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ORIGINAL ARTICLE

Effect of regular exercise on homocysteine concentrations: the HERITAGE Family Study

Tomohiro Okura · Tuomo Rankinen · Jacques Gagnon · Suzanne Lussier-Cacan · Jean Davignon · Arthur S. Leon · D. C. Rao · James S. Skinner · Jack H. Wilmore · Claude Bouchard

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Abstract We investigated whether regular aerobic exercise could affect plasma total homocysteine (tHcy), and whether there were sex-related or racial differences in tHcy changes. Data were available for 816 black and white men and women, aged 17–65 years, 711 of whom completed a 20 week aerobic exercise training program. The tHcy concentration was measured in frozen plasma samples by an HPLC method. In Blacks, tHcy did not change with exercise training [men −0.5 (SD 3.7) μmol/l, women 0.0 (2.2) μmol/l) but increased significantly in Whites (men +0.3 (1.7) μmol/l, women +0.2 (1.6) μmol/l). No sex-related differences were found in either racial group. Changes in tHcy correlated negatively with baseline homocysteine ($r = -0.40$, $P < 0.0001$). Homocysteine levels of the "High" (hyperhomocysteinemia) (≥15 μmol/l) group ($n = 30$) decreased significantly with regular aerobic exercise from 23.1 (12.1) to 19.6 (7.6) μmol/l. Homocysteine levels of the "Normal" group increased slightly from 8.2 ± 2.2 to 8.5 ± 2.4 μmol/l. Men exhibit racial differences for tHcy responses to exercise training. Regular aerobic exercise has favorable effects on individuals with hyperhomocysteinemia, but tHcy slightly increased in individuals within the normal range.

Keywords Aerobic exercise training · Sex · Homocysteine · Hyperhomocysteinemia · Racial differences

T. Okura · T. Rankinen · C. Bouchard (✉)
Human Genomics Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, USA
e-mail: BouchaC@pbrc.edu

J. Gagnon
Marine Biotechnology Research Centre, Remouski, Quebec, Canada

S. Lussier-Cacan · J. Davignon
Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montreal, Montreal, Quebec, Canada

A. S. Leon
Division of Kinesiology, University of Minnesota, Minneapolis, MN, USA

D. C. Rao
Division of Biostatistics and Departments of Genetics and Psychiatry, Washington University Medical School, St Louis, MO, USA

J. S. Skinner
Department of Kinesiology, Indiana University, Bloomington, IN, USA

J. H. Wilmore
Department of Kinesiology and Health Education, University of Texas at Austin, Austin, TX, USA

Introduction

Elevated plasma total homocysteine concentrations (tHcy) are thought to contribute to atherosclerosis and thrombosis in several ways: (a) endothelial cell injury and endothelial dysfunction, (b) increased vascular smooth muscle cell growth, (c) increased platelet adhesiveness, (d) enhanced low density lipoprotein oxidation and deposition in the arterial wall, and (e) direct activation of the coagulation cascade (Fonseca et al. 1999). Epidemiological studies have shown that elevated tHcy are independently associated with an

increased risk of coronary artery disease (Langman et al. 2000; Ridker et al. 1999). Further, several observational studies have found that lowering tHcy was associated with reduced incidence of heart attack and strokes (Homocysteine Studies Collaboration 2002; Boushey et al. 1995; Schnyder et al. 2001).

Little information is available on the effect of exercise on tHcy. Although a few studies on endurance trained men (Konig et al. 2003) and untrained young women (De Cree et al. 1999) have shown that a single bout of intensive exercise acutely increased tHcy, long-term (6 months) regular exercise may be associated with a reduction in tHcy in young overweight and obese women (Randeva et al. 2002). These studies were, however, too small to provide conclusive evidence for an effect of regular exercise on tHcy.

An epidemiological study (Ganji and Kafai 2003) showed that both sex and race were important predictors of tHcy. The difference in tHcy between men and women was explained by alcohol consumption and blood concentrations of folate, vitamin B_{12} (cyanocobalamin), creatinine and cotinine. On the other hand, racial differences are thought to be partly accounted for variation in allele frequency at the methylenetetrahydrofolate reductase gene (Cappuccio et al. 2002). To our knowledge, no data have been reported on race or sex differences for the changes in tHcy in response to exercise training. Therefore, the purpose of this study was to investigate the effects of relatively long-term regular exercise on tHcy in a large sample of black and white men and women.

