



## **Nicotine Replacement Therapy and Electronic Cigarettes: Awareness among Medical Students**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors ATK and JW designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors KAJ, SYAK, JZ, SRD, NSS, AEM and MKA managed the analyses of the study. Authors YHA, JLXS and IABS performed the statistical analysis and managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Whereas the use of electronic nicotine devices, such as e-cigarettes and nicotine replacement therapy, is on the rise, the awareness of these treatment options among health workers especially medical students is not well investigated.

**Objective:** This study was aimed to determine the knowledge and perception of the nicotine, nicotine replacement therapy (NRT) and e-cigarettes among medical students.

**Methodology:** This study is a descriptive study in which the research is measuring the knowledge and perception regarding tobacco cigarettes, nicotine, NRT and e-cigarettes, as well as observing

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the smoking rate in a given population simultaneously. A questionnaire was designed and applied to medical students in all 5 years. The sample size targeted was 200 with equal distribution among pre-clinical and clinical medical students. However, the number of responses obtained during the process of data collection was 184.

**Results:** The results of this study showed the knowledge and perception of the tobacco smoking hazards towards health and its substitutes had 46.0% and 53.6% on moderate knowledge levels and the majority 91.0% and 97.6% did not smoking among the preclinical and clinical respectively. The overall findings regarding opinion and knowledge on health risk among all participants are shown the majority participants 93 (76.9%) the tobacco cigarettes caused health risk. Regarding NRT, majority of preclinical 42(57.6%) and clinical 33 (69.8%) participants having low knowledge of NRT of health risk with a P value of 0.08 between the two groups. Also, majority of participants showed extremely agreed the smoking-related to the lung cancer, atherosclerosis in coronary and peripheral arteries. Majority of the participants in both preclinical and clinical agreed with the smoking addiction and agreed that facts on electronic cigarettes contain tobacco. Majority of preclinical and clinical students showed low knowledge of health risk and dependence potential.

**Conclusion:** medical students are not reasonable and overestimate the true hazards of tobacco smoking towards health. Additionally they are not knowledgeable about nicotine, NRT and e-cigarettes. Although, a large proportion of participants were exposed frequently to smokers, especially clinical phase students, they lack the knowledge and the correct perception regarding nicotine replacement therapy.

*Keywords: Medical students; nicotine; smoking reduction; e-cigarettes; NRT.*

## 1. INTRODUCTION

Smoking is a practice of inhalation and exhalation of fumes, produced by burning substances such as tobacco in cigars, cigarettes and pipes. Smoking is extremely harmful. Tobacco use is a risk factor for six out of the eight causes leading of death in the world. Smoking tobacco causes 87% of lung cancer diseases [1-4]. In Malaysia, there are above 27200 people who died annually from tobacco-caused disease, most deaths are among men age of 15 to 24 that they become a habit and the addiction to nicotine becomes unpredictable [5-8]. Cigarettes are made out of many ingredients and additives- approximately 600 that make tobacco products to be more acceptable and non-toxic. In fact, at least 69 of the chemicals are carcinogenic, agreed also by a research on the awareness of carcinogenic effect of tobacco smoke, while many others are poisonous. These harmful substances include nicotine, carbon monoxide, tar and many others [1-4]. Tobacco smoking leads to a dependence on nicotine that is indistinguishable from other forms of drug dependence. Nicotine Replacement Therapy (NRT) is a low-level nicotine substance, free of tar, carbon monoxide and other harmful chemicals found in tobacco smoke. NRTs, which are FDA-approved devices, act on nicotinic acetylcholine receptors to mimic or replace the effects of nicotine, the highly addictive chemical from tobacco products. NRTs are available over

the counter (OTC) and by prescription. NRTs provide only nicotine. No any other carcinogenic or toxic contents are contained in it, making it safer than tobacco cigarette smoking [9,10].

E-cigarettes are the most recent expansion in tobacco effect lessening. An electronic cigarette is an alternative to traditional smoking by using a battery-operated device which emits doses of evaporated nicotine, or non-nicotine solutions, that the smoker inhales to minimize the harmful effect of smoking. These battery operated gadgets create an airborne "smoke" by warming a fluid which may contain nicotine and other nourishment affirmed fixings, including flavours, nicotine is famously known to be addictive [9,10]. The six out of eight primary causes of deaths that tobacco smoking can cause are cancers of respiratory tract, ischemic heart disease, cerebra-vascular disease, chronic obstructive pulmonary disease, tuberculosis and lower respiratory tract infections. Besides the common lung cancer, it also causes 87% of lung cancer diseases, larynx, kidney, bladder, stomach, colon cancer, oral cavity and esophagus. However, it is preventable [5-8]. A research was issued in 2012 on NRT for smoking cessation among 50,000 participants to the primary comparison between any type of NRT and a placebo or non-NRT control group [11]. The effects were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. All the

commercially forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) are available and can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%, regardless of setting [9,10]. This study was aimed to determine the knowledge and perception of the nicotine, nicotine replacement therapy (NRT) and e-cigarettes among medical students. Thus, this study will help in continuing medical education for doctors which ensures that they possess indispensable knowledge to provide better health services for the community.

## **2. MATERIALS AND METHODS**

This research is implemented as a cross-sectional study, which is a type of observational study that involves the analysis of data collected from a population at one specific point in time. This type of study is a descriptive study in which the research is measuring the knowledge and perception regarding tobacco cigarettes, nicotine, NRT and e-cigarettes, as well as observing the smoking rate in a given population simultaneously. The study population of interest for the research includes medical students that are currently studying in SEGi University, hence the population size of participants was 374 a total number of pre-clinical (year 1 and 2) and clinical medical students (year 3,4 and 5) 170 and 204 respectively. Using sample size calculator from the Survey Monkey site, percentage of 95% is inserted as the confidence level and 5% as for margin of error. The inclusive criteria includes into two categories; clinical and pre-clinical year regardless of age, gender and ethnicity, or whether they are smokers or otherwise. However, the exclusion criteria was individuals which are not taking medicine and also the respondents that answered less than 80% of the questions.

### **2.1 Study Questionnaire**

A questionnaire was modified, printed out and circulated among the clinical and preclinical medical students. At first, members needed to read a brief presentation of the study purposes and agree to an informed consent. Then they were directed to the questions of the survey. The poll had five principle segments, requesting data about: (1) demographics of the members, including age, gender, phase of medical degree and ethnicity. 2) Smoking status, 3) knowledge and perception about the rate of involvement of nicotine to smoking-related diseases, 4) information about the adequacy and dependence

potential of nicotine replacement therapies and 5) knowledge about e-cigarettes. The survey was anonymous and participants were informed through the consent form that they could leave the poll at any time. The survey was included a serial number with the only purpose to remove double entries and easier recording of data. The questionnaire used in this research is referred to a public article which gives free authority for sharing and distribution of the material in any medium or format [12]. Modification was made to the existing questionnaire to accommodate into the research conducted and the area that the research is based on.

### **2.2 Independent/Dependent Variable**

The independent variables of the research were the participants' comparison of data between male and female, the dependable variables of the research were the rate of knowledge and perception of both of the groups of medical students.

## **3. RESULTS**

The results of this study showed the knowledge and perception of the tobacco smoking hazards towards health and its substitutes had 46.0% and 53.6% on moderate knowledge levels in the preclinical and clinical respectively. While majority 91.0% and 97.6% did not smoking in the preclinical and clinical respectively a P value of 0.059.

The overall findings regarding opinion and knowledge on health risk among all participants are shown the majority participants 93 (76.9%) the tobacco cigarettes caused health risk. About 60 (49.5%) mentioned the Electronic cigarettes caused high health risk. 75(60.0%) of participants have low knowledge on NRT and 48 (40.0%) have also low knowledge on oral smoking cessation. However, 126 (73.3%) of participants showed a highest knowledge on components of tobacco cigarettes and nicotine that caused health risk, while 69(40.1%) have low knowledge an inhaled smoke that caused health risk. While 96(55.8%), 83(48.3%) and 98(57.0%) of participants confirmed a highest knowledge on the tobacco, carbon monoxide and Tar that caused health risk (Table 2).

The overall results of Tobacco cigarettes health risk among pre-clinical 55(75.3%) answered that it has a high risk same result 38(79.2%) was confirmed from clinical participants. According to the snus, the preclinical confirmed that low health risk 20 (27.8%) and clinical participants showed

moderate 17(35.4%) of health risk. Majority of preclinical 23(31.5%) and clinical 15(31.3%) participants mentioned the highest knowledge of electronic cigarettes that caused health risk. Regarding NRT, majority of preclinical 42(57.6%) and clinical 33 (69.8%) participants mentioned the low knowledge of health risk to NRT users with a P value of 0.08 between the two groups. There was no difference between the two groups with regard to their lack of awareness of the health risks of tobacco smoking alternatives.

However, preclinical 34(46.6%) and clinical participants 37(77.1%) have low knowledge about oral smoking cessation with significant at *p-value* at 0.009. Majority of preclinical 61(68.5%) and clinical 65(78.3%) participants with highest agreement the nicotine caused the health risk. Both preclinical 40(44.9%) and clinical 46(55.4%) participants confirmed with low agreement the inhaled smoke caused the health risk, while the Tobacco showed the highest agreement in both preclinical 50 (56.2%) and clinical participants 46 (55.4%) mentioned the highest knowledge that tobacco caused the health risk. The health risk caused by Carbon monoxide and Tar showed highest confirmation from both preclinical 51(57.3%) and 54(60.7%), and clinical participants 32 (38.6%) and 44 (53.0%) with a P value of 0.07 and 0.08 respectively (Table 1).

Based on the participants' opinion regarding regulations of Malaysian Health Ministry on e-cigarettes, a substantial proportion of the preclinical participants agree for e-cigarettes to be available only through prescription the half disagree. More 72.6% among clinical participants also disagreed for it to be available only through prescription while only 27.4% agreed with the *p-value* of 0.001, 39% of the preclinical participants agree for e-cigarettes to be licensed as medicinal product, while more (61%) disagreed. More clinical participants (83.3%) also disagreed for it to be licensed as medicinal product while only 16.7% agreed to the opposite. Finally, with the *p-value* of 0.009, 35% of the preclinical participants agreed for e-cigarettes to be sold only in pharmacies, while more (65%) disagreed. More clinical participants (82.1%) also disagree.

The findings among the participants based on the cigarette smoking knowledge levels habits among genders showed the female more male in the moderate level of evaluation with significant at *p-value* of 0.003, while the male showed the highest level. Majority of male and female confirm no smoking and there significant

differences between smoking and nonsmoking at *p-value* of 0.007. About 6.5% of male participants admitted low, 37.7% as moderate, 35.1% as high and 20.8% as very high. 5.6% of female participants admitted low level of smoking knowledge, 57.9% as moderate, 31.8% as high and 4.7% as very high. On the current smoking status, a *p-value* of 0.007 was obtained. 11.7% of male participants are smokers, while 88.3% are not. 98.1% of female participants are not smokers (Table 2).

The results of study showed that majority with extremely agreed the diseases, smoking-related lung cancer, smoking related cancer in other organs, smoking-related atherosclerosis in coronary and peripheral arteries have strongly related to the smoking, these results also strongly confirmed among clinical phase students (Table 3).

Whereas the knowledge of electronic cigarettes and nicotine replacement therapy were compared to smoking. Majority of the participants in both preclinical and clinical agreed the smoking addiction while majority of participants did not recommend as a substitute for smokers and recommend to smokers those who failed to quit form the cigarettes smoking. In addition, a majority of preclinical and clinical students agreed that facts on electronic cigarettes contain tobacco and there is combustion and e-liquid ingredients approved for inhalation. While the majority of preclinical and clinical students did not agree that working temperature is lower than tobacco cigarettes, have official quality certificates and an e-cigarette has not nicotine (Table 4).

According to the knowledge of nicotine replacement therapy compared to smoking, the majority of preclinical and clinical students showed low knowledge of health risk, while majority of preclinical students did not show knowledge dependence potential, but the majority of the clinical students showed low knowledge about dependence potential risk. However, the majority of preclinical and clinical students showed high knowledge of health risk among beneficial for heavy smokers >15 cigarettes per day (Table 5).

The results of this study showed the knowledge of electronic cigarettes compared to smoking among preclinical and clinical students confirmed high knowledge of health risk, dependence potential and health risk of passive e-cigarette vapour lower than tobacco smoke exposure.

