HHS Public Access

Author manuscript

Hum Psychopharmacol. Author manuscript; available in PMC 2018 January 11.

Published in final edited form as:

Hum Psychopharmacol. 2014 July ; 29(4): 307–315. doi:10.1002/hup.2403.

Concurrent tobacco and khat use is associated with blunted cardiovascular stress response and enhanced negative mood: a cross-sectional investigation

Mustafa al'Absi[1,*], **Motohiro Nakajima**[1], **Anisa Dokam**[2], **Abed Sameai**[2], **Mohamed Alsoofi**[2], **Najat Saem Khalil**[3], and **Molham Al Habori**[3]

[1]Duluth Medical Research Institute, University of Minnesota Medical School, Duluth, Minnesota, USA

[2]Taiz University, Taiz, Yemen

[3]Sana'a University, Sana'a, Yemen

Abstract

Objectives—Khat (*Catha edulis*), an amphetamine-like plant, is widely used in East Africa and the Arabian Peninsula and is becoming a growing problem in other parts of the world. The concurrent use of tobacco and khat is highly prevalent and represents a public health challenge. We examined for the first time associations of the concurrent use of tobacco and khat with psychophysiological responses to acute stress in two sites in Yemen.

Methods—Participants ($N = 308$; 135 women) included three groups: users of khat and tobacco, users of khat alone, and a control group (nonsmokers/nonusers of khat). These individuals completed a laboratory session in which blood pressures (BP), heart rate, and mood measures were assessed during rest and in response to acute stress.

Results—Concurrent use of khat and tobacco was associated with attenuated systolic BP, diastolic BP, and heart rate responses to laboratory stress (ps <0.05) and with increased negative affect relative to the control group (ps <0.05).

Conclusions—Results demonstrated blunted cardiovascular responses to stress and enhanced negative affect in concurrent khat and tobacco users. These findings extend previous studies with other substances and suggest that adverse effects of khat use may lie in its association with the use of tobacco.

Keywords

tobacco; khat; cardiovascular response; negative affect; psychopharmacology

*Correspondence to: Mustafa al'Absi, University of Minnesota Medical School, 1035 University Drive, Duluth, Minnesota, USA 55812. Tel: (218) 726-7144; Fax: (218) 726-7559, malabsi@umn.edu.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

INTRODUCTION

Chronic exposure to drugs of addiction can have profound effects on the brain. The impact of this exposure may be particularly devastating in poor communities and in low-income countries where effects of drugs are complicated by other environmental hardship, including malnutrition, poverty, and poor health care. Khat (*Catha edulis*) is a natural amphetamine that is widely used in East Africa and the Arabian Peninsula with a prevalence reaching 75% of the adult population (Krikorian, 1984; World-Bank, 2007; Wedegaertner *et al.*, 2010; Reda *et al.*, 2012). Its use has been growing in North America, Western Europe, and other parts of the world (Kassim and Croucher, 2006; Griffiths *et al.*, 2010; Apps *et al.*, 2011; UK-Home-Office, 2011), although accurate epidemiological estimates are not available. The harm to health caused by this drug has long been established (Cox and Ramsay, 2003; Al Motarreb *et al.*, 2010; Ali *et al.*, 2011), but there is virtually no research addressing its effects on behavioral functions either acutely or chronically. This knowledge is critical in understanding the biobehavioral influences of khat use, for guiding efforts to combat its escalating use, addressing its adverse consequences on health.

Chewing khat leaves is the most common mode of intake (Kennedy, 1988), although a small number of users use dried leaves to make drinks (Pantelis *et al.*, 1989). Users fill their mouth with leaves and chew slowly and intermittently to release the active components of khat that are then swallowed (Nencini *et al.*, 1986). Khat chewing has a social and cultural tradition, and it may occur while in the company of others or alone (Kennedy, 1988). One of the major pharmacologically active constituents of khat is cathinone, an amphetamine-like sympathomimetic amine (Kalix, 1996). Similar to amphetamines, khat ingestion produces several central nervous system effects, including increased motor stimulation, euphoria, and sense of excitement and energy (Kalix, 1996; Nencini *et al.*, 1998), in addition to increased levels of alertness, ability to concentrate, confidence, friendliness, contentment, and flow of ideas (Kennedy, 1988; Brenneisen *et al.*, 1990; Widler *et al.*, 1994). It also results in decreased appetite and increased blood pressure (BP) and heart rate (HR) (Hassan *et al.*, 2000). Within 2 h after ingestion, chewers report excessive tension, anxiety, emotional instability, irritability, and restlessness, which are followed by feelings of low mood, numbness, lack of concentration, sluggishness, and insomnia (Kennedy, 1988; Al-Motarreb *et al.*, 2002). These effects suggest that khat acts through central mechanisms similar to amphetamine. Both cathinone and amphetamine increase the activity of the dopaminergic and noradrenergic transmission (Nielsen, 1985; Pehek and Schechter, 1990; Pehek *et al.*, 1990; Patel, 2000). Although the nature of khat dependence remains under active debate, accumulating evidence suggests the existence of a withdrawal syndrome and a low-level tolerance (Cox and Ramsay, 2003; Manghi *et al.*, 2009; Wedegaertner *et al.*, 2010). Withdrawal symptoms usually include inertia, nightmares, trembling, depression, sedation, and hypotension.

