Section: General Medicine

Original Research Article

ASSOCIATION OF VITAMIN B12 AND HOMOCYSTEINE LEVELS WITH 10-YEAR CARDIOVASCULAR DISEASE RISK IN AN INDIAN POPULATION: A CROSS-SECTIONAL ANALYTICAL STUDY

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ABSTRACT

Background: Elevated homocysteine and low vitamin B12 levels are independently associated with increased cardiovascular disease risk. Studies show an inverse relationship between serum homocysteine and vitamin B12. For instance, Raina et al. (2015) found that 77.42% of individuals with elevated homocysteine (>30 µmol/L) had suboptimal vitamin B12 (<200 pg/ml) levels (1). Patients with ischemic heart disease also had higher homocysteine and lower vitamin B12 compared to controls (2). Homocysteine correlates positively with the Framingham Risk Score (FRS), a tool for cardiovascular risk assessment (3). It is also significantly associated with coronary artery calcification (CAC) in individuals at intermediate coronary risk (4). These findings suggest plasma homocysteine may be a potential biomarker for cardiovascular risk, particularly in intermediate-risk individuals. However, studies in Indian populations have failed to establish a clear link between hyperhomocysteinemia and coronary artery disease, despite their high prevalence. **Objective:** To assess the relationship between homocysteine, vitamin B12 levels, and Framingham Risk Scores in an Indian population. **Materials and Methods:** A cross-sectional study of 76 participants aged 30–80 years without known cardiovascular disease. Blood samples were analyzed for vitamin B12, homocysteine, and lipid profiles. FRS was calculated using the Medscape calculator. **Results:** No statistically significant associations were found between homocysteine or vitamin B12 levels and FRS. A weak negative correlation existed between homocysteine and vitamin B12 but was not significant. Linear regression identified age, male sex, systolic blood pressure, smoking, diabetes, and low HDL as key risk factors. Thus, while important, homocysteine and vitamin B12 may not strongly predict cardiovascular risk.

INTRODUCTION

Recent studies have demonstrated a significant correlation between plasma homocysteine levels and various cardiovascular risk factors. Elevated homocysteine concentrations are associated with an increased risk of extracranial carotid artery stenosis and coronary artery calcification.[4,5] Additionally, homocysteine levels have shown a positive correlation with the Framingham Risk Score (FRS), a widely accepted tool for assessing cardiovascular risk.[3,6] This association is particularly evident among individuals with an intermediate 10-year risk of developing coronary heart disease.[4] However, research conducted in Indian populations has yielded inconsistent findings regarding the association between hyperhomocysteinemia and coronary artery disease, despite the high prevalence of both conditions. Although several studies report a significant inverse relationship between vitamin B12 levels and homocysteine, no consistent correlation has been found between vitamin B12 and the Framingham Risk Score.[7]

The relationship between vitamin B12, homocysteine, and cardiovascular risk is complex and multifactorial. Plasma homocysteine levels are inversely related to the intake of folate and vitamin B6, suggesting that deficiencies in these nutrients

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may contribute to elevated homocysteine and, consequently, increased cardiovascular risk.[5] Notably, vitamin B12 deficiency has been linked to more severe forms of coronary artery disease, as reflected in elevated SYNTAX scores.[8] Dietary factors play a significant role in maintaining adequate vitamin B12 levels, with fortified cereals, dairy products, and supplements offering protective benefits.[9] Elderly individuals are particularly vulnerable to vitamin B12 deficiency, with metabolic insufficiency affecting up to 12% of free-living older adults in the U.S.[10] Furthermore, hyperhomocysteinemia—frequently resulting from low vitamin B12 and folate levels—is prevalent in about 30% of the elderly population and has been associated with an increased risk of extracranial carotid-artery stenosis.[5]

Emerging evidence supports the utility of screening homocysteine levels, especially in individuals with unexplained thrombotic events or in younger patients presenting with coronary disease in the absence of traditional risk factors such as hypertension, smoking, hypercholesterolemia, or diabetes.[11] Although a definitive causal relationship between hyperhomocysteinemia and cardiovascular disease has not yet been established, growing data suggest potential benefits in reducing homocysteine levels among at-risk individuals.[3,5,12] Since homocysteine levels are inversely related to vitamin B12 status—a modifiable factor through dietary interventions—understanding this relationship becomes increasingly relevant.

