Published in final edited form as:

J Am Geriatr Soc. 2006 October ; 54(10): 1623–1625. doi:10.1111/j.1532-5415.2006.00903.x.

NORMAL HOMOCYSTEINE LEVELS IN WELL-FUNCTIONING OLDEST-OLD INDIVIDUALS DESPITE LOW KIDNEY FUNCTION

Michal Schnaider Beerli, PhD,

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

Jaime Uribarri, MD,

Dialysis Unit, Mount Sinai School of Medicine, New York, NY

James Schmeidler, PhD,

Department of Psychiatry, Department of Biomathematical Sciences, Mount Sinai School of Medicine, New York, NY

Rachel Lally, BA,

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

Joy Wang, BA,

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

Hillel T. Grossman, MD,

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

Erik Langhoff, MD,

Renal Clinic, Bronx Veteran Affairs Medical Center, Bronx, NY

Clive Rosendorff, MD, PhD, and

Department of Medicine, Bronx Veteran Affairs Medical Center, Bronx, NY

Jeremy M. Silverman, PhD

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

To the Editor: Homocysteine is a sulfur-containing metabolite of methionine that is emerging as an independent risk factor for atherosclerosis,¹ arterial and venous thrombosis,² and mortality.³ Previous studies, focusing on relatively young older people, have shown that homocysteine is higher in men and increases with age, smoking, lower vitamin B₁₂, folate, and renal function levels.⁴ Recently, we studied the relationships between homocysteine levels and the clinical and laboratory measures that have been typically associated with them in younger cohorts, using a sample of 117 well-functioning, cognitively intact community-dwelling oldest-old (aged ≥ 85). The relationship between change in homocysteine over time and these same factors was also examined in the subsample for whom follow-up data were available.

Nonfasting plasma homocysteine levels were measured according to a method previously described with minor modifications.⁵ Vitamin B₁₂, serum folate, serum creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and albumin were collected using standard techniques. Glomerular filtration rate (GFR), was estimated using the Cockcroft-Gault formula.⁶ Age, education, body mass index, and smoking information were also collected. Data on homocysteine, vitamin B₁₂,

Author Contributions: All of the authors contributed substantively to the conduct of the study and to the preparation of the letter.

folate, and creatinine levels were transformed using natural logarithms, to make the distributions approximately normal for statistical analysis purposes.

The means and standard deviations were 12.4 ± 3.4 $\mu\text{mol/L}$ for homocysteine, 1.0 ± 0.35 mg/dL for creatinine, and 45.1 ± 12.7 mL/min for GFR. Mean age was 89.2 ± 2.8 ; 70.5% were female. Approximately one-third of the sample had homocysteinemia (≥ 13 $\mu\text{mol/L}$ ⁷). GFR was impaired (<80 mL/min) in every subject, and serum creatinine levels were also high (creatinine >1.4 mg/dL in 29.7% of men and >1.1 mg/dL in 22.4% of women). None of the subjects had low folate levels, and only 1.7% had low vitamin B₁₂ levels (<200 pg/mL).

Table 1 presents the intercorrelations between homocysteine and other variables at baseline. Homocysteine was strongly correlated with creatinine and GFR but was significantly associated only with sex, with men having higher homocysteine levels (13.4 ± 4.2) than women (11.9 ± 2.8). Taking partial correlations, controlling for demographic, medical, and other laboratory measures, did not affect the associations of homocysteine with creatinine (0.63) and GFR (-0.57).

Of the 117 subjects, 44 had already had a second observation approximately 1 year after baseline. They were used to replicate all of the above analyses on an even older sample; results were similar. In addition, change scores were calculated; the intercorrelations between change variables are also presented in Table 1. Change in homocysteine levels was significantly associated with change in serum creatinine and GFR. Change in creatinine levels was significantly correlated with age and change in total cholesterol, but the partial correlation between change in homocysteine and change in creatinine, controlling for age and change in total cholesterol, remained significant (correlation coefficient (r) = 0.32, degrees of freedom (df) = 35, P = .05). Change in GFR was significantly correlated with age change. Partial correlation between change in homocysteine and change in GFR, controlling for change in age, also remained significant (r = -0.58 , df = 14, P = .04).

