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Vitamin D Status and Homocysteine Levels in Hormonal Contraceptive Users and Non-Users Among Women of Reproductive Age in Dhamar District, Yemen

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Abstract

Background: Vitamin D deficiency and elevated homocysteine are recognized contributors to cardiometabolic disorders; hormonal contraceptive use may influence both.

Methods: A case–control study was conducted among 200 apparently healthy married women aged 15–45 years in Dhamar District, Yemen (100 hormonal contraceptive users; 100 non-users). Serum 25-hydroxyvitamin D was measured by electrochemiluminescence immunoassay; homocysteine was analyzed enzymatically. Statistical analyses included independent t-tests, chi-square tests, Pearson correlation, one-way ANOVA, and multivariable linear regression.

Results: Hormonal contraceptive users had significantly higher homocysteine levels than non-users (7.41±2.72 vs. 6.33±2.02 µmol/L, p=0.002). Vitamin D levels were lower in users (14.99±11.38 vs. 18.18±12.03 ng/mL, p=0.056), and vitamin D deficiency was significantly more prevalent (57.9% vs. 42.1%, p=0.003). A significant inverse correlation between vitamin D and homocysteine was observed among users ($r=-0.217$, p=0.030). Multivariable regression identified age (β=0.067, p=0.002) and khat chewing duration (β=0.874, p<0.001) as independent predictors of homocysteine levels.

Conclusions: Hormonal contraceptive use was associated with higher homocysteine levels and greater vitamin D deficiency prevalence. The inverse vitamin D–homocysteine correlation among users suggests potential cardiovascular metabolic implications. Longitudinal studies and nutritional interventions targeting B vitamins and vitamin D status are warranted.

Keywords: vitamin D; homocysteine; hormonal contraceptives; women of reproductive age; Yemen; khat chewing

Introduction

Vitamin D_3 is a fat-soluble secosteroid essential for bone health, immune regulation, and cardiovascular processes, with primary synthesis occurring through UVB irradiation of skin [1]. Globally, vitamin D deficiency is a significant public health concern, particularly among women of reproductive age[2][3]. In Yemen, low vitamin D levels are paradoxically prevalent despite abundant sunlight, largely explained by cultural clothing practices, restricted outdoor activity, and nutritional limitations[4][5]. Beyond its skeletal role, vitamin D deficiency is increasingly implicated in cardiometabolic disorders [6-7].

Homocysteine, a sulfur-containing amino acid generated during methionine metabolism, is recognized as an independent cardiovascular risk factor through endothelial dysfunction, oxidative stress, and vascular inflammation[8][9]. Its metabolism is tightly regulated by folate and vitamins B_6 and B_{12} [10]. Emerging evidence suggests a potential interaction between vitamin D status and homocysteine metabolism that may compound cardiovascular risk[11-12].

In women of reproductive age, hormonal contraceptive use may influence vitamin D status [13]and homocysteine metabolism [14-15] and may contribute to changes in lipid and cardiovascular risk profiles[16-17]. Data from Yemen-particularly Dhamar-remains limited. This study, therefore, assessed vitamin D status and homocysteine levels among women of reproductive age in Dhamar and examined their association with hormonal contraceptive use.

Methods

Study Design and Setting

A case–control study was conducted from October 2023 to January 2024 at three public hospitals offering family planning services in Dhamar District, Yemen: The Maternity and Childhood Hospital, Al-Humeat Center, and Al-Wahda Center.

Study Population and Eligibility

A total of 200 apparently healthy married women aged 15–45 years were recruited and equally allocated into two groups: 100 hormonal contraceptive users (cases) and 100 non-users (controls). Cases had used hormonal contraceptives continuously for at least six months, including combined oral contraceptives (three formulations), injectable medroxyprogesterone acetate (150 mg), or subdermal etonogestrel implants (68 mg). Condom users were excluded from the control group. Controls were new attendees or accompanying visitors not using hormonal contraceptives. Exclusion criteria included pregnancy, lactation, chronic systemic disease (cardiovascular, renal, hepatic, endocrine, or metabolic), and use of vitamin/mineral supplements. Sample size was determined using G*Power (version 3.1.0) at 5% significance level, and 99% power; a 10% non-response adjustment yielded the final n=200.

