International Journal of Research in Medical Sciences
Al-Qader AF et al. Int J Res Med Sci. 2026 Apr;14(4):1467-1478
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20260954

Original Research Article

Metabolic cardiovascular risk profiles: a comparative study of khat-chewing and non-chewing women using hormonal contraception in Dhamar District, Yemen

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Received: 03 January 2026
Revised: 07 February 2026
Accepted: 21 February 2026

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ABSTRACT

Background: The concurrent use of khat (*Catha edulis*) and hormonal contraceptives (HC) is common among Yemeni women, yet its combined effect on novel metabolic cardiovascular risk markers is poorly understood. This study compared the impact of khat chewing on serum homocysteine (Hcy), c-reactive protein (CRP), the atherogenic index of plasma (AIP), and lipid profiles in HC.
Methods: A comparative cross-sectional study was conducted in Dhamar District, Yemen. One hundred women using HC were divided into 50 khat chewers and 50 non-chewers. Fasting blood samples were analyzed for Hcy, CRP, and lipid profiles, with calculation of AIP and (TC/HDL, LDL/HDL) ratios.
Results: Khat-chewing women exhibited a significantly more adverse metabolic profile. Key findings included elevated diastolic blood pressure (75.80±12.14 versus 68.40±11.13 mmHg, p=0.002), higher homocysteine (7.81±2.55 versus 6.77±2.53 µmol/l, p=0.04), elevated CRP (4.88±1.25 versus 4.26±1.32 mg/l, p=0.01), lower HDL-C (46.58±8.06 versus 49.96±8.35 mg/dl, p=0.04), higher triglycerides (159.99±41.44 versus 141.17±19.58 mg/dl, p=0.005), and a substantially higher AIP (0.38±0.12 versus 0.30±0.094, p<0.001). A dose-response relationship was observed, with heavy use linked to greater disturbances. A significant interaction was found between khat and contraceptive type on atherogenic ratios.
Conclusions: Among Yemeni women using hormonal contraception, khat chewing is a significant risk factor for an adverse cardiovascular profile, including hypertension, a pro-inflammatory and pro-thrombotic state, and atherogenic dyslipidemia. The harmful metabolic effects of khat were found to be modified by the type of contraceptive used. These effects also intensify with chewing duration, underscoring the critical need for targeted screening and personalized contraceptive counselling for khat-using women.

Keywords: Cardiovascular risk, Hormonal contraception, Khat, Yemen

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality among women globally.[1-3] Notably, these conditions have become increasingly common among young females.[4,5] In Yemen, the number of young women suffering from cardiovascular diseases is rising, with khat chewing identified as a primary risk factor.[6-8] The

incidence of myocardial infarction with non-obstructive coronary arteries (MINOCA) is notably high in Yemeni women, calling for an investigation into the synergistic effects of local risk factors like khat and medications.[9,10] Hormonal contraceptives (HCs) and the habitual chewing of khat are among the most significant exposures for women in Yemen. HCs are widely used, including Yemen.[11-15] Available as oral contraceptive pills (OCs), injectables, and implants.[16] OCs are the most prevalent method in the country, with a specific study in Dhamar Governorate finding that the rate of use reached 33% among users of both hormonal and non-hormonal contraceptives among married women.[17-19] In resource-limited settings like Dhamar, where healthcare access and availability of alternative methods are often constrained, hormonal contraceptives are a cornerstone of family planning.[16,20] However, HCs are associated with systemic metabolic alterations, including dyslipidemia and a prothrombotic state.[21,22] Specifically, the estrogen components in combined oral contraceptives (COCs) can stimulate the hepatic synthesis of angiotensinogen, leading to hypertension, and promote a hypercoagulable state by increasing clotting factors.[21]

Parallel to the widespread use of hormonal contraception is the deep-rooted cultural practice of khat chewing in Yemen, with estimates suggesting 50-60% of women engage in this habit, including very young women who use it daily.[7,23-25] The fresh leaves of the khat shrub contain cathinone, which induces sympathomimetic effects, leading to increased heart rate and blood pressure, and is linked to cardiovascular pathologies.[26,27] A large number of women in Yemen are simultaneously exposed to both factors. The potential for synergistic effects between the prothrombotic, hypertensive effects of HCs and the sympathomimetic effects of khat is plausible yet understudied. To effectively investigate this potential synergy, this study moved beyond traditional lipid panels to include a panel of advanced biomarkers that provide a more nuanced and comprehensive assessment of cardiovascular risk. These include:

Atherogenic ratios

The total cholesterol to HDL-C ratio (TC/HDL) and the LDL-C to HDL-C ratio (LDL/HDL) are recognized as more powerful predictors of cardiovascular risk than individual lipid parameters.[28,29]

The atherogenic index of plasma (AIP)

Calculated as Log_{10}(TG/HDL-C), the AIP is a robust indicator of plasma atherogenicity and the prevalence of small, dense LDL particles, serving as a superior predictor of CVD risk.[30-32]

Homocysteine (Hcy)

Hcy is a sulfur-containing amino acid derived from methionine metabolism, whose elevated plasma levels (hyperhomocysteinemia) are an independent marker of endothelial dysfunction and a pro-thrombotic state.[33,34] It promotes oxidative stress, damages the vascular endothelium, and stimulates smooth muscle proliferation, all of which accelerate atherosclerosis.[35-39] Increases in serum homocysteine are most frequently caused by dietary deficiencies of folic acid, vitamin B_{12}, and vitamin B_6, or genetic defects in its metabolic pathways.[40]

C-reactive protein (CRP)

CRP is an acute-phase protein synthesized by the liver in response to interleukin-6 (IL-6) and other inflammatory cytokines. Elevated CRP levels indicate systemic inflammation, a critical driver of all stages of atherosclerosis. Thus, CRP serves as a robust biomarker of cardiovascular inflammation and future event risk. While the individual effects of hormonal contraceptives and khat have been partially explored, their combined impact on this specific panel of metabolic and inflammatory cardiovascular risk markers remains unknown. Therefore, this study aimed to bridge this critical knowledge gap. The findings will provide vital insights for targeted screening and preventive healthcare strategies for this high-risk population.

METHODS

Study design and setting

A comparative cross-sectional study was conducted between October 2023 and January 2024 within a community in Dhamar District, where cultural traditions and Islamic principles strongly influence social life. The study was carried out in three primary government centers with family planning departments located in Dhamar District, the central district of Dhamar Governorate, approximately 100 km south of the capital, Sana'a.

Ethical considerations

The study received formal approval from the Dhamar Health and Population Office, and permission was obtained from the administration of each participating center. Due to high rates of illiteracy, verbal informed consent was acquired from all participants before their enrollment in the study.

Study population and sampling

A total of 100 healthy, married women of childbearing age (18-45 years) were randomly selected. The sample size was calculated a priori using G*Power software for an independent samples t-test. With a significance level (α) of 0.05, a statistical power (1-β) of 80%, and an allocation ratio of 1:1, a total sample of 100 participants was determined to be sufficient to detect a medium effect size (Cohen's d=0.57). Participants were required to have been consistently using one of the following hormonal

contraceptive methods for a minimum of six months before the study:

Combined oral contraceptives

Ethinylestradiol 0.02 mg/desogestrel 0.15 mg; ethinylestradiol 0.03 mg/gestodene 0.075 mg; or ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg.*injectables:* medroxyprogesterone acetate 150 mg.*implants:* etonogestrel 68 mg.

The participants were divided into two groups: Group 1 (Khat+): 50 daily khat users (history >4 years). Group 2 (Khat-): 50 women who had never used khat or had ceased use for >1 year.

Exclusion criteria

Exclusion criteria included tobacco use, history of cardiac, hepatic, renal, or metabolic diseases, diabetes, hypertension, and use of mineral/vitamin supplements or drugs affecting lipid profiles at least 12 months before enrollment, as well as those who had used hormonal contraceptives for less than six months.

Data collection and biochemical analysis

We collected data through face-to-face interviews using a structured questionnaire for demographics and khat chewing habits, alongside direct anthropometric measurements (weight, height, and BMI). Blood pressure was measured at rest, with systolic and diastolic readings taken on at least two occasions. Following a 12-hour overnight fast, a 6 ml venous blood sample was drawn. Serum was analyzed for lipid profile (total cholesterol, TG, HDL-C, LDL-C) using the enzymatic colorimetric method. C-reactive protein (CRP) using a Biosystems analyzer. Homocysteine using a Biosystems BA200 analyzer. Atherogenic indices (AIP, TC/HDL, LDL/HDL) were calculated.

Statistical analysis

Data were analysed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical variables were compared using the Chi-square test. One-way ANOVA and two-way ANOVA were employed for multiple group comparisons and interaction effects. A p value of <0.05 was considered significant.

RESULTS

Clinical and demographic characteristics

The baseline characteristics of the participants are detailed in Table 1. They were largely similar between the groups, with no significant differences in age, BMI, systolic blood pressure, place of residence, or education level. However, a significant difference was observed in that a significantly higher proportion of khat chewers were housewives (54.0% of housewives were chewers). In contrast, non-chewers were more likely to be employed (76.9% of employees were non-chewers) (p=0.037).

Table 1: Baseline demographic and clinical characteristics of khat-chewing and non-chewing women using hormonal contraception.*

Categories		Khat+ group (n=50) (%)	Khat-group (n=50) (%)	χ^2	P value
Age group (in years)	≤20	3 (33.3)	6 (66.7)	7.102	0.130
	21-25	9 (45.0)	11 (55.0)		
	26-35	26 (51.0)	25 (49.0)		
	36-45	12 (70.6)	5 (29.4)		
	>45	0 (0.0)	3 (100.0)		
BMI (kg/m^2)	Underweight- <18.5	4 (57.1)	3 (42.9)	1.469	0.690
	Healthy- 18.5-24.9	18 (45.0)	22 (55.0)		
	Overweight- 25-29.9	21 (56.8)	16 (43.2)		
	Obese- >30	7 (43.8)	9 (56.3)		
Systolic (mmHg)	≤120	46 (48.9)	48 (51.1)	0.710	0.400
	>120	4 (66.7)	2 (33.3)		
Diastolic (mmHg)	≤80	41 (46.1)	48 (53.9)	5.010	0.025*
	>80	9 (81.8)	2 (18.2)		
Place of residence	Urban	46 (50)	46 (50)	0.000	1.000
	Rural	4 (50)	4 (50)		
Occupation	Housewife	47 (54.0)	40 (46.0)	4.332	0.037*
	Employee	3 (23.1)	10 (76.9)		
Education	Illiterate	10 (66.7)	5 (33.3)	3.725	0.100
	Elementary	11 (50.0)	11 (50.0)		
	Intermediate	9 (52.9)	8 (47.1)		
	Secondary	14 (50.0)	14 (50.0)		

Continued.

Categories		Khat+ group (n=50) (%)	Khat-group (n=50) (%)	χ^2	P value
	University	6 (33.3)	12 (66.7)		
Khat chewing hours ^†^	≤ 3	33 (100)			
	>3	17 (100)			
Types of contraception	Pills	31 (47.0)	35 (53.0)	0.725	0.700
	Intramuscular Injection	13 (56.5)	10 (43.5)		
	Implant	6 (54.5)	5 (45.5)		
Pill Formulations^‡^	E1	11 (40.7)	16 (59.3)	0.920	0.630
	E2	7 (46.7)	8 (53.3)		
	E3	13 (54.2)	11 (45.8)		
Duration of use (Year)	<2	29 (43.9)	37 (56.1)	3.741	0.154
	2-4	11 (55.0)	9 (45.0)		
	>4	10 (71.4)	4 (28.6)		
Homocysteine (µmol/l)	Low <3	0	5 (100)	5.269	0.072
	Normal 3-15	49 (52.7)	44 (47.3)		
	High >15	1 (50)	1 (50)		
CRP (mg/l)	Optimal ≤5	34 (68.0)	39 (78.0)	1.268	0.260
	High >5	16 (59.3)	11 (40.7)		
Total cholesterol mg/dl	Normal <200	33 (50.8)	32 (49.2)	0.215	0.898
	Borderline 200-239	15 (50)	15 (50)		
	High ≥240	2 (40.0)	3 (60.0)		
LDLc mg/dl	Optimal <100	20 (54.1)	17 (45.9)	1.588	0.662
	Above optimal 100-129	11 (42.3)	15 (57.7)		
	Borderline high 130-160	9 (45.0)	11 (55.0)		
	High >160	10 (58.8)	7 (41.2)		
HDLc mg/dl	Low risk >60	2 (28.6)	5 (71.4)	2.558	0.278
	Normal risk 45-60	29 (47.5)	32 (52.5)		
	High risk <45	19 (59.4)	13 (40.6)		
Triglycerides mg/dl	Low <35	0	0	0.184	0.668
	Normal 35-135	15 (46.9)	17 (53.1)		
	High >135	35 (51.5)	33 (48.5)		
TC /HDL ratio	Optimal ≤3.5	19 (44.2)	24 (55.8)	1.020	0.312
	High risk >3.5	31 (54.4)	26 (45.6)		
LDL/HDL ratio	Optimal ≤3	36 (47.4)	40 (52.6)	0.877	0.349
	High risk >3	14 (58.3)	10 (41.7)		
Atherogenic index of plasma (AIP)	Low risk <0.1	0 (0)	3 (100)	4.121	0.100
	Intermediate risk 0.1-0.24	5 (38.5)	8 (61.5)		
	High risk >0.24	45 (53.6)	39 (46.4)		