Cigarettes and waterpipe tobacco smoking (shisha, nargile) are widely used during khat chewing sessions (Odenwald *et al.*, 2007; Tesfaye *et al.*, 2008; Kassim *et al.*, 2011; Regassa and Kedir, 2011; Nakajima *et al.*, 2012). Reports indicate high tobacco use reaching 65% among khat users (Bawazeer *et al.*, 1999; Odenwald *et al.*, 2007; Tesfaye *et al.*, 2008). Although effects of tobacco and khat use have been examined separately in previous studies and have been found to activate similar physiological systems, no study has evaluated acute or chronic influences of the combination, and factors contributing to concurrent use have not been explored. Furthermore, the extent to which concurrent use of khat and tobacco interacts to modulate stress-related biobehavioral functions is not known. Studies examining effects of tobacco alone have shown that long-term smoking contributes to dysregulation of the neurobiological stress response (e.g., diminished reactions in cortisol and BP (Kirschbaum *et al.*, 1993; al'Absi *et al.*, 2002; al'Absi, 2006), and these alterations have potential impact on treatment outcome (al'Absi *et al.*, 2005). Considering the complex interaction involved in the amphetamine-like effects of khat use and tobacco, it is possible that the use of both substances confers greater risk for impaired stress response regulation than the use of khat or tobacco alone. As such, this work is relevant to and could inform research focusing on concurrent addictive behaviors in other countries (Burns *et al.*, 2000; Lai *et al.*, 2000; John *et al.*, 2003; Humfleet and Haas, 2004).

We report here data obtained from a program conducted through a partnership between the University of Minnesota and two Yemeni universities to examine effects of the concurrent use of khat and tobacco. Concurrent khat and tobacco users, those who use khat alone, and those who were not using either of these two substances were recruited into this study. Cardiovascular and mood measures were assessed during rest and in response to acute stress. On the basis of previous work on nicotine and other psychostimulants (Kirschbaum *et al.*, 1993; al'Absi *et al.*, 2005; al'Absi, 2006), and previous data from a smaller group of khat users (al'Absi *et al.*, 2013), we predicted that khat use would be associated with blunted cardiovascular response and with exaggerated affective responses to stress. These response abnormalities would be more pronounced in khat users who also use tobacco than those who do not use tobacco.

METHODS

Participants

The current study used a cross-sectional design to examine the extent to which khat and tobacco use was associated with alterations with the stress response. Participants (concurrent users of khat and tobacco, users of khat alone, and a control group of nonsmokers/nonusers) were recruited between 2008 and 2010 on two university campuses and surrounding communities in two Yemeni cities, Sana'a and Taiz. Recruitment was conducted using flyers posted on both campuses and by word of mouth. Before enrolling in the study, participants attended a screening session to assess eligibility for the study and availability to participate in the protocol. The screening session included a brief medical history interview and assessment of current and past khat and tobacco use as well as the use of other substances. Participants were included if they were free from any medical or psychiatric conditions (e.g., high BP, cancer, heart disease, diabetes, major depression, anxiety disorders, and substance use disorders) and were not taking any medications. They also must have had a regular sleep/wake cycle. Khat users had to have been chewing khat on a daily basis. In addition to this, smokers had to have been smoking daily. We also assessed shisha smoking and used criteria for tobacco use status based on previously used methods (Maziak *et al.*, 2004). Three hundred and eight participants completed the laboratory session. These included 104 (39 women) who were concurrent users of tobacco and khat, 85 (30 women) who reported using khat only, and 119 (66 women) who reported no use of khat or tobacco.