These results demonstrate that in this very old sample, kidney function, assessed using serum creatinine or estimated GFR, was the main factor associated with serum homocysteine levels. Unlike findings in younger cohorts, lack of associations between homocysteine and B₁₂ and folate may be attributable to good nutrition in this highly educated sample.

In the present study, all subjects had abnormally low GFR values. Even after controlling for many possible confounders, its association with homocysteine remained essentially unchanged. The significant longitudinal associations between changes in homocysteine levels and renal function (creatinine and GFR) confirmed these associations. Previous evidence has suggested that, as renal function declines over the years, homocysteine levels increase.⁸ Despite this, it is noteworthy that homocysteine levels in this oldest-old sample were comparable with those of a younger cohort with normal kidney function (n = 52; mean age = 46, homocysteine = 12, GFR = 108; unpublished data). Nevertheless, homocysteine levels in the sample in the current study were lower than those of younger patients with renal failure who had comparable GFR (mean age = 53, homocysteine = 18, GFR = 55).⁹ Thus in these oldest-old individuals, although the reciprocal relationship with GFR was maintained, homocysteine levels were lower than in younger populations at any level of renal function. Therefore, it may be that this “adaptation” of homocysteine levels may contribute to longer survival in these very old individuals. This is consistent with the pleiotropic antagonism hypothesis of a continuous and complex reshaping of metabolism during physiological aging, likely contributing to successful aging.¹⁰ Such reshaping may have far-reaching consequences in therapeutic intervention for the oldest-old individuals. Future studies following younger cohorts for longer periods may clarify whether metabolic

changes over time provoke changes in homocysteine levels or whether the relatively normal levels in the oldest-old are characteristic of survivors.

Acknowledgments

Financial Disclosure: This research was supported by National Institute on Aging Grants 1 K01 AG023515–01A2 (Dr. Beeri), P50-AG05138 (Dr. Sano), and P01-AG02219 (Dr. Haroutunian).

Sponsor's Role: The supporting agency did not take part in any aspect of this letter.

REFERENCES

1. Nygard O, Vollset SE, Refsum H, et al. Total homocysteine and cardiovascular disease. *J Intern Med.* 1999; 246:425–454. [PubMed: 10583714]
2. Sauls DL, Wolberg AS, Hoffman M. Elevated plasma homocysteine leads to alterations in fibrin clot structure and stability: Implications for the mechanism of thrombosis in hyperhomocysteinemia. *J Thromb Haemost.* 2003; 1:300–306. [PubMed: 12871504]
3. Nygard O, Nordrehaug JE, Refsum H, et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med.* 1997; 337:230–236. [PubMed: 9227928]
4. Jacques PF, Bostom AG, Wilson PW, et al. Determinants of plasma total homocysteine concentration in the Framingham offspring cohort. *Am J Clin Nutr.* 2001; 73:613–621. [PubMed: 11237940]
5. Ubbink JB, Vermaak WJ, Bissbort SH. High-performance liquid chromatographic assay of human lymphocyte kynureninase activity levels. *J Chromatogr.* 1991; 566:369–375. [PubMed: 1939450]
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31–41. [PubMed: 1244564]
7. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med.* 2002; 346:476–483. [PubMed: 11844848]
8. Bates CJ, Mansoor MA, van der Pols J, et al. Plasma total homocysteine in a representative sample of 972 British men and women aged 65 and over. *Eur J Clin Nutr.* 1997; 51:691–697. [PubMed: 9347290]
9. Parsons DS, Reaveley DA, Pavitt DV, et al. Relationship of renal function to homocysteine and lipoprotein (a) levels: The frequency of the combination of both risk factors in chronic renal impairment. *Am J Kidney Dis.* 2002; 40:916–923. [PubMed: 12407635]
10. Rose, MR. *The Evolutionary Biology of Aging.* Oxford: Oxford University Press; 1991.