**Table 1. Opinion/knowledge on health risk**

Questionnaire parameters	Pre-clinical, <i>n</i> (%)				Clinical, <i>n</i> (%)				<i>p</i> -value*
	Low	Mod.	High	Highest	Low	Mod.	High	Highest	
Tobacco cigarettes	11(15.0)	3(4.1)	4(5.5)	55 (75.3)	2(4.2)	2(4.2)	6(12.5)	38(79.2)	0.19
Snus	29(40.3)	17(23.6)	18(25.0)	8(11.1)	12(25.0)	17(35.4)	16(33.3)	3(6.3)	0.13
Electronic cigarettes	18(19.5)	19(26.0)	13(17.8)	23(31.5)	10(20.8)	14(29.2)	15(31.3)	9(18.8)	0.36
NRT	42(57.6)	14(19.2)	6(8.2)	11(15.1)	33(69.8)	9 (18.8)	3(6.3)	3(6.3)	0.08
Oral smoking cessation	34(46.6)	13(17.8)	13(17.8)	13(17.8)	37(77.1)	1 (2.1)	6(12.5)	4(8.3)	0.009
Nicotine	14(15.7)	9(10.1)	5(5.6)	61(68.5)	13(15.6)	2(2.4)	3(3.6)	65(78.3)	0.29
Inhaled smoke	40(44.9)	13(14.6)	4(4.5)	32(36.0)	46(55.4)	3(3.6)	4(4.8)	30(36.1)	0.098
Tobacco	2(23.6)	9(10.1)	9(10.1)	50 (56.2)	20(8.4)	8(9.6)	9(10.8)	46(55.4)	0.95
Carbon monoxide	23(15.9)	6(6.7)	9 (10.1)	51 (57.3)	32(38.5)	7(8.4)	12(14.5)	32(38.6)	0.07
Tar	13(14.6)	7(7.9)	15(16.9)	54 (60.7)	21(24.3)	11(13.3)	7(8.4)	44(53.0)	0.08

*n* denotes number of participant, \* denotes Chi-Square test

**Table 2. Cigarette smoking habits of the participants**

Questionnaire parameters	Male, n (%)	Female, n (%)	Total, n (%)	p-value*
<b>Smoking knowledge levels</b>				
Low	5 (6.5)	6 (5.6)	11 (6.0)	0.003
Moderate	29 (37.7)	62 (57.9)	91 (49.5)	
High	27 (35.1)	34 (31.8)	61 (33.2)	
Very high	16 (20.8)	5 (4.7)	21 (11.4)	
<b>Current smoking status</b>				
Yes	9 (11.7)	2 (1.9)	11 (6.0)	0.007
No	68 (88.3)	105 (98.1)	173 (94.0)	
<b>Current smoker-smoking addiction</b>				
Low	1 (11.1)	1 (50.0)	2 (18.2)	0.233
Moderate	5 (55.6)	0 (0.0)	5 (45.5)	
High	1 (11.1)	1 (50.0)	2 (18.2)	
Very high	2 (22.2)	0 (0.0)	2 (18.2)	
<b>Past smoking status</b>				
Yes	5 (6.5)	2 (1.9)	7 (3.8)	0.106
No	72 (93.5)	105 (98.1)	177 (96.2)	
<b>Past smoker-method of quit smoking</b>				
Oral medication	0 (0.0)	0 (0.0)	0 (0.0)	0.495
Nicotine Replacement Therapy	1 (20.0)	0 (0.0)	1 (14.3)	
Systematic psychological support	0 (0.0)	0 (0.0)	0 (0.0)	
Other methods	0 (0.0)	0 (0.0)	0 (0.0)	
Without aid	4 (80.0)	2 (100.0)	6 (85.7)	