Methods

Subjects

The HERITAGE Family Study was designed to define the role of the genotype in cardiovascular, metabolic and hormonal responses to aerobic exercise training. The aim, design and measurement protocol of the HERITAGE Family Study has been previously described in details elsewhere (Bouchard et al. 1995).

The present study is based on baseline data from 816 sedentary subjects, who were recruited and studied at four clinical centers. They came from families that included parents (aged ≤65 years) and adult offspring (aged ≥17 years). They were required to be sedentary at baseline, with a body mass index (BMI) <40 kg/m^2 (a few cases with BMI ≥40 kg/m^2 were included with sufficient clinical justification), resting systolic blood pressure <160 mm Hg, resting diastolic blood pressure <100 mm Hg, plasma total cholesterol <350 mg/dl, and fasting plasma triglycerides <500 mg/dl. Subjects who had renal, hepatic or cardiac disease, were diabetic, or had hypothyroidism, or were being treated with lipid-lowering, hypertensive or hypoglycemic drugs were excluded. The study relies also on data from the response to a 20 week aerobic exercise training program in 730 subjects (90 black men, 159 black women including 18 post-menopausal and 46 who were taking hormones, 236 white men, and 245 white women including 45 post-menopausal and 105 who were taking hormones). The study protocol was approved by the Institutional Review Board at each clinical center. The aim and design of the study were explained to all subjects before they gave written informed consent.

Measures

Body weight, height, waist and hip circumferences were measured according to standardized procedures (Wilmore et al. 1997), and BMI was calculated as body weight (kg) divided by height (m^2). Body composition (fat mass and fat free mass) was estimated using the hydrostatic weighing technique. Details of the protocol of the hydrostatic weighing technique and body composition estimation are provided elsewhere (Wilmore et al. 1997).

Resting BP was measured using Colin STBP-780 automated units before 11 AM in the post-absorptive state (Rankinen et al. 2000). Subjects were asked to abstain from caffeine-containing or tobacco products for 2 h before measurements were made. Subjects rested for 5 min before the initial measurement. Blood samples were obtained after a 12 h fast. Cholesterol was determined in plasma by enzymatic methods (Despres et al. 2000).

The tHcy (the sum of homocysteine, homocystine, and homocysteine–cysteine mixed disulfides, free and protein bound) were measured in frozen plasma samples (−70°C) by an HPLC method (Durand et al. 1996). The intra- and inter-assay coefficients of variation for tHcy are 3.0% ($n = 12$) and 3.3% ($n = 50$), respectively. Plasma folate and vitamin B_{12} concentrations were determined by means of radioimmunoassay using a commercial kit (SimulTRAC-SNB_B_{12}/Folate, ICN Diagnostics, Orangeburg, NY). The intra- and inter-assay coefficients of variation are 6.3% ($n = 20$) and 10.3% ($n = 14$), respectively, for folate, and 4.9% ($n = 20$) and 4.3% ($n = 14$), respectively, for vitamin B_{12}. Plasma vitamin B_6 (pyridoxal phosphate) concentrations were also determined by means of a radioimmunoassay using a commercial kit (Vitamin B_6 (^{3}H) REA, American Laboratory Products Company, Windham, NH). The intra- and inter-assay coefficients

of variation for vitamin B_6 are 4.6% ($n = 9$) and 10.2% ($n = 8$), respectively.

Progressive maximal exercise tests to exhaustion were conducted both before and after the exercise training program on a stationary cycle ergometer (Ergo-Metrics 800S, SensorMedics, Yorba Linda, CA) connected to a SensorMedics 2900 metabolic cart.

Exercise training protocols

Each subject was trained three sessions per week for 20 weeks on stationary cycle ergometers that were computer controlled to automatically maintain the participant's target heart rates corresponding to heart rates associated with fixed percentages of the baseline VO_{2max} test (Skinner et al. 2000). The intensity and duration of the training program was adjusted each 2 weeks. Training began at a heart rate corresponding to 55% of each subject's baseline VO_{2max} for 30 min per session and progressed to an intensity of 75% for 50 min during the last 6 weeks. All training sessions were supervised on site.

Subjects were asked not to change their eating patterns (meals and supplement use) during the intervention period.

