Prognostic Value of Adiponectin for Cardiovascular Disease and Mortality

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Context: Low adiponectin concentrations are associated with the presence of an adverse cardiovascular disease (CVD) risk profile.

Objective: We studied the predictive value of adiponectin levels for all-cause and CVD mortality and CVD morbidity.

Design, Setting, and Participants: This was a population-based cohort study in Hoorn, The Netherlands, which started in 1989 and included 2484 participants, aged 50–75 yr.

Main Outcome Measures: Hazard ratios (HRs) with 95% confidence interval per SD change in log-adiponectin for all-cause and CVD mortality and CVD morbidity were calculated.

Results: Adiponectin was determined for 1077 men and 1248 women. Higher adiponectin reduced the risk of nonfatal CVD in women [HR with 95% confidence interval 0.72 (0.61–0.90) in women and 0.92 (0.79–1.06) in men], but not the risk of all-cause or CVD mortality. In contrast, after adjustment for cardiovascular risk factors, higher adiponectin was a significant predictor of all-cause and CVD mortality [HR for CVD mortality 1.45 (1.10–1.92) in women and 1.30 (1.04–1.63) in men]. Higher adiponectin was associated with an increased risk of CVD mortality in people with prevalent CVD [HR 1.27 (0.98–1.63)] and with reduced risk in people without [HR 0.90 (0.73–1.11)]. After adjustment for cardiovascular risk factors, the HRs for CVD mortality were 1.60 (1.14–2.23) for patients with and 1.38 (1.06–1.80) for patients without prevalent CVD.

Conclusions: High levels of adiponectin predict mortality, in particular in patients with prevalent CVD. We hypothesize that adiponectin protects against metabolic and vascular diseases, but in patients already afflicted with CVD, adiponectin is compensatory up-regulated and, therefore, indicates a high mortality risk. **(*J Clin Endocrinol Metab* 93: 1489–1496, 2008)**

Adiponectin is an adipocytokine, which is mainly produced by the adipose tissue (1). Although it is the most abundantly produced protein of the fat cell, plasma levels are reduced in obese patients. There is growing evidence that reduced adiponectin concentrations indicate an increased cardiovascular risk because hypoadiponectinemia is associated with the components of the metabolic syndrome, in particular with insulin resistance, elevated triglycerides, and low high-density lipoprotein (HDL) (1, 2). Apart from this, adiponectin possesses anti-inflammatory properties and exerts direct antiatherosclerotic and cardioprotective effects (2). Clinical studies have shown that low adiponectin concentrations are associated with endothelial

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Abbreviations: ALT, Alanine aminotransferase; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio.

dysfunction, increased carotid intima-media thickness, and coronary artery disease (2–4). High adiponectin concentrations are independent of other cardiovascular risk factors associated with a lower prevalence of acute coronary syndromes (4). Therefore, it was suggested that low adiponectin concentrations are a cardiovascular risk factor and that therapeutic strategies that enhance the secretion or action of this adipocytokine might reduce the incidence of cardiovascular diseases (CVDs) (1, 2).

However, several recently published studies on the prospective association between adiponectin and CVD events/mortality showed inconsistent results. Five studies reported that adiponectin was not independently associated with future CVD (5–9). Low adiponectin concentrations turned out as a risk factor for future CVD in some studies (10–16), whereas others showed that high adiponectin levels were associated with an increased risk of CVD and/or mortality (17–23). The underlying mechanisms for these contradictory results are still unclear but may be due to differences in the study populations. Toward this, it was speculated that low adiponectin predicts cardiovascular events in low-risk populations for CVD, whereas in high-risk populations, a counter-regulatory increase of adiponectin occurs that is responsible for the elevated cardiovascular risk associated with high adiponectin levels (24, 25). To test this hypothesis, we studied the association of adiponectin with 15-yr all-cause and CVD mortality and 10-yr nonfatal CVD in the Hoorn Study, a large population-based study, distinguishing subjects with and without a history of CVD.

Subjects and Methods

Study population

The Hoorn Study is a Dutch cohort study of diabetes and diabetes complications in the general population, which started in 1989. The cohort and the baseline measurements have been described in detail previously (26). Briefly, a random selection of 3553 men and women of 50–75 yr old was taken from the population register. A total of 2540 (71.5%) agreed to participate, and after exclusion of 56 non-Caucasian participants, the Hoorn Study population consisted of 2484 men and women. For the present study, we excluded 159 subjects with missing adiponectin data, leaving 1077 men and 1248 women for the analyses. This number of study probands was not determined by power calculations for specific hypotheses. All participants gave their written informed consent. The study was approved by the Ethics Committee of the Vrije Universiteit Medical Center.