*n* denotes number of participant, \* denotes Chi-Square test

**Table 3. Opinion/knowledge on contribution of nicotine to diseases development**

Questionnaire parameters/n (%)	Less important	Important	Very important	Extremely important
Smoking related diseases	14 (7.6)	37 (20.1)	66 (35.9)	67 (36.4)
Smoking-related lung cancer	16 (8.7)	32 (17.4)	55 (29.9)	81 (44.0)
Smoking related cancer in other organs	20 (10.8)	53 (28.8)	63 (34.2)	48 (26.1)
Smoking-related atherosclerosis in coronary and peripheral arteries	14 (7.6)	39 (21.2)	60 (32.6)	71 (38.6)
Smoking related wrinkling of skin	28 (15.7)	48 (26.1)	59 (32.1)	48 (26.1)
More hazardous type of nicotine/ Synthetically produced	57 (31.0)	64 (34.8)	62 (33.7)	

*n* denotes number of participant, \* denotes Chi-Square test

#### 4. DISCUSSION

Before fact-based questions were asked, the respondents were questioned on their smoking habits and their perceived knowledge regarding smoking in general. 6.0% of the respondents had rated low, 49.5% admitted to having moderate knowledge on smoking, 33.2% rated high and the remaining 11.4% of participants had rated themselves as having a high knowledge on smoking. This shows that most medical students had admitted to having moderate knowledge level on smoking and the lowest number shows they have only low level of knowledge on smoking. Smoking facts in general are common to be known to the public, since smoking is a norm in society. It is likely the participants

regarded themselves as moderately knowledgeable about smoking, considering that medical students should be more aware on the facts on smoking since they will be exposed to patients that smoke and smoking-related diseases.

The participants overestimated the relative risk of smoking and the hazards of nicotine towards health. Additionally, our study demonstrates that medical students have poor knowledge about alternative tobacco and nicotine delivery products and many would not recommend NRT therapy for long-term smoking cessation. The finding of our study is in consistent with studies conducted by other researchers in Europe and the United States [12,13-17], which also showed

overestimating of the harmful effects of cigarette smoking and a poor knowledge about the function and features of e-cigarettes. Studies conducted in Norway, Swedish and British showed that health workers overestimated the hazards of tobacco smoking and had little attention or understanding about alternative nicotine products, like electronic cigarettes. These findings are consistent with our study results [18-20]. However, a larger sample with more generalized healthcare professionals is advised for future studies.

Opinion on Malaysian Health Ministry Regulation on e-cigarettes was asked. The opinion that e-cigarettes should only be available only through prescription and in pharmacies is not quite well received by majority of the respondents. This might be because pharmacy and prescriptions generally reflect medicinal care, however the majority of them might not think of e-cigarettes as

a medicinal alternative to smoking cessation. Banning of nicotine from e-cigarettes is agreed upon by majority of the respondents (58.7%), which the respondents may take concern on the bad effects of nicotine to the body. However, banning of flavours is not highly recommended by them, which 65.8% had disagreed upon due to e-cigarettes being commercially known for their variety of flavours. Banning sales to youngsters aged younger than 18 years old and the prohibition of its use in public places are very much supported. Licensing e-cigarettes as a medicinal product is not agreed by the majority. This may be because the participants do not see e-cigarettes as a medicinal alternative to smoking cessation. Reducing the variability of the products in the market is not agreed by the majority. Banning advertisement of e-cigarettes as substitutes for smoking and including a warning as equally harmful to smoking are well received by the participants, because public

**Table 4. Knowledge of electronic cigarettes**

Questionnaire parameters	Pre-clinical, n (%)			Clinical, n (%)			p-value
	Yes	No	Do not know	Yes	No	Do not know	
Smoking addiction	66 (66.0)	18 (18.0)	16 (16.0)	61 (72.6)	12 (14.3)	11 (13.1)	0.625
Recommend as a substitute for smokers	23 (23.0)	60 (60.0)	17 (17.0)	18 (21.4)	50 (59.5)	16 (19.0)	0.92
Recommend to smokers who failed to quit	31 (31.0)	54 (54.0)	15 (15.0)	32 (38.1)	39 (46.4)	13 (15.5)	0.55
Questionnaire parameters	Pre-clinical, n (%)		Clinical, n (%)		p-value*		
	Yes	No	Yes	No			
Electronic Cigarettes, contain tobacco	45(45.0)	55(55.0)	27(32.1)	57(67.9)	0.075		
There is combustion	52(52.0)	48(48.0)	38(45.2)	46(54.8)	0.708		
E-liquid ingredients approved for inhalation	56(56.0)	44(44.0)	38(45.2)	46(54.8)	0.146		
Working temperature is lower than tobacco cigarettes	35(35.0)	65(65.0)	28(33.3)	56(66.7)	0.812		
Have official quality certificates	23(23.0)	77(77.0)	20(23.8)	64(76.2)	0.897		
Without nicotine	38(38.0)	62(62.0)	32(38.1)	52(61.9)	0.99		