Statistical analysis

General linear model analyses were used to test for differences between men and women as well as between the two ethnic groups. Paired *t*-tests were used to assess differences between variables before and after the exercise training program. Multiple regression analyses with the forward stepwise method were performed to estimate the independent contributions of age, sex, race, menopausal status, taking hormones, BMI, waist circumference, body composition, VO_{2max}, resting blood pressure, plasma levels of cholesterol, folate, vitamin B_6 and vitamin B_{12} to the variations in tHcy at baseline and changes in tHcy in response to aerobic exercise training. The relationship between two measurements was assessed by Pearson and Spearman rank correlation coefficients. Based on a position statement of the American Heart Association, we classified subjects into two groups: subjects with tHcy in the normal range (<15 μmol/l, "Normal" group) and subjects with elevated levels or hyperhomocysteinemia (≥15 μmol/l, "High" group) (Malinow et al. 1999). Probability values below 0.05 were regarded as significant. The data were analyzed with the Statistical Analysis System (SAS), version 9.1.

Results

Physical and biochemical characteristics of subjects at baseline are presented in Table 1 ($n = 816$). Detailed values of anthropometric and body composition measurements (Wilmore et al. 1997), resting blood pressure (Rankinen et al. 2000), and plasma lipids (Despres et al. 2000) were presented in previous reports. The tHcy levels were higher in men in both ethnic groups, and were higher in Blacks in both sexes.

For the whole sample ($n = 711$), the mean change in tHcy was only +0.1 μmol/l from baseline (8.8 ± 4.4 μmol/l) to post-exercise training (8.9 ± 3.6 μmol/l) ($P = 0.096$). Table 2 shows that tHcy did not change in Blacks but increased significantly in Whites. Vitamin B_6 remained unchanged, whereas vitamin B12 decreased significantly in all groups. Folate increased significantly in black men only. When the changes were compared between the two ethnic groups, we found a

Table 1 Comparison of baseline data between men and women, and between Blacks and Whites

	Blacks		Whites		Race difference	
	Women ($n = 191$)	Men ($n = 111$)	Women ($n = 260$)	Men ($n = 254$)	Women	Men
Age (years)	33.0 (11.4)	32.9 (12.3)	35.1 (14.1)	36.2 (14.9)	0.089	0.028
Height (m)	1.62 (6.6)	1.76 (6.7)[a]	1.64 (6.4)	1.78 (6.3)[a]	0.041	0.01
Weight (kg)	74.4 (17.9)	84.6 (18.6)[a]	67.2 (13.6)	84.4 (16.2)[a]	<0.0001	0.907
BMI (kg/m^2)	28.2 (6.5)	27.4 (5.6)	25.1 (5.0)	26.7 (4.9)[a]	<0.0001	0.218
Homocysteine (μmol/l)	8.5 (4.2)	11.0 (7.2)[a]	7.7 (2.7)	9.4 (3.7)[a]	0.01	0.004
Folate (nmol/l)	12.0 (8.3)	12.0 (8.5)	16.6 (15.0)	14.1 (10.3)	0.001	0.034
Vitamin B_6 (nmol/l)	40.6 (38.0)	64.9 (59.4)	56.2 (63.0)	60.9 (51.9)[a]	0.0001	0.763
Vitamin B_{12} (nmol/l)	332 (153)	328 (183)	286 (144)	289 (112)	0.0004	0.099
VO_{2max} (ml/min)	1,753 (365)	2,758 (490)[a]	1,912 (347)	3,026 (582)[a]	<0.0001	<0.0001

Data are expressed as mean (SD)

BMI body mass index, VO_{2max} maximal oxygen uptake

[a] $P < 0.001$ significantly different from women

Table 2 Comparison of changes in measurements between men and women, and between Blacks and Whites

	Blacks		Whites		Race difference	
	Women (n = 151)	Men (n = 87)	Women (n = 243)	Men (n = 230)	Women P-value	Men P-value
Weight (kg)	−0.4 (2.9)[a]	−0.8 (3.1)[a]	−0.1 (2.1)	−0.3 (2.1)[a]	0.224	0.252
BMI (kg/m^2)	−0.2 (1.1)	−0.2 (0.9)[a]	−0.0 (0.8)	−0.1 (0.7)[a]	0.279	0.376
Homocysteine (μmol/l)	+0.0 (2.3)	−0.5 (3.8)	+0.2 (1.6)[a]	+0.3 (1.7)[a]	0.407	0.04
Folate (nmol/l)	+0.9 (9.6)	+2.8 (7.9)[a]	−0.7 (9.0)	−0.3 (6.9)	0.111	0.003
Vitamin B_6 (nmol/l)	+3.3 (27.6)	+12.2 (76.2)	−1.5 (62.2)	+6.6 (64.7)	0.299	0.521
Vitamin B_{12} (nmol/l)	−17 (71)[a]	−14 (79)[a]	−23 (62)[a]	−18 (68)[a]	0.404	0.306
VO_{2max} (ml/min)	+336 (151)[a]	+411 (201)[a, b]	+349 (183)[a]	+450 (236)[a, b]	0.447	0.185

