The Impacts of Supervised Exercise Intervention on Tobacco Withdrawal Symptoms

Tobacco Use Insights
Volume 16: 1–10

DOI: 10.1177/1179173X231179811

Nur-Hasanah Ruslan[1], Siti Munira Yasin[2], Nadzimah Mohd Nasir[3] and Mohamad Rodi Isa[2]

[1]Faculty of Sports Science and Recreation, Universiti Teknologi MARA, Shah Alam, Malaysia. [2]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Malaysia. [3]Department of Pathology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Malaysia.

ABSTRACT

This study examined a supervised moderate-intensity aerobic exercise programme's effectiveness in regulating the Tobacco Withdrawal Symptoms (TWS) during temporary abstinence. This was a single group, pre and post-quasi intervention study. Thirty daily smokers participated in an 8-week supervised moderate-intensity aerobic exercise programme. We assessed the TWS, smoking urge, mood and stress-pleasure related hormonal variables after the aerobic exercise intervention. The measurements were conducted after overnight abstinence at baseline, post-intervention (at week-8) and post-detraining (at week-10). TWS components, smoking urge and mood were found to improve. For hormonal variables, cortisol and beta-endorphin except adrenaline showed insignificant changes at post-intervention and de-training. The findings suggest moderate-intensity exercise might help in reducing withdrawal symptoms and its adverse effects. Thus, exercise is an effective adjunct treatment in a smoking cessation programme.

KEYWORDS: tobacco withdrawal symptoms, beta endorphin, adrenaline, cortisol, mood, supervised exercise intervention, smoking urge

RECEIVED: November 29, 2022. **ACCEPTED:** May 17, 2023.

TYPE: Original Research Article

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by Fundamental Research Grant Scheme (FRGS FRGS/124/2015/SKK01/UITM/03/1) and FRGS5/3(124/2015).

SUPPLEMENTAL MATERIAL: Supplementary material for this article is available online.

CORRESPONDING AUTHOR: Nur-Hasanah Ruslan, Faculty of Sports Science and Recreation, Universiti Teknologi MARA, Seksyen 1, Shah Alam 40450, Malaysia.
Email: nur-hasanah@uitm.edu.my

Introduction

Smoking was reported to cause up to 8 million deaths globally annually.[1] By 2030, approximately 10 million mortalities from smoking-related diseases are expected.[2] In Malaysia, a recent survey reported that about 21.3% or 4.8 million adults (above 15 years old) used tobacco daily.[3] Annually, more than 27 200 deaths in Malaysia are related to smoking.[3] Thus, smoking cessation is a vital strategy in overcoming the burden of non-communicable diseases (NCD) and more importantly, achieving the National Tobacco Endgames 2045.

Behavioural and pharmacological treatment is the mainstay of management modality in smoking cessation programme.[4] There are various behavioural treatments for smoking cessation that work in multiple complex ways such as reward related functioning via motivational or comsumantory reward.[5] The evidence supporting the use of financial incentives in promoting smoking cessation. It demonstrates that financial incentives, as used in contingency management, can be an effective tool for promoting smoking cessation and maintaining abstinence.[6] For emotivational and cognitive interventions can be provided to enhance motivation and also working to decrease cognitions and likelihood of smoking intake.[7] For other behavioral therapy such as Contingency Management found to effective for short term abstinence and need combination of other therapy[8] wherease the CBT also effective therapeutic approach for assisting challenges to quitting tobacco smoking but there were several demographic factor could mediate and moderate the treatment efficacy.[9] Indeed, the behavioural treatment should be customised for individuals[10] based on their preferences because personalised treatment can be more effective.[11] Despite its clinically proven effectiveness, the uptake of these smoking cessation treatments remains poor.[12]

Apart from behavioural therapy, exercise was also reported to be an effective adjunct treatment for smoking cessation.[13] There were several reasons of choosing exercise as adjuct in smoking cessation because the previous studies found that exercise can alleviating withdrawal symptoms,[14] reduce cravings for cigarettes[15] due to the increased release of brain chemicals like dopamine and serotonin, which can help regulate mood and reduce the urge to smoke. Reducing TWS and craving will improving mood and well-being.[14] Improved mood can help prevent relapse by making it easier to cope with stress and other triggers associated with smoking. Moreover, quitting smoking can lead to weight gain in some individuals due to changes in metabolism and increased appetite. Exercise can help counteract weight gain and promote a healthier lifestyle, which can further

support smoking cessation efforts.[16] In addition, regular exercise can help build self-efficacy, or the belief in one's ability to succeed in quitting smoking can support the maintenance of long-term abstinence.[17] Several forms of exercise have been evaluated as a complementary treatment for smoking cessation, including yoga,[18] aerobic exercise,[19] and resistance exercise.[20] Continuous efforts should be taken to find other alternatives that can collectively improve treatment efficacy.

Previous evidences supported the fact that exercise positively improves participants' mood and feeling.[21,22] Exercise can exert mood-regulating effects[23] by increasing endogenous opiates, cognition, and hypothalamic-pituitary axis (HPA) hormones.[24] Indeed, a recent systematic review included 21 studies to report the effects of exercise on smoking cessation.[14] However, the studies involved different types of exercise and applied different methodological aspects and variables found inconclusive findings about the exercise to smoking cessation support improve abstinence compared with support alone, but the evidence is insufficient to assess whether there is a modest benefit. Thus, makes research on exercise as a smoking adjunct treatment is needed.

Previous studies have suggested that exercise can induce positive physical responses, particularly in cardiorespiratory fitness[25] and physiological benefit.[26] In this study, moderate-intensity exercise was selected as an introductory exercise for smokers. A study showed that moderate-intensity exercise would be more effective to manage TWS, besides producing greater psychological benefits and having higher adherence rates.[27] Since smokers in this study were likely to be minimally active and lead a sedentary lifestyle, moderate exercise is suitable to minimise the risk of cardiovascular events associated with exercise. Exercise can be performed anytime and anywhere, thus it should be considered as an adjunct therapy in a patient-centred approach for smoking cessation. However, there is a lack of high-quality studies on the incorporation of exercise as part of a smoking cessation programme in the literature.[28] Thus, there is a lack of consensus on the effects of regular exercise on tobacco withdrawal symptoms (TWS) and other related hormones.