Baseline examination and measurements

At the baseline medical examination, a blood sample was taken from all participants after overnight fasting. Adiponectin was determined in 2004 in spare baseline plasma samples that had been stored at −80 C and had never been thawed before. Adiponectin was determined with a latex turbidometric immunoassay. The interassay and intraassay coefficients of variation were less than 2.0% and less than 3.1%, respectively. A standard 75-g oral glucose tolerance test was performed in all subjects, except those using glucose-lowering medication. Plasma glucose was determined with a glucose dehydrogenase method (Merck, Darmstadt, Germany). Diabetes and impaired glucose metabolism were defined according to World Health Organization criteria of 1999 (27). Fasting insulin was determined with an insulin-specific double-antibody RIA (antibody: LINCO SP21; LINCO Research, Inc., St. Louis, MO). Fasting triglycerides, and total and HDL-cholesterol were determined by enzymatic techniques (Roche Molecular Biochemicals, Mannheim, Germany). Serum alanine aminotransferase (ALT) enzyme activity was measured according to the method of the International Federation of Clinical Chemistry from 1985, and expressed as U/liter. Serum creatinine level was determined in μmol/liter, and renal function [glomerular filtration rate (GFR)] was estimated by the Cockcroft-Gault formula in ml/min·1.73 m^2.

Waist and hip circumference, weight, and height were measured. Body mass index (BMI) was calculated as the ratio of weight and height squared. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer (Hawksley-Gelman Ltd., Lancing, UK), and the mean was used for computations. Information about use of medication, including antihypertensive medication, smoking status (nonsmokers, ex-smokers, and current smokers), and history of CVD at baseline (assessed by Rose Questionnaire) were determined by a self-administered questionnaire. Cigarette-years were calculated as the product of years smoked and mean number of cigarettes per day.

Follow-up of morbidity and mortality

The cohort was followed with respect to morbidity and mortality. Vital status was obtained from the population register of the city of Hoorn. Causes of death were coded by reviewing death certificates, and nonfatal CVD events were classified using medical records of general practitioners and the local hospital. Causes of death were coded according to the International Classification of Diseases, Injuries and Causes of Death, ninth revision.

CVD mortality was defined with International Classification of Diseases, Injuries and Causes of Death codes 390–459 (diseases of the circulatory system) or 798 (sudden death, cause unknown) because sudden death in general is of CVD origin. Vital status until January 2004 was known for all subjects. Cause of death could not be obtained for 35 men and 28 women.

Data on nonfatal outcomes were complete until 2000, for 845 men and 909 women who gave permission to access their hospital files and/or contact their general practitioners. Nonfatal CVD was defined as documented angina pectoris (chest pain, followed by coronary artery bypass surgery or angioplasty, or in the presence of more than 50% stenosis or electrocardiographic changes or positive exercise test), myocardial infarction (in the presence of at least two of the following: typical pain, elevated enzymes, and/or electrocardiogram changes), congestive heart failure (in the presence of at least two of the following: shortness of breath, cardiomegaly, dilated neck veins, or one of the former in the presence of edema or tachycardia), stroke or transient ischemic attack (sudden onset of symptoms, neurological symptoms, or change of consciousness), or peripheral disease (by procedure or typical pain accompanied by stenosis or ankle arm blood pressure ratio < 0.90 or positive vascular stress test).

Statistical analyses

Population characteristics were compared between sex-specific quartiles of baseline plasma adiponectin levels. Analyses were performed separately for men and women because of the different fat distribution in women and because women have higher levels of adiponectin than men. For proportions, trends over the quartiles were tested with the χ^2 test with P for linear-by-linear test. For continuous variables the Pearson and age-adjusted partial correlations with the log of adiponectin were determined. Survival curves of 15-yr all-cause mortality and CVD mortality and 10-yr nonfatal CVD in quartiles of adiponectin were plotted. Age-adjusted hazard ratios (HRs) for all-cause mortality, CVD mortality, and nonfatal CVD for the second through the fourth quartile relative to the lowest quartile of adiponectin were estimated with Cox proportional hazards analyses. We first adjusted for all possible mediating or confounding variables one by one, and then combined all these variables into one model. To study the possible modifying effect of the presence of diabetes or prevalent CVD, stratified analyses were performed. A P value less than 0.05 was considered statistically significant. Statistical analyses

were performed with SAS for windows, version 8.0 (SAS Institute Inc., Cary, NC) and with SPSS, version 15.0 (SPSS, Inc., Chicago, IL).