Therefore, this study aims to evaluate the strength of the relationship between homocysteine and vitamin B12—emerging risk factors—and their association with the Framingham Risk Score, which encompasses established cardiovascular risk markers. This investigation will help determine whether these newer biomarkers warrant consideration for inclusion in cardiovascular risk assessment tools such as the FRS.

MATERIALS AND METHODS

The study sample consisted of 76 participants aged 30–80 years, who were randomly selected from the General Medicine OPD and ward of a Tertiary Care Hospital, with no known cardiovascular diseases. Each subject completed a detailed questionnaire that captured demographic data, medical history, and lifestyle factors. Blood pressure was measured at two separate intervals, four hours apart. After obtaining informed consent, blood samples were collected in EDTA-coated vacutainers and sent to the central research laboratory at the University for analysis. Vitamin B12 and homocysteine levels were measured using GENLISA ELISA kits (Chrysgen Biosystems) with a multimode microplate fluorescent ELISA reader (Spark, Tecan). Lipid profiles (HDL cholesterol and total cholesterol) were assessed using the Agappe kit via a semi-automated analyser. Framingham Risk Scores were calculated using the Medscape Framingham Risk Score calculator. For the purposes of calculation, past smokers who had quit smoking more than 10 years ago were considered non-smokers.

Data analysis was conducted using SPSS, and statistical methods including Spearman's and Pearson's correlation tests, as well as chi-square tests, were used to assess relationships between variables.

INSTITUTIONAL ETHICAL COMMITTEE CLEARANCE

Institutional Ethical Committee Clearance was obtained before beginning the study.

Informed Consent

Written Informed consent was obtained from all subjects involved in the study for sample collection, analysis of results and for publishing this paper.

Sampling Method

- Purposive sampling

Sample Size

Sample Size Calculation Details:

- Effect size: 0.35
- Degrees of freedom: 3
- Significance level: 5%
- Statistical power: 80%
- Calculated using G*Power software (Version 3.1.9.7)
- Validated against reference cardiovascular research parameters [reference article: Cardiovascular manifestations of intermediate and major hyperhomocysteinemia due to vitamin B12 and folate deficiency and/or inherited disorders of one-carbon metabolism: a 3.5-year retrospective cross-sectional study of consecutive patients.[12]

Inclusion Criteria Clarification

- Age range: 30-80 years
- No known cardiovascular disease
- Ability to provide informed consent
- Resident of study region

Exclusion Criteria

- Age <30 or >80 years
- Diagnosed cardiovascular disease
- Gastrointestinal malabsorption disorders
- Concurrent medications affecting B12 metabolism.

RESULTS

Out of 90 participants initially screened, 14 were excluded due to factors known to affect homocysteine levels, such as existing coronary artery disease (CAD), hypothyroidism, age outside the inclusion criteria, or the use of multivitamin supplements or medications affecting cobalamin levels. Among the 76 participants included in the study, the mean homocysteine level was 5081.5 ng/ml (range: 500–8000 ng/ml), and the mean age was 56.08 years (range: 30–80 years). The mean total cholesterol level was 166.9 mg/dL (normal: <200 mg/dL), while the mean HDL cholesterol level was

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53.85 mg/dL (normal: >40 mg/dL). The median vitamin B12 level was 0.1800 pmol/ml (range: 0.118–0.701 pmol/ml), and the median Framingham Risk Score was reported with interquartile values (Q1: 4.65%, Q3: 19.2%). (Table 1; Figure 1)

Linear regression analysis (Figure 2) was performed to be able to predict the Framingham risk score (%) based on several clinical and demographic variables. The model demonstrates a strong fit, with an R^2 value of 0.869 and an adjusted R^2 of 0.853 (Table 2), indicating that approximately 85% of the variation in the Framingham score can be explained by the predictors included in the model.

The intercept of the model is -37.99, which represents the expected Framingham score when all predictors are at their reference or baseline values; although not meaningful on its own, it is necessary for the calculation of the final score. Among the predictors, being male (Sex: 1–0) significantly increases the risk score by 5.23%, while each additional year of age contributes to a 0.41% increase. Similarly, systolic blood pressure (SBP) is a significant predictor, with each mmHg increase raising the score by 0.19%. HDL cholesterol levels show a protective effect; for each unit increase, the risk score decreases by 0.11%, and this association is statistically significant. However, total cholesterol levels and being on blood pressure medications did not significantly affect the score, as their p-values were not statistically significant. On the other hand, smoking and having diabetes mellitus are both strong predictors of increased cardiovascular risk, with smokers having a 7.48% higher risk and individuals with diabetes showing a 7.62% higher score, both with p-values less than 0.001.

