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Serum adiponectin is associated with homocysteine in elderly men and women, and with 5,10-methylenetetrahydrofolate reductase (*MTHFR*) in a sex-dependent manner

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Abstract

Plasma homocysteine associates positively with cardiovascular disease. C-to-T substitution at base 677 of the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene associates with increased plasma homocysteine. The association of adiponectin with cardiovascular disease is unclear. This study of survivors of a 30-year cohort of the Jewish Israeli population, 310 men and 273 women (mean age, 70.5 ± 7.0 years for both), investigated the relationship between adiponectin and homocysteine, and between adiponectin and the *MTHFR* C677T genotype. Serum adiponectin associated positively with total homocysteine in both men ($r = 0.27$, $P < .001$) and women ($r = 0.22$, $P < .001$). In women, the TT *MTHFR* genotype associated with lower median adiponectin levels, 8.98 mg/L, compared with 9.88 and 10.57 mg/L for TC and CC, respectively ($P = .05$; CC vs TT, $P = .01$). In men, the trend was opposite, but not statistically significant: 7.90, 7.03, and 6.88 mg/L for TT, TC, and CC genotypes, respectively ($P = .5$). This study demonstrated a positive association between homocysteine and adiponectin in both elderly men and women and a statistically significant association between adiponectin and *MTHFR* C677T genotypes in women only.

1. Introduction

Adiponectin is found to associate negatively with insulin resistance [1] and inversely with the metabolic syndrome in nondiabetic men and women [2]. The relationship between adiponectin and cardiovascular disease is unclear. In men, hypoadiponectinemia was associated with impaired endothelial function [3-5] and with coronary heart disease and myocardial infarction [6]. Furthermore, in men, elevated levels of adiponectin were associated with reduced risk for myocardial infarction in a nested case-control study [7] and with a lower risk for coronary heart disease in a 10-year population study [8]. However, a recent meta-analysis of 7 prospective studies concluded that the association of adiponectin with coronary heart disease is minor [9]. In studies of women, neither total adiponectin nor high–molecular weight (HMW) adiponectin associated with coronary heart disease events [10,11]. Paradoxically, in patients at high risk for cardiovascular disease and in elderly populations, adiponectin has correlated positively with

There are no conflicts of interest to report.

Laboratory examinations were performed at the Institute of Chemical Pathology Laboratory at the Sheba Medical Center Medical Research Laboratories in Israel and in the Aarhus University Hospital in Denmark.

The Institutional Review Board at the Sheba Medical Center approved the study.

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pathology. In the former, adiponectin correlated positively with coronary heart disease events and mortality [12-14]. In the latter, high adiponectin levels associated with increased mortality in men [15] and with increased risk of incident coronary heart disease [16] and death from cardiovascular disease, as well as all causes, in both men and women [17].

Homocysteine has been positively associated with ischemic heart disease and stroke [18]. Plasma homocysteine is a product of genetic and lifestyle interactions, and the intake of folate and B vitamins. The 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, encoding the *MTHFR* enzyme, is required for the conversion of homocysteine to methionine. Individuals with a C-to-T substitution at base 677 of the gene (amino acid change A677V) have demonstrated reduced enzyme activity, increased levels of plasma homocysteine [19,20], and increased susceptibility to hyperhomocysteinemia [21,22]. We previously reported lower homocysteine levels for both men and women with the homozygous CC genotype, as compared with the heterozygous CT and homozygous TT *MTHFR* C677T genotypes [23].

In the current study, we investigated associations between adiponectin and homocysteine, as well as homocysteine's accompanying factors—folate, vitamin B12, and the *MTHFR* C677T common variant—in an elderly population of men and women, while controlling for demographic and lifestyle factors. In addition, we assessed the association of these 2 biomarkers with the prevalence of cardiovascular disease, hypertension, and type 2 diabetes mellitus.

