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Suppression of Homocysteine Levels by Vitamin B12 and Folates: Age and Gender Dependency in the Jackson Heart Study

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Abstract

Objectives—To examine factors potentially contributing to premature cardiovascular disease mortality in African Americans (40% versus 20% all other populations), plasma homocysteine, serum vitamin B12 and folate levels were examined for African American participants in the Jackson Heart Study.

Methods—Of 5,192 African American Jackson Heart Study participants (21–94 years), 5,064 (mean age, 55±13 years; 63% female) had homocysteine levels measured via fasting blood samples, with further assessments of participants' vitamin B12 (n=1,790) and folate (n=1,788) levels. We used regression analyses to examine age, gender, vitamin B12, and folate with homocysteine levels.

Results—Homocysteine levels, a purported surrogate risk factor for cardiovascular disease, increased with age, were inversely proportional to folate and vitamin B12 levels ($p<0.001$), and higher for men of all ages.

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Conclusions—Our results show that, as with other populations, age, gender, vitamin B12, and folate may predict homocysteine levels for African Americans. Diet may be an important predictive factor as well, given the relationships we observed between plasma homocysteine and serum B vitamin levels.

Keywords

Jackson Heart Study; African Americans; Homocysteine; Folic acid; Vitamin B12

Introduction

In the United States, 45.9% of African American men and women have been diagnosed with cardiovascular disease (CVD).¹ In Mississippi, the age-adjusted CVD mortality rate for all race-sex groups was the highest nationwide, at approximately 25% above the U.S. average.¹ However, African Americans, who comprise 37.2% of the state's population², were disproportionately affected, with the incidence of premature mortality (younger than 65 years) due to CVD at 20% for all populations, but at 40% for African Americans.³ For men in Mississippi, the age-adjusted CVD mortality rate was 47% higher for African Americans than for whites, while for women it was 75% higher for African Americans than for whites.⁴

Elevated homocysteine (tHcy) levels with increasing age, reportedly associated with increased total cholesterol and decreased high density lipoprotein (HDL),⁵ have long been discussed as an independent risk factor for CVD.^{6,7,8} A number of studies have explored the use of folic acid and vitamin B12 to decrease these levels,^{9,10} but this relationship may not be as straightforward as once hoped. The recent 'Vitamins to Prevent Stroke' (VITATOPS) trial¹¹ examined the long-term daily effects of folic acid, vitamin B6, and vitamin B12 in reducing tHcy through conversion and excretion;¹² the regimen proved safe, but not significantly more effective than placebo in reducing major vascular events.¹¹ Moreover, a prior report by other investigators suggests that harmful effects may occur with B vitamin supplements after myocardial infarction (MI).¹³

The role of age, gender and ethnicity in risk factor assessments and standard of care determinations for specific patients¹⁴ has been well understood, at least since 1999 data from the U.S. Atherosclerosis Risk in Communities (ARIC) Study demonstrated that African Americans with acute myocardial infarction had poorer survival after hospitalization than whites, and that African American men had greater short-term case fatality rates after coronary events compared to white men.¹⁵ A more recent ARIC report, on 3-year fatality rates after hospitalization for myocardial infarction, has also shown that socioeconomic status exerts a further significant impact on the effects of ethnicity.¹⁶

A number of studies demonstrate an association between tHcy, age, gender, race, and B vitamins.^{5,17,18} In 2003, the Framingham (Massachusetts) Offspring Study, which evaluated 5,135 local participants, reported gender effects on tHcy levels in its cohort, with a 15% elevation in men ($p < 0.001$) as compared to women, possibly owing to significantly higher plasma folate levels in women ($p < 0.001$).^{17,19} Other international population-based studies have also reported differences in associations of tHcy to CVD according to gender.^{20,21,22}

To further our understanding of the potential risk factors in cardiovascular disease for African Americans, we assessed and examined relationships between plasma tHcy, serum folate and vitamin B12 in a study sample of 5,064 African American participants in the Jackson (Mississippi) Heart Study. Associations of tHcy levels with age, gender, folate, and vitamin B12 were examined to help identify factors that might ultimately improve standards of care and reduce CVD risks for African American men and women as they age.

Methods

The protocol for the Jackson Heart Study, a longitudinal, population-based investigation initiated in 2000 for prospective research into the epidemiology and determinants of CVD in African Americans from the Jackson, Mississippi metropolitan area, was approved by the Institutional Review Board of the University of Mississippi Medical Center (UMMC). All participants (5,301), of both genders and ranging from 21–94 years of age, provided written, informed consent. The design and sampling of the Jackson Heart Study, which included participants from the Jackson cohort of the U.S. ARIC study, a random component, a family component, and a structured volunteer sample, have been previously described.²³ Study baseline data collection began in late 2000 and was completed in early 2004.

Our study of relationships between tHcy, folate, and vitamin B12, was approved by the UMMC Institutional Review Board for 5,192 participants from the Jackson Heart Study, owing to future research exclusions in 109 consents. A further 121 participants were excluded for ‘data missing at random’, and 7 for baseline homocysteine levels that were >50 $\mu\text{mol/L}$. After these exclusions, 5,064 subjects were included in our primary analysis, which evaluated relationships between plasma tHcy levels, gender, and age. A total of 1,787 participants were included in our secondary analysis, which evaluated relationships between the primary analysis findings and these serum levels. Participants excluded from the secondary analysis had missing folate ($n=3,276$) and vitamin B12 ($n=3,274$) values.

The Jackson Heart Study baseline examination included a home interview, a clinic visit, laboratory tests, and a physical examination. Fasting blood samples were collected and assayed for lipids, triglycerides and C-reactive protein (CRP). Blood pressure was assessed with standard laboratory protocol for random zero sphygmomanometry. Three blood pressure readings were taken at 5 minutes separation, with the average of the last two recorded. All tHcy, vitamin B12, and folate assays were performed at the University of Minnesota, in conjunction with the University of Minnesota Medical Center, Fairview. Plasma tHcy ($N=5,064$) was assayed by the fluorescence polarization immunoassay method, supplied by Abbott Diagnostics (Abbott Park, Illinois). Serum vitamin B12 ($N=1,790$) and folate ($N=1,788$) were measured by the homogenous enzyme immunoassay system using Hitachi 911 equipment (Roche Diagnostics, Indianapolis, Indiana).

For our study, all data analyses were performed using STATA computer software (STATA Corp, College Station, TX), with $p<0.05$ indicating statistical significance. Descriptive and summary statistics were used to characterize selected baseline characteristics, tHcy, folate, and vitamin B12, with findings stratified by age and gender ($\pm$ SD).

Linear regression was used to perform our primary analyses. For 5,064 participants, associations between tHcy levels, gender and age were examined, with a particular interest in exploring the effects of age on these levels by gender. Toward this end, plasma tHcy levels at age 50 were specifically analyzed in men and women (presumed menopausal).

For our secondary analyses, conducted for the 1,787 participants with vitamin B12 and folate data, simple linear regression was performed to determine whether or not age, vitamin B12, and folate were predictors of tHcy levels. Subgroup multivariable linear regression was also used to examine further relationships between folate, age, and vitamin B12 to tHcy levels.

Results

Baseline characteristics for the tHcy study cohort are displayed in Table 1. Mean age for our cohort was 55 ± 13 years, with 37% of its participants men, and 63% women.

Table 2 shows the ranges of tHcy, folate, and vitamin B12 for those participants for whom serum values were available. Levels of tHcy were higher in men, as compared to women, whereas levels of folate and vitamin B12 were higher in women, except among participants aged 21–34 years.

Multiple linear regression analysis showed that tHcy levels were significantly related to advancing age, as well as to low folate and vitamin B12 concentrations. Increased folate and vitamin B12 were also found to be associated with decreased tHcy levels, as shown in Figure 1.