Results

Mean adiponectin was higher in women than men, and was increasing with age and lower GFR in both genders (Tables 1 and 2). High adiponectin was strongly associated with a more favorable CVD risk profile, with lower weight, smaller waist, higher HDL cholesterol and lower triglycerides, lower insulin and glucose levels, and lower ALT. Associations were not significant for total cholesterol. In women there was a trend of lesser smoking and higher participation in sports activities with higher levels of adiponectin. In men the reverse was observed for smoking, and there was no significant association with sports activities. Adiponectin was not associated with prevalent CVD at baseline. The baseline characteristics according to adiponectin quartiles for study participants with and without prevalent CVD are shown in supplemental Tables A and B (published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Until January 2004, after 15-yr follow-up, 286 men and 219 women had died, among whom 121 men and 83 women due to CVD. Until January 2000, after 10-yr follow-up, 195 men and 128 women had a nonfatal CVD event. As shown in Fig. 1, all-cause mortality was highest in both men and women with the highest adiponectin levels. The higher risk of mortality could not be attributed to any particular causes, and the association was also observed for cancer mortality, and noncancer non-CVD mortality (data not shown).

As shown in Table 3, adjustment for age did not explain the positive association between adiponectin and all-cause mortality in men. In women, but not in men, there was a U-shaped association with all-cause and CVD mortality, and a significant negative association with nonfatal CVD was observed in women and a nonsignificant trend in men. Adjustment for possible mediating or confounding variables resulted in a strong and statistically significant increased risk of CVD mortality with higher adiponectin level for both men and women (Table 4). The same pattern was observed for all-cause mortality and for nonfatal CVD (data not shown).

When we stratified for the presence of type 2 diabetes, no differences were observed in the relationships for all-cause and CVD mortality, or for nonfatal CVD (data not shown). For all-cause and CVD mortality analyses of the entire study population, we observed *P* values for interaction terms of prevalent CVD with dummy variables of adiponectin quartiles all less than 0.15. Therefore, we performed subgroup analyses and found that high adiponectin was associated with increased mortality risk in both sexes with prevalent CVD at baseline (Table 5). In women without prevalent CVD, the mortality risk was reduced in higher adiponectin quartiles, and in men there was a U-shaped associ-

TABLE 1. Baseline characteristics for women according to quartiles of adiponectin

	Quartiles of adiponectin				Partial correlation[a]	*P* value[b]
	1 (n = 310)	2 (n = 314)	3 (n = 311)	4 (n = 313)		
Adiponectin (μg/liter)	8.10 ± 1.59	12.10 ± 1.07	16.01 ± 1.28	24.61 ± 5.87		
Age (yr)	61.2 ± 7.3	60.9 ± 7.4	61.7 ± 7.3	63.6 ± 7.5	0.154	<0.001
BMI (kg/m^2)	27.9 ± 4.0	27.5 ± 4.1	26.4 ± 4.1	25.7 ± 3.5	−0.235	<0.001
WHR	0.88 ± 0.07	0.85 ± 0.07	0.84 ± 0.07	0.82 ± 0.07	−0.360	<0.001
Waist (cm)	91.1 ± 10.3	88.6 ± 10.8	86.3 ± 10.1	83.3 ± 10.2	−0.307	<0.001
Hip (cm)	103.4 ± 7.5	103.8 ± 7.9	102.6 ± 7.7	101.9 ± 7.4	−0.090	0.004
Use of antihypertensives (%)	31.3	25.5	14.2	19.5		<0.001
Diastolic bp (mm Hg)	82.6 ± 10.7	80.9 ± 10.2	80.0 ± 10.4	79.7 ± 10.8	−0.121	<0.001
Systolic bp (mm Hg)	138.5 ± 21.5	134.4 ± 20.9	134.2 ± 20.6	133.4 ± 20.7	−0.143	<0.001
Cholesterol (mmol/liter)	7.02 ± 1.35	6.78 ± 1.18	6.88 ± 1.17	6.82 ± 1.15	−0.038	0.232
HDL cholesterol (mmol/liter)	1.23 ± 0.90	1.40 ± 0.33	1.50 ± 0.31	1.65 ± 0.39	0.449	<0.001
Triglycerides (mmol/liter)	2.09 ± 1.22	1.56 ± 1.02	1.33 ± 0.53	1.21 ± 0.54	−0.417	<0.001
Insulin (pmol/liter)	104.9 ± 52.0	88.8 ± 51.4	77.5 ± 33.2	76.3 ± 41.5	−0.260	<0.001
Glucose (mmol/liter)	6.23 ± 2.20	5.72 ± 1.67	5.53 ± 1.21	5.41 ± 1.40	−0.221	<0.001
2-h glucose (mmol/liter)	7.24 ± 3.84	6.34 ± 3.10	5.85 ± 2.92	5.50 ± 1.93	−0.275	<0.001
HbA_{1c} (%)	5.77 ± 1.16	5.49 ± 0.86	5.40 ± 0.70	5.35 ± 0.69	−0.190	<0.001
GFR (ml/min·1.73 m^2)	75.9 ± 18.2	73.7 ± 15.7	70.5 ± 14.6	67.6 ± 14.2	−0.155	<0.001
ALT (IU/liter)	12.7 ± 12.6	11.0 ± 5.8	11.2 ± 6.1	10.0 ± 4.8	−0.137	<0.001
Current cig smoker (%)	37.3	28.6	27.7	19.4		<0.001
Cig years[c]	270 ± 325	219 ± 319	212 ± 310	163 ± 264	−0.112	<0.001
Alcohol (g/d)	5.3 ± 8.5	5.8 ± 9.7	6.2 ± 9.9	5.0 ± 7.6	0.004	0.090
Sport activity (%)	25.7	26.3	30.3	33.9		0.013
CVD (%)	19.4	16.9	11.9	17.4		0.235

Continuous data are presented as means ± SD and categorical data as percentages. bp, Blood pressure; Cig, cigarette; HbA_{1c}, glycosylated hemoglobin; WHR, waist to hip ratio.

[a] Partial (Pearson) correlations are age adjusted, except for age.

[b] *P* values are for partial correlation coefficients for continuous variables, or for the χ^2 test with *P* for linear-by-linear test for proportions.

[c] Product of number of cigarettes per day and years smoked.

TABLE 2. Baseline characteristics for men according to quartiles of adiponectin

	Quartiles of adiponectin				Partial correlation[a]	*P* value[b]
	1 (n = 267)	2 (n = 261)	3 (n = 277)	4 (n = 272)		
Adiponectin (μg/liter)	5.54 ± 0.95	7.85 ± 0.60	10.27 ± 0.83	15.58 ± 3.71		
Age (yr)	58.3 ± 6.3	60.5 ± 6.8	61.7 ± 7.4	63.7 ± 7.2	0.208	<0.001
BMI (kg/m²)	27.0 ± 2.9	26.7 ± 2.9	25.9 ± 2.9	25.1 ± 2.7	−0.264	<0.001
WHR	0.96 ± 0.06	0.96 ± 0.06	0.94 ± 0.07	0.93 ± 0.06	−0.250	<0.001
Waist (cm)	97.1 ± 8.5	96.8 ± 8.7	94.6 ± 9.4	92.4 ± 8.7	−0.255	<0.001
Hip (cm)	101.0 ± 5.5	100.8 ± 5.3	100.1 ± 5.3	99.0 ± 5.3	−0.151	<0.001
Use of antihypertensives (%)	21.0	19.5	20.6	8.8		0.001
Diastolic bp (mm Hg)	84.6 ± 9.2	84.0 ± 9.2	83.0 ± 9.9	82.7 ± 11.0	−0.094	0.006
Systolic bp (mm Hg)	135.1 ± 18.1	134.8 ± 18.3	133.7 ± 17.7	136.9 ± 21.4	−0.084	0.015
Cholesterol (mmol/liter)	6.37 ± 1.12	6.47 ± 1.14	6.34 ± 1.08	6.48 ± 1.13	0.042	0.221
HDL cholesterol (mmol/liter)	1.07 ± 0.29	1.13 ± 0.24	1.18 ± 0.29	1.32 ± 0.34	0.304	<0.001
Triglycerides (mmol/liter)	2.06 ± 1.41	1.75 ± 0.87	1.53 ± 0.71	1.38 ± 0.70	−0.247	<0.001
Insulin (pmol/liter)	97.5 ± 53.2	95.3 ± 61.5	88.1 ± 59.6	74.2 ± 49.7	−0.190	<0.001
Glucose (mmol/liter)	5.95 ± 1.44	5.95 ± 1.57	5.71 ± 1.18	5.55 ± 1.15	−0.199	<0.001
2-h glucose (mmol/liter)	6.61 ± 3.40	6.07 ± 3.20	5.53 ± 2.45	5.27 ± 1.87	−0.220	<0.001
HbA_{1c} (%)	5.54 ± 0.84	5.51 ± 0.91	5.42 ± 0.66	5.47 ± 0.69	−0.096	0.006
GFR (ml/min·1.73 m²)	86.4 ± 16.9	80.8 ± 14.4	78.8 ± 16.5	74.5 ± 17.7	−0.133	<0.001
ALT (IU/liter)	17.8 ± 13.3	14.8 ± 8.9	13.6 ± 6.7	12.3 ± 7.8	−0.157	<0.001
Current cig smoker (%)	33.8	37.6	38.9	36.7		0.456
Cig years[c]	433 ± 405	505 ± 444	507 ± 422	563 ± 558	0.087	0.012
Alcohol (g/d)	14.4 ± 15.0	14.0 ± 16.2	11.1 ± 12.8	11.7 ± 13.2	−0.046	0.184
Sport activity (%)	28.6	23.9	25.8	21.8		0.117
CVD (%)	19.1	22.4	24.9	18.8		0.895

Continuous data are presented as means ± SD and categorical data as percentages. bp, Blood pressure; Cig, cigarette; HbA_{1c}, glycosylated hemoglobin; WHR, waist to hip ratio.