Prolonged exposure to addictive substances can modify brain adaptations and produce mesolimbic hypofunction.[29] Subsequent changes in the brain include the up-regulation of neural nicotinic acetylcholine receptors (nAChRs) and the nAChR desensitisation.[30] As a result, the effect of exercise among smokers on abstinence should be evaluated because they are adapting to sudden withdrawal from chronic exposure to nicotine. Previous studies have reported the possible hormonal changes in smokers, including cortisol dysregulation,[31] dysregulated reward pathways,[32] brain stress system,[33] and blunted cortisol when compared to non-smokers.[34] Chronic cigarette use can lead to the dysregulation of HPA[33] by causing a dramatic drop in the morning cortisol concentrations as a result of intense withdrawal symptoms and distress during abstinence.[34] Cortisol can interact with certain neurotransmitters and hormones such as acetylcholine, norepinephrine, dopamine, vasopressin, and beta-endorphin under the modulation of nicotine.[34] Indeed, beta-endorphin,[35,36] noradrenaline,[37] and other hormones such as leptin[38] could also become dysregulated following chronic exposure to nicotine.

Figure 1 shows the conceptual framework of this study. When undergoing smoking cessation or abstinece from smoking, smokers commonly experience mood disturbance as a result of hormonal dysregulation. The mood disturbance can intensify the TWS and increase the tendency of relapse. Figure 1 also illustrates the process of how exercise influences the secretion of selected hormones in reducing mood disturbance during smoking abstinence.

This study aimed to determine the impact of moderate-intensity exercise on TWS, smoking urge, and mood during temporary smoking abstinence associated with psychological and stress-pleasure related hormones. This study aimed to generate evidence on the impact of specific types of exercise intervention as an adjunct therapy for smoking cessation by predicting the changes of hormonal aspects associated with training programme. If proven so, the data can support the incorporation of exercise as part of the smoking cessation programme. First, this study hypothesises that exercise can exert both physiological and psychological impact, thus exercise should be considered as an important adjunct therapy for smoking cessation. Secondly, we also hypothesised that regular supervised exercise programme may positively improve the dysregulation of the HPA system in smokers. The stress hormones such as cortisol and adrenaline as well as "pleasure" hormones such as beta-endorphin can be potential biomarkers to assess the response to exercise training programmes as the changes in these hormones are directly correlated with the effects of smoking cessation. Examining the effects of exercise on TWS besides monitoring hormonal changes following exercise intervention can provide the necessary evidence to support public health interventions in the management of relapse during smoking cessation.

Methods

Study design

This study applied a single-group pretest-posttest quasi-experimental design. Study variables were measured at baseline (0 weeks), post-intervention (8 weeks), and post-detraining (10 weeks). Detraining is the partial or complete loss of training-induced anatomical, physiological, and performance adaptations, as a consequence of training cessation.[39] The sample size was calculated using online sample size calculation software[40] based on the formula of paired samples. The estimate was calculated based on the probability of an alpha value of .05 and a beta error value of .20, 80% power, and a 95% confidence interval for repeated measurements[41]. The sample size required was 30 participants. Ethical approval was approved from the UiTM Ethical Committee reference 600-RMI (5/1/16) and the

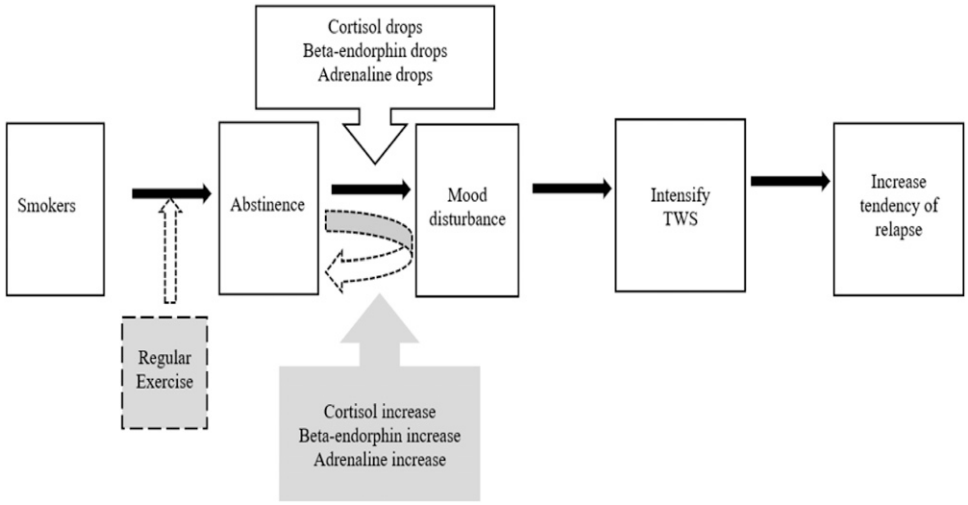

Figure 1. Possible mechanism of how exercise regulates abstinence.

Medical Register Ethical Register (MREC) ID NMRR-15-2070-28622. Participants were briefed before they provided written consent prior to the study. This study was also registered under the National Medical Research Registry (NMRR), Ministry of Health, Malaysia (NMRR-15-2070-28622) and the Iranian registery (IRCTID No: IRCT2015102121543N2) at https://www.irct.ir/search/result?query=tws.

Participants

Participants were recruited from 4 centres, including 2 higher education institutions, a government hospital, and a public clinic in Sungai Buloh, Selangor, Malaysia. Convenience sampling was used to recruit participants. The recruitment method included advertisements through email, letters to the heads of the department, posters, flyers, and bunting. Participants were screened to ensure that they met the inclusion criteria, ie males, aged 20-45 years, free from chronic diseases, smoked at least 10-20 cigarettes per day, minimally active or sedentary, and free from anxiety and depression. The exclusion criteria included participants who: 1) smoked more than 20 cigarettes per day, 2) had a nicotine dependence score of above 8, and 3) were at the preparation stage of quitting smoking.

