia, and severe dementia). The relationship between dichotomous cognitive impairment and smoking status was evaluated using the odds ratio (OR) and 95% confidence interval (CI) by logistic regression. Multiple logistic regression models adjusted potential confounders. The results are shown for the entire participants and not stratified by sex, as the relationship between cognitive impairment and smoking was relatively similar by sex in this present study. Multiple imputations linked the plausible values of missed data.[17] According to the 2020 census, Indonesia's population determined the post-stratification of weights. Statistical analyses were performed by IBM SPSS Statistics version 22 for Windows (IBM Corp. Armonk, NY, USA).

Results

The demographic profiles of this study, including 409 participants (264 male and 145 female), are displayed in **Table 1**. The majority (>50%) of education level and smoking status were illiterate-primary school and former-present smokers, respectively. Moderate dementia constituted the most cognitive impairment in this study (44.009%). The majority of participants had ≥20 pack-years cigarette consumer and/or passive smoking. Meanwhile, they mostly had lower BMI of <25 kg/m^2 and PASE of <100. Moreover, a participant might have multiple comorbidities of CVD, hypertension, or DM. The prevalence trend of moderate dementia and dementia increased with aged. However, MCI constituted the most cognitive impairment type in the 40-49 age group (**Figure 1**) and its prevalence declined as age increased.

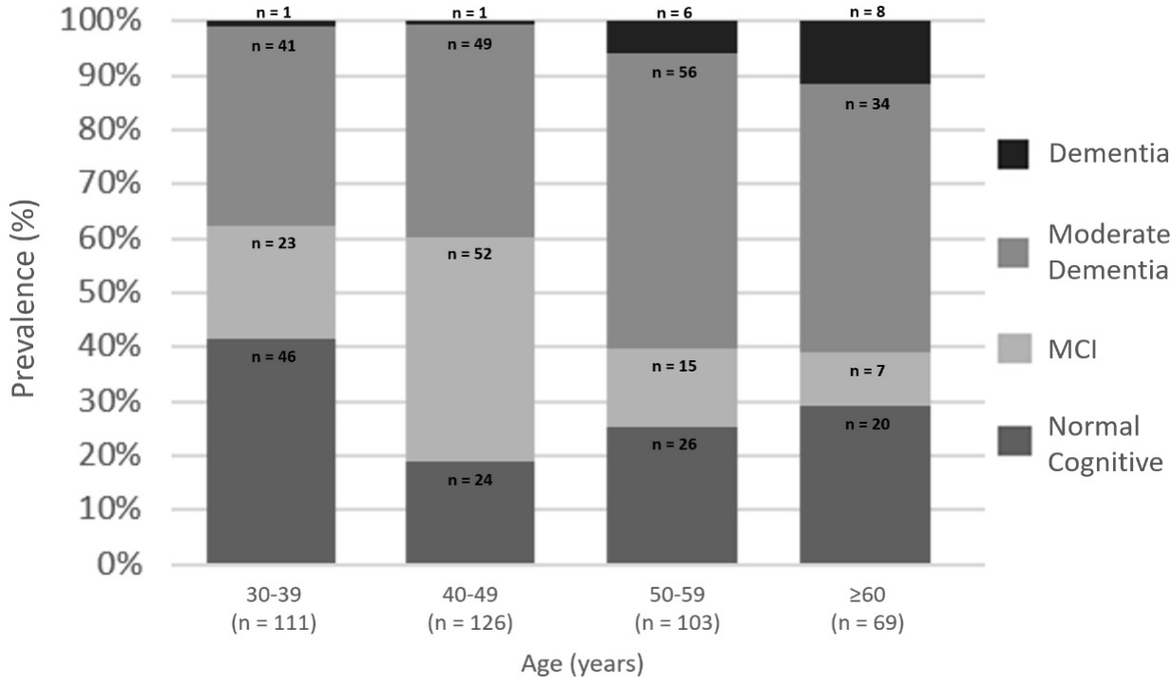

Figure 1: Prevalence of cognitive impairment according to age. MCI, Mild Cognitive Impairment.