Participants signed a consent form approved by the local Institutional Review Boards from Sana'a University and Taiz University. After that, they completed forms related to behavioral health and stress.

Apparatus and measures

Cardiovascular measures—An automated BP monitor (MicroLife Automatic BP monitor 3AC1; MicroLife, Widnau, Switzerland) was used to measure BP and HR. Such automated units have the advantages of enhanced reliability and freedom from differences in auscultatory practices between operators. This oscillometric device has been validated by the European Society of Hypertension's international protocol.

Self-report measures—We used the Subjective State measure to assess mood states during the laboratory session. This scale included 18 items that have been translated from previous adjective checklists used in lab experiments that is sensitive to acute mood changes (al'Absi *et al.*, 1997) and covers both negative and positive affect (Lundberg and Frankenhaeuser, 1980; al'Absi *et al.*, 1994a). Negative affect was assessed using items of anxiety, irritability, impatience, sadness, anger, and restlessness. Positive affect was assessed using items of cheerfulness, content, calmness, controllability, and interest. This scale has been previously validated and used in this population (Bongard *et al.*, 2011). The Cronbach's α values for negative affect and positive affect were 0.85 and 0.79, respectively (Bongard *et al.*, 2011). Each item was referenced to an 8-point scale anchored by the end points 'Not at All' and 'Very Strong'. Participants marked the scale at the point that best described how they felt during the previous 30 min. This measure was completed before and after performing an acute stress challenge.

Procedures

The laboratory session was conducted starting between 9:00 and 10:00 AM, and it lasted approximately 90 min. Prior to the laboratory session, a set of dietary guidelines and instructions about sleep were provided (e.g., participants were asked to have a light breakfast before the laboratory session). To minimize withdrawal symptoms, tobacco users continued to smoke at their regular rate until immediately before the laboratory session. Similarly, khat users continued their regular daily chewing habit (chewing the afternoon of the day before the session). At the beginning of the session, the participant was brought to a quiet room and sat in a comfortable chair. An inflatable BP cuff was attached to the subject's left upper arm. Procedures included resting baseline for 15 min, the acute stressful challenge for 10 min, and a recovery rest period for 15 min. The acute challenge was a mental arithmetic task that involved subtraction of a number 7 from a four-digit number. Participants were asked to perform as fast as they could. When a mistake was made, the participant was asked to go back to the previous correct number. This task has been previously used in multiple stress reactivity studies and has been found to be effective in activating the sympathetic system (Sherwood *et al.*, 1993; al'Absi *et al.*, 1994b; al'Absi *et al.*, 1997). BP and HR were measured every 3 min during resting baseline, the acute stressor, and during recovery.

Participants also completed the Subjective State measure after baseline, the stressor, and after recovery.

Data analysis

The primary dependent variables in this study were HR (bpm), systolic BP (mmHg), diastolic BP (mmHg), and self-report measures of negative affect and positive affect. Rate pressure product (RPP, mmHg beat/min, calculated as HR × systolic BP) was included as an index of myocardial oxygen demand. Cardiovascular measures were averaged across three periods (baseline, stress, and recovery). Cardiovascular and self-report data were analyzed using 3 (groups: concurrent users of khat and tobacco, khat-only users, and nonusers) × 2 (gender: men, women) × 3 sampling times (baseline stress, and recovery) analysis of covariance with Greenhouse–Geisser corrections. Site variable was included as a covariate. Demographic variables such as age and body mass index [BMI; weight (kg)/height (m^2)] were analyzed using 3 groups × 2 gender analysis of variance (ANOVA) as well as chi-square tests. Khat-user variables were analyzed using 2 groups (concurrent users and khat-only users) × 2 gender ANOVA and chi-square tests. Tobacco use among concurrent users was analyzed by one-way ANOVAs with gender as a factor and chi-square tests. For main effect comparison, we used the Bonferroni correction.

RESULTS

Participant characteristics

Concurrent and khat-only users were older than nonusers (group effect: $F(2, 302) = 9.99$, $p < 0.01$; Table 1). Men were taller ($F(1, 295) = 227$, $p < 0.001$) and heavier ($F(1, 295) = 37.1$, $p < 0.001$) than women; however, BMI did not differ by groups or gender (ps >0.16). Concurrent users reported fewer average hours of sleep than nonusers ($F(2, 105) = 5.13$, $p < 0.01$). Years of education did not differ by group or by gender (ps >0.25). Khat-only and concurrent users did not differ in patterns of khat use, with one exception that concurrent users reported longer hours of chewing per session than khat-alone users ($F(1, 184) = 8.39$, $p < 0.01$). Reported age started was earlier, and hours and days of khat chewing were greater in men than in women (Fs(1, 181) = 16.4, ps <0.001). Reported number of cigarettes smoked per day was greater in men than in women ($F(1, 101) = 94$, $p < 0.001$), whereas waterpipe use was greater in women than in men ($F(1, 71) = 40$, $p < 0.001$). Because of observed differences in age across groups, age was included as a covariate where appropriate.