*n* denotes number of participant.\* denotes Chi-Square test

**Table 5. Opinion/knowledge of nicotine replacement therapy compared to smoking**

Questionnaire parameters	Pre-clinical, n (%)			Clinical, n (%)			p-value*
	Lower	Higher	Do not know	Lower	Higher	Do not know	
Health risk	46 (46.0)	28(28.0)	26(26.0)	43(51.2)	12(14.2)	29(34.5)	0.13
Dependence potential	28 (28.0)	40(40.0)	32(32.0)	33(39.3)	25(29.8)	26(31.0)	0.373
Beneficial for heavy smokers (>15 cigarettes per day)	18 (18.0)	59(59.0)	23(23.0)	19(22.6)	50(59.5)	15(17.9)	

*n* denotes number of participant,\* denotes Chi-Square test

should know that even e-cigarettes have their own bad effects. Banning e-cigarettes as a leading step to smoking cessation was not agreed by the majority and the remaining 16.8% is unsure of the regulation [21-23].

Less than the half of both preclinical and clinical medical students are sufficiently knowledgeable regarding NRT and e-cigarettes. It is not clarified whether they overestimated or underestimated it due to their answers. Additionally, they have poor knowledge about it. In the genders comparison of both genders having moderate level of knowledge, admitting that they do not really know about tobacco smoking although there has been advertisements and awareness campaigns done by the government. It has always been advertised that smoking causes all kinds of fatal diseases, but what it specifically causes and how it affects the health or the presence of any substitutes for tobacco smoking is admittedly not clear to the participants. Moreover, more male participants are having higher knowledge regarding this matter than female participants. In addition, more than 80% of both genders were non-smokers. This is a pleasingly good phenomenon as medical students who are future doctors should show good decent examples of not smoking to society. According to a study nicotine is known to have major systemic side effects instead, besides the addictive characteristic that it inputs in its users [20]. It can negatively affect the heart, lung, kidney and even the reproductive system etc. Nicotine only causes a minimal contribution to those cancers as in the questionnaire. Tobacco in cigarettes is the actual cause for most of the cancers as surveyed in the questionnaire, mainly lung cancer [9-12,21]. However, WHO estimated around 1.27 billion tobacco users throughout the world [2].

On the perception of e-cigarettes, male participants more than females thinking that the health risk of passive e-cigarette vapor is not lower than tobacco smoke exposure but this is wrong. Male and females participants both would rather not recommend e-cigarettes as a substitute to smokers who are not willing to take medication as a step in smoking cessation. This is, in reality, a mistaken perception. As another point, most female participants agree to ban e-cigarettes as the leading step to smoking cessation in Malaysia while the male participants mostly disagree. This shows a contraindicating opinion to take note on. There was also a small group of participants that chose "do not know" when answering. It was stated that e-cigarettes

doesn't have tobacco but they have nicotine substance. Although, some packaging of these cigarettes were labelled as nicotine-free, but from the initial FDA lab tests conducted in 2009, there were traceable levels of nicotine found [11,12].

## **5. CONCLUSION**

Medical students are not reasonable and overestimate the true hazards of tobacco smoking towards health. Additionally they are not knowledgeable about nicotine, NRT and e-cigarettes. Although, a large proportion of participants were exposed frequently to smokers, especially clinical phase students, they lack the knowledge and the correct perception regarding nicotine replacement therapy.

## **CONSENT AND ETHICAL APPROVAL**

The proposed questionnaire had been approved for distribution after it was inspected by the assessor. The consent form by the Faculty of Medicine of SEGi University has been given to proceed with the data collecting process, the consent form along with a brief detail of the group member, also been given to participants. The questionnaire also informs the participants about the confidentiality of the participant if they were to participate in the questionnaire. The research proposal was approved by the Ethics Committee of SEGi University.

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## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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