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Research Article

# Demographic Influences on Folate and Homocysteine Status in Women of Reproductive Age Attending the Maldives National University

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## Abstract

Folate and homocysteine levels affect both reproductive health and well-being in pregnancy. The aim of this study is to evaluate the involvement of demographic factors in the folate and homocysteine status of women of reproductive age. The findings show that young age, single marital status, and higher educational levels are all associated with increased folate deficiency, as was found before.

In addition, women with menstrual irregularities had elevated homocysteine levels, and this link between homocysteine metabolism and reproductive health has not been explored. Several previous studies have emphasized the importance of further study of the impact of homocysteine and vitamin B12 deficiency on recurrent pregnancy loss.

Also, being previously related to cardiovascular and reproductive risks, the MTHFR C677T polymorphism was taken into consideration. A meta-analysis showed that people with the TT genotype are at high risk of coronary heart disease, especially if folate intake is low. The key to metabolic health, this finding puts forth, is also genetic and nutritional crosstalk.

The study points to the need for directed intervention to increase folate intake and control the levels of homocysteine among at-risk populations. Education based on diet, supplementation programs, and genetic screening are some strategies that can facilitate reproductive health outcomes. There is much more groundwork to be laid in understanding biological mechanisms undergirding these associations and the evidence for public health guidelines that follow.

Folate, homocysteine, women's health, demographic factors, menstrual irregularities

**Keywords:** Folate Deficiency; Homocysteine; MTHFR C677T Polymorphism; Nutritional Interventions

## Introduction

Folate and homocysteine play an important role in DNA synthesis in women of reproductive age (WRA) and red blood cell formation, as well as cardiovascular health. WRA has problems regarding health due to its elevated homocysteine levels and inadequate folate levels.

Folate, or vitamin B9, is a necessary nutrient for DNA synthesis, blood cell formation, and DNA division (Shelton., *et al.,* 2020) [6]. That is all the more true while pregnant, as it's important to take proper folate so that you prevent neural tube defects (NTDs) in your developing fetus. Folate is not only essential in expressing genetics, preventing birth defects of the brain and spinal cord, or neural tube defects, in pregnancy, needed for pregnancy, and low in food and blood, but it is also important to optimal health beyond pregnancy and aids in pregnant and non-pregnant people's cognitive function, immune response, and cardiovascular health.

In addition, the study suggested that homocysteine levels are related to abnormal periods. Even though much has not been explored about this topic, the results suggest that homocysteine metabolism plays a role in reproductive health. Similarly, homocysteine deficiency and vitamin B12 deficiency are related to recurrent pregnancy loss (RPL), as mentioned by Frosst., *et al*. (1995) [2], and should be further taken seriously when taking serum homocysteine imbalances during pregnancy recovery.

It is the sticky amino acid intermediate of the methionine metabolism, the homocysteine. The amino acid is controlled by folate, vitamin B12, and vitamin B6. With a risk for cardiovascular disease, stroke, endothelial dysfunction, and thrombosis, homocysteine is a condition. The condition is hyperhomocysteinemia, or high homocysteine. All groups are not equally and widely available to the same quantity of the same folate-rich foods and folate-poor foods, which increases the risk for deficiency and potentially harmful health consequences. Additionally, genetic variants of the MTHFR gene, which cause mutations of the gene and lead to changes in the way the body processes folate, cause an increase in levels of homocysteine, which lowers health risks.

A meta-analysis of Klerk., *et al*. (2002) [8] shows an increased risk of CHD among the TT genotype, especially in folate-deficient participants. Thus, it suggests that identification of the genetic and nutritional interaction on folate and homocysteine metabolism is warranted.

Whenever there are factors related to folate and homocysteine levels in the WRA, it is important to understand because they will contribute to targeted interventions aimed at improving health outcomes. This study aimed to establish an association of demographic factors with the folate and homocysteine levels in a sample of WRA with the view of looking for ways health policy should go about in reducing risk and improving the whole reproductive health.

## Methods

The study was conducted in a cross-sectional study of women aged 18 to 49 years at levels of higher education institutions in the Maldives. Data were collected using a structured questionnaire. Furthermore, the parameters were determined by means of the analysis of the blood samples. In the questionnaire, demographic characteristics, socioeconomic status, dietary habits, and medical history were inquired about. Either way, the responses were collected in person, and trained healthcare workers were interviewed to minimize bias and accuracy of responses. Upon arrival on the given day and at the given place, participants were asked to arrive and obtain blood as per standard phlebotomy procedures at the designated collection centers. Bukowski., *et al*. (2009) [1] processed and analyzed the laboratory measures of serum folate and homocysteine on samples using validated laboratory techniques. To make the assays as precise and reliable as possible, the ELISA and HPLC were used in the assays. In all the laboratory procedures, a quality control measure was instigated in order to ensure data integrity.

Demographic data were described using descriptive statistics. Analyses were carried out by appropriate statistical tests (t-tests, ANOVA, and regression), and associations with folate and homocysteine levels and demographic factors were sought. The Shapiro-Wilk test was used to assess the normality of data distribution. Before analysis, variables with skewed distribution were log transformed. To control for possible confounders, including age, BMI, and dietary intake, multivariate regression models were used. $p < 0.05$ was taken as statistical significance, and all calculations were carried out using SPSS 20 version.

## Results

The result shows that folate deficiency was more prevalent in younger women (18-25 years). Folate deficiency was more common among single women than among married or ever-married women. Surprisingly, women with a higher degree of education in terms of university or postgraduate had more of a folate deficiency. Furthermore, homocysteine levels were found to be related to menstrual irregularity (amenorrhea/oligomenorrhea and metrorrhagia).

In our case, the AUC of 0.770 indicates that the test for homocysteine (Hcy) levels has good discriminatory ability, with a statistically significant result (p-value = 0.000).

Age, marital status, educational level, physical activity, fruit and vegetable intake, and tobacco use correlated significantly with serum folate irregular menstrual patterns are associated with higher level of homocysteine.

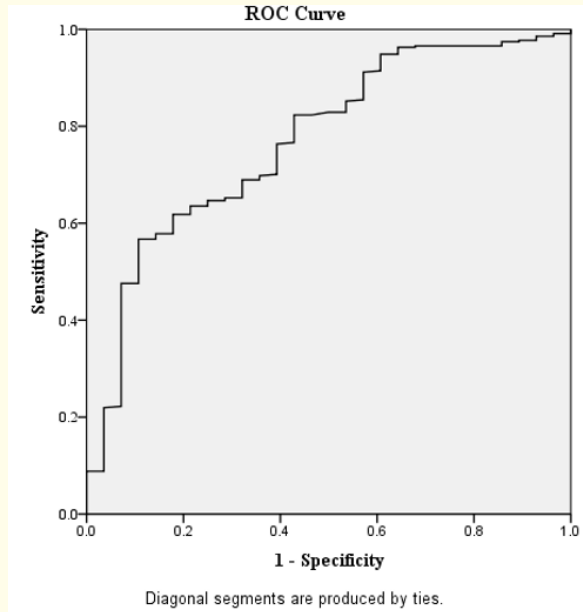


**Figure a**

| Characteristics | | Serum Homocysteine ≥11.63 nmol/L | | Serum Folate <4ng/dL | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p value | OR (95% CI) | p value |
| Menstrual Regularity (n=380) | | | | | |
| | Regular (ref.) | | | | |
| | Irregular/Abnormal | 1.76 (1.16-2.69) | 0.009 | 1.94 (0.80-4.68) | 0.141 |
| Menstrual abnormalities (n=374) | | | | | |
| | Regular (ref.) | | | | |
| | Amenorrhea/Oligomenorrhea | 2.09 (1.02-4.29) | 0.044 | ---- | --- |
| | Menorrhagia | 0.36 (0.10-1.37) | 0.136 | 1.09 (0.13-8.86) | 0.936 |
| | Metrorrhagia | 2.10 (1.26-3.50) | 0.004 | 1.35 (0.53-3.47) | 0.529 |

**Figure b:** Menstrual Regularity: Irregular menstrual cycles are significantly associated with elevated Hcy levels (OR = 1.76, p = 0.009).

Menstrual Abnormalities: Both amenorrhea/oligomenorrhea (OR = 2.09, p = 0.044) and metrorrhagia (OR = 2.10, p = 0.004) are significantly associated with elevated Hcy levels.

There is no significant association between having CVD, HTN and DPL; and elevated Hcy levels (p = 0.142).

| Cardiovascular Disease (n=380) | Serum Homocysteine (≥11.63 nmol/L) | p-value | Serum Folate (<4ng/dL) | p-value |
|---|---|---|---|---|
| Cardiovascular Disease | 0.70 (0.43-1.13) | 0.142 | 0.50 (0.22-1.13) | 0.096 |
| Coronary Heart Disease | 0.58 (0.10-3.51) | 0.554 | 0.31 (0.03-2.89) | 0.305 |
| Diabetes Mellitus | 1.43 (0.49-4.45) | 0.539 | 0.16 (0.05-0.55) | 0.004 |
| Hypertension | 0.88 (0.18-4.41) | 0.876 | 0.39 (0.04-3.48) | 0.401 |
| Dyslipidemia | 0.65 (0.31-1.38) | 0.265 | 0.48 (0.16-1.49) | 0.204 |

**Figure c**

This, however, is not reflected in significant associations between demographic factors Influences on Folate and Homocysteine and either vitamin B12 levels or MTHFR genotype distribution.

| Area | Std. Error[a] | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| .770 | .045 | .000 | .681 | .859 |

**Table a:** Area Under the Curve

Test Result Variable(s): Hcy

The test result variable(s): Hcy has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

| Characteristics | Total | Serum Folate | | | | p value |
|---|---|---|---|---|---|---|
| | | ≥10 nmol/L | | <10 nmol/L | | |
| | | n | % | n | % | |
| Age (years) | | | | | | 0.002 |
| 18 to 25 | 239 | 6 | 2.51 | 233 | 97.49 | |
| 26 to 34 | 92 | 7 | 7.61 | 85 | 92.39 | |
| ≥ 35 | 48 | 7 | 14.58 | 41 | 85.42 | |
| Marital status | | | | | | 0.002 |
| Married/Ever married | 142 | 14 | 9.86 | 128 | 90.14 | |
| Single | 237 | 6 | 2.53 | 231 | 97.47 | |
| Geographical Region | | | | | | 0.397* |
| HA, HDh and Sh | 57 | 3 | 5.26 | 54 | 94.74 | |
| N, R, B and Lh | 63 | 1 | 1.59 | 62 | 98.41 | |
| K, AA, ADh and V | 93 | 9 | 9.68 | 84 | 90.32 | |
| M, F and Dh | 31 | 1 | 3.23 | 30 | 96.77 | |
| Th and L | 27 | 1 | 3.70 | 26 | 96.30 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| GA, GDh, Gn and S | 107 | 5 | 4.67 | 102 | 95.33 | |
| Educational level | | | | | | 0.015 |
| Primary/Secondary completed | 79 | 1 | 1.27 | 78 | 98.73 | |
| High School completed | 131 | 4 | 3.05 | 127 | 96.95 | |
| University/post-graduate | 167 | 15 | 8.98 | 152 | 91.02 | |
| Profession | | | | | | 0.017 |
| Student | 195 | 5 | 2.56 | 190 | 97.44 | |
| Administrative/Managerial | 67 | 6 | 8.96 | 61 | 91.04 | |
| Education | 32 | 5 | 15.63 | 27 | 84.38 | |
| Health | 45 | 2 | 4.44 | 43 | 95.56 | |
| Others | 8 | 1 | 12.50 | 7 | 87.50 | |
| Monthly income (MVR) | | | | | | 0.089 |
| ≤ 30000 | 211 | 8 | 3.79 | 203 | 96.21 | |
| > 30000 | 137 | 11 | 8.03 | 126 | 91.97 | |
| Physical Activity | | | | | | 0.961 |
| <150 minutes /week | <150 | 94 | 8 | 8.51 | 86 | |
| ≥ 150 minutes /week | >150 | 156 | 13 | 8.33 | 143 | |
| Fruit and vegetable intake | | | | | | <0.001 |
| Daily intake | 37 | 10 | 27.03 | 27 | 72.97 | |
| 3 to 6 days in a week | 248 | 11 | 4.44 | 237 | 95.56 | |
| 2 days or less or nil | 94 | 7 | 7.45 | 87 | 92.55 | |
| Tobacco use | | | | | | 0.098 |
| Never | 362 | 25 | 6.91 | 337 | 93.09 | |
| Ever/Current/ Occasional | 17 | 3 | 17.65 | 14 | 82.35 | |

**Table b**

| | | | | |
|---|---|---|---|---|
| 11.4850 | .581 | .179 | 0.821 | 0.403 |
| 11.5050 | .578 | .179 | 0.821 | 0.400 |
| 11.5200 | .578 | .143 | 0.857 | 0.435 |
| 11.5400 | .575 | .143 | 0.857 | 0.433 |
| 11.5600 | .573 | .143 | 0.857 | 0.430 |
| 11.5750 | .570 | .143 | 0.857 | 0.427 |
| 11.5850 | .567 | .143 | 0.857 | 0.424 |
| 11.6300 | .567 | .107 | 0.893 | 0.460 |
| 11.6750 | .564 | .107 | 0.893 | 0.457 |
| 11.6850 | .561 | .107 | 0.893 | 0.454 |
| 11.7000 | .558 | .107 | 0.893 | 0.451 |
| 11.7150 | .553 | .107 | 0.893 | 0.446 |
| 11.7350 | .550 | .107 | 0.893 | 0.443 |
| 11.7850 | .547 | .107 | 0.893 | 0.440 |
| 11.8250 | .538 | .107 | 0.893 | 0.431 |

**Table c**

## Discussion

The study found that demographic factors are associated with folate and homocysteine status in women of reproductive age (WRA). More specifically, the research found that younger age (18-25 years), having no marriage status, and higher educational level were related to increasing prevalence of folate deficiency. This is consistent with Lee and Jung (2022) [3], which found more folate deficiency risk for younger women and higher-educated individuals.

The study also found that homocysteine levels are correlated with menstrual irregularities. This association is not presently looked into much more, but our results suggest a possible part of homocysteine metabolism in reproductive fitness. Roberts and Roberts (2004) [5] explored the effects of homocysteine and vitamin B12 deficiency in recurrent pregnancy loss (RPL) and associated homocysteine and vitamin B12 deficiency of RPL. It is consistent with our findings and emphasizes the intricacy between homocysteine, vitamin B12, and reproductive outcomes.

Furthermore, the MTHFR C677T polymorphism is related to various cardiovascular and reproductive health issues. Klerk., *et al*. (2002) [8] presented a meta-analysis of the MTHFR polymorphism on CHD, which showed a 16% increased risk of CHD among persons with the TT genotype, especially in combination with low levels of folate (Raghavan., *et al.* 2016) [4]. With this in mind, we agree that folate deficiency in particular demographic groups may be responsible for far more than just folate deficiency-a contributing factor to CHD, for example.

Previous studies showing an association between high homocysteine levels and menstrual irregularities couldn't confirm the exact mechanism, but the vast majority of such studies had been unable to do so. Further investigation of the actual mechanisms that are of clinical importance for the management of menstrual disorders is needed for these findings. Supplemental, diet-related, or public health interventions in dietary folate or in imbalances of homocysteine may protect against some reproductive health problems that afflict WRA.

Further in terms of overall findings, our work adds to the burgeoning line of investigations between demographic factors and folate, homocysteine, and health outcomes of WRA (Raghavan., *et al*. 2016) [4]. Such associations can help in developing targeted strategies to have better nutritional status and reproductive health outcomes in the vulnerable populations. Future work will characterize the biological relevance of the folate, homocysteine, and WRA relationship and determine ways that may improve folate and homocysteine levels in WRA.

## Limitations

The design of the study used for this study was a cross-sectional design, hence making it impossible to establish causality. However, generalizability of the findings to the whole population is limited as this is a cross-sectional study, and only the women of reproductive age linked to the high education institutions were taken up in the study sample. The use of self-reported data on various aspects relating to dietary intake and health status often generates recall errors, influencing the results. Moreover, the study did not assess genetic variations, including MTHFR polymorphism, that influence folate metabolism and homocysteine levels. Research into the future should be longitudinal in design, biochemical/objective in assessment, and genetic screening of the findings.

## Conclusion and Recommendations

There is a large dependence of the folic acid and homocysteine status in women of reproductive age on demographic factors. Targeted interventions and additional research are needed for younger, single, well-educated women with menstrual irregularities, due mainly to folate deficiency and the elevation of homocysteine levels.

### Targeted Interventions

Public health initiatives, such as increased folate intake, especially among younger women and women of low education, should be advanced to impact public health outcomes, including improved folate intake (Stevenson., *et al*. 2000) [7]. It is useful in that it prevents deficiencies from folate status, allowing educational programs to focus on the importance of having food rich in folates. The use of folic acid supplements for high-risk groups like younger women or less well-educated people can help marginally reduce these risks.

### Screening and MONITORING

Blood should be collected for the measurement of serum folate and homocysteine levels three or four times per year in people with menstrual irregularity. MTHFR polymorphism genetic screening is also useful for identifying people at a greater risk of having a folate deficiency and its complications and getting treated at the right time.

### Dietary Guidance

To augment folate status, it is necessary to encourage the consumption of foods that contain folate, i.e., fruits and vegetables. The need to increase promotion of folate status for smoking cessation is made on the basis that smoking either has a negative impact on serum folate levels or can result in increased homeostasis levels. This additional support includes the raising of awareness of alcohol consumption on folate metabolism.

## Further research

In a longitudinal fashion, the serum folate and homocysteine levels should be studied as to their causation relationships with cardiovascular diseases and menstrual disorders. It is helpful to understand how homocysteine is addressed when intervention, to reduce it, is used to address concerns regarding menstrual health.

## Policy development

Advocacy for policies that will improve access to nutritional supplements as well as resources for groups at risk of folate deficiency should be undertaken. Learning about folate should be included in reproductive health programs exposed in order to make women of reproductive age aware of it and earlier intervention for better reproductive health outcomes.

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