Cardiovascular and self-report measures

We found significant differences in the magnitude of cardiovascular responses to stress as demonstrated by significant group × sampling time interactions (Fs(4, 513) >2.57, ps <0.05) in systolic BP, diastolic BP, HR, and RPP. To further explore these interactions, change scores (the value during baseline period was subtracted from the value during stress period) were obtained. A series of 3 groups × 2 gender analyses of covariance including site as a covariate found significant group differences across all cardiovascular measures (Fs(2, 295) >3.28, ps <0.05) reflecting attenuated response among concurrent users relative to nonusers (ps <0.05; Figure 1). Khat-only users exhibited smaller RPP response to stress ($p < 0.01$) and tended to show smaller systolic BP ($p < 0.07$) than nonusers. Concurrent users of khat and tobacco did not differ from khat-only users (*p*s >0.99; Figure 2). Men showed greater systolic BP and RPP than women (*F*s(1, 294) >4.13, *p*s <0.05).

Exposure to the acute stressor was associated with increased negative affect and decreased positive affect (time effects: *F*s(2, 574) >9.64, *p*s <0.001, specific comparisons: *p*s <0.001; Figure 3). A significant group effect was also found for these measures (*F*s(2, 297) >5.68, *p*s <0.01). This was due to greater negative affect and lower positive affect in concurrent users than the nonusers (*p*s <0.05). In addition, lower positive affect was reported by khat-only users compared with the nonusers (*p* <0.01). Concurrent users of khat and tobacco did not differ from khat-only users (*F*s <1). Women reported lower positive affect than men (*F*(1, 297) = 4.71, *p* <0.05).

Correlational analysis

A series of correlational analyses were conducted to examine the extent to which patterns of khat use were associated with cardiovascular measures. These analyses included concurrent users and khat-only users. Daily khat use was positively related to systolic BP and RPP during all periods (*r*s 0.16–0.26, *p*s <0.05). The frequency of khat chewing sessions per week was positively linked with HR during baseline and recovery (*r*s 0.14–0.15, *p*s <0.05), and years of chewing were positively correlated with systolic BP during stress and recovery (*r*s 0.17–0.24, *p*s <0.05). Years of khat use were inversely associated with HR response (change score from baseline to stress; *r* = −0.15, *p* <0.05). Similarly, correlational analyses were conducted to test the relationships between tobacco use patterns and cardiovascular measures. The number of cigarettes per day was positively associated with systolic BP during stress and RPP during all periods (*r*s 0.19–0.26, *p*s <0.05). In contrast, the number of waterpipe heads was inversely related to HR during baseline (*r* = −0.30, *p* <0.01). Daily tobacco use was inversely associated with systolic BP, diastolic BP, and RPP responses (*rs* > −0.19, *ps* ≤ 0.05) (Figure 4).

Correlational analyses were also conducted to examine whether self-report mood measures were linked with cardiovascular measures. When analyses were conducted including all participants, we found positive correlations between positive affect at all periods (baseline, stress, and recovery) and systolic BP and diastolic BP during stress (*r*s 0.11–0.24, *p*s ≤ 0.05). When the analyses were conducted in each group, similar patterns of results were obtained in nonusers and khat-only users. That is, there were correlations between positive affect at all periods and systolic BP during stress (*r*s 0.18–0.32, *p*s <0.05) and correlations between baseline positive affect and diastolic BP during stress (*r* = 0.22, *p* <0.05) in nonusers. Also, positive affect during baseline as well as recovery was related to systolic BP and diastolic BP during stress in khat-only users (*r*s 0.21–0.31, *p*s <0.05). In contrast, these findings were not found in concurrent users (*p*s >0.12; Figure 4).