*Data are presented as the number of participants and percentage (n% %). Percentages are calculated by row for each category. P values were derived from Chi-square (χ^2) tests comparing the distribution of characteristics between the Khat+ and Khat- groups. A p value <0.05 was considered statistically significant (*). ^†^ The category "khat chewing hours" applies only to the Khat+ group (n=50) and is presented as a simple count (N); it was not statistically tested against the non-chewing group. ^‡^ Pill Formulations: E1 = Ethinylestradiol 0.02 mg/Desogestrel 0.15 mg; E2 = Ethinylestradiol 0.03 mg/Gestodene 0.075 mg; E3 = Ethinylestradiol 0.03 mg/Levonorgestrel 0.15 mg (with ferrous and malate). Abbreviations: BMI- body mass index; BP- blood pressure; CRP- c-reactive protein; LDL- Low-density lipoprotein; HDL- High-density lipoprotein; VLDL= very low-density lipoprotein.

Education: a trend suggested that non-chewers had higher educational attainment, with 66.7% of university-educated women being non-chewers, compared to 33.3% who were chewers (p=0.100).

Blood pressure: a significantly higher proportion of women with elevated diastolic blood pressure (>80 mmHg) were khat chewers (81.8% versus 18.2%, p=0.025).

Contraceptive profile: the type of hormonal contraception (pills, injections, implants) and the specific formulation of pills used were similarly distributed between the groups (p>0.05). However, a higher percentage of long-term users (>4 years) were khat chewers (71.4%).

Metabolic risk markers: khat chewing versus non-chewing (continuous data)

As shown in Table 2, analysis of continuous variables confirmed a significantly more adverse metabolic profile in khat chewers. They exhibited elevated diastolic blood pressure (75.80±12.14 versus 68.40±11.13 mmHg, p=0.002), higher homocysteine levels (7.81±2.55 versus

6.77±2.53 µmol/l, p=0.04), and higher CRP levels (4.88±1.25 versus 4.26±1.32 mg/l, p=0.01). Crucially, khat chewers had a more atherogenic lipid profile, characterized by significantly lower HDL-c (46.58±8.06 versus 49.96±8.35 mg/dl, p=0.04), higher triglycerides (159.99±41.44 versus 141.17±19.58 mg/dl, p=0.005), elevated VLDL (31.99±8.29 versus 28.23±3.92 mg/dl, p=0.005), an increased TC/HDL ratio (4.08±0.96 versus 3.69±0.79, p=0.03), and a substantially higher atherogenic index of plasma (AIP) (0.38±0.12 versus 0.30±0.094, p<0.001).

Dose-response relationship with khat chewing duration

When the Khat+ group was subdivided by daily chewing duration (≤3 hours versus >3 hours), a dose-response relationship was evident (Table 3). Heavy khat use (>3 hours/day) was associated with the most pronounced metabolic disturbances. Women who chewed khat for more than 3 hours had significantly higher homocysteine (8.91±2.90 µmol/l, p=0.011) and markedly elevated CRP (6.11±1.25 mg/L, p<0.001) compared to non-chewers and moderate users (≤3 hours). Diastolic blood pressure remained elevated in both khat-chewing subgroups compared to non-chewers (p=0.008). A complex, non-linear relationship was observed for the lipid profile. Both khat-chewing subgroups had significantly elevated triglycerides and VLDL compared to non-chewers (p=0.018). The Atherogenic Index of Plasma (AIP) was significantly different across the groups (p<0.001), being highest in the moderate-duration group (≤3 hours). Furthermore, HDL-c was lowest, and the TC/HDL ratio was highest in the shorter-duration chewing group (≤3 hours).

Impact of contraceptive-related factors

Women using implants had a significantly higher BMI (p=0.001). However, the type of contraceptive, pill formulation, or duration of use did not independently significantly affect lipid profiles, inflammatory markers, or atherogenic indices (Tables 4-6).

Interaction effects between khat chewing and contraceptive factors

A two-way analysis of variance (ANOVA) was employed to test for interaction effects. The results, detailed in Table 7, revealed a significant interaction between khat chewing and the type of contraceptive method used on several lipid parameters. This interaction significantly affected: Total Cholesterol [F (2,94) =6.300, p=0.003, partial η^2=0.118], LDL-c [F (2,94) =6.522, p=0.002, partial η^2=0.122], and the atherogenic ratios TC/HDL [F (2,94) =5.448, p=0.006, partial η^2=0.104] and LDL/HDL [F (2,94) =5.913, p=0.004, partial η^2=0.112]. No significant interactions were found for other Metabolic Markers (Table 7, Figures 1 and 2).