Table 1: The variable profiles of the study demographic.

Variables	n	%
Sex		
Male	264	64.547
Female	145	35.453
Education		
Illiterate	197	48.166
Primary	109	26.650
Secondary	77	18.826
Higher	25	6.358
Cognitive Impairment (MMSE)		
Normal	116	28.361
MCI	97	23.716
Moderate Dementia	180	44.009
Dementia	16	3.914
Smoking		
Never	101	24.694
Former	150	36.674
Present	158	38.632
Pack-years		

Variables	n	%
None	91	22.249
<10	67	16.381
10-19	92	22.493
≥20	158	38.877
Passive Smoking		
No	138	33.740
Yes	271	66.260
BMI (kg/m^2)		
<25	186	45.476
25-30	121	29.584
≥30	102	24.940
Physical activity (PASE)		
<100	232	56.723
100–249	118	28.850
≥250	59	14.427
Comorbidities		
CVD	175	36.997
Hypertension	239	50.528
DM	59	12.473

BMI, Body Mass Index; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; MMSE, Mini-Mental State Examination; PASE, Physical Activity Scale for the Elderly.

The age-adjusted effect of passive smoking status on cognitive impairment by three active smoking statuses such as never, former, and current are presented in **Figure 2**. Each comparison within three active smoking categories showed a significant difference ($p < 0.05$) in the MMSE score. They also showed that the age-adjusted mean is consistently lower among passive smokers. However, the impact of leaving smoking could not be evaluated directly because the smoking cessation date was not gathered. Few significant differences between current and former active smokers are noticed, while mean MMSE scores declined as pack-years increased (**Table 2**).