Overall, the model identifies age, male sex, higher systolic BP, smoking, diabetes, and lower HDL as significant contributors to higher cardiovascular risk, aligning with known clinical risk factors in cardiovascular disease prediction.

Correlation analysis (Table 3) was done to explore the relationships between Homocysteine, Vitamin B12, HDL Cholesterol, and Age using both Spearman rank correlation (for non-normally distributed data) and Pearson's correlation coefficient (for normally distributed data). The results indicate that none of the observed correlations are statistically significant, as all p-values are greater than 0.05.

A weak negative correlation was found between Homocysteine and Vitamin B12 (r = -0.170, Spearman), suggesting that as Vitamin B12 levels increase, Homocysteine levels tend to decrease; however, this relationship is not statistically significant. Similarly, Homocysteine showed a weak positive correlation with HDL Cholesterol (r = 0.143, Spearman) and a very weak negative correlation with Age (r = -0.048, Pearson), both of which were also not significant.

Vitamin B12 demonstrated a moderate positive correlation with HDL Cholesterol (r = 0.681, Pearson), which might imply a potential association between these two variables, though this too lacked statistical significance. Additionally, the correlation between Vitamin B12 and Age was very weak (r = 0.078, Pearson), indicating no meaningful relationship. HDL Cholesterol showed a moderate positive correlation with Age (r = 0.503, Pearson), suggesting that HDL levels may increase slightly with age, but this was not statistically significant either.

The table presents the results of a correlation analysis between homocysteine levels and three variables—Vitamin B12, HDL cholesterol, and age—as well as the correlation between HDL cholesterol and Vitamin B12. Two types of correlation coefficients are reported: Spearman rank correlation (denoted by #) and Karl Pearson's correlation (denoted by ##), with * indicating a p-value > 0.05, i.e., not statistically significant.

Homocysteine levels show a weak negative correlation with Vitamin B12 (Spearman's ρ = -0.170), though this relationship is not statistically significant. There is a weak positive correlation between homocysteine and HDL cholesterol (Spearman's $\rho = 0.143$), which is also not significant. Similarly, a very weak negative correlation is observed between homocysteine and age (Pearson's r = -0.048), lacking statistical significance. On the other hand, a moderate positive correlation exists between age and HDL cholesterol (Pearson's r = 0.681), though it, too, is statistically not significant. Lastly, HDL cholesterol and Vitamin B12 are weakly negatively correlated (Spearman's ρ = -0.095), with no statistical significance.

Overall, none of the observed correlations reached statistical significance ($p > 0.05$), suggesting that within this dataset, there is no strong or meaningful linear or monotonic association between homocysteine and the parameters studied (Vitamin B12, HDL cholesterol, and age), nor between HDL cholesterol and Vitamin B12.

Association was analysed between Homocysteine, Vitamin B12 and the Framingham Risk Scores. For association study, homocysteine, vitamin B12 and framingham were risk stratified as-

Vitamin B12 (normal range:0.118-0.701 pmol/ml)

- Low normal-0.118-0.200 pmol/ml
- Normal-0.201-0.701 pmol/ml

Homocysteine (normal range: 500-8000 ng/ml)

- Low normal-500-3000 ng/ml
- Moderate Normal-3001-6000 ng/ml
- High normal-6001-8000 ng/ml

Framingham risk scores- risk was described as per the medscape Framingham risk scores-10 year risk calculator (2008).

Outcomes-

- Pearson chi square value of 1.087 with p-value of 0.581. Hence, there is no significant association between smoking history and homocysteine levels. (Table 4)
- Pearson chi square value of 2.805 with p-value of 0.591. Hence, there is no significant

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association between framingham risk scores and homocysteine levels. (Table 5)

- Pearson chi square value of 0.0508 with p-value of 0.975. Hence, there is no significant association between framingham risk scores and vitamin B12 levels. (Table 6)

Table 1: Descriptive statistics of the study parameter (N=90)

Parameter	Mean±SD
Systolic blood pressure	124±17
Diastolic blood pressure	76.9±9.6
Age	56.08±12
Total Cholesterol	166 (147,188)[#]
HDL Cholesterol	49.6 (45.5,60.5)[#]
Cobalamin(in pmol/ml)	0.18(0.17, 0.21)[#]
Framingham risk scores	9.40(4.65, 19.2)[#]
Homocysteine	4997 (4707,5582)[#]