[a] Partial (Pearson) correlations are age adjusted, except for age.

[b] *P* values are for partial correlation coefficients for continuous variables, or for the χ^2 test with *P* for linear-by-linear test for proportions.

[c] Product of number of cigarettes per day and years smoked.

ation with reduced risk in the second and increased risk in the third and fourth adiponectin quartile. After adjustments for cardiovascular risk factors (according to the fully adjusted model in Table 4), the HR [with 95% confidence interval (CI)] for cardiovascular mortality including both sexes was 1.38 (1.06–1.80) for patients without and 1.60 (1.14–2.23) for patients with CVD per SD change in log adiponectin. Accordingly, the HR for all-cause mortality was 1.33 (1.15–1.55) for patients without and 1.69 (1.33–2.16) for patients with prevalent CVD, with similar results for sex-stratified analyses (data not shown).

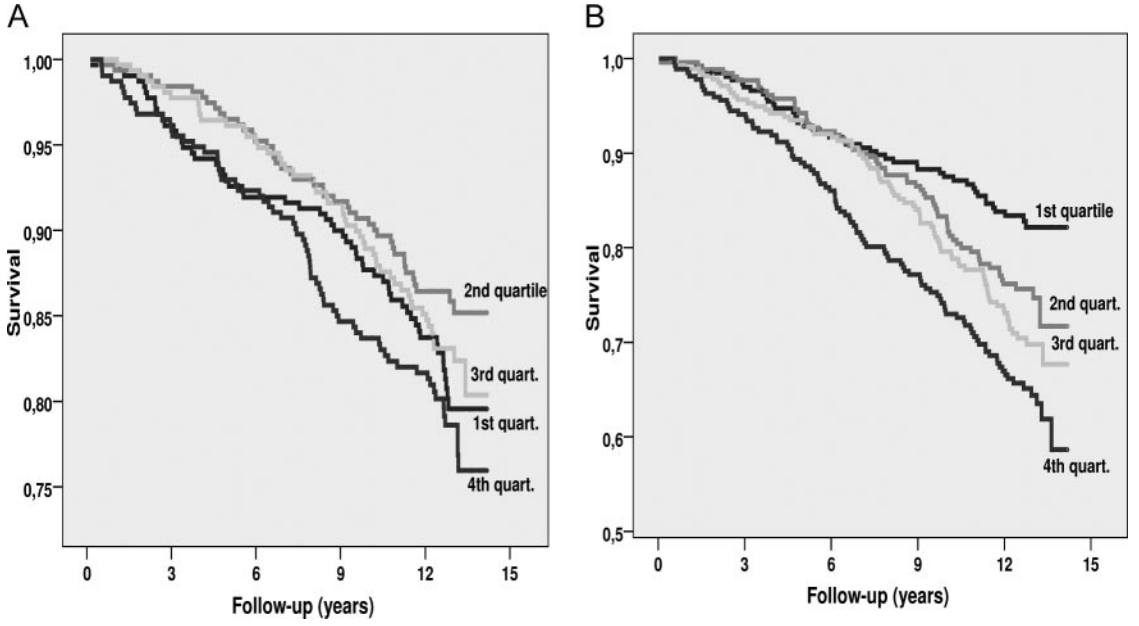

FIG. 1. A, Fifteen-year all-cause mortality according to quartiles (quart) of adiponectin in women. B, Fifteen-year all-cause mortality according to quartiles of adiponectin in men.

TABLE 3. Age-adjusted HRs (with 95% CI) for 15-yr all-cause mortality, 15-yr CVD mortality, and 10-yr nonfatal CVD in sex-specific quartiles of adiponectin