Data Collection and Measurements

Structured face-to-face interviews captured sociodemographic data (age, education, occupation, residence), lifestyle factors (sun exposure, khat chewing, tea/coffee consumption), and contraceptive history. Anthropometric measurements (height, weight, BMI) and blood pressure were recorded by trained personnel per WHO criteria[18]. A pilot study (n=20) was conducted to validate the questionnaire; pilot participants were excluded from the main analysis.

Biochemical Analysis

Fasting venous blood (6 mL) was collected after 8–12 hours of overnight fasting. Serum 25-hydroxyvitamin D [25(OH)D] was measured by electrochemiluminescence immunoassay (Elecsys 2010/cobas e 411). Homocysteine was determined enzymatically (Biosystems BA200). Vitamin D status was classified as deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL) [38]. Hyperhomocysteinemia was defined as >15 µmol/L [19].

Statistical Analysis

Data were analyzed using SPSS v26/27. Continuous variables are expressed as mean ± SD; categorical variables as frequencies and percentages. Group comparisons used independent t-tests, chi-square tests, and one-way ANOVA. Pearson correlation evaluated vitamin D–homocysteine relationships. Multivariable linear regression (Enter method) identified independent predictors of vitamin D and homocysteine. Two-tailed $p<0.05$ was considered statistically significant.

Ethical Considerations

Permission was obtained from the Dhamar Health and Population Office and participating healthcare centers. Verbal informed consent was obtained from all participants, given the high rate of illiteracy. Participation was voluntary, and confidentiality was maintained. A formal institutional ethics review committee was unavailable locally; all procedures adhered to the principles of the Declaration of Helsinki.

Results

Continuous Characteristics

Volume 9, Issue 5; September-October 2026; Page No 46-55

Hormonal contraceptive users were significantly younger than non-users (30.44±7.11 vs. 34.68±7.88 years, p<0.001; Table 1). Combined tea and coffee intake was higher among users (3.90±1.73 vs. 2.92±1.23 cups/day, p<0.001). BMI, blood pressure, and khat chewing duration did not differ significantly (p>0.05). Vitamin D levels were lower in users (14.99±11.38 vs. 18.18±12.03 ng/mL, p=0.056), while homocysteine was significantly elevated (7.41±2.72 vs. 6.33±2.02 µmol/L, p=0.002).

Figure 1. Mean serum vitamin D and homocysteine levels in hormonal contraceptive users and non-users. Values are presented as mean ± standard deviation (SD). Blue bars = users (n=100); green bars = non-users (n=100). NS = not significant; ** p < 0.01.

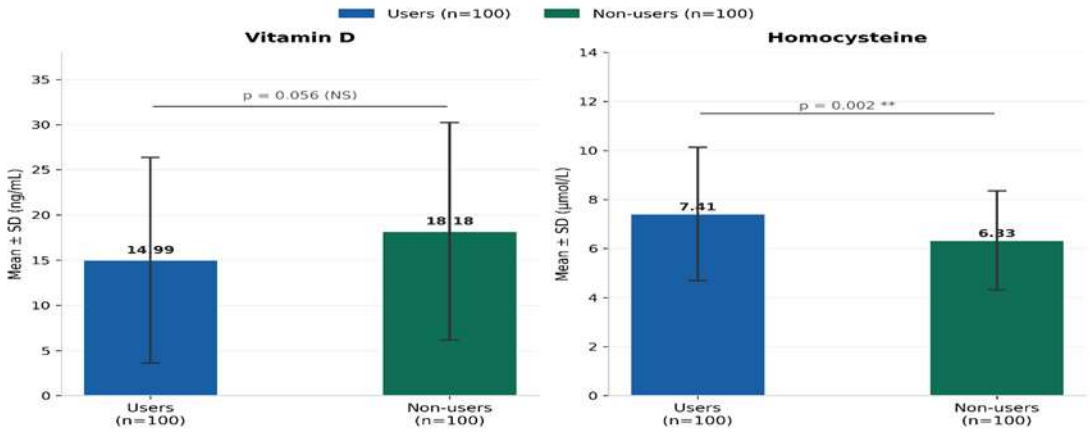


Table 1. Comparison of Continuous Characteristics Between Hormonal Contraceptive Users and Non-Users

Variable	n	Users Mean±STD	n	Non-Users Mean±STD	Mean Diff.	P-value
Age (years)	100	30.44±7.11	100	34.68±7.88	−4.24	<0.001**
BMI (kg/m²)	100	25.39±4.68	100	26.32±4.12	−0.93	0.137
Systolic BP (mmHg)	100	99.30±14.44	100	102.40±12.24	−3.10	0.103
Diastolic BP (mmHg)	100	68.10±13.16	100	67.20±10.06	0.90	0.587
Khat chewing (hours)	50	4.45±2.06	34	4.17±1.86	0.28	0.523
Tea (cups/day)	41	2.59±2.14	50	2.70±1.92	−0.115	0.789
Tea+Coffee (cups/day)	59	3.90±1.73	50	2.92±1.23	0.978	<0.001**
Vitamin D (ng/mL)	100	14.99±11.38	100	18.18±12.03	−3.19	0.056
Homocysteine (µmol/L)	100	7.41±2.72	100	6.33±2.02	1.08	0.002**

Volume 9, Issue 5; September-October 2026; Page No 46-55

Values: Mean±STD. Independent samples t-test. *p<0.05, **p<0.01. BMI: body mass index; BP: blood pressure.

Sociodemographic Characteristics and Clinical Profiles

Age distribution differed significantly (p=0.002), with younger women predominating among users (Table 2). Skin colour (p=0.011), occupation (p=0.013), education (p=0.014), and khat chewing (p=0.022) also differed significantly between groups. Vitamin D deficiency was more prevalent among users (57.9% vs. 42.1%, p=0.003). Homocysteine category distribution did not differ significantly (p=0.404), with most participants in the normal range (5–15 µmol/L). Among users, oral contraceptive pills were most common (66.0%), followed by injection (23.0%) and implant (11.0%). No significant differences in vitamin D or homocysteine were observed across contraceptive type, formulation, or duration of use (all p>0.05).

Table 2. Sociodemographic Characteristics, Vitamin D Status, and Homocysteine Levels Among Hormonal Contraceptive Users and Non-Users

Variable	Category	Users n (%)	Non-users n (%)	χ^2	P-value
Age group (years)	≤20	9 (64.3)	5 (35.7)	16.878	0.002**
	21–25	20 (66.7)	10 (33.3)		
	26–35	51 (56.7)	39 (43.3)		
	36–45	17 (32.7)	35 (67.3)		
	>45	3 (21.4)	11 (78.6)		
BMI (kg/m²)	<18.5 (Underweight)	7 (77.8)	2 (22.2)	3.704	0.295
	18.5–24.9 (Healthy)	40 (50.6)	39 (49.4)		
	25–29.9 (Overweight)	37 (45.1)	45 (54.9)		
	>30 (Obese)	16 (53.3)	14 (46.7)		
Skin Color	Fair	30 (66.7)	15 (33.3)	6.452	0.011*
	Wheatish	70 (45.2)	85 (54.8)		
Sun exposure	Exposed	30 (50.0)	30 (50.0)	0.000	1.000
	Non-exposed	70 (50.0)	70 (50.0)		
Residence	Urban	92 (52.0)	85 (48.0)	2.407	0.121
	Rural	8 (34.8)	15 (65.2)		
Occupation	Housewife	87 (54.4)	73 (45.6)	6.125	0.013*
	Employee	13 (32.5)	27 (67.5)		
Education	Illiterate	15 (55.6)	12 (44.4)	12.524	0.014*
	Elementary	22 (48.9)	23 (51.1)		
	Intermediate	17 (77.3)	5 (22.7)		
	Secondary	28 (52.8)	25 (47.2)		
	University	18 (34.0)	35 (66.0)		
Khat chewing	Yes	50 (59.5)	34 (40.5)	5.255	0.022*

Volume 9, Issue 5; September-October 2026; Page No 46-55

	No	50 (43.1)	66 (56.9)		
Vitamin D status	<20 ng/mL (Deficiency)	73 (57.9)	53 (42.1)	11.483	0.003**
	20–29 ng/mL(Insufficiency)	22 (43.1)	29 (56.9)		
	30–60 ng/mL (Sufficiency)	5 (21.7)	18 (78.3)		
Homocysteine	<5 µmol/L (Low)	21 (44.7)	26 (55.3)	1.637	0.404
	5–15 µmol/L (Normal)	79 (51.6)	74 (48.4)		

Values: frequency (n) and percentage (%). Chi-square test. *p<0.05, **p<0.01. BMI: body mass index; BP: blood pressure.

Correlation Between Vitamin D and Homocysteine

No significant correlation was observed in the whole sample (r=−0.116, p=0.101; Table 3). Among hormonal contraceptive users, a weak but significant negative correlation was found (r=−0.217, p=0.030). No significant association was identified among non-users (r=0.082, p=0.417).

Figure 2. Correlation between serum vitamin D and homocysteine levels in hormonal contraceptive users and non-users. Dashed line represents the regression line for users. * p < 0.05; NS = not significant.

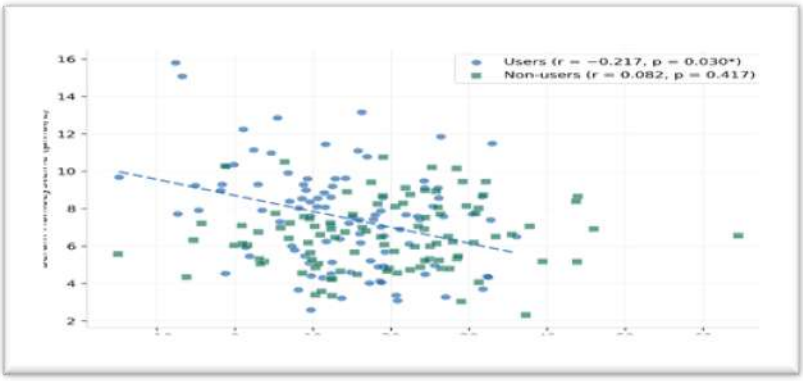


Table 3. Pearson Correlation Between Serum Vitamin D and Homocysteine Levels

Group	r	P-value
All participants	−0.116	0.101
Hormonal contraceptive users	−0.217	0.030*
Non-users	0.082	0.417

Homocysteine Levels Across Vitamin D Status Categories

Mean homocysteine levels did not differ significantly across vitamin D status categories in either group (p>0.05; Table 4), although contraceptive users with vitamin D deficiency had numerically higher values (7.80±3.15 µmol/L).

Table 4. Mean Homocysteine Levels Across Vitamin D Status Categories

Volume 9, Issue 5; September-October 2026; Page No 46-55

Vitamin D Status	All (Mean±STD)	Users (Mean±STD)	Non-users (Mean±STD)
<20 ng/mL (Deficiency)	7.11±2.88	7.80±3.15	6.16±2.15
20–29 ng/mL (Insufficiency)	6.53±2.27	6.68±2.65	6.42±1.98
30–60 ng/mL (Sufficiency)	6.62±1.95	6.48±2.82	6.66±1.74
P-value	0.363	0.552	0.640

Values: Mean±STD. One-way ANOVA.

Multivariable Linear Regression

No independent predictors of serum vitamin D were identified ($p>0.05$ for all variables; Table 5). For homocysteine, age (β=0.067, 95% CI: 0.025–0.108, p=0.002) and khat chewing duration (β=0.874, 95% CI: 0.721–1.028, p<0.001) were significant independent predictors. After controlling for confounders, hormonal contraceptive use was negatively associated with homocysteine (β=−1.408, 95% CI: −2.062 to −0.753, p<0.001), reflecting the confounding influence of age and khat chewing rather than an independent contraceptive effect.

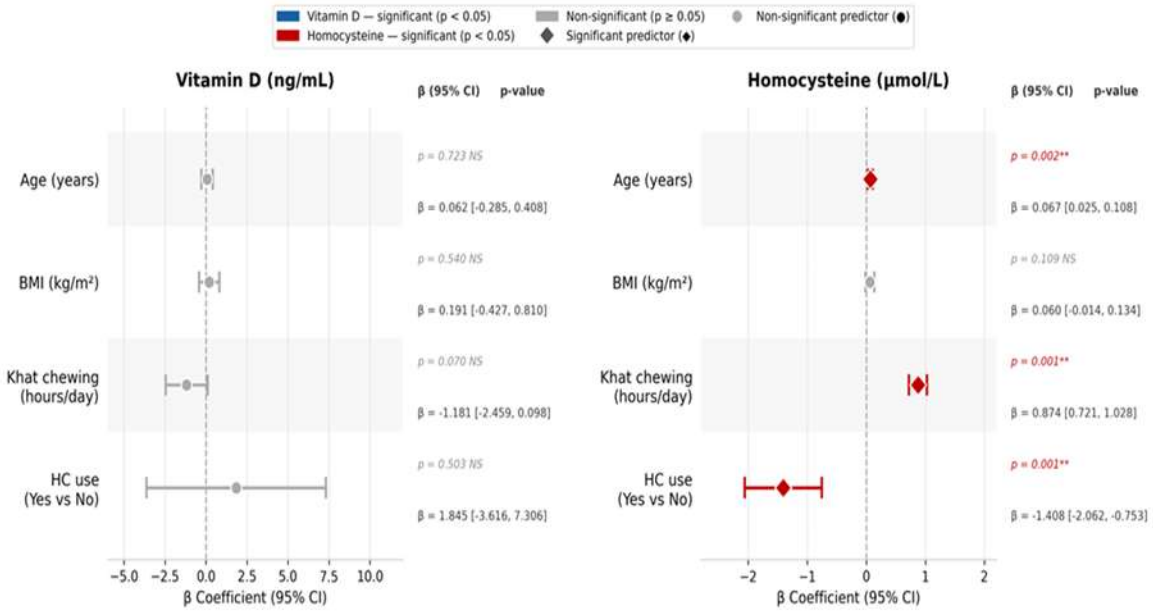
Table 5. Multivariable Linear Regression Analysis of Factors Associated with Serum Vitamin D and Homocysteine Levels

Variable	VitD β	95% CI	P	Homo. β	95% CI	P
Age (years)	0.062	−0.285 to 0.408	0.723	0.067	0.025 to 0.108	0.002**
BMI (kg/m²)	0.191	−0.427 to 0.810	0.540	0.060	−0.014 to 0.134	0.109
Khat chewing (hours)	−1.181	−2.459 to 0.098	0.070	0.874	0.721 to 1.028	<0.001**
HC use (Yes, vs No)	1.845	−3.616 to 7.306	0.503	−1.408	−2.062 to −0.753	<0.001**

β: unstandardized coefficient; CI: confidence interval. All variables are entered simultaneously. **p<0.01. BMI: body mass index; HC: hormonal contraceptive use

Figure 3. Forest plot of multivariable linear regression coefficients for predictors of serum vitamin D and homocysteine levels. β = unstandardized regression coefficient; CI = 95% confidence interval; HC = hormonal contraceptive use. Diamonds (◆) = significant predictors; Circles (●) = non-significant predictors. * $p < 0.05$; ** $p < 0.01$.

Volume 9, Issue 5; September-October 2026; Page No 46-55



Discussion

This study examined vitamin D status and homocysteine levels in relation to hormonal contraceptive use among women of reproductive age in Dhamar, Yemen, a context underrepresented in existing literature. The key findings are that hormonal contraceptive users had significantly higher homocysteine levels and a significantly higher prevalence of vitamin D deficiency, while age and khat chewing duration emerged as the primary independent predictors of homocysteine in multivariable analysis.

Hormonal contraceptive users were significantly younger, consistent with the greater demand for contraception during peak reproductive years[20]. Age was an independent predictor of homocysteine (β=0.067, p=0.002), aligning with established evidence that homocysteine concentrations rise with advancing age in females[21-22]. BMI and blood pressure did not differ significantly between groups, consistent with reports that low-dose formulations have minimal effects on these parameters[23-24]

Khat chewing was more prevalent among users (59.5% vs. 40.5%, p=0.022) and was the strongest independent predictor of homocysteine (β=0.874, p<0.001). The active alkaloids cathinone and cathine may elevate homocysteine through sympathetic activation, oxidative stress, and disruption of one-carbon metabolism[25-26]. Although khat chewing duration was inversely associated with vitamin D (β=−1.181), this did not reach significance (p=0.070), possibly reflecting khat-related indoor sedentary behavior limiting UVB exposure and appetite suppression, reducing dietary vitamin D intake[26-27].