[#] ***Median(Q1, Q3)***

Table 2: Model fit measures in this model

Model Fit Measures-					
Model		**R^2**		**Adjusted R^2**	
1		0.869		0.853	

Table 3: Correlation analysis of the parameters

Variable	Vitamin B12	HDL Cholesterol	Age
Homocysteine	-0.170[#] 0.143*	-0.048[##] 0.681*	0.078[##] 0.503*
HDL Cholesterol	-0.095[#] 0.415*		

#Spearman rank correlation coefficient, ##Karl-Pearson's correlation coefficient, *p-value>0.05, statistically not significant

Table Association between smoking and homocysteine

SMOKING HISTORY	Homocysteine-low normal (frequency %)	homocysteine-Moderate normal (frequency %)	homocysteine-High normal (frequency %)	Pearson-chi square coefficient 1.087	p- value 0.581
yes	0	20.6%	33.3%		
no	100%	79.4%	66.7%		

Table 5: Association between framingham risk scores and homocysteine

FRAMINGHAM RISK STRATIFICATION	Homocysteine-low normal (frequency %)	homocysteine-Moderate normal (frequency %)	homocysteine-High normal (frequency %)	Pearson-chi square coefficient 2.805	p-value 0.591
High	0	26.5%	33.3%		
Moderate	50%	17.6%	33.3%		
Low	50%	55.9%	33.3%		

Table 6: Association between framingham risk scores and vitamin B12

FRAMINGHAM RISK STRATIFICATION	vitamin B12-low normal (frequency %)	vitamin B12-normal (frequency %)	Pearson-chi square coefficient 0.0508	p-value 0.975
High	70%	30%		
Moderate	73.3%	26.7%		
Low	70.7%	29.3%		

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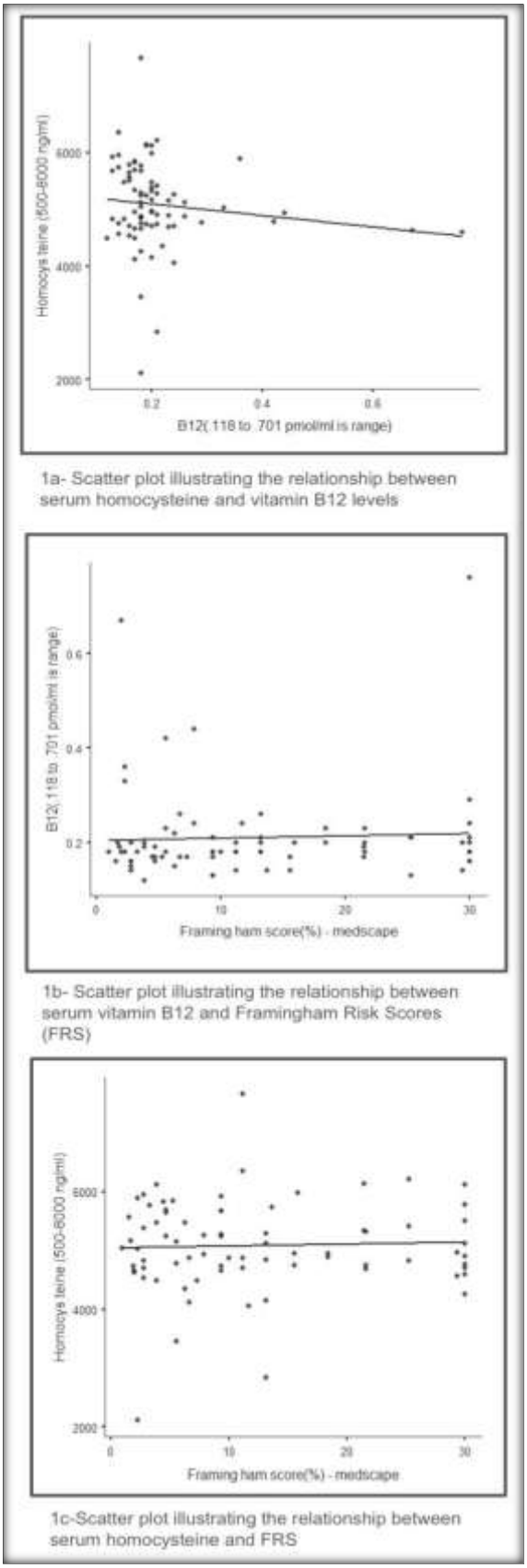
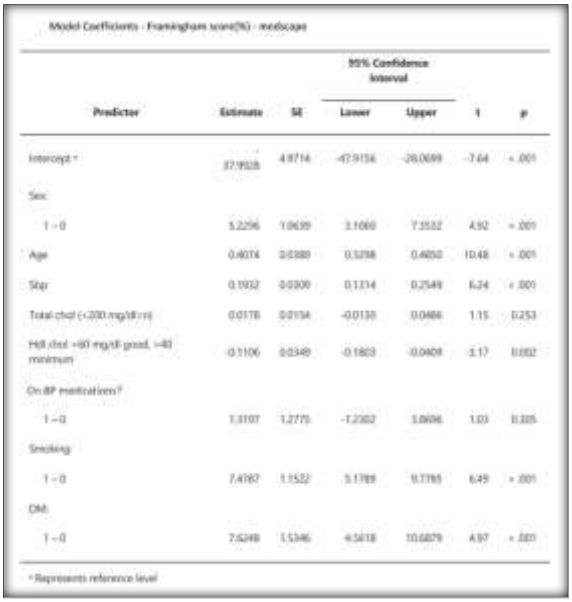