2. Materials and methods

2.1. Study population

This cross-sectional study comprised 583 eligible individuals of the Israel Study of Glucose Intolerance, Obesity, and Hypertension (The Israel GOH Study). The original cohort comprised individuals whose names were drawn from the Israel Central Population Registry in an ongoing nationwide longitudinal study of the Jewish Israeli population that was started in 1968. Stratification was according to sex (50% male and 50% female), age (33% from each 10-year increment of subjects born between 1912 and 1941), and ethnic origin (Yemen, Middle East, North Africa, Europe/America). The detailed sampling procedure and design of this study have been reported previously [24]. Country of birth determined ethnic origin. For Israeli-born subjects, the father's country of birth determined ethnic origin. Europe/America origin characterizes subjects born in Europe or with ancestors who immigrated from Europe to America. The original cohort comprised 1288. Of 948 survivors, 31 did not have a total homocysteine (tHcy) result, 49 did not have an adiponectin measurement, and 96 completed a telephone interview but not laboratory examinations; and of the 189 nonrespondents, 94 (49.7%) were not located, 64 (33.9%) refused to participate, 13 (6.9%) had communication problems, and 18 (9.5%) were too ill to participate. The Institutional Review Board at the Chaim Sheba Medical Center in Israel approved the study. Each participant signed an informed consent form.

2.2. Interview and laboratory examinations (measurements of biochemical analysis)

Trained nurses in local clinics interviewed the participants about demographic variables (age, ethnic origin), lifestyle characteristics (smoking and physical activity habits), medical history, and use of medications. Blood pressure was measured 3 times during the interviews. Weight and height were measured with subjects wearing light clothing and no shoes. Central obesity was defined according to waist circumference. Body mass index (BMI; in kilograms per square meter) was calculated. Blood was drawn after 12 hours of fasting and tested for lipid, creatinine, vitamin B12, folic acid, tHcy, and adiponectin. DNA analysis was performed for the *MTHFR* C677T common variant.

All blood samples were collected during 2000-2004 and stored at −70° until analysis. Serum adiponectin was determined at Medical Research Laboratories in Aarhus, Denmark, by a validated novel in-house time-resolved immunofluorometric assay based on 2 antibodies and recombinant human adiponectin (R and D Systems, Abingdon, United Kingdom), as previously described [25,26]. Both antibodies are capable of detecting several adiponectin polymers in serum, including the 3 major molecular forms: trimers, hexamers, and highly congregated multimers of 300 kd [27]. Within and in-between assay coefficients of variation of standards and unknown samples averaged less than 5% and 10%, respectively.

All other laboratory examinations were performed at the Institute of Chemical Pathology Laboratory at the Sheba Medical Center. For assessing tHcy, fasting blood samples were drawn in tubes containing EDTA and put in crushed ice. Plasma was separated immediately. Total Hcy levels were measured by fluorescent detection after separation by high-performance liquid chromatography following labeling of plasma by monobromobimane, as previously described [28]. Normal values for adults range between 5.0 and 15.0 μmol/L.

Levels of high-density lipoprotein (HDL) cholesterol and triglycerides were determined using an automated enzymatic technique (Boehringer Mannheim, Mannheim, Germany) and standardized against reference materials supplied by the standardization program of the Centers for Disease Control and Prevention. Folic acid and B12 assays were performed on the Access Immunoassay system kit (AxSYM Abbott Laboratories, Abbott Park, IL). Creatinine was measured in venous plasma by the Jaffe spectroscopic method using an Olympus AU2700 analyzer (Olympus American Inc, Melville, NY) [29].

DNA was isolated from blood samples using a DNA blood PureGene kit (Gentra, Minneapolis, MN) according to the manufacturer's protocol. *MTHFR* C677T single nucleotide polymorphism genotyping was performed using

polymerase chain reaction amplification of genomic DNA, a short extension reaction across the polymorphic site, and mass spectrometry to detect allele-specific mass differences of the extension. Allele detection and genotype calling were performed using the MassARRAY system from Sequenom (San Diego, CA) [30].

Presence of cardiovascular disease, hypertension, and diabetes was determined based on participants' self-report and use of medication for the specific disease.