Table 2: Metabolic and cardiovascular risk profile of khat-chewing and non-chewing women using hormonal contraception.*

Variable	Khat- Group Mean±STD (n=50)	Khat+ Group Mean±STD (n=50)	Mean difference	P value
Age(years)	29.64±7.55	31.24±6.61	1.61	0.3
Weight (Kg)	59.28±12.94	61.12±11.93	1.84	0.5
Height(cm)	152.14±7.13	154.100±5.37	1.96	0.1
BMI (kg/m^2)	25.32±5.10	25.45±4.26	0.13	0.1
Systolic (mmHg)	101.40±13.10	106.60±14.37	5.20	0.06
Diastolic (mmHg)	68.40±11.13	75.80±12.14	7.40	0.002*
Homocysteine (µmol/l)	6.77±2.53	7.81±2.55	1.04	0.04*
CRP (mg/l)	4.26±1.32	4.88±1.25	0.62	0.01*
Total Cholesterol (mg/dl)	182.10±40.53	185.64±37.51	3.54	0.7
LDL c (mg/dl)	114.18±46.26	118.49±40.54	4.31	0.6
HDLc (mg/dl)	49.96±8.35	46.58±8.06	-3.38	0.04*
Triglycerides (mg/dl)	141.17±19.58	159.99±41.44	6.48	0.005*
TC/HDL	3.69±0.79	4.08±0.96	0.38	0.03*
LDL/HDL	2.31±0.90	2.60±0.92	0.29	0.1
AIP	0.30±0.094	0.38±0.12	0.08	<0.001*

*Data are presented as mean±standard deviation (SD). The mean difference was calculated as (Khat+ Group Mean - Khat- Group mean). P values were derived from independent samples t-tests (two-tailed). A p value <0.05 was considered statistically significant (*). Abbreviations: BMI- body mass index; CRP- c-reactive protein; LDL- low-density lipoprotein; HDL- high-density lipoprotein; VLDL- very low-density lipoprotein; TC- total cholesterol; AIP- atherogenic index of plasma

Table 3: Comparison of metabolic and cardiovascular risk profiles by khat-chewing duration.*

Variables	Non-chewer (n=50) Mean±SD	Khat+ (≤3 hours) (n=33) Mean±SD	Kha+(>3 hours) (n=17) Mean±SD	P value
BMI (kg/m²)	25.32±5.10	25.92 ±3.66	24.53±5.25	0.606
Systolic BP (mmHg)	101.40±13.10	106.67±14.72	106.47±14.12	0.176
Diastolic BP (mmHg)	68.40±11.13	76.36±12.703	74.71±11.246	0.008
Homocysteine (µmol/l)	6.77±2.53	7.24±2.19	8.91±2.90	0.011*
CRP (mg/l)	4.26±1.32	4.24±0.61	6.11±1.25	<0.001*
Total cholesterol (mg/dl)	182.10±40.53	182.30±39.21	192.12±34.16	0.635
LDL- c (mg/dl)	114.18±46.26	113.87±35.78	127.46±48.39	0.513
HDL-c (mg/dl)	49.96±8.35	44.00±7.06	51.59±7.68	<0.001*
Triglycerides (mg/dl)	141.17±19.58	160.30±44.03	159.38±37.16	0.018*
TC/HDL	3.69±0.79	4.24±1.05	3.76±0.66	0.018*
LDL/HDL	2.31±0.90	2.66±0.94	2.49±0.91	0.243
AIP	0.30±.094	0.40±0.12	0.33±0.10	<0.001*

*Data are presented as Mean±Standard Deviation. P values were derived from a one-way analysis of variance (ANOVA) test comparing the means across the three groups (Non-Chewer, Khat+ ≤3 hours, Khat+ >3 hours). A p value <0.05 was considered statistically significant.

Table 4: Comparison of metabolic and cardiovascular profiles by hormonal contraceptive type.*

Variables	Pills (n=66) Mean±SD	Injection (n=23) Mean±SD	Implants (n=11) Mean±SD	P value
BMI (kg/m²)	25.38±4.48	23.41±4.68	29.57±3.12	0.001*
Systolic BP (mmHg)	103.64±15.26	102.17±10.43	110.00±10.95	0.292
Diastolic BP (mmHg)	71.67±13.20	70.87±9.49	77.27±10.09	0.319
Homocysteine (µmol/l)	7.173±2.260	7.21±2.90	8.13±3.66	0.517
CRP (mg/l)	4.68±1.49	4.41±0.99	4.21±0.58	0.449
Total Cholesterol (mg/dl)	185.88±35.92	178.09±46.73	183.91±41.048	0.714
LDL- c (mg/dl)	118.80±43.60	109.31±41.31	116.22±48.156	0.669
HDL-c (mg/dl)	48.56± 8.08	48.26±9.45	46.55±7.97	0.763
Triglycerides (mg/dl)	150.71±31.83	148.96±42.16	153.18±25.88	0.943
TC/HDL	3.89±0.765	3.80±1.14	4.05±1.09	0.753
LDL/HDL	2.48±0.86	2.33±0.94	2.61±1.25	0.698
AIP	0.34±0.11	0.33±0.14	0.37±0.08	0.701

*Data are presented as mean±standard deviation. P values were derived from a one-way analysis of variance (ANOVA) test comparing the means across the three groups (pills, injections, and implants). A p value <0.05 was considered statistically significant (*).

Table 5: Comparison of metabolic and cardiovascular profiles by pill formulations.*

Variable	E1 (n=27) Mean±SD	E2 (n=15) Mean±SD	E3 (n=24) Mean±SD	P value
BMI (kg/cm²)	24.92±4.61	24.29±4.75	26.58±4.06	0.239
Systolic BP (mmHg)	104.07±16.23	100.00±13.09	105.42±15.60	0.556
Diastolic BP (mmHg)	72.96±14.89	70.67±12.80	70.83±11.77	0.806
Homocysteine (µmol/l)	6.76±2.46	6.99±2.09	7.75±2.09	0.288
CRP (mg/l)	4.61±1.49	5.09±1.29	4.50±1.61	0.466
Total cholesterol (mg/dl)	191.41±38.21	177.13±34.49	185.13±34.42	0.47
LDL-c (mg/dl)	126.15±42.74	108.55±45.58	116.94±43.67	0.447
HDL-c (mg/dl)	48.30±9.60	48.47±6.85	48.92±7.19	0.963
Triglycerides (mg/dl)	148.97±26.47	142.83±27.78	157.59±38.82	0.352
TC/HDL	4.06±0.84	3.69±0.77	3.82±0.66	0.295
LDL/HDL	2.66±0.82	2.26±0.97	2.41±0.81	0.306
AIP	0.34±0.12	0.32±0.11	0.35±0.10	0.610

*Data are presented as mean ± standard deviation. P values were derived from a one-way analysis of variance (ANOVA) test comparing the means across the three groups (E1, E2, and E3). A p value <0.05 was considered statistically significant (*). Abbreviations: E1 = Ethinylestradiol 0.02 mg / Desogestrel 0.15 mg; E2 = Ethinylestradiol 0.03 mg/Gestodene 0.075 mg; E3 = Ethinylestradiol 0.03 mg / Levonorgestrel 0.15 mg (with ferrous and malate).