1a- Scatter plot illustrating the relationship between serum homocysteine and vitamin B12 levels

1b- Scatter plot illustrating the relationship between serum vitamin B12 and Framingham Risk Scores (FRS)

1c-Scatter plot illustrating the relationship between serum homocysteine and FRS

Figure 1: Scatter Plotting of the 3 prime parameters- homocysteine, vitamin B12 and Framingham Risk Scores (FRS)



Model Coefficients - Framingham score(%) - medscape

Predictor	Estimate	SE	95% Confidence Interval Lower	Upper	t	p
Intercept *	37.9928	4.9714	-47.9154	-26.0699	-7.64	< .001
Sex						
1 - 0	5.2256	1.0639	3.1060	7.3532	4.92	< .001
Age	0.4074	0.0388	0.3298	0.4850	10.48	< .001
Stop	0.1932	0.0309	0.1314	0.2549	6.24	< .001
Total chol (<200 mg/dl = n)	0.0178	0.0154	-0.0130	0.0486	1.15	0.253
HdI chol. >60 mg/dl good, >40 minimum	-0.1106	0.0349	-0.1803	-0.0409	-3.17	0.002
On BP medications?						
1 - 0	1.3107	1.2775	-1.2382	3.8696	1.03	0.305
Smoking						
1 - 0	7.4787	1.1522	5.1789	9.7785	6.49	< .001
DM:						
1 - 0	7.6248	1.5346	4.5618	10.6879	4.97	< .001

* Represents reference level

Figure 2: Linear regression analysis of the variables

DISCUSSION

Homocysteine (Hcy), a sulfur-containing amino acid, has been recognized as an independent risk factor for cardiovascular disease (CVD). Elevated plasma Hcy levels are associated with endothelial dysfunction, increased arterial stiffness, and atherosclerosis. Numerous studies have consistently demonstrated a correlation between higher Hcy levels and an increased risk of coronary heart disease (CHD), stroke, and other cardiovascular events. Specifically, elevated plasma homocysteine levels have been linked to a heightened risk of carotid artery stenosis, coronary artery calcification, and new- onset heart failure.[4,5,13,14]

A meta-analysis of prospective cohort studies reported that every 5 µmol/L increase in homocysteine levels is associated with a roughly 20% increase in the risk of CHD. Notably, this association remains significant even after adjusting for traditional CVD risk factors, indicating that homocysteine provides additional predictive value beyond conventional risk assessments.[15] However, some studies in Indian populations have found no clear relationship between hyperhomocysteinemia and coronary artery disease, despite a high prevalence of both conditions.[7]

The Framingham Risk Score (FRS) is a well-established tool **for** estimating CVD risk; however, it has limitations, particularly among older adults or individuals at intermediate risk. Incorporating biomarkers such as homocysteine into the FRS has been proposed to enhance its predictive accuracy. Several studies have supported this approach, showing that combining homocysteine levels with the FRS significantly improves CVD risk prediction. For instance, in a study involving elderly patients with type 2 diabetes, the combination of Hcy and FRS yielded a higher predictive value (AUC = 0.852) compared to either measure alone (AUC = 0.741 for