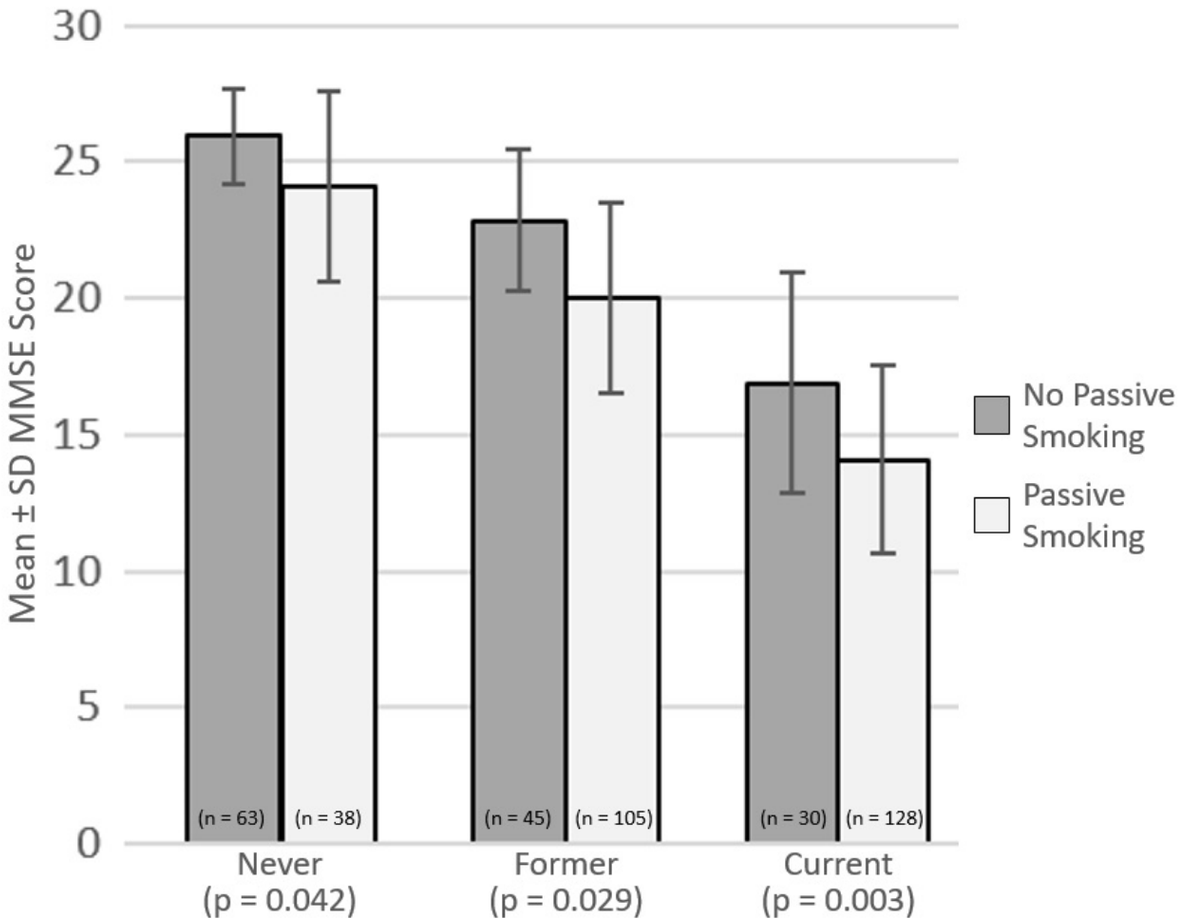

Figure 2. The effect of passive smoking status on cognitive impairment by three active smoking status categories. MMSE, Mini-Mental State Examination; SD, standard deviation.

Table 2: The relationship between smoking and cognitive impairment presents a dose-response fashion with increased pack-years.

	MMSE continuous					
	Unadjusted		**Age-adjusted**		**Multivariate-adjusted [a]**	
	β [b]	**95% CI**	**β [b]**	**95% CI**	**β [b]**	**95% CI**
Constant	22.27		23.09		22.03	
Never smoking/No passive smoking	Reference		Reference		Reference	
Never smoking/ Passive smoking	-0.71	-1.91 - 0.95	-0.61	-1,98 - 0.93	-0.38	-1.68 - 1.02
Pack-years <10	-0.42	-0.98 - 0.62	-0.23	-1.06 - 0.66	0.09	-0.79 - 0.92
Pack-years 10-19	-0.92	-2.01 - 0.26	-0.53	-1.75 - 0.92	-0.72	-1.86 - 0.68
Pack-years ≥20	-4.25	-5.32 - -2.96	-2.69	-3.28 - -1.06	-2.08	-2.36 - -0.45
Overall p-value of F-test	<0.001		0.029		0.041	
Trend test p-value [c]	<0.001		0.002		0.038	
	Cognitive impairment (MMSE ≤ 23, MCI or worse)					
	Unadjusted		**Age-adjusted**		**Multivariate-adjusted [a]**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Never smoking/No passive smoking	1.00		1.00		1.00	
Never smoking/ Passive smoking	2.19	1.43 - 2.89	2.08	1.43 - 2.88	2.01	1.37 - 2.70
Pack-years <10	1.93	1.52 - 2.41	1.78	1.29 - 2.32	1.53	1.02 - 2.11
Pack-years 10-19	2.05	1.38 - 2.70	1.65	1.01 - 2.25	1.86	1.24 - 2.42
Pack-years ≥20	4.01	2.94 - 5.10	1.86	0.98 - 2.73	1.61	0.98 - 2.31
Overall p-value of F-test	<0.001		0.072		0.098	
Trend test p-value [c]	<0.001		0.004		0.023	

95% CI, 95% confidence intervals; β, regression coefficient; OR, odd ratio; MMSE, Mini-Mental State Examination; MCI, Mild Cognitive Impairment.