In addition to the positive association observed between tHcy and age, gender exerted an important influence among all age groups, as shown in Figure 2, with higher tHcy levels consistently observed for men. At age 50, men had over a $1.5 \pm 10 \mu\text{mol/L}$ higher average tHcy level than women ($9.9 \pm .55 \mu\text{mol/L}$ vs $8.4 \pm .73 \mu\text{mol/L}$, $p < 0.001$).

A summary of age and vitamin measures are presented in Table 3. Simple linear regression showed that, for each 10 year increase in age, tHcy increased by $0.8 \mu\text{mol/L}$ ($p < 0.001$). For every 10 unit increase in folate, tHcy decreased by $2.2 \mu\text{mol/L}$ ($p < .0001$). Finally, for every 100 unit increase in vitamin B12, tHcy decreased by $0.2 \mu\text{mol/L}$ ($p < 0.001$).

Multivariate regression demonstrated that tHcy, age, vitamin B12, and folate were significantly correlated ($p < 0.001$) (Table 4). For each 10 year increase in age, tHcy levels increased by $1 \mu\text{mol/L}$. Moreover, for every 100 unit increase in vitamin B12, tHcy levels decreased by $0.2 \mu\text{mol/L}$. Both folate and vitamin B12 were correlated to tHcy concentrations, although vitamin B12 demonstrated a lesser effect. The decrease in tHcy ($0.2 \mu\text{mol/L}$) for each increase in vitamin B12 (100 units) was deemed clinically insignificant, so vitamin B12 was removed from multivariable regression analysis. After this exclusion, age and folate remained statistically significantly ($p < 0.001$) (Table 5).

Discussion

Although the literature indicates that tHcy levels may be adversely altered by age¹ and race²², our analysis of the Jackson Heart Study cohort showed that mean tHcy concentrations in a large African American population cohort were in the normal literature range ($< 10 \mu\text{mol/L}$)²⁴, with increases linked to male gender and advancing age. However, geriatricians and others supervising the care of older men and post-menopausal women from the African American community may wish to monitor tHcy levels in tandem with lipid profiles, as elevations in tHcy may accompany changes in hormones, believed to be strong contributors to cardiovascular health and disease, and so signal increased risk.

In addition to our finding that serum vitamin level, age, and gender were significant determinants of plasma tHcy levels, we observed a relationship between folate, vitamin B12, and tHcy. Where these serum levels were elevated, tHcy levels decreased, findings consistent with reports from the Framingham study (described above), the Netherlands, and Ontario, Canada.^{8,9,17}

The relationship between elevated tHcy levels, ethnicity, age, gender, and disease is complex, even with a well-documented gender difference reported across the literature. Higher levels of tHcy have been correlated with coronary heart disease (CHD),²⁵ but the mechanism by which tHcy poses an independent risk factor has not been fully explained. A New Mexico study found that elderly Hispanics had a higher serum tHcy level than did elderly non-Hispanic Whites,²⁶ with the direct link between tHcy levels and prevalence of CHD most significant among elderly (65 years) Hispanic women. Another study, conducted in an African American cohort, showed that premenopausal women (aged 30–40

years) with hypertension had a statistically significant, higher mean tHcy than the same group with normal blood pressure; no correlation was seen for men of the same age. These researchers also observed a significant inverse relationship between tHcy, folate, and vitamin B12 in women.²¹ Iranian investigators found that men had significantly higher tHcy levels than women ($19.02 \pm 1.46 \mu\text{mol/L}$ vs. $14.05 \pm 1.45 \mu\text{mol/L}$, $p = 0.004$), with hyperhomocysteinemia identified as an independent CVD risk factor among young patients (< 45 years of age), and men with vitamin B12 deficiency determined to be at particular risk.²⁰

For non-Hispanic black men and women, the National Health and Nutrition Examination Survey (NHANES) III observed a higher, age-adjusted geometric mean for total tHcy levels (9.8 and $8.2 \mu\text{mol/L}$, respectively) than that seen for non-Hispanic white men and women (9.6 and $7.9 \mu\text{mol/L}$, respectively).²² Across all ethnicities, this study further reported lower age-adjusted geometric mean total tHcy levels for women than for men ($p < 0.01$).²² These findings were more recently supported by Russo et al. and Cappuccio et al., who also observed higher tHcy concentrations for men than for women^{19,27}. Of note, the most recent NHANES IV reported that men had higher reductions in the prevalence of elevated tHcy levels than did women, at 6.8% and 3.1% , respectively²⁸.