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Hcy and AUC = 0.717 for FRS).[16] Similarly, a Taiwanese study reported that higher homocysteine levels were associated with higher FRS values, and their combination significantly increased the odds ratio for cardiovascular risk.[17]

The correlation between homocysteine levels and FRS has been investigated in multiple studies. A study involving 675 adults reported a positive correlation between serum Hcy levels and FRS ($r = 0.292$, $P < 0.05$).[6] This was echoed by another study in a Taiwanese cohort, which also found that elevated Hcy levels were associated with higher FRS values . Although the correlation is not particularly strong, it underscores that homocysteine contributes unique information beyond traditional cardiovascular risk factors.[17] In some studies, no clear association between homocysteine and the Framingham Risk Score has been established.[7]

Vitamin B12 plays a crucial role in the metabolism of homocysteine. Deficiency in vitamin B12 results in elevated homocysteine levels, thereby indirectly increasing cardiovascular risk. Studies have shown that low levels of vitamin B12 are associated with a higher risk of cardiovascular events. For example, a study on hypertensive patients found that lower vitamin B12 levels corresponded to higher cardiovascular risk as measured by the FRS.[18] Another study identified vitamin B12 deficiency as a significant predictor of large-artery atherosclerosis stroke, further highlighting its relevance in vascular health.[19]

Elevated homocysteine levels have been shown to correlate with higher FRS values, suggesting that vitamin B12 deficiency may contribute to increased cardiovascular risk via homocysteine metabolism.[18] Furthermore, vitamin B12 deficiency has been linked to inflammation and oxidative stress—key mechanisms in CVD development.[13] A study done on mice by Domínguez-López I suggests that vitamin B12 levels are associated with elevated inflammatory markers, which in turn are linked to higher FRS values.[20]

Randomized controlled trials have demonstrated that supplementation with low-dose B vitamins, including vitamin B12, can reduce FRS. For instance, a study involving healthy elderly Chinese participants found that daily B-vitamin supplementation for 12 months significantly reduced FRS, particularly among individuals with folate deficiency. This supports the potential role of B-vitamin supplementation in cardiovascular risk management, especially in at-risk populations.[21]

Interestingly, the association between homocysteine and coronary artery calcification has been shown to be strongest in individuals with intermediate risk (6–20%) based on the Framingham Risk Score. This suggests that homocysteine may be particularly valuable in refining cardiovascular risk assessments in this subgroup.[4]

The current study's findings align with prior research indicating a negative correlation between vitamin B12 and homocysteine levels. However, the absence of statistically significant results in this study may be attributed to a small sample size or unaccounted confounding factors. While the correlation between homocysteine levels and FRS has been established in some studies—such as the one by Kim et al, involving 675 adults that reported a moderate correlation ($r = 0.292$, $P < 0.001$) or the study that showed that individuals in the highest quartile of plasma homocysteine had an odds ratio of 17.45 for high-risk FRS (≥20%) compared to those in the lowest quartile, further supporting a strong association,[6] —the present study did not replicate these findings.

Despite evidence in the literature, the lack of any association between FRS and homocysteine or vitamin B12 levels in this study suggests that other factors may play a more significant role in determining cardiovascular risk within the studied population. These findings imply that while homocysteine and vitamin B12 may offer additional insight, they may not serve as reliable standalone biomarkers for cardiovascular risk in all cohorts.

CONCLUSION

This study examined the relationship between emerging cardiovascular biomarkers—homocysteine and vitamin B12—and the established Framingham Risk Scores (FRS). A weak negative correlation was observed between homocysteine and vitamin B12 levels, with additional weak correlations involving HDL cholesterol and age; however, none of these reached statistical significance. Moreover, neither homocysteine nor vitamin B12 showed a significant association with FRS. These findings suggest that while emerging biomarkers like homocysteine and vitamin B12 do play a role in cardiovascular health, their independent contribution within this study was not strong enough to enhance the predictive accuracy of the FRS. The regression analysis reinforced the significance of established risk factors—age, sex, systolic blood pressure, smoking, diabetes, and HDL cholesterol—in cardiovascular risk prediction. Further studies with larger sample sizes and comprehensive adjustment for confounding variables are needed to determine whether emerging biomarkers offer sufficient incremental value to be considered for inclusion in existing cardiovascular risk models.

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