2.3. Statistical analysis

Demographic and clinical characteristics were analyzed by sex using the χ^2 test for categorical variables and Fisher exact test as appropriate. The 2-sample *t* test was used for assessing differences in quantitative parameters. We applied logarithmic transformation to adiponectin because of its nonnormal distribution.

The association of adiponectin to continuous parameters (eg, plasma vitamin B12 and folate) was assessed by Pearson correlation. We used Wilcoxon rank sum test to examine differences in median values of adiponectin by physical activity levels and the use of vitamin B supplements, and Kruskal Wallis test for ethnic origin categories, smoking, and *MTHFR* C677T. A multiple linear regression model with adiponectin level as the dependent variable was applied using GLM procedure (SAS version 9.13; SAS, Cary, NC). Before building the multiple regression model, we established a univariate model for each explanatory variable: sex, age, ethnic origin, physical activity, smoking, waist circumference, creatinine, plasma vitamin B12, plasma folate, tHcy, vitamin B supplements, and *MTHFR* C677T. We entered variables that were significant at a 20% level into a backward elimination procedure, except for *MTHFR* C677T, which was retained in the multiple regression model. We eliminated the least significant variables sequentially until all remaining variables were significant at a 5% level. Interactions between sex and the independent variables were all tested.

Associations were investigated between both adiponectin and homocysteine values, and between the presence and absence of cardiovascular disease, hypertension, and diabetes using the Wilcoxon test for continuous variables with a nonnormal distribution.

3. Results

Table 1 presents demographic, anthropometric, and biochemical characteristics of the study subjects by sex. There were no significant differences between the sexes in age, ethnic origin, physical activity, or blood pressure. Among the men, there were significantly more past smokers. Waist circumference, plasma homocysteine levels, and creatinine levels were significantly higher in men than in women. In women, BMI and plasma levels of HDL cholesterol, plasma vitamin B12, plasma folate, and adiponectin were significantly higher. The proportion of men reporting use of vitamin B supplementation was less than half that of women (20.7% vs 43.8%, $P < .0001$). The homocysteine median value was lower in the men using vitamin B supplementation than in the nonusers (9.75 vs 11.6 μg/dL, $P = .03$). In the women, the same trend was observed, but without statistical significance (9.1 vs 9.7 μg/dL, $P = .41$). There were no statistically significant differences in the distribution of the *MTHFR* C677T genotypes by sex.

Table 1
Demographic, anthropometric, and biochemical characteristics of Jewish Israelis by sex, 2000-2004

	Men n = 310	Women n = 273	*P*
Age (y)	70.5 ± 7.0	69.6 ± 6.4	.1
Ethnic origin (n, %)			
Yemen	58 (18.7)	54 (19.8)	.9
Middle East	87 (28.1)	73 (26.7)	
North Africa	48 (15.5)	42 (15.4)	
Europe/America	117 (37.7)	104 (38.1)	
Smoking (n, %)			
Never	113 (36.7)	204 (74.7)	<.001
Past	163 (52.9)	44 (16.1)	
Current	32 (10.4)	25 (9.2)	
BMI (kg/m^2)	27.8 ± 4.0	29.1 ± 5.2	<.001
Waist circumference (cm)	100.0 ± 10.7	97.1 ± 11.7	.002
Physical activity (n, %)			
Sedentary	144 (46.8)	137 (50.2)	.4
Active	164 (53.3)	136 (49.8)	
Vitamin B supplement use (n, %)	62 (20.3)	120 (44.1)	<.001
Blood pressure (mm Hg)			
Systolic	143.3 ± 22.7	143.5 ± 23.0	.9
Diastolic	79.4 ± 11.6	79.6 ± 11.4	.9
HDL cholesterol (mg/dL)	42.7 ± 11.1	54.7 ± 13.7	<.001
Triglycerides (mg/dL)	135.4 ± 72.3	146.1 ± 81.8	.1
Homocysteine (μmol/dL)	12.1 ± 5.7	10.0 ± 4.4	<.001
Plasma vitamin B12 (pg/mL)	352.3 ± 206	440 ± 278	<.001
Plasma folate (μg/L)	4.8 ± 3.2	5.6 ± 3.7	.005
Creatinine (mg/dL)	1.12 ± 0.26	0.90 ± 0.26	<.001
Median Adiponectin (mg/L) [range]	7.9 [2.2-32.4]	10.22 [2.9-35.1]	<.001
MTHFR genotypes (n, %)			
CC	134 (43.6)	119 (44.2)	.3
TC	137 (44.6)	108 (40.1)	
TT	36 (11.7)	42 (15.6)	

Data are mean ± SD if not specified otherwise.

Table 2 presents median adiponectin concentrations by selected characteristics and sex. No differences were found in median values of adiponectin according to ethnic origin. The lowest median values of adiponectin were in current smokers and the highest median values were in past smokers, in men only ($P = .003$). In women, higher median adiponectin values presented in the CC, followed by the TC and TT *MTHFR* C677T genotypes. In men, this association was reversed, but not statistically significant.

Table 3 presents Pearson correlation coefficients by sex. In both men and women, adiponectin associated negatively with the 2 measures of adiposity (BMI, waist circumference) and positively with age, plasma B12, and tHcy. Plasma folate was significantly associated to adiponectin for men only.

Table 2
Median adiponectin concentration (in milligrams per liter) by selected characteristics and sex in Jewish Israelis, 2000-2004

	Men n = 310	Women n = 273	Total N = 583
Total [range]	7.09 [2.2-32.4]	10.22 [2.9-35.1]	8.50 [2.2–35.1]
Ethnic origin			
Yemen	7.55	10.03	8.82
Middle East	6.59	9.76	8.09
North Africa	7.03	10.06	8.28
Europe/America	7.42	10.52	9.16
P	.3	.7	.3
Physical activity			
Sedentary	7.63	10.49	9.16
Active	6.71	9.88	8.23
P	.1	.6	.05
Smoking			
Never	6.82	10.52	9.41
Past	7.85	8.87	8.10
Current	5.62	10.35	7.06
P	.002	.3	.002
MTHFR genotypes			
CC	6.88	10.57	8.88
TC	7.03	9.88	8.42
TT	7.90	8.98	8.20
P	.5	.05	.8
Vitamin B supplement use			
Yes (62/120)	7.28	10.55	10.29
No (243/152)	7.03	10.02	9.39
P	.4	.3	.001

Adiponectin values are after logarithmic transformation.

Neither systolic nor diastolic blood pressure associated with adiponectin. The association between homocysteine and adiponectin was statistically significant for both men and women who did not take vitamin B supplementation. For those who took vitamin B supplementation, statistical significance was borderline for women and absent for men.

Table 3
Pearson correlation coefficients for the relationships between plasma adiponectin concentration and various parameters by sex for Jewish Israelis, 2000-2004

Variable	Men n = 310		Women n = 273		Total N = 583	
	r	*P*	*r*	*P*	*r*	*P*
Age	0.33	<.001	0.18	.004	0.23	<.001
BMI	−0.23	<.001	−0.11	.08	−0.11	.01
Waist circumference	−0.21	<.001	−0.14	.002	−0.21	<.001
Systolic BP	−0.01	.8	−0.01	.9	−0.01	.8
Diastolic BP	−0.01	.9	0.01	.9	0.002	.9
Creatinine	0.07	.2	0.09	.1	−0.05	.2
Plasma vitamin B12	0.06	.3	0.08	.2	0.12	.01
Plasma folate	0.15	.01	0.07	.3	0.14	.001
Homocysteine total	0.27	<.001	0.22	<.001	0.17	<.001
Homocysteine + B suppl	−0.004	.97	0.18	.05	0.08	.3
Homocysteine no B suppl	0.33	<.001	0.25	.003	0.23	<.001

Adiponectin values are after logarithmic transformation. BP indicates blood pressure; +B suppl, those who took vitamin B supplementation; no B suppl, those who did not take vitamin B supplementation.