In participants from the Jackson Heart Study, African American men had higher tHcy levels than did African American women at all ages, irrespective of menopause. Neither the exact mechanism of protection among women, nor the mechanism for the increase in tHcy seen post-menopausally is clear. However, hormonal effects, which lessen with advancing age, may play a role in this elevation,²⁹ as may hormonal therapies and other treatment regimes not captured by our data. Moreover, the impact of diet and nutritional supplements is important, particularly given the United States Food and Drug Administration's 1996 mandate to fortify each 100 g of enriched flour, rice, pasta, corn meal and other grain products (such as cereal) with $140 \mu\text{g}$ of folic acid.³⁰ A comparison of Jackson Heart Study Food Frequency Questionnaires with participant serum levels could help provide important information on diet and dietary supplements that may differ by gender.

Genetic pathways may indeed play a role in the relationship between elevated tHcy and CVD, supporting the need for further studies among families and within ethnic groups. For example, a significant association between the genetic polymorphism MTR 2756A>G and CVD was reported by researchers in Tunisia.³¹ As remethylation involves 5-methyltetrahydrofolate, which results from the conversion of dietary folate to 5,10-methyltetrahydrofolate reductase (MTHFR),³² polymorphisms in this enzyme can increase the risk for CVD.

In the African American population we studied, the inverse relationship seen between plasma tHcy and serum folate and vitamin B12 provides considerable evidence that this cohort's remethylation pathway is unaltered. Protective genetic factors may be involved, as investigators have proposed that MTHFR TT genotypes, which reduce MTHFR activity and increase tHcy levels, are lowest in the African American population and highest in Hispanic Americans.^{33,34}

Conclusions

Our study results support those of previous researchers who have suggested that an association exists between the risk of cardiovascular disease and high plasma tHcy concentrations, and who have proposed the utility of clinically assessing plasma tHcy in determining a patient's risk of underlying vascular disease.

Results from our investigation further showed that age, gender, vitamin B12, and folate are predictors of tHcy levels in a large African American cohort. Plasma tHcy levels increased with age and were found to be gender dependent. The inverse relationship of serum folate and vitamin B12 with tHcy demonstrates that dietary factors are significant determinants of plasma tHcy levels in African Americans. Our findings suggest the need for a comprehensive surveillance study to assess the relationship between tHcy and cardiovascular disease morbidity and mortality.

Study Limitations

This study, a well-characterized cross-sectional study of a large African American cohort living in the same geographical area, utilized standardized data collection and laboratory methods to minimize systematic bias. As our study population was limited to African Americans, our findings may not apply to other ethnic groups. Also, covariates, such as education, socioeconomic status, and co-morbidities, were not assessed. Moreover, in our study, information on participants' vitamin, as well as complementary and alternative medicine, usage was not analyzed. In particular, vitamin B6 was not included in the baseline examination for the Jackson Heart Study, and so could not be analyzed here; however, it too may contribute to elevated tHcy levels.

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Figure 1. Jackson Heart Study (JHS) participant associations between homocysteine and vitamin B12 (n=1,790), and between homocysteine and folate (n=1,788).

Figure 2.

Associations between homocysteine and age, as well as between homocysteine, age and gender, for Jackson Heart Study participants (n=5,064).