[a] *Adjusted for sex, education, physical activity based on Physical Activity Scale for the Elderly (PASE) score, comorbidities such as cardiovascular disease, hypertension, and diabetes mellitus.*

[b] *Coefficient of linear regression*

[c] *The p-value of linear trend test covering pack-year variable accompanied by variable of never smoker/no passive smoking group as category of reference.*

The relationship between cognitive impairment (evaluated using the continuous MMSE) and smoking (using six categorical variables integrating passive and active smoking status and pack-years information) is shown in **Table 2**. It indicates that elevated pack-years smoking was accompanied by lower MMSE score or higher severity of cognitive impairment, with the bold effect seen amidst those with smoking exposure ≥20 pack-years. Furthermore, its effect persisted significantly (coefficient of regression excludes 0 with 95% CI) after adjusting sex, education level, PASE, and comorbidities such as CVD, hypertension, and DM.

A declined trend of MMSE score over smoking pack-years continued to remain significant following possible confounders adjustment (trend test p-value = 0.038). A few significant passive smoking effects were noticed across never-active smoking with the extent of passive smoking effect (multivariate-adjusted regression coefficient, β = -0.38, 95%CI, -1.68 - -1.02) was proportional with 10-19 pack-years (β = -0.72, 95%CI, -1.86 - 0.68). Indistinguishable results were noticed at repeated analyses, and cognitive impairment was interpreted as a dichotomous variable with an MMSE score cutoff of ≤23. Increased pack-years followed an increased OR that caused a dose-response effect (trend test p-value = 0.023) and 1.61 OR (95%CI, 0.98 - 2.31) for those ≥20 pack-years of exposure. The extent of the relationship for passive smoking across never smoking with 2.01 OR (95%CI, 1.37 - 2.70) was proportional towards 10-19 pack-years with OR of 1.86 (95%CI, 1.24 - 2.42).

Discussion

Regarding active smoking and cognitive impairment, this present study's result is similar to previous reports on different countries. In American elderly population showed that tobacco smoking is related to the risk of cognitive dysfunction, including former smokers (>100 cigarettes in life and quit smoking) 3.12 (95% CI, 1.51 to 4.73).[18] Furthermore, a case-control study in Poland regarding the association between tobacco smoking and cognitive performance in psychosis patients showed that schizophrenic smokers revealed lower scores on delayed memory tests and immediate memory than schizophrenic non-smokers (p = 0.002; 47.1±6.4 vs. 52.0±4.0, p = 0.001, respectively).[19] A study in the Pakistani population aged 18-30 about the effect of nicotine smoking on cognitive performance showed that the correct attention-switching tasks percentage trials was significantly higher (p = 0.001) in non-smokers (96.95±2.18) than in smokers (83.75±11.22).[20] Tobacco smokers aged 18-29 in the United Kingdom also showed a significant cognitive decline in sustained attention (p= 0.005), executive planning (p= 0.002), and spatial working memory (p= 0.004) compared to non-smokers after the matching of education, income, and gender covariates.[21] However, there were no data regarding the effect of passive smoking on cognitive decline.

In general, this present study resulted in a dose-response effect of ≥20 pack-years associated with cognitive impairment even following covariates risk factors adjustments such as older age, CVD, hypertension, diabetes, and higher BMI. Severe smoking is related to cognitive decline in young-to-middle age. High concentrations of nicotinic

acetylcholine receptors (nAChRs), nicotinic α4β2, and α7 receptors in the brain might be caused by nicotine-containing tobacco smoking.[22] They cause changes in the hemostasis of dopamine, serotonin, and norepinephrine. As a downstream consequence, high α4β2, α7 receptors, and nAChRs lead to significant cognitive deficits in learning-memory, attention, executive, and sensory-motoric function.[23]