Considering both sexes together, the median serum adiponectin levels for *MTHFR* C677T genotypes CC, TC, and TT of 8.88, 8.42, and 8.20 mg/L, respectively, show no significant trend. However, stratification of *MTHFR* C677T by sex (Fig. 1) reveals an association in women of the TT genotype with lower median levels of adiponectin as compared with the TC and CC *MTHFR* C677T genotypes (8.98, 9.88, and 10.57 mg/L, respectively; $P = .05$; CC vs TT, $P = .01$). In contrast, the TT genotype in men associated with higher, though not statistically significant, median levels of adiponectin (7.90 mg/L), as compared with the TC and CC genotypes (7.03 and 6.88 mg/L, respectively; $P = .5$). Homocysteine correlated positively and significantly with adiponectin in both men and women for each *MTHFR* C677T genotype. The highest correlation coefficients were for homozygote TT men ($r = 0.41$, $P = .01$) and for wild-type CC women ($r = 0.38$, $P < .001$). These associations remained when stratifying for waist circumference of 94 cm for men and 88 cm for women (data not shown).

Table 4 presents the multiple linear regression analysis model of the association between adiponectin and the variables tHcy, plasma vitamin B12, *MTHFR* C677T genotype, age, sex, and waist circumference. Ethnic origin and creatinine were not candidates for the multiple regression model because they were not significant ($P > .2$) in the univariate model. The variables vitamin B supplementation, smoking, physical activity, and plasma folate were entered into the backward elimination procedure, but were excluded from the final model because of nonsignificance. After adjusting for all other variables, the model shows the increases in adiponectin levels expected for incremental increases in age, tHcy, and plasma vitamin B12 and the decrease in adiponectin level expected for an increase in waist circumference. A significant interaction was found between sex and *MTHFR* C677T genotype ($P = .006$). Women with the TT *MTHFR* C677T genotype are expected to have 24% lower adiponectin levels than those

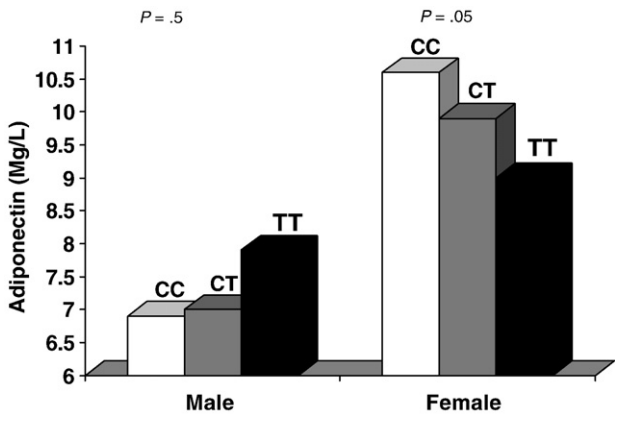

Fig. 1. Median adiponectin levels (in milligrams per liter) according to the *MTHFR* C677T genotypes CC, CT, and TT for male and female Jewish Israelis, 2000-2004. *P* values are calculated for the differences between the 3 genotypes for each sex.

Table 4
The effect of age, waist circumference, plasma homocysteine, vitamin B12, and *MTHFR* C677T genotype-sex interaction on adiponectin plasma levels in a multiple linear regression of Jewish Israelis, 2000-2004

Variable	Rate ratio	95% CI	*P*
Age (increment of 1 y)	1.02	1.01-1.02	<.001
Waist circumference (increment of 5 cm)	0.96	0.95-0.98	<.001
Homocysteine (increment of 1 μm/dL)	1.02	1.01-1.02	<.001
Plasma vitamin B12 (increment of 50 pg/mL)	1.01	1.00-1.02	.01
Interaction between *MTHFR* C677T gene and sex			
Genotype			.006
Men: CC	1.00	–	
TC	1.06	0.96-1.17	
TT	1.07	0.92-1.26	
Women: CC	1.00	–	
TC	0.92	0.82-1.03	
TT	0.76	0.65-0.88	

with the CC C677T genotype. The expectation for men is reversed, though not statistically significant.