DISCUSSION

The present study was prompted by the high prevalence of concurrent use of tobacco and khat in many countries around the world and by reports indicating that up to two thirds of khat users also smoke (Bawazeer *et al.*, 1999; Odenwald *et al.*, 2007; Tesfaye *et al.*, 2008; al'Absi and Grabowski, 2012). The results showed that concurrent use of khat and tobacco was associated with attenuated cardiovascular responses to acute stress. Concurrent users also reported greater negative affect and less positive affect during the acute stress laboratory session relative to the control group. This is the first study to examine the influences of concurrent use of the psychostimulant khat and tobacco on physiological and mood responses to acute stress. Although increased reported negative affect by the concurrent khat and tobacco users may reflect a greater predisposition for using these substances, it is possible that these changes reflect long-term effects of chronic exposure to these substances. Previous research has shown that chronic tobacco use is associated with enhanced negative affect (al'Absi *et al.*, 2003). Population studies in khat users have also indicated the association of chronic khat use with various psychological problems, including major psychiatric disorders such as psychotic disorders and mania (Yousef *et al.*, 1995; Odenwald *et al.*, 2007; Bhui and Warfa, 2010).

The patterns of associations between khat and tobacco use with cardiovascular measures implicate these substances in altering the stress response. Furthermore, results showing significant associations between subjective reports and cardiovascular responses in the nonusers and the khat-only users but not in the concurrent users demonstrate the disrupted connection of motivational states with stress physiological responding in the concurrent use group. Mechanisms responsible for these results in concurrent users likely involve dysregulation at multiple levels, including sympathetic nervous system, vagal tone, and baroreceptor-reflex sensitivity. Although little research has focused on the effects of chronic khat use, studies focusing on chronic tobacco use have shown the role of reduced beta-adrenergic receptor functions as a potential mediator of the effects of chronic tobacco use (Laustiola *et al.*, 1988; Laustiola *et al.*, 1991). It is possible that repeated responses of these systems to these substances would impose increased allostatic load leading to altered responses to the acute challenges and possibly contributing to the development of cardiovascular diseases in this population. Indeed, this possibility may explain the recent findings of increased risk for cardiovascular morbidity among khat users (Cox and Ramsay, 2003; Al Motarreb *et al.*, 2010; Ali *et al.*, 2011).

The established reactivity hypothesis indicates that repeated and exaggerated increases in cardiovascular activity in response to stress may increase or accelerate risk for cardiovascular diseases (Harris and Matthews, 2004; Chida and Steptoe, 2010). Similar to acute stress, both tobacco and khat acutely increase cardiovascular activity (Benowitz *et al.*, 1984; Hassan *et al.*, 2000). Ongoing and repeated exposure to these substances, however, may lead to long-term hemodynamic adjustment, contributing to poor responsiveness to acute stress. Consistent with this hypothesis, previous research has demonstrated that chronic use of addictive substances, such as alcohol, opiate, and amphetamine, is associated with blunted physiological responses to a wide range of psychological (e.g., mental arithmetic and public speaking) and physical stressors (e.g., cold pressor and isometric handgrip) (Bernardy *et al.*, 1996; Gerra *et al.*, 2003a; Gerra *et al.*, 2003b). Research focusing on polysubstance use has also demonstrated pronounced dysregulation of the stress hormonal response (Lovallo, 2007). Findings of the current study demonstrate a similar pattern among concurrent users of khat and tobacco.

Both khat and tobacco are likely to exert their effects through common central and peripheral pathways, including the dopaminergic and adrenergic systems (Mereu *et al.*, 1983; Kalix, 1984; Kalix and Braenden, 1985). These pathways are involved in various affective, motivational, and cognitive processes that directly and indirectly mediate the influence of drug use and participate in coordinating the stress response. Indeed, previous work has demonstrated the convergence of these processes during stress, showing clear connections between the sympathetic responses, hormonal activity, and negative affect during stress (Lovallo *et al.*, 1990; Cacioppo, 1994; al'Absi *et al.*, 1997). Frequent and repeated activation of these processes in response to chronic drug use may influence motivational processes during stress, possibly contributing to stress response dysfunction (al'Absi, 2007). It is also possible that this dysregulation process in the stress response precedes or increases risk for drug use. For example, there is evidence to suggest a connection between physiological (attenuated) response to stress and propensity to using drugs (al'Absi, 2007; Lovallo, 2007; Sinha, 2008). Studies on individuals with family history of drug use show a reduction in their physiological response to stress (Lovallo, 2007). The extent to which altered stress response predisposes these individuals to use drugs and/or draw greater benefit from drug use is not known, particularly in the context of tobacco and khat use.