Although the pathomechanism of passive smoking on cognition has not been extensively reported, several pathomechanism in other body systems have been reported. Long-term SHS exposure increased the concentration of inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-17A in the lungs and impaired adaptive immunity.[24] In general, cigarette smoking deteriorates adaptive immune cells of CD4+ and CD25+ regulatory T cells, T helper cells (Th1/Th2/Th17), B cells and memory T/B lymphocytes, and CD8+ T cells. On the other hand, it impacts dendritic cells, NK cells, and macrophages of innate immunity.[25,26] Respectively, those immunity declines cause an increase in the neurodegenerative components such as quinolinic acid and 3-hydroxykynurenine and a decrease in the kynurenic acid neuroprotective of the kynurenine pathway. These processes are believed cause pathological neural changes.[27] Cigarette smoking also damages the cortical neurons and causes neuronal necrosis. Consequently, chronic active smoking may lead to brain structural changes, especially in the insula and superior frontal gyrus, compared to non-smokers ($p = 0.02$ and $p = 0.05$, respectively) according to the resting-state functional magnetic resonance imaging and global brain connectivity method.[28] The well-established role of both insula frontal lobes is for managing the higher executive function of memorization, and their damage may cause amnesia or forgetfulness.[29]

Regarding research covariates, males smoke tobacco at higher rates than females. Across the US population, approximately 16.7% of adult men and 13.6% of women smoked tobacco in 2015.[30] In 2021, about 29% of the Indonesian population aged 15 or more were smokers. The rate of female smokers in Indonesia tends to decline from 6.9% in 2000 to 3.7% in 2020. Meanwhile, the Global Youth Tobacco Survey 2014 revealed that 20.3% of Indonesian students aged 13-15 were active smokers, including 19.4% smoking tobacco, 18.3% smoking cigarettes, and 2.1% consuming smokeless tobacco.[9,31] Participants with lower education levels, lower PASE scores, and higher BMI, especially active and passive smokers with comorbidities, tend to have cognitive impairment.

A significant impact of lower socioeconomic and education on risk for cognitive impairment was reported across 51 studies. This population is likely unaware of the long-term consequences of cigarette or tobacco smoking.[32] Thus, Indonesian authorities should carry out a number of capacity-building initiatives for nationwide smoke-free taskforces, for example Human-Centered Design (HCD) approaches. These initiatives will create a cleaner and better environment, opening the door to a healthier Indonesia. Obesity and physical inactivity accompanied by tobacco consumption, hypertension, and DM cause lectin-like oxidized-LDL (ox-LDL) receptor-1 (LOX-1) upregulation, leading to neuronal damage and apoptosis. The expression of LOX-1 also stimulates TNF-α, IL-1, and IL-10.[33] Furthermore, LOX-1 causes ox-LDL degradation, increasing the risk of cerebral and coronary plaque formation.[34] This study has two main limitations. First, quantifying dose association was formulated and adapted based on previous study regarding smoking, SHS, and erectile dysfunction.[35] However, due to the huge study population coverage, the dose association was quantified solely from MMSE questionnaires. Second, cognitive impairment can be influenced by numerous confounding factors beyond the scope of this study. Thus, the authors recommend further similar study to evaluate more confounding factors.

Conclusion

This present study shows a relationship between smoking and cognitive impairment and strengthens a dose-response association between pack-years cumulative and cognitive impairment risk. These verify previous studies from the reports confirming the relationship between smoking and cognitive impairment. Thus, this study highlights the urgency of smoking cessation and avoiding cigarettes from a young age. At last, a significant effect of passive smoking or chronic SHS exposure shows a potential impact on cognitive impairment.

Acknowledgment

The authors have no competing interests. The authors are grateful to Aisyah F. Putri, MD and Beata Nino, MD for assisting data entry process; and Neurologist colleagues in Dr. Moewardi and UNS Hospital for providing technical support of manuscript feedback and proofreading. The research dataset is available on reasonable request. Please contact faizal9m@student.uns.ac.id.

Disclosure

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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