Table 6: Comparison of metabolic and cardiovascular profiles by duration of contraceptive use.*

Variables	<2 yrs. (n=66) Mean±SD	2-4 yrs. (n=20) Mean±SD	>4 yrs. (n=14) Mean±SD	P value
BMI (kg/m²)	25.31±4.59	24.01±4.92	24.01±4.92	0.073
Systolic BP (mm Hg)	103.18±12.67	104.00±17.59	107.86±14.24	0.526
Diastolic BP (mm Hg)	71.52±10.99	71.50±15.99	75.71±11.58	0.492
Homocysteine (µmol/L)	6.100±2.51	7.713±2.58	8.04±2.88	0.278
CRP (mg/L)	4.52±1.30	4.59±1.20	4.77±1.60	0.813
Total Cholesterol (mg/dl)	184.89±38.86	169.60±31.81	199.43±43.69	0.082
LDL-c (mg/dl)	119.28±45.25	101.56±36.42	123.56±40.100	0.223
HDL-c (mg/dl)	47.64±8.52	49.10±9.12	50.07±6.27	0.545
Triglycerides (mg/dl)	146.37±24.23	150.79±41.53	170.14±51.38	0.054
VLDL (mg/dl)	29.27±4.85	30.16±8.31	34.03±10.28	0.054
TC/HDL	3.95±0.87	3.54±0.80	4.05±1.06	0.147
LDL/HDL	2.54±0.91	2.15±0.86	2.53±0.99	0.251
AIP	0.34±0.11	0.33±0.12	0.37±0.11	0.593

*Data are presented as mean±standard deviation. P values were derived from a one-way analysis of variance (ANOVA) test comparing the means across the three duration-of-use groups (<2 years, 2-4 years, >4 years).

Table 7: Results of two-way ANOVA examining the interaction effects of khat chewing with contraceptive type, pill type, and duration of use on metabolic cardiovascular risk profiles.*

Metabolic markers	Interaction effect khat * contraceptive type (pills, injection, implant)			Interaction effect khat * pill type (E1, E2, E3)			Interaction effect khat * duration of use (<2, 2-4, >4 yrs)		
	F-value (df)	P value	Partial η^2	F value (df)	P value	Partial η^2	F value (df)	P value	Partial η^2
Anthropometric measures									
BMI (kg/cm²)	(2, 94) =0.384	0.682	0.008	(2, 66) =0.779	0.463	0.025	(2, 94) =1.912	0.153	0.039
Blood Pressure									
Systolic BP (mmHg)	(2, 94) =0.392	0.677	0.008	(2, 60) =0.685	0.508	0.022	(2, 94) =2.863	0.062	0.057
Diastolic BP (mmHg)	(2, 94) =0.052	0.949	0.001	(2, 60) =1.340	0.270	0.043	(2, 94) =2.470	0.090	0.050
Inflammatory and metabolic markers									
CRP (mg/l)	(2, 94) =0.149	0.861	0.003	(2,60) =1.713	0.189	0.054	(2,94) =2.038	0.136	0.042
Homocysteine (µmol/l)	(2,94) =0.661	0.519	0.014	(2,60) =1.638	0.203	0.052	(2, 94) =1.135	0.326	0.024
Lipid profile									
T. cholesterol (mg/dl)	(2, 94) =6.300	0.003	0.118	(2, 60) =0.324	0.725	0.011	(2, 94) =0.955	0.388	0.020
LDL-c (mg/dl)	(2, 94) =6.522	0.002	0.122	(2, 60) =0.205	0.816	0.007	(2, 94) =0.497	0.610	0.010
HDL-c (mg/dl)	(2, 94) =0.060	0.941	0.001	(2,60) =0.0358	0.701	0.012	(2, 94) =1.086	0.342	0.023
Triglycerides (mg/dl)	(2, 94) =0.149	0.862	0.003	(2,60) =1.875	0.162	0.059	(2,94) =0.023	0.977	0.000
Atherogenic Indices									
TC/HDL ratio	(2, 94) =5.448	0.006	0.104	(2,60) =0.003	0.997	0.000	(2,94) =0.202	0.817	0.004
LDL/HDL ratio	(2, 94) =5.913	0.004	0.112	(2,60) =0.465	0.631	0.015	(2,94) =0.175	0.840	0.004
Atherogenic index of plasma (AIP)	(2, 94) =0.115	0.891	0.002	(2,60) =0.402	0.671	0.013	(2,94) =0.837	0.436	0.018

*A two-way analysis of variance (ANOVA) was conducted to examine the interaction effects between khat chewing status and three contraceptive factors. The F-value, degrees of freedom (df), p-value, and partial eta-squared (Partial η^2) are reported for each interaction term. Partial η^2 is interpreted as the proportion of variance in the dependent variable explained by the interaction effect, with values of 0.01, 0.06, and 0.14 generally considered small, medium, and large effect sizes, respectively. A p-value < 0.05 was considered statistically significant (*).