Screening

The physical activity level of the participants was assessed using the short version of the International Physical Activity Questionnaire (IPAQ-M) to determine the participants with a sedentary lifestyle who were minimally active. Smoking-related information was assessed in the self-administrated questionnaires by asking the number of cigarettes smoked per day. Nicotine dependence was determined using the Malay Fagerstrom Test of Nicotine Dependence (FTND) by.[42] Next, the stage of readiness to change and to quit smoking was assessed based on a single question with 3 options to indicate the current stage of change[43]. Participants would only be recruited among moderate smokers with mild addiction because heavy smokers were perceived to experience more intense TWS. Furthermore, only smokers with no intention to quit were recruited and classified into different cessation stages.[44] The Malay version of the Physical Activity Readiness Questionnaire (PAR-Q) was used to determine the readiness and safety of participants to participate in physical activity as retrieved from the Sport Singapura website (www.sportsingapore.gov.sg/).[45] The Atherosclerotic Cardiovascular Disease risk factors checklist developed by the American College of Sports Medicine (ACSM)[46] was used to assess the CVD risk during the exercise as a precaution when dealing with smokers who perform exercise. Participants with a history of diabetes mellitus and hypertension were also excluded. Mental health status was also screened using a self-developed checklist with 'Yes' and 'No' responses for common psychological problems. Lastly, the anxiety and depression status were assessed using the Malay version of the Beck Anxiety Inventory (BAI-M)[47] and the Beck Depression Inventory (BDI-M).[48] The participants were excluded if the BAI score was more than 21 or the BDI score was more than 17.

Intervention

The intervention for this study was a supervised, moderate-intensity aerobic exercise training programme for 8 weeks in a gymnasium as in Figure 2. The frequency of exercise training was 3 times per week while the exercise intensity was set at a moderate level of 64-75% of the Predicted Maximal Heart Rate (% HRmax). The type of exercise was supervised running on a motorised treadmill. The progression principle was applied by increasing 5 minutes of exercise time every 2 weeks.[49] The intervention started with 30 minutes of exercise time before progressing to 45 minutes after the programme. This progression enabled the participants to maintain the prescribed exercise training intensity stimuli without reaching a training plateau state (no exercise stimulus benefits). The

Components	Week 1-2	Week 3-4	Week 5-6	Week 7-8	Week 9-10 Detraining
Warm-up	3-5 min				Exercise cessation Reversibility principle
Frequency	3times/ week	3times/ week	3times/ week	3times/ week	
Intensity	moderate	moderate	moderate	moderate	
Time	30 min/session	35 min/session	40 min/session	45 min/session	
Type	Running on treadmill				
Cooling down	3-5 min (passive/ active)				

	Progression principle
	Reversibility principle

Figure 2. Exercise intervention based on frequency, intensity, type and time components.

exercise intensity was prescribed using the heart rate percentage of the Individual Target Heart Rate Zone (THR) zone.[46] It was calculated to monitor the exercise intensity during the exercise programme. The intervention also followed the detraining principle. This principle was applied to remove at least half of the effect of adaptation to training. The detraining period for this study would be 2 weeks after the final week of the intervention.

Data Collection

Before the data collection at baseline, post-training and detraining were conducted, the abstinence verification determine the carbon monoxide level via smokerlyzer (Micro + smokerlyzer©Bedfont Scientific Ltd, England) and expressed in parts per million (ppm). If it is more than 10 ppm, the participants were asked to re-abstinence from smoking.

Self-administered questionnaires

The demographic characteristics included age, occupation, smoking history, current smoking habits, and the relevant instruments. TWS was assessed using the validated Malay version of the Shiffman and Jarvick Withdrawal Scale (SJWS-M)[50] that consisted of five-factor categories, ie craving (5 items), psychological symptoms (5 items), physical symptoms (3 items), sedation (1 item), and appetite (1 item) evaluated on a seven-point Likert scale ranging from "very definitely" to "very definitely not". The Malay version showed good internal consistency with Cronbach alpha value ranging from .66 to .79 for each factor. The smoking urge was assessed using the short Malay version of the Questionnaire for Smoking Urge (QSU-M) that has been translated and validated locally with good internal consistency.[51] The QSU-M brief consists of 10 items with 2 factors: desire and intention to smoke as well as anticipation of relief from negative effects on an 'agree-disagree' Likert scale. The mood profile was assessed using a 12-item Malay translated and validated Subjective Exercise Experience Scale (SEES-M).[52]

Hormonal variables

Blood samples were collected to determine serum cortisol, serum beta-endorphin, and plasma adrenaline. After overnight smoking abstinence, 10 ml of the antecubital venous blood was collected from each participant using a syringe attached to a 21G × 1 ¼" needle (TERUMO© Tokyo, Japan). The blood was taken around 8.00 AM to 10.00 AM to minimise diurnal variation. For serum cortisol and beta-endorphin analysis, whole blood was transferred into a plain tube (Becton Dickinson (BD) and silicon-coated tube (Vacutainer, USA). The samples were left to clot for 2-3 hours before centrifugation at 1300×g and 4°C for 10 minutes for serum cortisol and at 1000×g and RCF for 20 minutes for beta-endorphin using the centrifuge (EBA20 Hettich, USA). The blood sample for adrenaline analysis was collected using EDTA tube (BD vacutainer® K2 EDTA 5.4 mg USA) and was centrifuged at 1300×g and 4°C for 10 minutes. The serum and plasma were stored in triple aliquots at −20°C and −80°C respectively for analysis later on. The serum cortisol analysis was performed using the electrochemiluminescence immunoassay technique (Cobas e 411, Roche, USA). The serum beta-endorphin level and plasma adrenaline were analysed using the competitive inhibition enzyme-linked immunosorbent assay (ELISA) method from (Cloud-Clone Corp, USCN, China) and (Demeditec Diagnostics GmbH, Germany) respectively. The optical density of the microplate reader (Tecan Safire 2, Austria) was set at 450 nm wavelength. Only concentrations with a coefficient-variation of less than 10% for intra-assay and less than 20% for inter-assay were reported.

Statistical analysis

Data were analysed using SPSS (Version 27.0, IBM SPSS Statistics, IBM Corporation). Descriptive statistics were presented using frequency and percentage. Repeated measures analysis of variance (ANOVA) within the subject's statistical test was used to determine the impact of a supervised exercise intervention on TWS and other variables between different time points. Normal distribution and homogeneity of variance were also checked in the analysis. The statistical difference level was set at $P < .05$. The effect size was presented in partial η^2.

Table 1. Sociodemographic information's of study participants.

	MEAN (SD)	N (%)
Age	28.5 (5.08)	
Marital status		
Single		14 (46.7%)
Married		16 (53.3%)
Educational level		
Primary		1 (3.3%)
Secondary		15 (50%)
Certificate		2 (10%)
University		11 (36.7%)
Job categories		
Support staff		23 (76.6%)
Professional		3 (10%)
Student		4 (17.3%)
Salary		
<RM1000.00		6 (20%)
RM1000.00-RM2999.99		12 (40%)
RM3000.00-RM4999.99		8 (26.7%)
>RM5000.00		3 (10%)
Smoking History		
Age when start smoking	15.5 (3.5)	
Age when become a daily smoker	16.9 (2.4)	
Duration of smoking	12.9 (5.2)	
No. of cigarette smoke per day	16.2 (4.1)	

Results

Among the 30 participants, their average age was 28.5 ± 5.08 years old with an average duration of smoking of 12.9 ± 5.25 years. The majority of the participants were married (53.3%), graduated from university (36.7%), and worked as support staff (76.6%). Most of the participants (40.0%) had a monthly income of RM 1000-RM3000. Table 1 shows the sociodemographic characteristics of the participants.

Table 2 shows the impact of exercise intervention. There was a statistically significant exercise intervention effect for craving (F [2, 58] = 5.26, P = .01, partial η^2 = .15) with significant differences between baseline and post-intervention, desire to smoke (F [1.39, 40.42] = 4.19, P < .04, partial η^2 = .13), with significant differences between baseline and post-detraining. For mood subscales, physical well-being (PWB) (F [1.64, 47.61] = 4.03, P = .03, partial η^2 = .12) showed significant differences between baseline and post-intervention. Psychological distress (PD) (F [1.30, 37.75] = 3.93, P = .04, partial η^2 = .12), fatigue (F [1, 29] = 3.70, P = .03, partial η^2 = .11), and adrenaline (F [2, 58] = 4.42, P = .04, partial η^2 = .14) recorded significant differences between baseline and post-detraining.The trend of changes in mood, TWS, smoking urge, and hormones are shown in graphs in supplement materials.

Discussion

This study focused on the impact of a supervised aerobic exercise intervention on psychological aspects (TWS and psychological symptoms) and associated biomarkers of stress-pleasure related hormones during temporary smoking abstinence. On the craving subscale of TWS, there was a significant post-intervention difference for psychological components. The reduction of withdrawal symptoms was also demonstrated in all subscales, similar to another study.[53] The improvement may be due effects of exercise that helps smokers to cope with the withdrawal symptoms and hence, facilitated smoking cessation.[53] However, the effect of the exercise intervention was less favourable for physical symptoms based on the increasing symptom severity post-intervention.

Next, the subscale of smoking urge also recorded a reduction post-intervention. Both the strong desire to smoke and the anticipation of negative effects were decreased following the exercise intervention, thus indicating a decrease in a negative mood. Our result was similar to another study that highlighted a reduced smoking urge after exercise.[54] One of the possible reasons could be the moderate intensity of the aerobic exercise in the intervention was deemed comfortable and within the acceptable physical load, especially for participants who were used to a sedentary lifestyle.[55] In addition, the exercise was found to be enjoyable, hence increasing motivation and promoting a sense of pleasure.[53,54]

In addition, there was a significant increase in positive wellbeing, decreased fatigue, and reduced physiological distress post-intervention in the mood subscales. The subsequent positive mood was due to the reduction of depression and increased vigour after exercise. This finding was similar to.[53] In many instances, the mood is closely related to the magnitude of withdrawal symptoms.[56] Thus, any interventions that can regulate mood would also be able to reduce the severity of withdrawal symptoms. In other words, mood reduction can be a result of exercise-induced changes in stress-pleasure related hormones such as cortisol and beta-endorphin.

During the early abstinence phase, acute nicotine withdrawal stimulates cholinergic receptors to activate cortisol production via the HPA axis pathway. As a result, the static stress system becomes unresponsive.[57] The cortisol release is closely associated with the abstinence-induced reduction phenomenon that affects nicotine metabolism as well as the cortisol sensitivity that is related to nicotine withdrawal.[58] The reduced secretion of cortisol can happen following different responses on endocrine or neural

Table 2. The impact of exercise on TWS, smoking urge, mood and hormones.

FACTORS	TIME OF MEASUREMENT	MEAN (SD)	FSTAT (DF)	*P-VALUE*	PARTIAL η^2
TWS					
Appetite	Baseline	4.70 (1.84)	.77 (1.64, 47.76)	.44	.03
	Post-intervention	4.33 (2.12)			
	Post-detraining	4.27 (1.93)			
Craving	Baseline	4.53 (.55)	5.26 (2, 58)	.01*	.15
	Post-intervention	4.33 (.37)			
	Post-detraining	4.22 (.45)			
Physical symptoms	Baseline	3.46 (1.37)	.09 (2, 58)	.91	.01
	Post-intervention	3.89 (1.25)			
	Post-detraining	3.46 (1.16)			
Psychological symptoms	Baseline	3.82 (.96)	1.86 (2, 58)	.17	.06
	Post-intervention	3.55 (.95)			
	Post-detraining	3.69 (1.05)			
Sedation	Baseline	3.23 (1.72)	1.36 (2, 58)	.26	.05
	Post-intervention	2.77 (1.48)			
	Post-detraining	3.03 (1.35)			
Smoking urge					
Desire to smoke	Baseline	8.25 (2.22)	4.19 (1.39, 40.42)	.04*	.13
	Post-intervention	7.65 (2.12)			
	Post-detraining	7.53 (2.25)			
Anticipation of pleasure of smoking	Baseline	7.29 (2.32)	1.26 (1.49, 43.19)	.28	.04
	Post-intervention	6.89 (2.22)			
	Post-detraining	7.07 (2.13)			
Mood					
Positive well-being	Baseline	4.54 (.93)	4.03 (1.64, 47.61)	.03*	.12
	Post-intervention	4.91 (.96)			
	Post-detraining	4.90 (.99)			
Psychological distress	Baseline	2.73 (1.08)	3.93 (1.30, 37.75)	.04*	.12
	Post -intervention	2.39 (.86)			
	Post-detraining	2.26 (.88)			
Fatigue	Baseline	3.98 (1.22)	3.70 (1, 29)	.03*	.11
	Post-intervention	3.82 (1.28)			
	Post-detraining	3.41 (1.37)			

HORMONES	TIME OF MEASUREMENT	MEAN (SD)	FSTAT(DF)	*P-VALUE*	PARTIAL η^2

(Continued)

Table 2. Continued.

HORMONES	TIME OF MEASUREMENT	MEAN (SD)	FSTAT(DF)	*P-VALUE*	PARTIAL η^2
Serum cortisol (nmol/L)	Baseline	249.90 (100.11)	.51 (1, 29)	.51	.03
	Post-intervention	236.80 (90.70)			
	Post-detraining	227.98 (82.46)			
Serum beta-endorphin (pg/ml)	Baseline	132.71(94.15)	1.96 (1.13, 32.72)	.17	.29
	Post-intervention	152.40 (98.14)			
	Post-detraining	231.73 (341.39)			
Plasma adrenaline (pg/ml)	Baseline	.23 (.22)	4.42 (2, 58)	.04*	.57
	Post-intervention	.59 (.97)			
	Post-detraining	.22(.28)			

Note: TWS, Tobacco Withdrawal Symptom.
Note: *P < .05 = significant difference.

mediators as a result of the adaptation of the HPA axis functioning in the event of regular exercise and smoking cessation.[59]

Secondly, a recent study reported that reduced cortisol in the exercise intervention could be due to the desensitised nicotine in the body metabolism that enhances corticosteroid activity.[53] The cortisol may have interacted with several neurotransmitters that mediate the effects of nicotine that were associated with stress-neurocircuit dysregulation of the addiction cycle.[33] In addition, the reduction might also be associated with an increase in the adrenocortical activity in smokers as compared to non-smokers, thus indicating the possibility that smokers are less adept at responding to stressful conditions.[34] In this study, the cortisol reduction trend during smoking abstinence is not a favourable sign because it is might be associated with early relapse.[53] The cortisol level should be high enough to stimulate a reduction of craving as shown in vigorous exercise[15]. In this study, we found that the cortisol concentration continuously decreased at post-intervention and detraining, thus indicating a possibility of the prolonged positive impact of exercise intervention for up to 10 weeks. Our findings also support the previous findings by.[53] The reduction of cortisol also highlighted the potential and possibility that the dysregulation of cortisol levels had been corrected based on the significant reduction in craving and improvement in mood among smokers.

The beta-endorphin is a marker related to HPA activity. It can be used to establish a response of pleasure or euphoric effects, as well as reward regulations.[36] Normally, smoking abstinence leads to reduced beta-endorphin and dopamine. Altered levels of these hormones will create a vulnerability to the effects of nicotine reward.[36] In this study, there was no significant difference in the serum beta-endorphin concentration after the exercise intervention. However, there was an increased trend from baseline to detraining. Our finding closely resembled[60]; in which the researchers found an increased level of beta-endorphin in the exercise group. Nevertheless, even though the increasing levels of serum beta-endorphin was not significant in our study, it could have still led to reduced stress and cortisol level during smoking abstinence. In other words, exercise, when performed for a longer duration, could maintain the beta-endorphin level and reduce drug-seeking behaviour during smoking cessation. In addition, the changes in beta-endorphin might be associated with the stress reflex of long-term allosteric adjustment due to chronic nicotine consumption.[36]

This study provided a potential piece of evidence of the impact of exercise programmes. It also highlighted the possibility that regular exercise can maintain an optimal serum beta-endorphin level even during abstinence. This hormone is supposed to be suppressed in chronic exposure to nicotine[61] due to the alteration of the dopaminergic and opioid system centre, subsequently promoting drug dependence in smokers.[62] In contrast, the attenuated beta-endorphin may reinforce smoking urges and exaggerate negative mood.[36] We also speculated that regular exercise could maintain the beta-endorphin level due to a significant improvement in craving and mood. Therefore, the inability to detect any significant beta-endorphin changes in this study might be due to several factors, such as small sample size, moderate-intensity exercise, and individuals' training status. A low level of lactate concentration[63] as a result of moderate-intensity or adaptation to regular exercise can explain the insignificant increase in the fatigue factors of the mood component. In addition, exercise intensity is known to positively influence beta-endorphin release whereby a high exercise intensity (> 60% VO_2max) causes high lactic acid concentration. The elevated lactate threshold can promote the surge of beta-endorphin. It is also closely related to the sympathoadrenal axis hormone.[63] As our intervention was moderate-intensity exercise, it may not be sufficient to induce further training stimulus, depending on the participants' adaptation and fitness level. Therefore, the possible explanation for the incremental trend of this hormone could be the acute effect of exercise from the

previous day, because this hormone tends to remain longer in the blood circulation, especially in light smokers.[64] The circulating beta-endorphin hormone would have enhanced the coping mechanism, especially since cortisol and nicotine would have been reduced during abstinence. Hence, the enhancement of beta-endorphin is the therapeutic target of exercise training to modulate mood and stress during smoking cessation.

More importantly, there was a significant increase in plasma adrenaline post-intervention that subsequently returned to baseline at detraining. This was likely due to the activation of sympathetic effects[65] and the release of dopamine and its derivative, adrenaline. An increase in adrenaline indicates a high dopamine concentration. A previous study reported that TWS severity was related to decreased levels of dopamine and catecholamine.[66] In this context, most pharmacotherapy treatment targets the actions of dopamine as its reduction can promote intense withdrawal.[66] Indirectly, this demonstrated the beneficial effects of our exercise intervention, as reported by.[15] Furthermore, exercise intervention can help to maintain the catecholamine homeostasis to increase the pleasure effect during abstinence from smoking.[66] In a previous study, heavy smokers were found to face difficulty in regulating immediate brain catecholamine release as mediated by decreases in dopamine and noradrenaline, thus predisposing them to more severe withdrawal symptoms.[66] To counteract these negative effects, antidepressants were prescribed to increase the catecholamine level during abstinence. When taken, the synergistic effect between antidepressants and catecholamines can contribute to more severe TWS. As shown in this study, exercise intervention increased the levels of adrenaline and thus exercise can be considered as an potential adjunct to overcome TWS during abstinence. Furthermore, the increase in the plasma adrenaline level may be related to a significant reduction in their craving and desire to smoke. Our finding was aligned with a study[15] in which noradrenaline was identified as a potential biomarker in reducing cigarette cravings and TWS.