We must note the limitations of this study. First, we measured only BPs and HR; a comprehensive assessment of hemodynamic measures would have informed this study to explain the attenuated BP response in concurrent users. Second, although we collected measures to assess subjective state after exposure to the task, it would have been useful to also collect data on subjects' perception of the tasks per se to assess engagement and perception of task difficulty. Third, the directional sequence and causality cannot be inferred from this cross-sectional study. We note the challenge in recruiting smokers who do not chew khat, suggesting the possibility that khat is a significant cue for tobacco use (al'Absi and Grabowski, 2012; Nakajima *et al.*, 2012). In light of this limitation, we cannot completely rule out the possibility that the observed attenuation in the cardiovascular response to stress may have been due to smoking. Nevertheless, patterns of changes in cardiovascular measures (Figure 1) were different between nonuser and the two khat using groups. Nonusers showed the expected increase in BP levels in response to stress, whereas this was not observed in the two khat groups: they exhibited blunted responses. These results indicate similarity in stress response patterns between concurrent users and khat-only users, suggesting that alterations in central stress regulatory systems may not be due to tobacco use alone. Although not statistically significant, results of changes score analyses suggest a dose–response relationship in cardiovascular measures. Replicating our protocol with larger and balanced sample may improve the results. We note that the study has several strengths including the inclusion of a large sample size, the novelty of the results in this unique population, and the use of a controlled setting to examine effect of acute stress. Future studies should address the impact of the acute effects of khat and tobacco use alone and in interaction with stress on emotion-regulation-related biobehavioral systems. In addition, it will be critical to examine the effects of abstinence from khat to determine intensity of withdrawal symptoms.

In conclusion, this study has demonstrated for the first time attenuated cardiovascular responses to stress and enhanced negative affect among khat users and those who also concurrently use tobacco relative to nonsmokers/ nonkhat users. The patterns of associations between khat and tobacco use with cardiovascular measures implicate these substances in altering the stress response. The results confirm and extend previous studies with other substances and indicate that adverse effects of khat use may be exacerbated by the use of other stimulants such as tobacco. To this end, successful efforts to combat the high prevalence of tobacco use in this population must take into consideration the concurrent use of khat and must address the dynamics of polysubstance use in sociocultural contexts.

Acknowledgments

Research reported in this publication was supported by the Fogarty International Center FIRCA grant award number R03TW007219 and by the Fogarty International Center and National Institute for Drug Abuse under award number R21 DA024626. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank the following for their help with this project: Amal Alanisi, Tawfeek Alharazi, Ashrak Al-Awdari, Bakeer Dahmash, Essa Oumairi, Basma Ali Thabe, and Khaled Al-Sahmiry for assisting with data collection.

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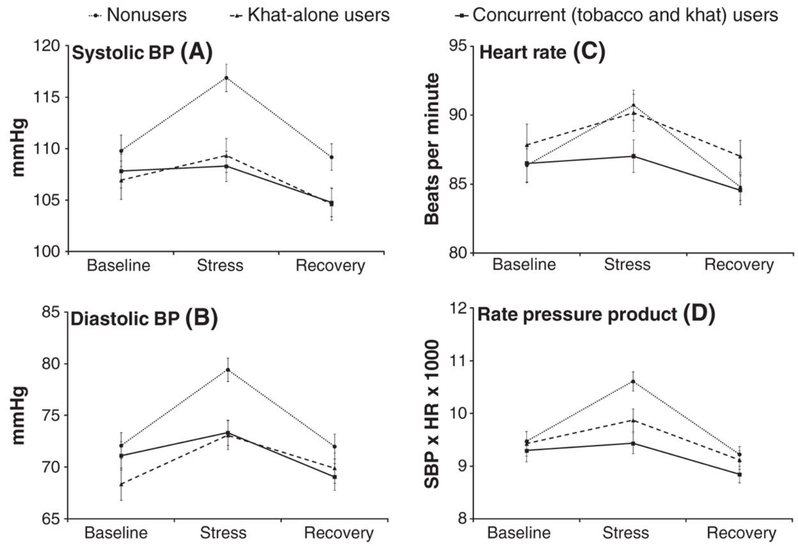

Figure 1.