Table 5 presents morbidity data according to median adiponectin and tHcy. When men and women are considered together, adiponectin values were lower in those having cardiovascular disease, hypertension, or type 2 diabetes mellitus; tHcy values were higher for those with hypertension and similar for those with cardiovascular disease or type 2 diabetes mellitus.

4. Discussion

The main findings in this study are the positive association between circulating adiponectin and plasma tHcy in both men and women in an elderly population, and the association of adiponectin and *MTHFR* C677T, which was statistically significant in women only. To the best of our knowledge, this is the first study to investigate the association between adiponectin and homocysteine in a healthy elderly population. This association was statistically significant in both men and women who did not take vitamin B supplementation, and obscured in those who did take supplementation. In another study, a positive correlation between adiponectin and homocysteine was detected in patients who had undergone coronary angiography [13]. By contrast, no correlation was found in hypertensive men with coronary artery disease [31], in men with type 2 diabetes mellitus [32], or in overweight individuals [33].

We report a significantly higher mean adiponectin level and a significantly lower mean homocysteine level in women compared with men. Others have documented lower levels of homocysteine [34] and higher levels of adiponectin in women [27,35-39]. In a study of healthy adults, adiponectin was highest in men older than 70 years, followed by women of all ages and then men younger than 70 years [40]. A 20-year prospective study suggests that adiponectin may function differently between the sexes. Higher adiponectin concentrations predicted reduced risk of nonfatal myocardial infarction in men only [17].

The associations observed in this study between *MTHFR* C677T and adiponectin underscore the sex differences detected in homocysteine and adiponectin levels. Associations of *MTHFR* C677T genotype with adiponectin were in opposing directions in men and in women. In women, the TT genotype associated negatively with adiponectin. In men, the positive association of the TT genotype did not remain significant in a multiple linear regression model.

We will now explore 3 possible explanations for the positive association observed between adiponectin and homocysteine in elderly men and women: a detrimental effect of adiponectin, a compensatory role for adiponectin, and the existence of a common underlying factor that influences both adiponectin and homocysteine.

Pilz et al [13] suggested a detrimental effect of adiponectin as an explanation for the positive correlation they detected between adiponectin and homocysteine. This is consistent with studies that have demonstrated associations between adiponectin and morbidity or mortality [12,14-17].

Table 5
Morbidity according to median adiponectin and median tHcy values

	Adiponectin (mg/L) (n) median plasma value			Homocysteine (μmol/L) (n) median plasma value		
	Total	Male	Female	Total	Male	Female
Cardiovascular disease						
Yes	(176) 7.72	(118) 6.58	(58) 9.25	(175) 10.7	(117) 11.4	(58) 8.95
No	(407) 9.10	(192) 7.48	(215) 10.49	(396) 9.9	(186) 10.9	(210) 9.40
P value	.001	.15	.14	.097	.5	.9
Hypertension						
Yes	(265) 8.04	(141) 6.55	(124) 9.75	(260) 10.3	(138) 11.8	(122) 9.5
No	(318) 9.12	(169) 7.71	(149) 10.55	(311) 9.8	(165) 10.8	(146) 8.75
P value	.03	.02	.14	.005	.18	.007
Type 2 diabetes mellitus						
Yes	(98) 7.46	(52) 6.23	(46) 8.31	(96) 10.0	(51) 10.2	(45) 9.5
No	(485) 8.94	(258) 7.37	(227) 10.50	(475) 10.1	(252) 11.6	(223) 9.2
P value	.001	.03	.005	.6	.13	.5

The association we found in women between adiponectin and *MTHFR* C677T supports a compensatory role for adiponectin. Because *MTHFR* C677T genotype evidently precedes adiponectin expression, our data suggest that *MTHFR* C677T may mediate adiponectin through homocysteine, at least in women. Interestingly, homocysteine was recently proposed as a mediator of adiponectin levels in alcoholic liver disease, albeit in the opposite direction as to what we found; high levels of homocysteine were considered to contribute to decreased adiponectin production [41]. Our findings are congruent with Sattar and Nelson's [41] hypothesis that elevated levels of adiponectin may reflect a compensatory response and not a modifying role. In addition, Prior et al [42] proposed a compensatory role for adiponectin in their recently published study of individuals with long-standing type 1 diabetes mellitus.