In summary, several important findings including a significant improvement in the observed psychological variables such as mood, urge, and adrenaline following the exercise intervention emerged from our study. Nonetheless, the effectiveness of others variables following the exercise intervention may only be established with a bigger sample size and the presence of a control group. Thus, making generalisations based on this study cannot be made at this moment. Nonetheless, our findings on TWS and hormonal changes following exercise intervention serve as important preliminary data for future studies on psychophysiological and addiction-related hormone dysregulation. Future studies are strongly recommended to include a control group and additional measurements of other related hormones such as dopamine and serotonin. Moreover, the application of a supervised exercise programme as an adjunct non-pharmacological therapy for smoking cessation may be considered in future investigations, with or without the combination of religious or spiritual-related psychotherapy.

There are several limitations to this study. First, certain factors could not be controlled, such as the physical activity performed and the number of cigarettes smoked throughout the exercise intervention by the participants. Secondly, no control group could be established because of poor participation even though we extended the recruitment to several centres. Thus, the study finding might not be able to detect the actual effects of supervised moderate-intensity exercise. Similar to other smoking-related research[67]; we faced great challenges to achieve the sample size even though the process was extended for more than 2 years (from February 2016 until June 2018) and to 11 centres. Thus, the cross-over study design might overcome the challenges of this similar future study. Lastly, the low participation rate from smokers restricted a randomisation process. Additionally, the measure of withdrawal during the 12-h overnight abstinence might not have achieved the peak point of withdrawal. Future studies should implement the gold standard study design with at least a cross-over study to better quantify the actual effect of an exercise intervention on TWS and hormonal variables.

Acknowledgements

We want to thank the Director-General of Health for his permission to recruit the participant from their facility. We also thank the smokers who participated in the study and the laboratory research assistance for the laboratory analysis.

Author Contributions

The authors confirm contribution to the paper as follows: NHR contributed to the study conception, design, analysis, interpretation and the first draft of manuscript writing. SMY contributed to study conception and design, MRI involved in study methodology and data interpretation, NMN involved in laboratory analysis and interpretation of results. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. World Health Organization (WHO). *Launches New Report on Global Tobacco Use Trends*; Geneva, WHO, 2019. https://www.who.int/news-room/detail/19-12-2019-who-launches-new-report-on-global-tobacco-use-trends.
2. Lim KH, Teh C, Pan S, et al. Prevalence and factors associated with smoking among adults in Malaysia: Findings from the national health and morbidity survey (NHMS) 2015. *Tob Induc Dis*. 2018;16(1):01-12. doi:10.18332/tid/82190.
3. IPH, Institute for Public Health Malaysia, M. of HChan Ying Ying JSMS, Norzawati Y, et al. National health and morbidity survey (NHMS) 2019: NCDs—non-communicable diseases, healthcare demand and health literacy. In: Tania Gayle R, (ed). *Dr Thamil Arasu Saminathan, Cheong Siew Man, Lalitha Palanivello, Dr Fazila Haryati Ahmad*. Institute for Public Health, National Institutes of Health (NIH), Ministry of Health Malaysia, 1; 2019. https://www.iku.gov.my/nhms-2019.
4. U.S. Department of Health and Human Services, Health C. for C. D. P., H. P. (*U. S. Smoking Cessation: A Report of the Surgeon General*; U.S. Department of Health and Human Services, Health, Washington, DC, 2020.
5. Wardle MC, Lopez-Gamundi P, LaVoy EC. Effects of an acute bout of physical exercise on reward functioning in healthy adults. *Physiol Behav*. 2018;194:552-559. doi:10.1016/j.physbeh.2018.07.010.
6. Sigmon SC, Patrick ME. The use of financial incentives in promoting smoking cessation. *Prev Med*. 2012;55(suppl):24-32. doi:10.1016/j.ypmed.2012.04.007.

7. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. *Psychiatr Clin North Am*. 2010;33(3):511-525. doi:10.1016/j.psc.2010.04.012.
8. Aonso-Diego G, González-Roz A, Krotter A, García-Pérez A, Secades-Villa R. Contingency management for smoking cessation among individuals with substance use disorders: In-treatment and post-treatment effects. *Addict Behav*. 2021;119:106920. doi:10.1016/j.addbeh.2021.106920
9. Nwosu NC, Ede MO, Onah NG, et al. Cognitive behavioral therapy for challenges to quitting tobacco smoking among social science and religion students. *Medicine (United States)*. 2022;101(47):E31913. doi:10.1097/MD.0000000000031913.
10. Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: A review of reviews for the U.S. preventive services task force. *Ann Intern Med*. 2015;163(8):608-621. doi:10.7326/M15-0171.
11. Garcia-Gomez L, Hernández-Perez A, Noe-Diaz V, Riesco-Miranda JA, Jimenez-Ruiz C. Smoking cessation treatments: Current psychological and pharmacological options. *Rev Invest Clin*. 2019;71(1):7-16. 10.24875/RIC.18002629.
12. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Individual differences in adoption of treatment for smoking cessation: Demographic and smoking history characteristics. *Drug Alcohol Depend*. 2008;93(1-2):121-131. doi:10.1016/j.drugalcdep.2007.09.005.
13. Vander Weg MW, Coday M, Stockton MB, et al. Community-based physical activity as adjunctive smoking cessation treatment: Rationale, design, and baseline data for the lifestyle enhancement program (LEAP) randomized controlled trial. *Contemp Clin Trials Commun*, 2018;9, 50–59. doi:10.1016/j.conctc.2017.11.013.
14. Ussher MH, Faulkner G, Angus K, Hartmann-Boyce J, Taylor AH Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*, 2019, 2019(10), 51-121. doi:10.1002/14651858.CD002295.pub6.
15. Roberts V, Gant N, Sollers JJ, Bullen C, Jiang Y, Maddison R. Effects of exercise on the desire to smoke and physiological responses to temporary smoking abstinence: A crossover trial. *Psychopharmacology*. 2015;232(6):1071-1081. doi:10.1007/s00213-014-3742-8.
16. Hartmann-Boyce J, Theodoulou A, Farley A, et al. Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev*. 2021;10(10):CD006219. doi:10.1002/14651858.CD006219.pub4.
17. Taylor AH, Ussher MH, Faulkner G. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behaviour: a systematic review. *Addiction*. 2007;102:534-543. doi:10.1111/j.1360-0443.2006.01739.x.
18. Bock BC, Fava JL, Gaskins R, Morrow KM, Williams DM, Jennings E, Becker BM, Tremont G, Marcus BH. Yoga as a complementary treatment for smoking cessation in women. *J Womens Health*. 2012;21(2):240-248. doi:10.1089/jwh.2011.2963.
19. Marcus B, Albrecht A, Niaura R, et al. Exercise enhances the maintenance of smoking cessation in women. *Addict Behav*. 1995;20:87-92.
20. Ho JY, Kraemer WJ, Volek JS, et al. Effects of resistance exercise on the HPA axis response to psychological stress during short-term smoking abstinence in men. *Addict Behav*. 2014;39(3):695-698. doi:10.1016/j.addbeh.2013.10.027.
21. Ciccolo JT, Williams DM, Dunsiger SI, et al. Efficacy of resistance training as an aid to smoking cessation: Rationale and design of the strength to quit study. *Mental Health and Physical Activity*. 2014;7(2):95-103. doi:10.1016/j.mhpa.2014.05.004.
22. Everson ES, Daley AJ, Ussher M. The effects of moderate and vigorous exercise on desire to smoke, withdrawal symptoms and mood in abstaining young adult smokers. *Ment Health Phys Act*. 2008;1:26-31.
23. Olutende M, Wekesa J, Mogaka E, WabuyaboKweyu I. Effects of aerobic exercise on mood state of university students : A quasi- experimental approach. *Int J Curr Res*. 2017;9(11):61107-61112.
24. Basso JC, Suzuki WA. The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: a review. *Brain Plast*. 2017;2(2):127-152. doi:10.3233/bpl-160040.
25. Korhonen T, Goodwin A, Miesmaa P, Dupuis EA, Kinnunen T. Smoking cessation program with exercise improves cardiovascular disease biomarkers in sedentary women. *J Womens Health*. 2011;20(7):1051-1064. doi:10.1089/jwh.2010.2075.
26. Peluso MA, Guerra de Andrade LHS. Physical activity and mental health: the association between exercise and mood. *Clinics*. 2005;60(1):61-70. doi:10.1590/S1807-59322005000100012.
27. Pérez CA. Prescribing Exercise in Tobacco Smoking Cessation Therapy. *Arch Bronconeumol*. 2009;45(11):556-560. (English Edition) doi:10.1016/s1579-2129(09)73417-2.
28. Klinsophon T, Thaveeratitham P, Sitthipornvorakul E, Janwantanakul P. Effect of exercise type on smoking cessation: A meta-analysis of randomized controlled trials. *BMC Res Notes*. 2017;10(1):1-21. doi:10.1186/s13104-017-2762-y.
29. Lynch WJ, Peterson A, Sanchez VAJ, Abel J, Smith MA. Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis. *Neurosci Biobehav Rev*. 2013;37:1622-1644. doi:10.1016/j.neubiorev.2013.06.011.
30. Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: Nicotine addiction. *Sci Adv*. 2019;5(10):eaay9763. doi:10.1126/sciadv.aay9763.
31. Wardle MC, Munafò MR, De Wit H. Effect of social stress during acute nicotine abstinence. *Psychopharmacology*. 2011;218(1):39-48. doi:10.1007/s00213-010-2150-y.
32. Bruijnzeel AW. Tobacco addiction and the dysregulation of brain stress systems. *Neurosci Biobehav Rev*. 2012;36(5):1418-1441. doi:10.1016/j.neubiorev.2012.02.015.
33. Koob G, Kreek MJ. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry*. 2007;164(8):1149-1159. doi:10.1176/appi.ajp.2007.05030503.
34. al'Absi M, Hatsukami D, Davis GL, Wittmers LE. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. *Drug Alcohol Depend*. 2004;73:267-278. doi:10.1016/j.drugalcdep.2003.10.014.
35. Berrendero F, Robledo P, Trigo JM, Martín-García E, Maldonado R. Neurobiological mechanisms involved in nicotine dependence and reward: Participation of the endogenous opioid system. *Neurosci Biobehav Rev*. 2010;35(2):220-231. doi:10.1016/j.neubiorev.2010.02.006.
36. Shaw D, al'Absi M. Attenuated beta endorphin response to acute stress is associated with smoking relapse. *Pharmacol Biochem Behav*. 2008;90(3):357-362. doi:10.1016/j.pbb.2008.03.020.Attenuated.
37. Jensen EW, Espersen K, Kanstrup IL, Christensen NJ. Plasma noradrenaline and ageing: effects of smoking habits. *Eur J Clin Invest*. 1996;26(10):839-846.
38. Al'Absi M., Hooker S., Fujiwara K., et al. Circulating leptin levels are associated with increased craving to smoke in abstinent smokers. *Pharmacol Biochem Behav*. 2011;97(3):509-513. doi:10.1016/j.pbb.2010.10.004.
39. Mujika I, Padilla S. Cardiorespiratory and metabolic characteristics of detraining in humans. *Med Sci Sports Exerc*. 2001;33(3):413-421. doi:10.1097/00005768-200103000-00013.
40. Kohn M A, Senyak J. *Sample Size Calculators*. National Center for Advancing Translational Sciences, National Institutes of Health; 2021.
41. Harper T., Fitzgeorge L., Tritter A., Prapavessis H., Harper T., Fitzgeorge L., Tritter A., Prapavessis H.. Acute Exercise Effects on Craving and Withdrawal Symptoms among Women Attempting to Quit Smoking Using Nicotine Replacement Therapy Acute Exercise Effects on Craving and Withdrawal Symptoms among Women Attempting to Quit Smoking Using Nicotine Replacement. *Journal of Smoking Cessation* 2012;7(2):72-79. https://doi.org/10.1017/jsc.2012.15.
42. Anne Yee H, Ng C, Rusdi A. Validation of The malay version of fagerstrom test for nicotine dependence (FTND-M) among a group of male staffs in a university hospital. *MJP Online Early*. 2011;20(1):1-7.
43. DiClemente C. C., Prochaska J. O., Fairhurst S. K., Velicer W. F., Velasquez M. M., Rossi J. S.. The Process of Smoking Cessation: An Analysis of Precontemplation, Contemplation, and Preparation Stages of Change. *Journal of Consulting and Clinical Psychology* 1991;59(2):295-304. https://doi.org/10.1037/0022-006X.59.2.295.
44. Mbulo L, Murty KS, Husain MJ, et al. Contrasting Trends of Smoking Cessation Status: Insights From the Stages of Change Theory Using Repeat Data From the Global Adult Tobacco Survey, Thailand (2009 and 2011) and Turkey (2008 and 2012). *Preventing Chronic Disease*; 2017:14, E42, doi:10.5888/pcd14.160376, PARQ.
45. Malay.Pdf Sport Singapura:Retrieved February 1, 2016. www.sportsingapore.gov.sg/ (2022).
46. Pescatello L, Arena R., Riebe D, Thompson P. In: Pescatello L, Arena R, Riebe D., Thompson P, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. (Ninth ed.). Wolters Kluwer Lippincott Williams & Wilkins; 2014.
47. Mukhtar F., Zulkefly N. The beck anxiety inventory for Malays (BAI-Malay): a preliminary study on psychometric properties. *Malaysian J Med Health Sci*. 2011;7(1):73-79.
48. Oei TPO, Mukhtar F. Exploratory and confirmatory factor validation and psychometric properties of the automatic thoughts questionnaire for Malays (ATQ-Malay) in Malaysia. *J Hong Kong Coll Psychiatr*. 2008;18:92-100.
49. Riebe D. General principles of exercise prescription. In: *ACSM's Guide to Exercise Testing and Prescription*. 9th ed. Lippincott,William & Wilkins; 2014:22-38.
50. Teo EW, Lee YY, Khoo S, Morris T. Translation and validation of the Malay version of Shiffman-Jarvik withdrawal scale and cessation self-efficacy questionnaire: a review of psychometric properties. *Health Qual Life Outcomes*. 2015;13(1):45. doi:10.1186/s12955-015-0238-0.
51. Blebil AQ, Sulaiman SAS, Hassali MA, Dujaili JA, Zin AM. The Malay version of the brief questionnaire on smoking urge: Translation and psychometric properties of the questionnaire. *J Epidemiol Glob Health*. 2015;5(1):15-22. doi:10.1016/j.jegh.2014.10.006.
52. Ruslan NH, Yasin S, Mohd Nasir N, Isa MR, James A, Rajikin M (2020). Reliability and construct validity of the Malay version of subjective experience exercise scale (SEES) among smokers. *J. Soc. Sci. Res* 2018, 5(13), 305–310. https://cssr.uitm.edu.my/2018/
53. Al-Eisa E, Alghadir AH, Gabr SA, Iqbal ZA. Exercise intervention as a protective modulator against metabolic disorders in cigarette smokers. *J Phys Ther Sci*. 2016;28(3):983-991. doi:10.1589/jpts.28.983.