Data are expressed as mean (SD)

BMI body mass index, VO_{2max} = maximal oxygen uptake

[a] Training response (post–pre) $P < 0.05$

[b] $P < 0.01$ significantly different from women

significant difference in males for folate and homocysteine. No sex difference was found for any of the variables. After exercise training, the mean (SD) values of tHcy were 8.6 (3.4) μmol/l for black women, 10.8 (5.4) μmol/l for black men, 8.0 (2.4) μmol/l for white women, and 9.6 (3.4) μmol/l for white men. Sex and racial differences were identical to those at baseline.

We quantified the independent contributions of the variables considered here to the variance in tHcy. At baseline (Table 3), folate was the best predictor of tHcy in both sexes, and both races. Age, ethnicity and vitamin B_{12} were also significant predictors of tHcy. When exercise training induced changes in tHcy were used as the dependent variable, baseline homocysteine levels, and changes in folate were the strongest predictors in the whole sample as well as in the sex and race subgroups (Table 3). Although VO_{2max} was not selected as a significant predictor, increases in VO_{2max} tended to associate with decreases in tHcy ($P = 0.06$) in the whole sample.

Figure 1 illustrates the relationship between baseline tHcy and change in tHcy in response to exercise training. Changes in tHcy were negatively correlated with baseline tHcy (Pearson correlation coefficient = −0.40, $P < 0.0001$ and Spearman rank correlation coefficient = −0.25, $P < 0.0001$).

Figure 2 displays individual tHcy data for the High group ($n = 30$) at baseline and after training. Mean values of tHcy decreased from 23.1 (SD 12.1) μmol/l to 19.6 (7.6) μmol/l ($P = 0.01$). After training, 21 (70%) individuals (3 black women, 9 black men, 3 white women, and 6 white men) decreased their tHcy. Eight of the 21 individuals decreased their tHcy to less than 15 μmol/l. On the other hand, in the Normal group ($n = 681$), only 8 (1%) individuals (2 black women, 3 black men, 1 white women, and 2 white men) increased their tHcy to more than 15 μmol/l. The Normal group had a statistically significant increase in tHcy from 8.2 (2.2) μmol/l to 8.5 (2.4) μmol/l ($P < 0.0001$).

Figure 3 compares tHcy changes between the Normal and High groups. A significant ($P < 0.0001$) difference was observed between the Normal [+0.3 (1.5) μmol/l] and High [−3.5 (7.0) μmol/l] groups for the tHcy response to exercise training. The difference was still found after adjustment for age, sex, race and baseline tHcy ($P = 0.0028$). Folate levels increased significantly (+1.1 ± 3.0 nmol/l, $P < 0.05$) during the exercise training in the High group but remained unchanged in the Normal group. Vitamin B_{12} levels did not change in the High group but decreased significantly (−16.5 ± 97.8 pmol/l, $P < 0.0001$) in the Normal group.

Discussion

We found that the 20 week aerobic exercise training program reduced significantly tHcy (−3.5 μmol/l, $P = 0.01$) in those with elevated tHcy at baseline. Moreover, a significant difference in tHcy changes remained between the Normal and High groups even after adjustment for age, sex, race and baseline tHcy ($P = 0.0028$). Boushey et al. (1995) have reported that about 10% of the population's coronary artery disease risk was attributable to tHcy, and Ueland et al. (2000) found that an increase of 5 μmol/l in tHcy could be associated with a 20% increased risk of cardiovascular disease. Schnyder et al. (2001) found that lowering tHcy from 11.1 to 7.2 μmol/l reduced significantly the rate of coronary restenosis after angioplasty and decreased the incidence of major adverse cardiac events. In a more recent study, lowering tHcy by 25% (3 μmol/l) was associated with an 11% lower ischemic heart disease and 19% lower stroke risk (Homocysteine

Table 3 Results of multiple regression analysis

Independent variable	Homocysteine at baseline					Independent variable	Homocysteine training response				
	Beta	*F*	*P*	Partial R^2	Model R^2		Beta	*F*	*P*	Partial R^2	Model R^2
[All]											
Folate	−0.18	118.1	<0.0001	14.2	14.2	B_homocysteine	−5.36	72.8	<0.0001	10.5	10.5
Sex[a]	−0.1	77.4	<0.0001	8.4	22.6	ΔFolate	−0.04	21.5	<0.0001	3.0	13.5
Age	0.002	73.8	<0.0001	7.3	29.9	Age	0.02	7.9	0.005	1.1	14.6
B_{12}	−0.17	44.9	<0.0001	4.2	34.1	B_folate	−0.78	8.9	0.003	1.2	15.8
Race[b]	−0.04	18.6	<0.0001	1.7	35.8	B_VO_{2max}	0.0004	11.4	0.0008	1.5	17.3
						ΔB12	−0.002	4.5	0.036	0.6	17.9
						B_B6	−0.004	4.4	0.036	0.6	18.5
[Male]											
Folate	−0.23	65.6	<0.0001	16.7	16.7	B_homocysteine	−5.9	44.4	<0.0001	13.4	13.4
Age	0.002	48.3	<0.0001	10.8	27.5	ΔFolate	−0.05	15.3	0.0001	4.4	17.8
B_{12}	−0.16	14.6	0.0002	3.1	30.6	ΔB12	−0.004	5.7	0.018	1.6	19.4
Race	−0.05	13.4	0.0003	2.8	33.4	Age	0.03	4.1	0.044	1.2	20.6
Fat%	0.002	8.6	0.004	1.7	35.1	B_VO_{2max}	0.0006	5.9	0.015	1.6	22.2
						B_folate	−0.9	5.1	0.025	1.4	23.6
[Female]											
Folate	−0.15	60.3	<0.0001	13.6	13.6	B_homocysteine	−4.61	32.2	<0.0001	8.9	8.9
B_{12}	−0.18	35.9	<0.0001	7.4	21.0	ΔFolate	−0.03	8.9	0.003	2.4	11.3
Age	0.002	22.1	<0.0001	4.3	25.3	B_B6	−0.84	6.2	0.013	1.6	12.9
Race	−0.03	6.8	0.009	1.3	26.6	ΔB6	−0.003	4.9	0.028	1.3	14.2
						Age	0.02	5.3	0.021	1.4	15.6
[Blacks]											
Folate	−0.26	50.9	<0.0001	17.4	17.4	B_homocysteine	−8.0	61.0	<0.0001	25.0	25.0
Sex	−0.17	34.3	0.0001	10.3	27.7	ΔFolate	−0.05	8.4	0.004	3.3	28.3
Age	0.002	21.9	0.0027	6.0	33.7	ΔB6	−0.006	5.4	0.021	2.1	30.4
B_{12}	−0.17	14.6	0.0096	3.8	37.5						
Cholesterol	0.02	4.2	0.041	1.1	38.6						
[Whites]											
Folate	−0.16	66.2	<0.0001	12.4	12.4	B_homocysteine	−0.03	42.0	<0.0001	8.8	8.8
Age	0.002	61.3	<0.0001	10.2	22.6	ΔFolate		10.2	0.0015	2.1	10.9
Sex	−0.07	45.0	<0.0001	6.8	29.4	Sex		9.2	0.0026	1.8	12.7
B_{12}	−0.17	42.2	<0.0001	5.9	35.3	B_B6		9.8	0.0019	1.9	14.6
Resting DBP	0.002	7.0	0.008	1.0	36.2	B_folate		6.8	0.009	1.3	16.0
						Age		12.1	0.0006	2.3	18.3
						ΔB6		4.4	0.036	0.8	19.1

[a] 1 = men, 2 = women

[b] 1 = blacks, 2 = whites

Studies Collaboration 2002). Therefore, our observation that tHcy can be lowered by regular exercise in those with high levels is coherent with a number of studies indicating that it may reduce significantly the risk of events in individuals with hyperhomocysteinemia.

Sex difference

The tHcy concentrations are known to be higher in men than in women (Ganji and Kafai 2003; Carmel et al. 1999; Fukagawa et al. 2000; Lussier-Cacan et al. 1996; Morris et al. 2000; Nygard et al. 1995). Ganji et al. (2003) and Carmel et al. (1999) found that the sex-related difference could be explained by alcohol consumption, and concentrations of plasma folate, vitamin B_{12}, creatinine and cotinine. Folic acid and vitamin B_{12} are involved as co-factors in metabolic pathways catalyzed by the enzymes 16,2methylenetetrahydrofolate reductase and methionine synthase, respectively, whereas vitamin B_6 is a cofactor for cystathionine beta synthase (Kang et al. 1992). A number of studies have shown inverse relationships of tHcy with plasma/serum levels of folate, vitamin B_6 and vitamin B_{12} (Robinson et al. 1998; Selhub et al. 1993). Moreover, differences in rates of homocysteine remethylation (Fukagawa et al. 2000) and estrogen concentrations (Morris et al. 2000) may also contribute to the homocysteine sex dimorphism. Remethylation is one of the major pathways for homocysteine metabolism. In remethylation, homocysteine is salvaged by acquisition of a methyl group from N^5-methyl-tetrahydrofolate in a vitamin B_{12} dependent pathway or from betaine in a pathway occurring primarily in the liver (McKeever et al. 1991). Fukagawa et al. (2000) and

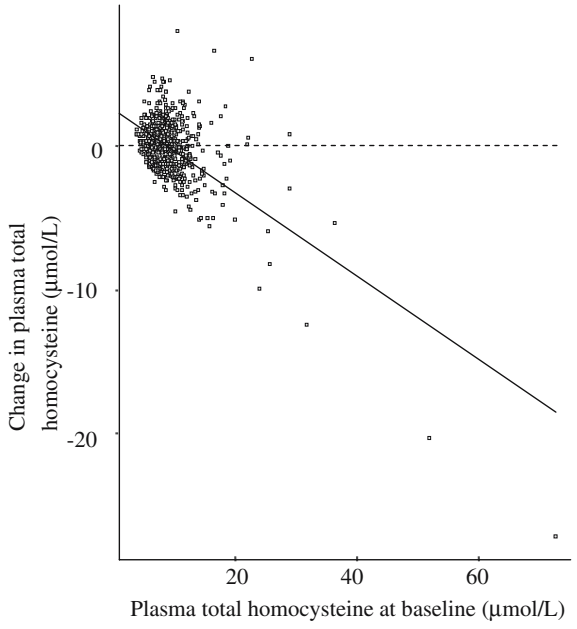

Fig. 1 Association between baseline homocysteine and regular exercise-induced changes in homocysteine. Pearson correlation coefficient = −0.40 ($P < 0.0001$), Spearman correlation coefficient = −0.25 ($P < 0.0001$)

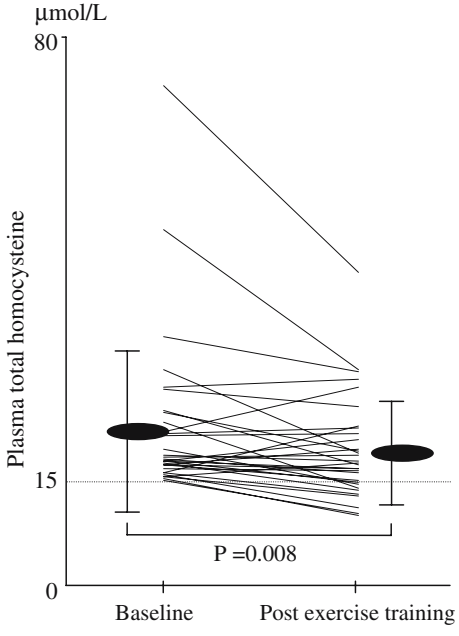

Fig. 2 Plasma total homocysteine levels in the High group at baseline and post-exercise training. *Vertical lines* indicate means (*filled circle*) and SD

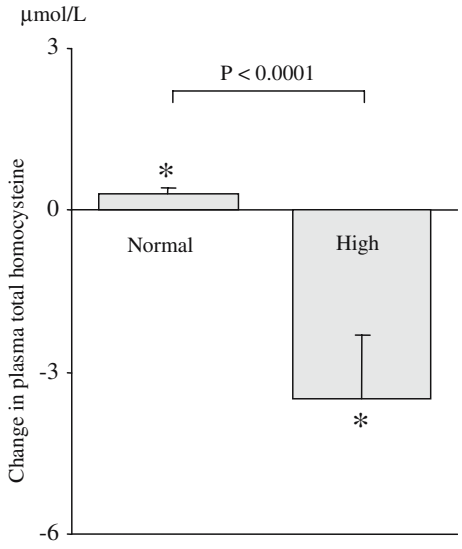

Fig. 3 Comparison of changes in plasma homocysteine levels between the "Normal" and "High" groups. Data are expressed as means ± SEM. *$P < 0.01$, within group difference (pre vs post)