It is also possible that a common underlying factor may explain a positive correlation between adiponectin and homocysteine. Age-related factors could conceivably explain the coincident increase of homocysteine and adiponectin observed in our study. Homocysteine in both sexes [34] and adiponectin in men only [40] have been shown to increase with age. The age-dependent increase in renal insufficiency has been proposed as a possible cause. Positive associations between creatinine and both adiponectin and homocysteine [34,43], and between BUN and adiponectin, [44] and a negative association between glomerular filtration rate and adiponectin [38,40,43] are all consistent with such an explanation. In the present study, we did not find a correlation between adiponectin and plasma creatinine. Of importance, a recent study dismissed renal insufficiency as a confounder for the association between elevated levels of adiponectin and coronary heart disease [16]. Moreover, although age-related renal insufficiency could contribute to both elevated homocysteine and adiponectin [45], it does not explain the sex differences we observed in the *MTHFR* C677T genotype.

Sarcopenia, the degenerative loss of skeletal muscle mass and strength associated with aging, is an age-related factor proposed to raise adiponectin [15], with different expression in men and women. In mice, skeletal muscle activity that simulated sarcopenia was shown to differ by sex [46], as did the expression of adiponectin in skeletal muscle [47]. Age-related decreases in muscle mass and increases in fat mass are less pronounced in women than in their male counterparts [48]. In addition, women have less intraabdominal fat and more peripheral fat [48]. Adiponectin has been shown to correlate negatively with intraabdominal fat [36] and positively with peripheral fat [37]. We chose waist circumference, and not BMI, as a measure of adiposity in the multiple linear regression model and found it to be significantly associated to adiponectin levels. The significantly higher mean waist circumference in men is consistent with their lower mean level of adiponectin. In contrast, the significantly higher BMI levels in women would predict lower adiponectin levels than for men, which were not found. Thus, the present study supports fat distribution, as assessed by waist circumference, as a better predictor of adiponectin than BMI. Sex differences in fat distribution in the elderly may explain at least in part the sex differences in adiponectin levels for this population.

The associations in the present study between morbidity (cardiovascular disease, type 2 diabetes mellitus, and hypertension) and both adiponectin and homocysteine concur with those of previous studies. As with all epidemiologic studies of elderly populations, survival bias is a limitation. Nevertheless, the association between adiponectin and homocysteine remained positive and significant in analysis of the younger, less than 65-year-old participants of this study ($r = 0.27$, $P = .02$, n = 136).

Another limitation of this study is that we measured total adiponectin and not its isoforms. Recently, the HMW isoform has been distinguished as the most involved in the increased level of adiponectin in individuals with type 1 diabetes mellitus without nephropathy [49]. This isoform has been suggested to be a better marker for coronary heart disease extent than total adiponectin [50]. At low levels, the HMW isoform was shown to be an independent determinant of the metabolic syndrome in middle-aged men and women [51]. Testosterone was found to inhibit the HMW form of adiponectin and not the other forms [52]. It has been proposed that measurement of the different isoforms of adiponectin and of the HMW form in particular, may clarify the paradox between experimental data suggesting a vascular protective effect of adiponectin, and the ambiguous epidemiologic evidence suggesting both beneficial and detrimental effects [53].

In this study of a large well-defined population, we demonstrate a positive association between homocysteine and adiponectin for both elderly men and women. This association remained after adjustment for ethnic origin. The association we found between adiponectin and *MTHFR* C677T in women suggests that homocysteine may have a mediating role for adiponectin. Although we have no biological explanation for these findings, there may be clinical implications, particularly for sex differences in morbidity. Furthermore, vitamin B supplementation, in addition to its effect on homocysteine reduction, may have an influence on adiponectin values, a suggestion calling for further research.

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