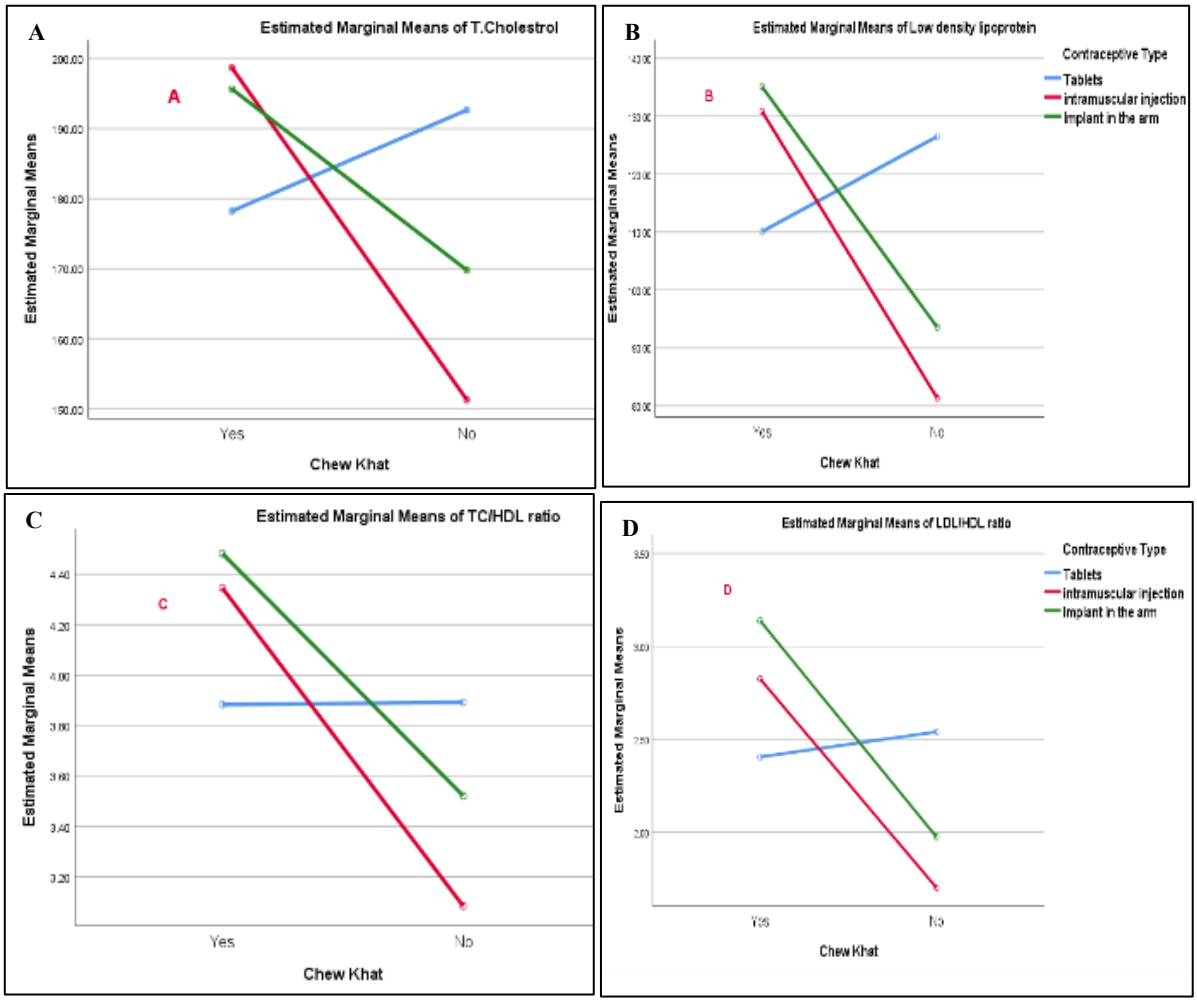

Figure 1 (A-D): Significant interaction effects of khat chewing and contraceptive type on TC, LDL-C, TC/HDL, LDL/HD.

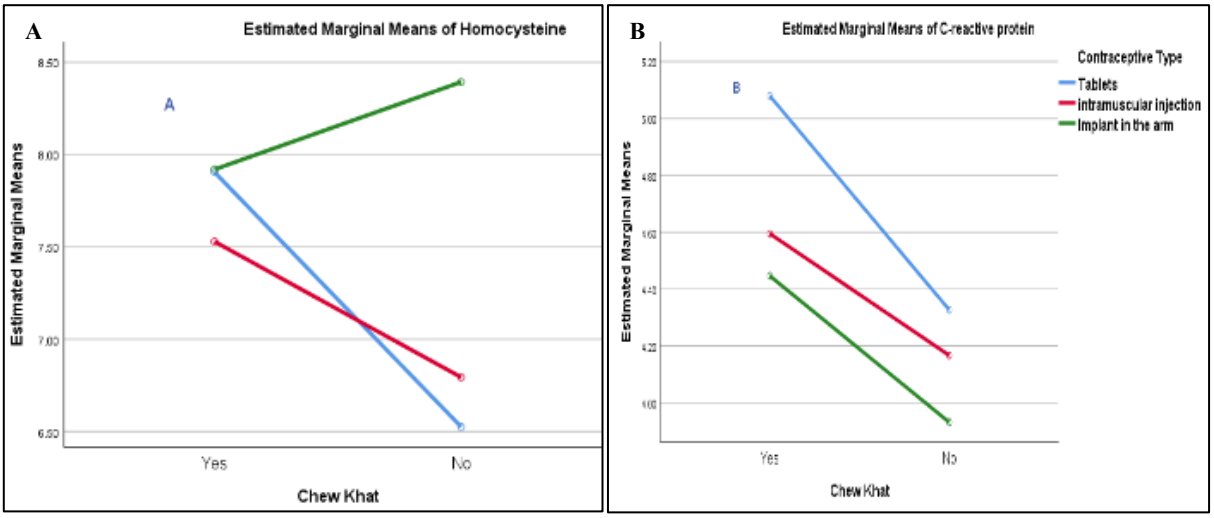

Figure 2 (A and B): Non-significant interaction effects on homocysteine and CRP.

Visualization of interaction effects

To further elucidate the nature of these interactions, the estimated marginal means for key outcome variables are plotted in Figures 1 and 2.

Estimated marginal means of key lipid parameters showing a significant interaction ($p<0.01$) between khat chewing status and the type of hormonal contraceptive method (Two-way ANOVA). The divergent patterns of the lines indicate that the effect of khat on these lipid measures depends on the contraceptive method used. (A) Total cholesterol, (B) LDL-C, (C) TC/HDL ratio, (D) LDL/ HDL ratio.