McKeever et al. (1991) found that the remethylation rate was significantly higher in women than in men. They concluded that the sex-related difference is partially explained by homocysteine remethylation rates. Morris et al. (2000) found that higher estrogen concentrations are associated with lower tHcy, independent of nutritional status and muscle mass.

In the Hordaland Homocysteine Study (Nygard et al. 1995), tHcy levels were 19% higher in men (10.8 μmol/l) than in women (9.1 μmol/l) in middle age participants but only 11% (men 12.3 μmol/l and women 11.0 μmol/l) in elderly subjects. Although our data also indicated that baseline tHcy was higher in men than in women, there was no difference in exercise-induced changes in tHcy between men and women.

Racial differences

Several studies (Carmel et al. 1999; Ganji and Kafai 2003; Morris et al. 2000) have reported that Whites have 7–8% higher tHcy than Blacks. For instance, Ganji and Kafai (2003) found that tHcy was 8% higher in Whites (10.4 μmol/l) than in Blacks (9.6 μmol/l). Carmel et al. (1999) speculated that the higher tHcy in Whites might be explained by their lower vitamin B_{12} status compared with Blacks. On the other hand, the third National Health and Nutrition Survey in the United States (Jacques et al. 1999) found no racial difference in tHcy.

The present study indicates that baseline homocysteine levels were higher in Blacks than in Whites, and differences were also found for the training changes in homocysteine levels between Black and White men. Several investigators have reported that folate and vitamin B_{12} were predictors of blood homocysteine concentrations (Koehler et al. 2001; Morris et al. 2000).

Using multiple regression analyses, folate was found to be the strongest predictor of homocysteine in the present study. Our results also showed that folate levels were higher in Whites than in Blacks although vitamin B_{12} levels were higher in Blacks.

The present study has some limitations. First, since the primary goal of the HERITAGE Family Study is to study the role of genotype in the responsiveness to regular exercise, a control group was not deemed necessary. Second, subjects were asked not to change their eating patterns during the 20 week intervention period, but we have no direct assessments of folic acid, vitamin B_6 and B_{12} intakes over the duration of the exercise protocol.

In summary, we have examined the effects of exercise training on tHcy concentrations in both sexes and in Blacks and Whites. Baseline tHcy is higher in men than in women, consistent with previous studies. However, no difference between men and women was found for the changes in tHcy levels as a result of regular exercise. Baseline tHcy was higher in Blacks than in Whites, and in men, differences were also found for the changes in tHcy between the two ethnic groups. Twenty weeks of regular exercise reduced tHcy in individuals with baseline hyperhomocysteinemia, although tHcy slightly increased in individuals who were in the normal range of tHcy at baseline.

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References

Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J (1995) The HERITAGE family study. Aims, design, and measurement protocol. Med Sci Sports Exerc 27:721–729

Boushey CJ, Beresford SA, Omenn GS, Motulsky AG (1995) A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA 274:1049–1057

Cappuccio FP, Bell R, Perry IJ, Gilg J, Ueland PM, Refsum H, Sagnella GA, Jeffery S, Cook DG (2002) Homocysteine levels in men and women of different ethnic and cultural background living in England. Atherosclerosis 164:95–102

Carmel R, Green R, Jacobsen DW, Rasmussen K, Florea M, Azen C (1999) Serum cobalamin, homocysteine, and methylmalonic acid concentrations in a multiethnic elderly population: ethnic and sex differences in cobalamin and metabolite abnormalities. Am J Clin Nutr 70:904–910

De Cree C, Malinow MR, van Kranenburg GP, Geurten PG, Longford NT, Keizer HA (1999) Influence of exercise and menstrual cycle phase on plasma homocyst(e)ine levels in young women—a prospective study. Scand J Med Sci Sports 9:272–278

Despres JP, Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C (2000) Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the health, risk factors, exercise training, and genetics (HERITAGE) family study. Arterioscler Thromb Vasc Biol 20:1932–1938