	15-yr all-cause mortality	15-yr CVD mortality	10-yr nonfatal CVD
Women			
Participants at risk	1248	1220	909
Events	219	83	128
First quartile	1.00 Reference	1.00 Reference	1.00 Reference
Second quartile	0.74 (0.50–1.10)	0.74 (0.40–1.39)	0.66 (0.42–1.06)
Third quartile	0.84 (0.58–1.23)	0.60 (0.31–1.15)	0.56 (0.36–0.91)
Fourth quartile	0.92 (0.64–1.31)	0.88 (0.51–1.53)	0.44 (0.27–0.72)
Continuous[a]	0.98 (0.86–1.12)	0.93 (0.75–1.15)	0.72 (0.61–0.90)
Men			
Participants at risk	1077	1042	845
Events	286	121	195
First quartile	1.00 Reference	1.00 Reference	1.00 Reference
Second quartile	1.17 (0.80–1.73)	1.14 (0.64–2.03)	0.86 (0.57–1.30)
Third quartile	1.26 (0.87–1.82)	1.34 (0.77–2.33)	0.99 (0.67–1.46)
Fourth quartile	1.41 (0.98–2.03)	1.13 (0.64–2.00)	0.73 (0.47–1.11)
Continuous[a]	1.13 (1.00–1.28)	1.07 (0.89–1.29)	0.92 (0.79–1.06)

[a] HR per SD change in log-transformed adiponectin.

The results for the subgroup with available data for nonfatal CVD events were similar to those from the entire study population. In this subgroup, the age-adjusted HRs for all-cause mortality were 0.98 (0.79–1.23) for women and 1.17 (0.92–1.49) for men with no history of CVD at baseline, and 1.35 (0.98–1.86) for women and 1.16 (0.86–1.57) for men with prevalent CVD, and the age-adjusted HRs for CVD mortality were 0.81 (0.58–1.13) for women and 0.93 (0.64–1.34) for men without CVD, and 1.26 (0.80–1.99) for women and 1.10 (0.75–1.62) for men with prevalent CVD. For nonfatal events the age-adjusted HRs per SD change in log adiponectin were 0.74 (0.59–0.93) for women and 0.91 (0.73–1.14) for men without CVD at baseline, and 0.73 (0.54–0.99) in women and 0.86 (0.65–1.14) in men with prevalent CVD. Baseline characteristics for the subgroup with available data for nonfatal CVD events were approximately identical to those of the entire study population (data not shown).

Discussion

High adiponectin was associated with a higher age and a beneficial CVD risk profile at baseline in the general Dutch population. Risk of nonfatal CVD was significantly reduced in women with higher adiponectin, and there was a nonsignificant trend for such an association in men. In contrast, high adiponectin was not associated with lower CVD mortality and all-cause mortality, but after adjustment for cardiovascular risk factors, high adiponectin was significantly associated with increased all-cause and cardiovascular mortality. This association of high adiponectin and increased mortality risk was more pronounced in patients with prevalent CVD than in those without. Adiponectin is considered to protect against CVD, mediated by direct effects on the cardiovascular system and by its association with a favorable cardiovascular risk profile (2). Adiponectin inhibits pro-atherogenic processes in endothelial cells, suppresses macrophage tofoam cell formation, and exerts antiinflammatory effects, *e.g.* through inhibition of nuclear factor-κB. Stimulation of AMP-activated kinase by adiponectin reduces insulin resistance, and recent data from the Hoorn Study show that high adiponectin levels are associated with a reduced risk of impaired glucose tolerance and type 2 diabetes (1, 28). Furthermore, several cross-sectional and genetic studies support the notion that low adiponectin levels are associated with all components of the metabolic syndrome and serve as a risk factor for coronary artery disease (1, 2).

TABLE 4. Multivariate-adjusted HRs (with 95% CI) for 15-yr CVD mortality in sex-specific quartiles of adiponectin

Adjusted for	Age, BMI, WHR	Age, HDL, triglycerides	Age, glucose, 2 h-glucose	Age, insulin	Age, ALT	Age, GFR, smoking[a]	All previous
Women (1220 study participants at risk with 83 deaths due to CVD)							
First quartile	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Second quartile	0.79 (0.42–1.51)	0.94 (0.49–1.79)	0.88 (0.42–1.86)	0.74 (0.39–1.41)	0.75 (0.40–1.41)	0.86 (0.45–1.69)	1.07 (0.49–2.34)
Third quartile	0.69 (0.36–1.34)	0.91 (0.45–1.82)	0.95 (0.46–1.93)	0.67 (0.34–1.29)	0.61 (0.32–1.17)	0.64 (0.33–1.24)	1.30 (0.60–2.81)
Fourth quartile	1.13 (0.63–2.02)	1.52 (0.81–2.84)	1.36 (0.72–2.65)	0.98 (0.56–1.72)	0.90 (0.52–1.57)	1.01 (0.57–1.78)	2.36 (1.13–4.95)
Continuous[b]	1.04 (0.88–1.31)	1.15 (0.90–1.46)	1.11 (0.87–1.41)	0.99 (0.80–1.23)	0.94 (0.76–1.16)	0.97 (0.79–1.20)	1.45 (1.10–1.92)
Men (1042 study participants at risk with 121 deaths due to CVD)							
First quartile	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Second quartile	1.13 (0.63–2.03)	1.31 (0.72–2.56)	1.20 (0.66–2.18)	1.12 (0.62–2.01)	1.13 (0.63–2.03)	1.10 (0.61–1.97)	1.21 (0.65–1.97)
Third quartile	1.54 (0.88–2.69)	1.61 (0.91–2.86)	1.44 (0.81–2.57)	1.30 (0.74–2.27)	1.33 (0.76–2.03)	1.30 (0.74–2.26)	1.59 (0.88–2.89)
Fourth quartile	1.43 (0.81–2.57)	1.51 (0.82–2.77)	1.24 (0.68–2.56)	1.17 (0.60–2.08)	1.13 (0.63–2.01)	1.12 (0.63–2.01)	1.71 (0.90–3.26)
Continuous[b]	1.19 (0.98–1.45)	1.20 (0.98–1.47)	1.10 (0.91–1.34)	1.09 (0.90–1.33)	1.07 (0.88–1.29)	1.08 (0.89–1.31)	1.30 (1.04–1.63)