Estimated marginal means of homocysteine and c-reactive protein (CRP) showing no significant interaction ($p>0.05$) between khat chewing status and contraceptive type. The near-parallel lines indicate that the pro-thrombotic and pro-inflammatory effects of khat are consistent across different contraceptive methods. (A) Homocysteine, (B) c-reactive protein.

DISCUSSION

This study provides compelling evidence that khat chewing is a significant, independent risk factor for an adverse metabolic cardiovascular profile among Yemeni women using hormonal contraception. The results demonstrate synergistic detriments associated with concurrent exposure.

Hemodynamic impact

The hypertensive effect of khat is well-documented in general populations; however, its specific interaction with HCs has been largely unexamined. Our findings address this critical gap, revealing a significant elevation in diastolic blood pressure among khat-chewing women (75.80±12.14 mmHg) compared to their non-chewing counterparts (68.40±11.13 mmHg; $p=0.002$). Categorically, 81.8% of women with clinically elevated diastolic pressure (>80 mmHg) were khat chewers ($p=0.025$). This aligns with established literature linking khat use to hypertension), and the mechanism is attributed to the sympathomimetic amines cathinone and cathine, which induce vasoconstriction and increased peripheral vascular resistance.[27] A two-way ANOVA confirmed no significant interaction between khat chewing and contraceptive type on blood pressure ($p>0.05$, partial $\eta^2<0.01$), indicating that the pressor effect of khat is a consistent and independent phenomenon, unmodified by the specific hormonal contraceptive method used.

Demographic and anthropometric considerations

The analysis revealed no significant difference in mean age between khat-chewing and non-chewing participants, indicating that chronological age was not a primary confounding factor for khat-use status in this cohort. The observed concentration of khat chewers within the 26-45-year age bracket aligns with broader epidemiological patterns, where khat use among women is frequently associated with established adult social roles, such as marriage and spousal chewing habits, rather than initiation in adolescence. Consequently, the adverse cardiovascular risk profile observed in khat chewers is more likely attributable to the behaviour itself and its interaction with contraception than to age-related metabolic changes. Similarly, no significant difference in body mass index (BMI) was observed between khat-chewing and non-chewing women, with both cohorts falling within the overweight range (Khat+: 25.45±4.26 kg/m^2; Khat-: 25.32±5.10 kg/m^2). This result is consistent with a recent cross-sectional study of female students at Al Yemeni University in Sana'a City, which also found no significant difference in BMI between khat chewers and non-chewers. Our finding partially aligns with an Ethiopian study that reported a statistically significant, though clinically small, higher median BMI in female khat chewers (20.6 versus 20.4 kg/m^2, $p<0.05$), with both values remaining in the normal weight range, but contrasts with a body of literature suggesting an appetite-suppressant effect of khat, leading to lower BMI. The absence of a leaner phenotype in our khat-chewing cohort indicates that the metabolic consequences of khat are not secondary to weight differences. Furthermore, a two-way ANOVA confirmed no significant interaction between khat chewing and any contraceptive-related variable on BMI (all $p>0.05$). This indicates that the null association between khat use and BMI is consistent and is not modified by the type or duration of contraceptive use, thereby reinforcing that the documented metabolic perturbations are direct effects of khat exposure.

Atherogenic dyslipidaemia and the central role of the AIP

The most robust biochemical finding of this study is the significantly more atherogenic lipid profile in women who chew khat, most accurately captured by the atherogenic index of plasma (AIP). The mean AIP in the khat-chewing group was 0.38, substantially exceeding the high-risk threshold of 0.24 and indicating a pronounced risk for small, dense LDL particles and future atherosclerotic events.[30] A clear dose-response relationship was evident, with heavy khat use (>3 hours/day) associated with a higher mean AIP. This pattern of dyslipidaemia-characterized by elevated triglycerides and reduced HDL-C-is consistent with findings predominantly from male populations, but has been less consistently documented in women. Our research demonstrated that this atherogenic effect is potentiated in the presence of hormonal contraception, which is itself known to elevate triglycerides.

The atherogenic impact of khat chewing was not fully captured by traditional lipid measures, which showed only non-significant elevations in total cholesterol (TC) and LDL-C. This finding is consistent with the limited and

conflicting data available for women and mirrors the inconclusive picture from studies on men. The collective evidence suggests that the impact of khat on these traditional lipid parameters is inconsistent and may not be a primary driver of dyslipidaemia, underscoring the need for more sensitive, integrated risk indices.

In contrast, the pro-atherogenic impact was accurately captured by a significant elevation in the total cholesterol to HDL-C ratio (TC/HDL: 4.08 ±0.96 versus 3.69±0.79, p=0.03). This ratio is a well-established, integrated atherogenic index where a higher value signifies a critical imbalance between atherogenic and protective lipoproteins and is a recognized superior predictor of cardiovascular risk.[29] Our finding is reinforced by a recent Ethiopian study that also reported a significant increase in the TC/HDL ratio among khat users.

Similar, though non-significant, trends were observed for the LDL-C/HDL-C ratio, which is another accurate predictor of cardiovascular risk which aligns with reports of khat's tendency to affect this atherogenic index adversely. Contrary to a simple dose-response model, the most atherogenic TC/HDL profile was unexpectedly identified in the moderate-duration chewing group (≤3 hours/day), which exhibited a mean ratio of 4.24. This observation suggests a potentially rapid and potent disruption of lipid homeostasis, which appears to occur with even moderate daily khat exposure. While previous research has linked long-term khat use over many years to adverse lipid profiles. The distinct pattern observed in our cohort highlights a previously unreported complexity and a potentially nonlinear relationship between chewing duration and cardiovascular risk. The clinical gravity of a TC/HDL ratio of 4.24 is substantial, as this range has been associated with a significantly higher likelihood of acute myocardial infarction in women and by local evidence demonstrating a strong association between khat chewing and acute coronary syndrome in Yemeni women.[7]

Hormonal contraceptives (HCs) have well-documented but inconsistent effects on lipid profiles. some studies report increased atherogenic markers and others show no significant change. In our cohort of khat-chewing women, the independent effect of HCs on lipid parameters was non-significant, showing no substantial impact on AIP, LDL-c, TC, or their ratios. A trend of increasing TC and LDL-c with longer-term use (>4 years) was observed, aligning with duration-dependent effects noted in other studies, but this did not reach statistical significance. This suggests that in populations with concurrent, potent risk factors like khat chewing, the dyslipidemic signature of HCs may be attenuated or obscured, highlighting the critical need to analyze these exposures in tandem.