Table 1

Baseline characteristics of Jackson Heart Study participants (n = 5064)

Clinical Variables	Values ^a
Women, n (%)	3,186 (63)
Men, n (%)	1,878 (37)
Age, y	55±13
tHcy $\mu\text{mol/L}$ ^b	9.32±3.4
Folate ng/mL	13.5±3.6
Vitamin B12 pg/mL	639.0±287.8
Body mass index, kg/m ²	31.8
HDL mg/dL	52.0±15.0
LDL mg/dL	126.0±37.0
Triglycerides mg/dL	108.0±8.0
CRP mg/dL	0.51±0.9
Systolic Blood Pressure, mmHg	127±18.0
Diastolic Blood Pressure, mmHg	79.0±11.0

^aData expressed as mean $\pm$ SD^bExclusion criteria for reference sample, which consisted of participants with tHcy concentrations $> 50 \mu\text{mol/L}$

The overall mean age was 55±13 years (63% women, 37% men). The mean age for men was 54 $\pm$ 13 (n=1,878) and the mean age for women was 55 $\pm$ 13 (n=3,186). The mean tHcy for the cohort was in the normal value range (9.32 $\pm$ 3.4 $\mu\text{mol/L}$). All of the lipid profile variable means were in the normal value range for participants.

Table 2

Characteristics of Jackson Heart Study (age and gender)

Age (y)	Homocysteine $\mu\text{mol/L}^a$		Folate ng/mL ^a		Vitamin B12 pg/mL ^a	
	Males	Females	Males	Females	Males	Females
21–34	8.8±2.3	7.3±3.2	13.3±3.2	12.5±3.5	571.4±124.9	513.6±26.9
35–44	9.1±2.4	7.5±2.2	11.7±3.5	12.1±2.2	554.1±178.6	650.2±298.2
45–54	9.8±3.4	8.23±2.5	12.8±3.5	12.5±3.6	608.1±267.4	639.6±270.2
55–64	10.4±3.6	9.1±3.1	13±3.7	14.2±3.2	592.6±259.4	691.5±310.1
65–74	11.5±4.1	10.0±3.5	13.5±3.5	14.6±3.4	568.1±267.2	697.5±308.2
75–84	12.6±4.6	11.3±3.7	14±3.9	14.7±3.2	522.8±302.7	627.6±258.6
85	16.1±1.4	13.5±4.7	N/A	17.5±1.2	N/A	765.5±503.4
Overall	10.2±3.6	8.7±3.2	12.9±3.6	13.8±3.5	579.4±257.6	672.4±297.8

^aRepresents values at baseline mean $\pm$ SD

Plasma tHcy levels were higher in men compared to women, and tHcy increased with each age group, as expected. In contrast, serum levels of folate and vitamin B12 were higher in women compared to men except in the 21–34 year old age group.

Table 3

Simple linear regression for homocysteine, age, folate and vitamin B12 status for participants in the JHS

Variable	Slope	Confidence Intervals	p-value
Age	0.08	0.07, 0.09	<0.001
Vitamin B12 pg/mL	-0.002	-0.003, -0.002	<0.001
Folate ng/mL	-0.22	-0.26, -0.17	<0.001

JHS=Jackson Heart Study

For every 10 unit increase in age, tHcy increased by 0.8 $\mu\text{mol/L}$ ($p<0.001$); for every 10 unit increase in folate, tHcy decreased 2.2 $\mu\text{mol/L}$ ($p<0.001$); and for every 100 unit increase in vitamin B12, tHcy decreased by 0.2 $\mu\text{mol/L}$ ($p<0.001$).

Table 4

Multivariable regression for homocysteine, age, vitamin b12, and folate for participants in the JHS.

Variable	Slope	Confidence Intervals	p-value
Age	0.106	0.092, 0.121	<0.001
Vitamin B12 pg/mL	-0.002	-0.002, -0.001	<0.001
Folate ng/mL	-0.257	-0.305, -0.209	<0.001

JHS=Jackson Heart Study

Both folate and vitamin B12 were correlated to tHcy concentrations; however, vitamin B12 demonstrated less of an effect.

Table 5

Multivariable regression for homocysteine, age and folate for participants in the JHS.

Variable	Slope	Confidence Intervals	p-value
Age	0.108	0.939, 0.123	<0.001
Folate ng/mL	-0.298	-0.344, -0.252	<0.001

JHS=Jackson Heart Study

After excluding vitamin B12, age and folate are still significant ($p<0.001$).