WHR, Waist to hip ratio.

[a] Adjustment for current smokers (yes/no) and product of number of cigarettes per day and years smoked.

[b] HR per 1 SD change in log-transformed adiponectin.

TABLE 5. Age- and sex-adjusted HRs (with 95% CI) for 15-yr all-cause mortality and 15-yr CVD mortality in subjects with and without CVD at baseline in sex-specific quartiles of adiponectin

	All		Women		Men	
	15-yr all-cause mortality	15-yr CVD mortality	15-yr all-cause mortality	15-yr CVD mortality	15-yr all-cause mortality	15-yr CVD mortality
No history of CVD						
Participants at risk	1886	1839	1040	1015	846	824
Deaths	340	115	160	51	180	64
First quartile	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Second quartile	0.73 (0.52–1.01)	0.64 (0.37–1.12)	0.58 (0.37–0.93)	0.64 (0.30–1.37)	0.96 (0.59–1.55)	0.73 (0.33–1.64)
Third quartile	0.89 (0.65–1.21)	0.72 (0.43–1.21)	0.70 (0.46–1.07)	0.42 (0.19–0.95)	1.19 (0.76–1.87)	1.18 (0.57–2.41)
Fourth quartile	0.96 (0.71–1.29)	0.77 (0.47–1.27)	0.73 (0.48–1.10)	0.64 (0.32–1.31)	1.32 (0.85–2.04)	1.03 (0.51–2.12)
Continuous[a]	1.00 (0.89–1.13)	0.90 (0.73–1.11)	0.90 (0.76–1.06)	0.79 (0.32–1.31)	1.14 (0.96–1.36)	1.07 (0.80–1.48)
History of CVD						
Participants at risk	433	417	204	201	229	216
Deaths	164	88	59	32	105	56
First quartile	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference	1.0 Reference
Second quartile	1.52 (0.92–2.50)	1.39 (0.71–2.74)	1.38 (0.64–2.99)	1.08 (0.36–3.22)	1.57 (0.80–3.05)	1.64 (0.67–4.04)
Third quartile	1.36 (0.82–2.26)	1.35 (0.68–2.66)	1.75 (0.77–3.99)	1.70 (0.59–5.32)	1.23 (0.63–2.39)	1.32 (0.54–3.27)
Fourth quartile	1.89 (1.16–3.06)	1.64 (0.85–3.17)	1.85 (0.91–3.76)	1.70 (0.67–4.29)	1.87 (0.95–3.67)	1.60 (0.63–4.11)
Continuous[a]	1.29 (1.07–1.55)	1.27 (0.98–1.63)	1.31 (1.00–1.72)	1.32 (0.91–1.91)	1.27 (0.99–1.63)	1.22 (0.87–1.73)

[a] HR per 1 SD change in log-transformed adiponectin.

However, several recent studies on the prospective association between adiponectin and CVD events/mortality showed inconsistent results (5–23). Unexpectedly, several of these studies, in particular those including patients already afflicted with or at high risk for CVD, found that high adiponectin was associated with an increased risk of mortality (17, 18, 20–23). As an explanation for these results, it was hypothesized that in CVD, a counter-regulatory increase of adiponectin occurs that represents a defense mechanism of the body against the cardiovascular alterations and the pro-inflammatory state associated with CVD (24, 25). This is in line with our results because we show that high adiponectin is significantly associated with an increased mortality risk, in particular, in patients with prevalent CVD. These findings fit well with observations that adiponectin exerts protective functions in early atherosclerosis by reducing a pro-atherogenic endothelial activation, but in patients with vascular diseases, adiponectin was positively correlated with serum concentrations of markers of endothelial activation/injury like CD146 or vascular cell adhesion molecule-1, suggesting a possible up-regulation of adiponectin in response to endothelial damage (2, 29, 30). It was also implicated that inflammation, lipotoxicity, and oxidative stress increased adiponectin expression, whereas adiponectin counteracts these pro-atherogenic influences by its antiinflammatory and antioxidative properties (1, 2, 31–33). Furthermore, it was shown that adiponectin increases in patients with myocardial dysfunction, although adiponectin is suggested to protect against heart failure because it attenuates cardiac hypertrophy (2, 18, 22, 23). All these data suggest that adiponectin protects against CVD, but it may be compensatory up-regulated in response to cardiovascular damage, or due to the wasting process in heart failure with elevation of adiponectin as a consequence of weight loss (22). Weight loss and malnutrition, both associated with high adiponectin, predict mortality in patients with CVD, and could, therefore, partially account for the relationship between high adiponectin and mortality (1, 34, 35). Our results of an association between adiponectin and mortality in patients with CVD fit well with the concept of "reverse epidemiology," a term that is used to describe the inverse association between traditional cardiovascular risk factors (*e.g.* BMI) and mortality in patients with heart and renal failure (34, 35). However, in the present study, adjustment for BMI did not explain the associations between adiponectin and mortality. Alternatively, "adiponectin resistance," possibly due to down-regulation of adiponectin receptors as reported in obesity and insulin resistance, could also trigger a counter-regulatory increase of adiponectin in high-risk patients with prevalent CVD (1).

It should also be noted that adiponectin serum concentrations are inversely correlated with GFR and are increased in patients with albuminuria (18, 21, 29, 30). Underlying mechanisms for the elevation of adiponectin in chronic kidney disease remain unclear but may at least in part be due to reduced renal clearance (36). However, GFR in the present study could not explain the association between high adiponectin and high mortality risk. Apart from this, adiponectin correlates with age and might, therefore, also be compensatory up-regulated in the aging process of the body.

Finally, it cannot be excluded that adiponectin also exerts harmful effects that contribute to the increased mortality risk associated with high adiponectin. Toward this, it could be speculated that beneficial effects of adiponectin might become deleterious in advanced disease stages of CVD, in particular when the compensatory increase of adiponectin is overwhelming. In this context the ability of adiponectin to decrease body weight, mediated by increases in energy expenditure and by central effects in the brain, might be harmful in advanced stages of CVD, when a decline in body weight is associated with an adverse cardiovascular outcome (1, 34, 35, 37). Considering that adiponectin-mimetic therapies have been suggested to be introduced in the treatment of metabolic and CVD (1, 2), it will be important to elucidate the underlying mechanisms for the asso-

ciation between adiponectin and mortality, and to monitor carefully therapeutic interventions that aim to enhance the secretion or action of adiponectin.

Apart from low concentrations of a globular form that is cleaved from the full-length protein, adiponectin forms multimers that circulate in plasma in a low-, middle-, and high-molecular weight form (1, 2). These isoforms have different binding affinities to the adiponectin receptors (AdipoR1 and AdipoR2) and may, therefore, exert different bioactivities. Recent data indicate that the high-molecular weight form is the most active and clinically relevant form, at least for the metabolic and vascular-protective effects of adiponectin (1, 2, 38, 39). However, it was shown that globular adiponectin may contribute to myocardial hypertrophy, suggesting that not all isoforms of adiponectin protect against CVD (40).

A limitation of the present study may be that the different isoforms of adiponectin were not determined because at the time of our measurements, the recently developed ELISA systems were not available (39). Furthermore, information on nonfatal CVD was available for a subpopulation, and for a shorter follow-up period. To exclude the possibility that the differences in population size and follow-up duration explain the differences in the associations between adiponectin and nonfatal CVD and mortality, we also studied 10-yr all-cause and CVD mortality in the same subcohort. The associations did not differ from those observed in the total cohort, and for a longer follow-up duration.

During the revision process of our manuscript, other data from older men were published that confirm a positive association between adiponectin and mortality, with the most significant results for patients with heart failure (41).

In conclusion, high plasma adiponectin level is associated with a favorable lipid and glucose metabolism, and with a reduced risk of CVD events in women. However, higher adiponectin was associated with an increased risk of mortality, in particular in people with a history of CVD. We hypothesize that adiponectin protects against metabolic and vascular diseases, but in patients already afflicted with CVD, adiponectin is compensatory up-regulated in advanced disease stages and, therefore, indicates a high mortality risk in these patients. It remains a challenge for the near future to elucidate further the underlying mechanisms for our results.

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