Interaction effects between khat chewing and contraceptive factors

Our analysis revealed a novel and significant interaction between khat chewing and the type of hormonal contraceptive method on specific lipid parameters, a finding previously unreported in the literature. The two-way ANOVA revealed a significant interaction between khat chewing and the type of hormonal contraceptive method (pills, injection, and implant) on specific lipid parameters. The interaction significantly affected total cholesterol [F (2,94) =6.300, p=0.003], LDL-c [F (2,94) =6.522, p=0.002], and the atherogenic ratios TC/HDL [F (2,94) =5.448, p=0.006] and LDL/HDL [F (2,94) =5.913, p=0.004]. The partial eta-squared values (0.104-0.122) indicate that the combination of khat use and contraceptive type explains a moderate (10-12%) and clinically meaningful proportion of the variance in these measures. This finding, visualized by the divergent patterns in Figure 1, demonstrates for the first time that the route of hormonal administration significantly modifies the dyslipidemic effect of khat. In contrast, no such interaction was observed for other lipid markers, including the atherogenic index of plasma (AIP), triglycerides, or HDL-C, nor with the specific pill formulation or duration of contraceptive use. This specificity underscores that the synergistic effect is confined to particular atherogenic pathways and is dependent on the broad category of contraceptive method.

CRP and homocysteine: markers of inflammation and pro-thrombotic state

Our analysis established khat chewing as the principal factor elevating c-reactive protein (CRP) levels. Khat-chewing women exhibited significantly higher mean CRP (4.88 mg/l) than non-chewers (4.26 mg/l; p=0.01). A pronounced dose-response relationship was evident, with heavy users (>3 hours/day) showing markedly elevated CRP (6.11 mg/l, p<0.001), indicating that the intensity of khat exposure is a key driver of systemic inflammation. This finding, derived using a standard latex-enhanced assay (not hsCRP), underscores khat-induced systemic inflammation, likely driven by cathinone's sympathomimetic effects, which cause physiological stress and microvascular injury, triggering CRP production. While our results contrast with a null finding from another Sana'a study, they align with a study on Yemeni women. Critically, a two-way ANOVA revealed no significant interaction between khat chewing and contraceptive type, pill type, or duration of use on CRP levels (p>0.05), indicating that khat's pro-inflammatory effect is robust and consistent across different contraceptive methods. Although a non-significant trend of higher CRP was observed with combined oral contraceptives, consistent with the literature on their pro-inflammatory potential this effect was likely overshadowed by the dominant impact of khat. These findings highlight khat chewing as a major, independent inflammatory risk factor in this population.

This study found a significant elevation in serum homocysteine levels in khat-chewing women compared to non-chewers (7.81±2.55 versus 6.77±2.53 µmol/l, p=0.04), adding a pro-thrombotic risk dimension to their already heightened cardiovascular risk profile.[38] A robust dose-response relationship was evident, with the highest homocysteine levels (8.91±2.90 µmol/l) observed in heavy khat users (>3 hours/day), underscoring chewing intensity as a key determinant. Although a direct mechanism is

unconfirmed, the sympathomimetic effects of cathinone, khat's primary active component which induces chronic cardiovascular stress provide a plausible pathway for increased homocysteine production. While the mean levels were below traditional hyperhomocysteinemia thresholds, they approach a more sensitive cut-off (9.45 µmol/l) linked to increased coronary artery calcification, suggesting that even moderate elevation may accelerate atherosclerosis in this vulnerable population. In contrast, homocysteine levels were not significantly influenced by the type, formulation, or duration of hormonal contraceptive use. This finding aligns with studies showing no consistent link although the broader literature remains contradictory, reporting both higher and lower levels, indicating that homocysteine regulation is complex and influenced by factors beyond contraceptive exposure.[12,13,15] Critically, this study is the first to investigate the interaction between khat and hormonal contraceptives on homocysteine. A two-way ANOVA confirmed no significant interaction with contraceptive type, formulation, or duration of use ($p>0.05$), demonstrating that the hyperhomocysteinemic effect of khat is a robust and independent phenomenon. Therefore, khat chewing itself emerges as the primary and unmitigated driver of elevated homocysteine, representing a significant independent cardiovascular risk factor for women using hormonal contraception.

This study acknowledges several limitations, including its cross-sectional design which prevents establishing causality, and a sample size that, while adequate for main comparisons, may have been underpowered for detecting smaller effects in subgroup analyses. Furthermore, the use of a standard CRP assay instead of a high-sensitivity test may have limited the precision in measuring inflammation, and the reliance on self-reported data for khat and contraceptive use introduces potential recall bias. Finally, the findings from women in the Dhamar District may not be generalizable to other populations.

CONCLUSION

Among Yemeni women using hormonal contraception, khat chewing is a major, independent risk factor for an adverse metabolic cardiovascular profile, inducing hypertension, atherogenic dyslipidemia, systemic inflammation, and hyperhomocysteinemia. A clear dose-response relationship exists, and a significant interaction with contraceptive type was identified. These findings underscore the critical need for integrating khat-use screening into family planning and cardiovascular risk assessment programs in Yemen. Public health initiatives should educate women on the compounded cardiovascular risks of concurrent khat and hormonal contraceptive use.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the staff of the Maternity and Childhood Hospital, Al-Homeat Hospital, and Al-Wahda Center in Dhamar Districtfor their cooperation and for allowing us to collect samples and take data from the female participants in the study. We also thankfully appreciate the study population for their participation in this study. We also extend our thanks to Al-Jarfi Laboratories and the Taiba Hospital Laboratory in Dhamar for analyzing the study samples.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Al-Qader AF, Ahad A, Alans A, Alsumaiee JMAN, Hivrale VK. Metabolic cardiovascular risk profiles: a comparative study of khat-chewing and non-chewing women using hormonal contraception in Dhamar District, Yemen. Int J Res Med Sci 2026;14:1467-78.