Mean cardiovascular measures during baseline, acute stress, and recovery. Note: Means and standard errors for systolic BP (A); diastolic BP (B); heart rate (C); and rate pressure product (D)

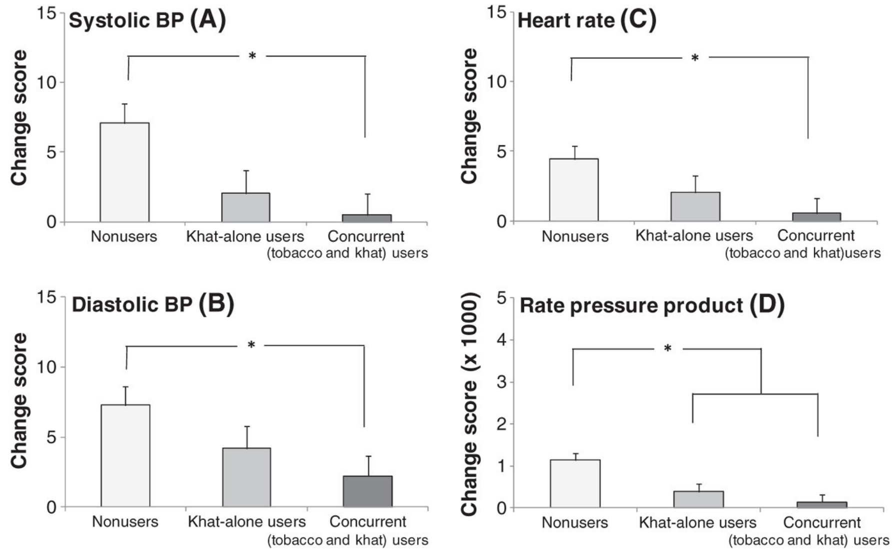

Figure 2.

Changes in cardiovascular measures in response to laboratory stress (differences between baseline and stress periods). Note: Means and standard errors for systolic BP (A); diastolic BP (B); heart rate (C); and rate pressure product (D). Asterisks reflect significant group differences

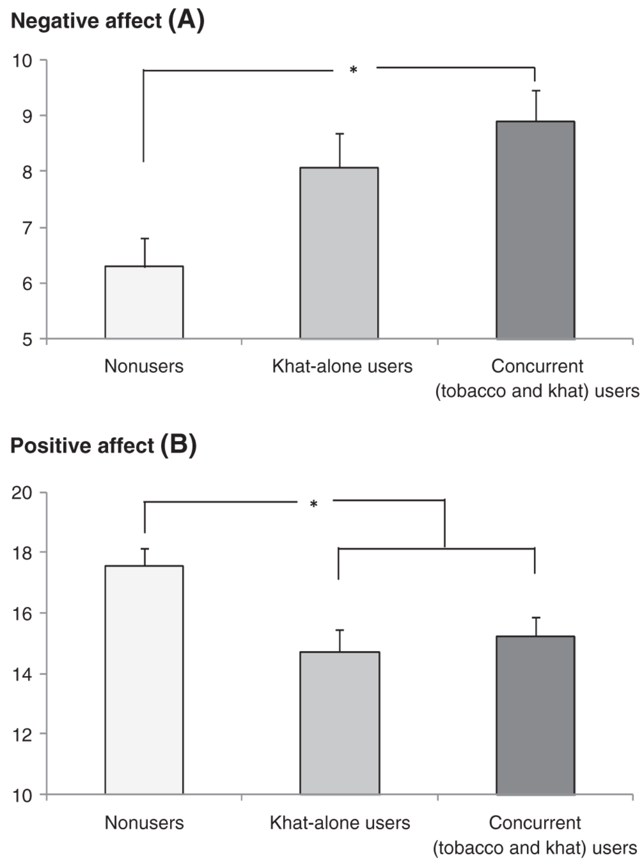

Figure 3.

Negative affect (A) and positive affect (B) during the laboratory session. Note: Means and standard errors of reported negative affect and positive affect. Asterisks reflect significant group differences