54. Zourbanos N, Hatzigeorgiadis A, Tsiami A, et al. An initial investigation of smokers' urges to smoke and their exercise intensity preference: A mixed- methods approach, 1-9; 2016. doi:10.1080/2331205X.2016.1149043.
55. Garber CE, Blissmer B, Deschenes MR, et al. American college of sports medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7): 1334-1359. doi:10.1249/MSS.0b013e318213fefb.
56. Morrell HER, Cohen LM, al'Absi M. Physiological and psychological symptoms and predictors in early nicotine withdrawal. *Pharmacol Biochem Behav*. 2008;89(3): 272-278. doi:10.1016/j.pbb.2007.12.020.
57. Seyler LE, Fertig J, Pomerleau O, Hunt D, Parker K. The effects of smoking on ACTH and cortisol secretion. *Life Sci*. 1984;34:57-65.
58. Wong JA, Pickworth WB, Waters AJ, Al'Absi M, Leventhal AM. Cortisol levels decrease after acute tobacco abstinence in regular smokers. *Hum Psychopharmacol*. 2014;29:152-162. doi:10.1002/hup.
59. Kirschbaum C, Wust S, Hellhammer D. Consistent sex differences in cortisol responses to psychological stress. *Psychosom Med*. 1992;54(6):648-657. doi:10.1097/00006842-199211000-00004.
60. Leelarungrayub D, Pratanaphon S, Pothongsunun P, Sriboonreung T, Yankai A, Bloomer RJ. Vernonia cinerea Less. supplementation and strenuous exercise reduce smoking rate: relation to oxidative stress status and beta-endorphin release in active smokers. *J Int Soc Sports Nutr*. 2010;7:21. doi:10.1186/1550-2783-7-21.
61. Rasmussen DD, Boldt BM, Bryant CA, Mitton DR, Larsen SA, Wilkinson CW. Chronic daily ethanol and withdrawal: 1. Long-term changes in the hypothalamo-pituitary-adrenal axis. *Alcohol Clin Exp Res*. 2000;24(12):1836-1849. doi:10.1111/j.1530-0277.2000.tb01988.x.
62. Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. *Curr Top Med Chem*. 2004;4(1):39-50. doi:10.2174/1568026043451573.
63. Goldfarb AH, Jamurtas AZ. Beta-endorphin response to exercise. An update. *Sports Med*. 1997;24:8-16. https://www.ncbi.nlm.nih.gov/pubmed/9257407
64. del Arbol JL, Raya Muñoz J, Ojeda L, et al. In: Plasma concentrations of beta-endorphin in smokers who consume different numbers of cigarettes per day. *Pharmacol Biochem Behav*, 67; 2000:25-28. doi:10.1016/S0091-3057(00)00291-4.
65. Goldstein DS. Catecholamines and stress. *Endocr Regul*. 2003;37(2):69-80. doi:10.1002/9783527628346.ch2.
66. Kawai A, Kurita M, Nishino S, Hirata E, Sato T, Okubo Y. Need for medication to complement catecholamines in smoking cessation of hardcore smokers. *Neuropsychiatr Dis Treat*. 2017;13:2419-2424. doi:10.2147/NDT.S144181.
67. Lee YY, Khoo S, Morris T, et al. A mixed-method study of the efficacy of physical activity consultation as an adjunct to standard smoking cessation treatment among male smokers in Malaysia. *SpringerPlus*. 2016;5(1):1-12. doi:10.1186/s40064-016-3675-2.