Although combined tea and coffee intake was not retained in the final regression model — as it did not independently predict homocysteine levels and its inclusion destabilized other model coefficients-this is consistent with its known mediation through B-vitamin pathways already captured by age and khat chewing duration in the model [28-29].Furthermore, moderate coffee and tea consumption has been associated with neutral or protective cardiovascular effects in some populations, attributable to antioxidant polyphenol content [30-31], which may partly explain the inconsistencies reported across studies on caffeine and homocysteine.

Vitamin D deficiency was more prevalent among users than non-users (57.9% vs. 42.1%, p=0.003), and mean levels were lower in users, though not significantly so (p=0.056). The literature is divided: some studies report higher total vitamin D among users due to elevated vitamin D-binding protein[13,32], while others document lower levels in specific populations[33]. The current findings are clinically relevant, as users showed markedly lower sufficiency

Volume 9, Issue 5; September-October 2026; Page No 46-55

rates (21.7% vs. 78.3%), despite no formulation- or duration-dependent differences. Paradoxically, fair-skinned women were more common among users. Yet, vitamin D deficiency was still more prevalent in this group, underscoring the dominance of behavioural, hormonal, and sociocultural factors over skin pigmentation [33-34].

Contraceptive-induced depletion of folate, vitamins B6, and B12 plausibly explains homocysteine elevation in hormonal contraceptive users [10,17,35] , cofactors essential for homocysteine remethylation. Despite higher mean homocysteine among users, the regression analysis showed a negative beta coefficient for contraceptive group membership after controlling for age and khat chewing, indicating that these confounders—rather than contraceptive use itself—drive the observed elevation[21][36].This pattern is consistent with established evidence that homocysteine concentrations increase progressively with age in females and that age remains a dominant independent predictor across reproductive life stages[36-37]. This finding has important implications for cardiovascular risk profiling in Yemeni women.

A significant inverse correlation between vitamin D and homocysteine was observed exclusively among contraceptive users ($r=-0.217$, $p=0.030$), consistent with proposed mechanisms involving vitamin D's anti-inflammatory effects and role in one-carbon metabolic pathways [11-12]. This interaction was absent in non-users, suggesting contraceptive exposure may modulate the vitamin D–homocysteine relationship. Potential cardiovascular relevance follows from the coexistence of elevated homocysteine and vitamin D deficiency, both independently associated with endothelial dysfunction and atherogenesis[9,34,38,39], in a population already using agents linked to thrombotic risk[16,40].

Limitations

This study has notable strengths, including simultaneous evaluation of two cardiovascular biomarkers alongside comprehensive lifestyle data in an understudied population. Limitations include the cross-sectional design precluding causal inference, modest sample size limiting subgroup power, and non-assessment of folate, B6, and B12 intakes. Free vitamin D and vitamin D-binding protein were not measured, which is relevant given contraceptive effects on binding protein. Residual confounding from unmeasured dietary, physical activity, and sociocultural variables cannot be excluded.

Conclusion

Hormonal contraceptive use was associated with higher homocysteine levels and greater vitamin D deficiency prevalence in women of reproductive age in Dhamar, Yemen. Age and khat chewing duration were the primary independent predictors of homocysteine, while an inverse vitamin D–homocysteine correlation was identified specifically among contraceptive users. These findings suggest a combined cardiometabolic risk in this population. Longitudinal studies and targeted nutritional interventions addressing vitamin D and B-vitamin status among hormonal contraceptive users are recommended.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethical approval: Permission was obtained from the Dhamar Health and Population Office and participating healthcare centers. All procedures were conducted in accordance with the Declaration of Helsinki.

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Volume 9, Issue 5; September-October 2026; Page No 46-55

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Volume 9, Issue 5; September-October 2026; Page No 46-55

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Volume 9, Issue 5; September-October 2026; Page No 46-55