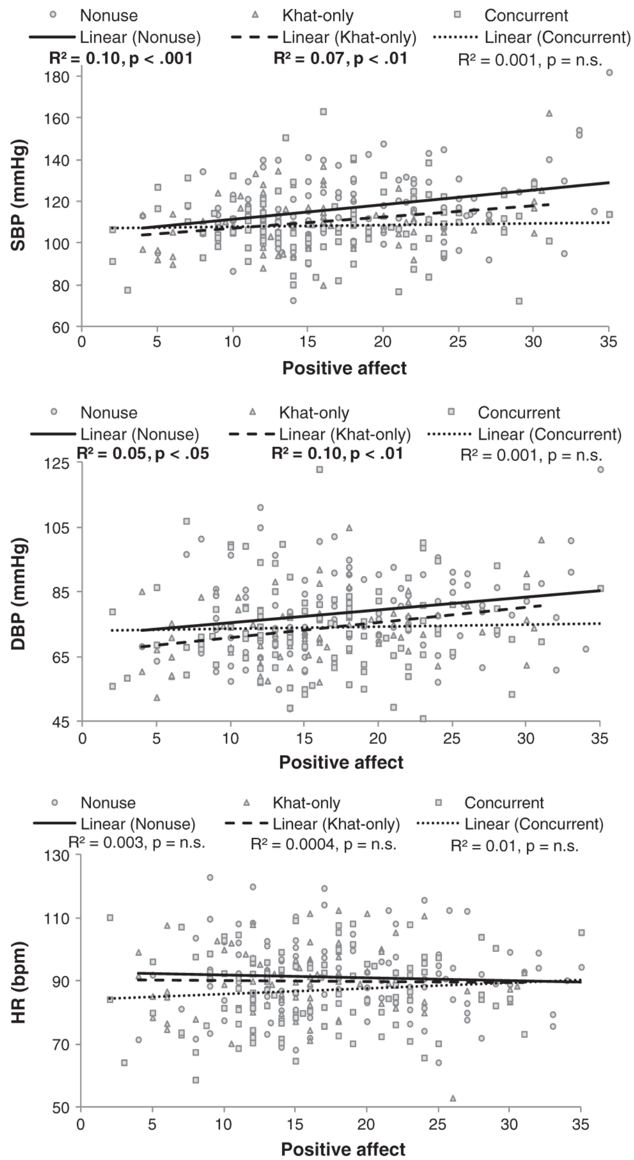

Figure 4.

Associations between positive affect scores and cardiovascular measures during stress. Note: Positive affect is presented on the *x*-axis, and cardiovascular measures are presented on the *y*-axis

Table 1

Sample characteristics

	Nonusers		Khat-only users		Concurrent (tobacco and khat) users	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
	(*n* = 66)	**(*n* = 53)**	**(*n* = 30)**	**(*n* = 55)**	**(*n* = 39)**	**(*n* = 65)**
Demographic variables						
Age (years)[c]	22.1 (0.6)	22.2 (0.7)	25.2 (0.9)	23.7 (0.7)	25.5 (0.8)	24.5 (0.6)
Height (cm)[d]	153.2 (0.9)	167.0 (1.0)	155.1 (1.3)	163.1 (0.9)	150.2 (1.1)	166.1 (0.9)
Weight (kg)[d]	49.3 (1.2)	59.6 (1.4)	53.1 (1.8)	56.5 (1.3)	49.9 (1.6)	57.4 (1.2)
Body mass index (kg/m^2)	21.1 (0.5)	21.3 (0.5)	22.1 (0.7)	21.3 (0.5)	22.1 (0.6)	20.8 (0.5)
Education (years)[a]	11.4 (0.7)	13.1 (0.8)	12.8 (1.4)	12.7 (0.8)	9.0 (3.2)	11.5 (0.8)
Sleep (average hours per day)[a]	8.0 (0.3)	7.2 (0.3)	6.8 (0.6)	6.9 (0.3)	5.9 (0.8)	6.8 (0.4)
Khat use						
Age started (years)[d]	n/a	n/a	17.1 (0.7)	15.6 (0.5)	18.4 (0.6)	15.3 (0.5)
Daily use (%)[d]	n/a	n/a	56.7	80.0	48.7	92.3
Duration (years)	n/a	n/a	5.3 (0.9)	7.0 (0.7)	5.8 (0.8)	6.5 (0.6)
Length of use (h/session) [c]	n/a	n/a	3.7 (0.4)	4.9 (0.3)	4.5 (0.3)	5.9 (0.3)
Times (per week)[d]	n/a	n/a	5.0 (0.3)	5.9 (0.3)	4.4 (0.3)	6.5 (0.2)
Tobacco use						
Daily tobacco use (%)[d]	n/a	n/a	n/a	n/a	33.3	67.7
Duration (years)	n/a	n/a	n/a	n/a	4.3 (0.7)	5.4 (0.5)
Cigarettes (per day)[d]	n/a	n/a	n/a	n/a	1.4 (1.0)	13.5 (0.7)
Waterpipe (per day)[b,d]	n/a	n/a	n/a	n/a	2.0 (0.2)	0.2 (0.2)

n/a, not applicable.

[a]Data collected in Sana'a component only.

[b]Data collected in Taiz component only.

[c]Group effect was significant.

[d] Gender effect was significant.