Durand P, Fortin LJ, Lussier-Cacan S, Davignon J, Blache D (1996) Hyperhomocysteinemia induced by folic acid deficiency and methionine load–applications of a modified HPLC method. Clin Chim Acta 252:83–93

Fonseca V, Guba SC, Fink LM (1999) Hyperhomocysteinemia and the endocrine system: implications for atherosclerosis and thrombosis. Endocr Rev 20:738–759

Fukagawa NK, Martin JM, Wurthmann A, Prue AH, Ebenstein D, O'Rourke B (2000) Sex-related differences in methionine metabolism and plasma homocysteine concentrations. Am J Clin Nutr 72:22–29

Ganji V, Kafai MR (2003) Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 77:826–833

Homocysteine Studies Collaboration (2002) Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 288:2015–2022

Jacques PF, Rosenberg IH, Rogers G, Selhub J, Bowman BA, Gunter EW, Wright JD, Johnson CL (1999) Serum total homocysteine concentrations in adolescent and adult Americans: results from the third National Health and Nutrition Examination Survey. Am J Clin Nutr 69:482–489

Kang SS, Wong PW, Malinow MR (1992) Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. Annu Rev Nutr 12:279–298

Koehler KM, Baumgartner RN, Garry PJ, Allen RH, Stabler SP, Rimm EB (2001) Association of folate intake and serum homocysteine in elderly persons according to vitamin supplementation and alcohol use. Am J Clin Nutr 73:628–637

Konig D, Bisse E, Deibert P, Muller HM, Wieland H, Berg A (2003) Influence of training volume and acute physical exercise on the homocysteine levels in endurance-trained men: interactions with plasma folate and vitamin B12. Ann Nutr Metab 47:114–118

Langman LJ, Ray JG, Evrovski J, Yeo E, Cole DE (2000) Hyperhomocyst(e)inemia and the increased risk of venous thromboembolism: more evidence from a case-control study. Arch Intern Med 160:961–964

Lussier-Cacan S, Xhignesse M, Piolot A, Selhub J, Davignon J, Genest J Jr (1996) Plasma total homocysteine in healthy subjects: sex-specific relation with biological traits. Am J Clin Nutr 64:587–593

Malinow MR, Bostom AG, Krauss RM (1999) Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation 99:178–182

McKeever MP, Weir DG, Molloy A, Scott JM (1991) Betaine-homocysteine methyltransferase: organ distribution in man, pig and rat and subcellular distribution in the rat. Clin Sci (Lond) 81:551–556

Morris MS, Jacques PF, Selhub J, Rosenberg IH (2000) Total homocysteine and estrogen status indicators in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 152:140–148

Nygard O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland M, Kvale G (1995) Total plasma homocysteine

and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 274:1526–1533

Randeva HS, Lewandowski KC, Drzewoski J, Brooke-Wavell K, O'Callaghan C, Czupryniak L, Hillhouse EW, Prelevic GM (2002) Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. J Clin Endocrinol Metab 87:4496–4501

Rankinen T, Rice T, Perusse L, Chagnon YC, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C (2000) NOS3 Glu298Asp genotype and blood pressure response to endurance training: the HERITAGE family study. Hypertension 36:885–889

Ridker PM, Manson JE, Buring JE, Shih J, Matias M, Hennekens CH (1999) Homocysteine and risk of cardiovascular disease among postmenopausal women. JAMA 281:1817–1821

Robinson K, Arheart K, Refsum H, Brattstrom L, Boers G, Ueland P, Rubba P, Palma-Reis R, Meleady R, Daly L, Witteman J, Graham I (1998) Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. Circulation 97:437–443

Schnyder G, Roffi M, Pin R, Flammer Y, Lange H, Eberli FR, Meier B, Turi ZG, Hess OM (2001) Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 345:1593–1600

Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH (1993) Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA 270:2693–2698

Skinner JS, Wilmore KM, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C (2000) Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. Med Sci Sports Exerc 32:157–161

Ueland PM, Refsum H, Beresford SA, Vollset SE (2000) The controversy over homocysteine and cardiovascular risk. Am J Clin Nutr 72:324–332

Wilmore JH, Stanforth PR, Domenick MA, Gagnon J, Daw EW, Leon AS, Rao DC, Skinner JS, Bouchard C (1997) Reproducibility of anthropometric and body composition measurements: the HERITAGE Family Study. Int J Obes Relat Metab Disord 21:297–303