Table 1

Baseline (Below Diagonal) and Change Scores (Above Diagonal) Intercorrelations Between Homocysteine (Hcy) and Other Variables

	Hcy	Hcy_2	B ₁₂	Folate	Creatinine	GFR	Age	Sex	Education	BMI	TC	LDL	HDL	TG	Albumin	Smoking
Hcy	1	—	−0.09	−0.08	.34*	−.77 [†]	.021	—	—	0.02	−0.11	−.05	.05	−	−0.08	−.01
N			44	44	44	17	44			17	39	39	39	39	39	0.33
Hcy_2	.98 [†]	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
N	117															
B ₁₂	−.09	−.12	1	.16	−.13	.29	−.27	—	—	−.21	.22	−.06	−.20	.07	−.03	—
N	117	117		44	44	17	44			17	39	39	39	39	39	
Folate	−.06	−.06	.16	1	.21	−.33	.05	—	—	.19	−0.05	−.10	.05	.06	−.14	—
N	117	117	117		44	17	44			17	39	39	39	39	39	
Creatinine	.64 [†]	.54 [†]	−.13	−.22*	1	−.94 [†]	.38*	—	—	−.17	−.41 [†]	−.24	.20	−.21	−.05	—
N	117	117	117	117		17	44			17	39	39	39	39	39	
GFR	−.52 [†]	−.50 [†]	−.03	.00	−.63 [†]	1	−.68*	—	—	.38	.50	.50	.05	−.02	−.21	—
N	55	55	55	55	55		17			17	16	16	16	16	16	
Age	.13	.05	.1	−.28 [†]	.17	−.31*	1	—	—	−.21	−.28	.04	−.23	−.07	.18	—
N	117	117	117	117	117	55				17	39	39	39	39	39	
Sex	−.20*	−.08	.14	.13	−.41 [†]	−.17	.001	1	—	—	—	—	—	—	—	—
N	117	117	117	117	117	55	117									
Education	.03	−.12	.19*	.06	.11	−.06	.07	−.14	1	—	—	—	—	—	—	—
N	117	117	117	117	117	55	117	117								
BMI	.01	.01	.21	.04	.10	.28	−.17	.02	.05	1	−.33	−.06	.63*	−.21	−.82 [†]	—
N	55	55	55	55	55	55	55	55	55		16	16	16	16	16	
TC	−.02	−.07	.04	−.09	−.11	.10	.04	.33 [†]	−.09	.23	1	.30	.24	.29	.43 [†]	—
N	110	110	110	110	110	54	110	110	110	54		39	39	39	39	
LDL	.06	.02	.01	−.11	.10	.01	−.04	.16	−.06	.26	.89 [†]	1	−.16	.16	−.08	—
N	111	111	111	111	111	55	111	111	111	55	110		39	39	39	
HDL	−.17	−.16	.01	.04	−.39 [†]	.19	.09	.43 [†]	−.06	.01	.47 [†]	.12	1	−.45 [†]	.12	—
N	111	111	111	111	111	55	111	111	111	55	110	111	111	39	39	

	Hcy	Hcy_2	B ₁₂	Folate	Creatinine	GFR	Age	Sex	Education	BMI	TC	LDL	HDL	TG	Albumin	Smoking
TG	.02	-.01	.09	-.05	.01	.09	.07	-.04	-.06	.05	.19*	.07	-.34 [‡]	1	.20	—
N	111	111	111	111	111	.53	111	111	111	55	110	111	111		39	
Albumin	.07	.08	-.13	-.04	-.12	-.01	-.12	.13	-.02	.03	.15	.09	.09	.13	1	—
N	111	111	111	111	111	.55	111	111	111	55	110	111	111	111		
Smoking	.02	-.02	-.11	.14	.08	-.04	-.13	.07	-.20*	.08	.10	.18	-.08	.09	-.04	1
N	104	104	104	104	104	53	104	104	104	53	101	102	102	102	102	

P ≤ .05;

[‡].01;

[‡].001.

Hcy_2 = homocysteinemia; GFR = glomerular filtration rate; BMI = body mass index; TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides.