

# Serum Adiponectin Is a Predictor of Coronary Heart Disease: A Population-Based 10-Year Follow-Up Study in Elderly Men

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**Context:** Cross-sectional and nested case-control studies indicate a relationship between adiponectin, obesity, and coronary heart disease (CHD).

**Objective:** Our objective was to investigate whether adiponectin could predict CHD in a population-based cohort of elderly men.

**Design and Setting:** From 1991–1995 a baseline investigation was carried out in 832 healthy men aged 70 yr in the Uppsala Longitudinal Study of Adult Men (ULSAM study). They were followed up to 10.4 yr using Swedish national registry data. The baseline investigation included anthropometry, blood pressure, smoking, serum lipids, a euglycemic insulin clamp, and fasting serum adiponectin.

**Main Outcome Measures:** Main outcome measures were defined as death or first-time hospitalization for CHD (n = 116), recorded in the Cause of Death Registry or in the Hospital-Discharge Registry of the National Board of Health and Welfare, Sweden. Associations were

analyzed using Cox's proportional hazards regression, presented as hazard ratios (HR) with 95% confidence intervals (CI) for 1 SD increase in the predictor variable.

**Results:** In a multivariable analysis including total cholesterol (HR, 1.24; CI, 1.02–1.50), high-density lipoprotein cholesterol (HR, 0.72; CI, 0.58–0.89), smoking (HR, 1.39; CI, 0.91–2.14), and systolic blood pressure (HR, 1.26; CI, 1.05–1.52), serum adiponectin was associated with lower risk for CHD (HR, 0.81; CI, 0.66–0.99). The association was independent of BMI and remained significant after adjustment for insulin sensitivity index.

**Conclusions:** In this population-based cohort of healthy men, elevated serum levels of adiponectin were associated with a lower risk for CHD. Importantly, the association between adiponectin and CHD was independent of other well-known risk factors. (*J Clin Endocrinol Metab* 92: 571–576, 2007)

**A**DIPONECTIN IS AN adipocyte-derived protein that has gained considerable interest due to its positive effects on insulin sensitivity (1), atherosclerosis (2, 3), and inflammation (3, 4), hereby linking adipose tissue with the cornerstones of the metabolic syndrome.

There is substantial experimental and clinical evidence that adiponectin protects the vascular endothelium against the processes leading to atherosclerosis (5, 6). Experimentally, adiponectin knockout animals show an increased neointimal formation after vascular injury as compared with wild-type littermates (7), whereas adiponectin-deficient mice infected with an adenovirus overexpressing mouse adiponectin showed a normal vascular response to injury (3). Furthermore, in the ApoE-deficient mouse, a model of accelerated atherosclerosis, breeding with adiponectin transgenic mice inhibited the progression of atherosclerosis despite an unaltered glucose and lipid metabolism, suggesting that adiponectin possessed direct antiatherogenic actions (8).

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Abbreviations: BMI, Body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval(s); CV, coefficient(s) of variation; HDL, high-density lipoprotein; HR, hazards ratio(s); ICD, International Classification of Diseases; M/I, insulin sensitivity index; OR, odds ratio.

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In keeping with the experimental support for a vasoprotective effect of adiponectin, several clinical investigations based on cross-sectional study cohorts have reported on reduced circulating adiponectin levels in patients with verified coronary heart disease (CHD) (9–11). However, some studies have not been able to demonstrate an association between low levels of adiponectin and an increased risk for CHD (12), and others have shown that the relationship becomes insignificant after adjustment for high-density lipoprotein (HDL) cholesterol (13, 14). On the other hand, nested case control studies have shown that healthy subjects with adiponectin levels within the upper 20% range have a 2-fold reduced risk for myocardial infarction (15) and a 7-fold reduced risk for progression of coronary artery calcification (16). We are not aware of studies describing the relationship between adiponectin and the risk for CHD in population-based cohorts.

Insulin resistance is a major risk factor for the development of atherosclerosis (17, 18), and it also affects plasma levels of adiponectin, which become gradually decreased with increasing insulin resistance (6, 19). Although adiponectin exerts potent insulin-sensitizing actions in experimental *in vivo* models (1, 8, 20), it remains to be clarified whether the inverse association between adiponectin and insulin sensitivity is a cause-effect relationship (6). Thus, it could be speculated that the observed relationship between adiponectin and the risk for CHD simply reflects changes in insulin sensitivity. Based on these considerations, we found it of interest to study the

risk for CHD and its relationship with plasma adiponectin and measures of insulin sensitivity in a population-based cohort of healthy 70-yr-old men followed for more than 10 yr.

## Subjects and Methods

### Subjects

In 1970, all men (predominantly Caucasians) born between 1920 and 1924 and residing in Uppsala, Sweden, were invited to a health survey. Eighty-two percent ( $n = 2322$ ) agreed to participate (21). After 20 yr, at age 70, they were invited for reinvestigation performed between August 1991 and May 1995. This reinvestigation formed the baseline of the present study and comprised 1221 men of 1681 still alive (73%) (17, 22, 23).

CHD mortality and morbidity data were collected from the official Swedish registries held by The Centre for Epidemiology, National Board of Health and Welfare, in Sweden. At the reinvestigation, all information on medical history and ongoing current pharmacological treatment was registered using the original protocol questionnaire (21). The study was approved by the Ethics Committee at the Faculty of Medicine at Uppsala University, Sweden. Written informed consent was obtained from all subjects.

### Cross-sectional study population

Prevalent CHD at baseline (*i.e.* from August 1991 to May 1995) was defined as first-time hospitalization for CHD, which was diagnosed according to International Classification of Diseases (ICD), ninth revision (ICD-9), codes 410–414 and 10th revision (ICD-10), codes I20–25, as recorded in the Hospital-Discharge Registry.

### Longitudinal study population, follow-up, and outcome

To select subjects free from cardiovascular disease at baseline, 351 men were excluded due to the presence of 1) prior myocardial infarction or angina pectoris; 2) Q or QS complexes or left bundle branch block (Minnesota codes 1.1–1.3 or 7.1, respectively) in the baseline ECG registration; 3) previous or incident cardiovascular disease (ICD codes 390–459 in the ICD-9, equivalent to ICD codes I00–I99 in the ICD-10) up to 1 yr after baseline or current treatment with nitroglycerine or cardiac glycosides. After these exclusions, the main analysis comprised 870 men. An additional 38 subjects were excluded due to lack of baseline data, leaving 832 subjects with complete baseline data to be included in the follow-up study.

**Follow-up data.** Cases were defined as subjects dying from CHD or subjects with first-time hospitalization due to CHD. Deaths from CHD were identified using records from the Cause of Death Registry. First-time hospitalizations due to CHD were identified using records from the Hospital Discharge Registry (censor date December 31, 2001) and based on ICD-9 codes 410–414 and ICD-10 codes I20–25 (censor date December 31, 2001). CHD morbidity defined by combining data from the Hospital Discharge Registry and the Cause of Death Registry represents an efficient, validated alternative to revised hospital discharge notes and death certificates (24, 25). No subject was lost during follow-up due to missing registry data.

### Immunoassay for adiponectin

Serum was collected in the morning after fasting overnight and stored at  $-70^{\circ}\text{C}$  from baseline to the time of assay. Serum adiponectin was analyzed blinded to outcome using a validated in-house time-resolved immunofluorometric assay based on commercial reagents from R&D Systems (Abingdon, UK) as recently described (26). All samples were analyzed in duplicate in a final dilution of 1 in 206. Within-assay coefficients of variation (CV) of standards and unknown samples averaged less than 5%. Between-assay CV were estimated by repetitive analysis of a control sample diluted 1:2500, 1:500, and 1:50, respectively. After 111 set-ups, between-assay CV averaged 5.9% at  $4.8\ \mu\text{g/liter}$  (final dilution 1:2500), 3.6% at  $23\ \mu\text{g/liter}$  (final dilution 1:500), and 2.7% at  $234\ \mu\text{g/liter}$

(final dilution 1:50). The recovery of exogenously added adiponectin to serum was  $101 \pm 1\%$  (means  $\pm$  SEM based on 10 samples). Repetitive thawing and freezing of serum for up to seven cycles did not alter the immunoreactive levels of adiponectin significantly (data not shown).

### Other measurements

Insulin sensitivity was determined with the euglycemic insulin clamp technique as previously described (17, 27). The insulin sensitivity index (M/I) was calculated as glucose disposal rate (milligrams glucose infused per minute per kilogram body weight) divided by the mean plasma insulin concentration  $\times 100$  (mU/liter) during the last 60 min of the 2-h clamp. Concentrations of plasma glucose were analyzed by the glucose dehydrogenase method (Gluc-DH; Merck, Darmstadt, Germany). The concentrations of intact proinsulin and 32–33 split proinsulin were analyzed using the two-site immunometric assay technique as previously described (22). Specific insulin concentrations were also determined in these samples using the Access Immunoassay System (Sanofi Pasteur Diagnostics, Marnes La Coquette, France) (22). In the present study cohort, data derived from the euglycemic insulin clamp as well as measurements of proinsulin and insulin and their longitudinal relationships with CHD have previously been published (17).

Serum total and HDL cholesterol, supine systolic and diastolic blood pressure (BP), weight, height, body mass index (BMI) ( $\text{kg}/\text{m}^2$ ), and waist circumference were measured and an electrocardiogram was recorded under standardized conditions (22, 23).

For both study cohorts, the presence of diabetes, hypertension, and dyslipidemia was defined as follows: diabetes, a fasting plasma glucose of at least  $7.0\ \text{mmol/liter}$  and/or diabetes medication (insulin or oral); hypertension, a systolic BP of at least  $140\ \text{mm Hg}$  and/or diastolic BP of at least  $90\ \text{mm Hg}$  and/or hypertension treatment; dyslipidemia, serum triglyceride of at least  $1.7\ \text{mmol/liter}$  and/or HDL cholesterol less than  $0.9\ \text{mmol/liter}$  and/or drugs for dyslipidemia.

### Statistical analyses

All statistical tests were specified *a priori*. Skewed variables (adiponectin, M/I, insulin, insulin propeptides, HDL cholesterol, and glucose) were log transformed to achieve normal distribution. Normally distributed variables were used in all statistical analyses, performed using the statistical software package SAS 8.0 for PC (SAS Institute, NC). All tests were two tailed, and  $P$  values  $< 0.05$  were considered significant. In a hierarchical order, primary and secondary analyses were performed. Primary analyses concerned the univariate cross-sectional and longitudinal associations between adiponectin and CHD, respectively. Secondary cross-sectional and longitudinal association analyses with CHD were performed on the other variables presented in Tables 1 and 2 because these may be related to the outcome CHD or to adiponectin concentrations.

In the cross-sectional analyses, logistic regression analyses were used on standardized variables (standardized to 1 SD) to determine the magnitude of the relationship to, and the statistical significance of, the predictor adiponectin of the defined outcome. For a number of variables of secondary interest, we have performed similar analyses. In the multivariable models investigating associations with adiponectin and CHD, separate analyses were made with adjustments for the conventional risk factors for CHD and the possible confounding effects of M/I, proinsulin, waist circumference, and BMI. To study possible multiplicative effects of significant predictors, interaction terms between significant predictors of CHD were tested within the multivariable models.

In the prospective analyses, Cox's proportional hazard regression models were used. Hazard ratios (HR) with two-tailed 95% confidence intervals (CI) were estimated for a 1 SD increase in a continuous variable and for a one-step increase in the dichotomous variable smoking to determine the magnitude of the relationship to, and the statistical significance of, the predictors of the defined outcome. All analyses were adjusted for age at baseline. A Kaplan-Meier graph was also performed for adiponectin below compared with adiponectin above the median and CHD as the outcome.

**TABLE 1.** Cross-sectional study comparing subjects with and without CHD at baseline

	Mean $\pm$ SD (n = 1221)	OR (95% CI), P value	Mean $\pm$ SD (non-CHD) (n = 1073)	Mean $\pm$ SD (CHD) (n = 148)
Age (yr)	71.0 $\pm$ 0.6	1.07 (0.90–1.26), 0.45	71.0 $\pm$ 0.6	71.0 $\pm$ 0.7
Adiponectin (mg/liter)	10.4 $\pm$ 4.3	0.84 (0.71–1.00), 0.049	10.4 $\pm$ 4.4	9.7 $\pm$ 4.0
Serum total cholesterol (mmol/liter)	5.8 $\pm$ 1.0	1.11 (0.93–1.31), 0.26	5.8 $\pm$ 1.0	5.9 $\pm$ 1.1
Serum HDL cholesterol (mmol/liter)	1.28 $\pm$ 0.35	0.68 (0.57–0.82), 0.001	1.30 $\pm$ 0.35	1.18 $\pm$ 0.31
Systolic BP (mm Hg)	147 $\pm$ 18	0.77 (0.64–0.92), 0.005	147 $\pm$ 18	143 $\pm$ 18
Diastolic BP (mm Hg)	84 $\pm$ 9	0.69 (0.58–0.82), 0.001	84 $\pm$ 9	81 $\pm$ 10
M/I (mg·min <sup>-1</sup> ·kg <sup>-1</sup> /100 mU/liter)	5.0 $\pm$ 2.5	0.68 (0.57–0.82), 0.001	5.1 $\pm$ 2.5	4.2 $\pm$ 2.2
Intact proinsulin (pmol/liter)	8.5 $\pm$ 8.6	1.56 (1.31–1.84), 0.001	8.2 $\pm$ 8.5	11.0 $\pm$ 8.5
32–33 split proinsulin (pmol/liter)	11.0 $\pm$ 12.0	1.53 (1.28–1.82), 0.001	10.5 $\pm$ 11.6	15.1 $\pm$ 14.4
Specific insulin (pmol/liter)	52.7 $\pm$ 45.2	1.55 (1.30–1.85), 0.001	50.9 $\pm$ 44.5	66.2 $\pm$ 48.5
Fasting plasma glucose (mmol/liter)	5.8 $\pm$ 1.5	1.22 (1.05–1.42), 0.009	5.7 $\pm$ 1.4	6.0 $\pm$ 1.6
BMI (kg/m <sup>2</sup> )	26.3 $\pm$ 3.4	1.44 (1.22–1.69), 0.001	26.1 $\pm$ 3.4	27.5 $\pm$ 3.8
Waist circumference (cm)	94.8 $\pm$ 9.7	1.34 (1.13–1.59), 0.001	94.4 $\pm$ 9.6	97.4 $\pm$ 10.0
Smoking (%)	21	0.76 (0.48–1.21), 0.24	22	17

Data are arithmetic mean  $\pm$  SD and odds ratios with 95% CI and *P* values. Logistic regression was applied to variables standardized to 1 SD (except smoking) and adjusted for age at baseline. Means for subjects with and without CHD events during follow-up are also shown. The *P* values were not corrected for multiple testing because we found this correction too conservative (*i.e.* the level of significance would be as low as 0.004). However, we acknowledge that the lack of correction increases the possibility of type 1 errors.

## Results

### Cross-sectional study at the age of 70

The clinical baseline characteristics for the entire population and for subjects with and without CHD are presented in Table 1. As can be seen, the baseline prevalence of CHD was 12.1% (148 of 1221). Of the 1221 subjects, 131 (10.7%) suffered from diabetes, 908 (74.4%) from hypertension, and 443 (36.3%) from dyslipidemia.

Adiponectin concentrations were slightly but significantly lower in subjects with than without CHD (*P* < 0.05). HDL cholesterol and systolic and diastolic BP were lower among subjects with CHD (*P* < 0.005), whereas neither total cholesterol nor smoking habits differed significantly. M/I was lower, whereas plasma levels of intact proinsulin, 32–33 split proinsulin, intact insulin, and fasting glucose as well as waist circumference and BMI were higher in subjects with CHD (*P* < 0.05; Table 1).

In multivariable regression analyses modeling, adiponectin [odds ratio (OR), 0.81; CI, 0.67–0.97; *P* = 0.021] significantly predicted CHD after adjustment for classical risk factors such as systolic BP (OR, 0.75; CI, 0.62–0.91; *P* = 0.003), total cholesterol (OR, 1.15; CI, 0.96–1.38; *P* = 0.12) and smok-

ing (OR, 0.73; CI, 0.46–1.17; *P* = 0.19). However, when the relationship between adiponectin and CHD was adjusted for significant CHD predictors such as HDL cholesterol (OR, 0.69; CI, 0.56–0.84; *P* = 0.001), M/I (OR, 0.68; CI, 0.55–0.84; *P* = 0.001), fasting proinsulin (OR, 1.57; CI, 1.31–1.89; *P* = 0.001), BMI (OR, 1.41; CI, 1.19–1.67; *P* = 0.001), and waist circumference (OR, 1.31; CI, 1.10–1.57; *P* = 0.003), adiponectin was no longer a significant predictor of CHD (all *P* values > 0.35).

### Longitudinal 10.4-yr follow-up study

Baseline clinical characteristics at the age of 70 and standardized crude HR for a first CHD event during follow-up are shown in Table 2. Of the 832 subjects, 71 (8.5%) suffered from diabetes, 411 (49.4%) from hypertension, and 172 (20.7%) from dyslipidemia.

Median follow-up was 7.9 yr (maximum 10.4 yr), with a total of 5972 person-years at risk. During follow-up, 116 of 832 subjects had a CHD event (rate 1.94 per 100 person-years at risk; incidence, 13.9%). The mortality of CHD was 44.0% (51 of 116). Baseline concentrations of adiponectin were negatively associated with CHD development, and 1 SD increase

**TABLE 2.** Longitudinal study: clinical characteristics at baseline and HR for CHD (n = 116) over the 10.4-yr follow-up period

	Mean $\pm$ SD (n = 832)	HR (95% CI)	<i>P</i> value
Age (yr)	71.0 $\pm$ 0.6	1.02 (0.73–1.14)	0.92
Adiponectin (mg/liter)	10.3 $\pm$ 4.2	0.77 (0.64–0.92)	0.005
Total cholesterol (mmol/liter)	5.8 $\pm$ 1.0	1.14 (0.95–1.36)	0.15
HDL cholesterol (mmol/liter)	1.31 $\pm$ 0.35	0.74 (0.61–0.88)	0.001
Systolic BP (mm Hg)	147 $\pm$ 18	1.20 (1.01–1.43)	0.041
Diastolic BP (mm Hg)	84 $\pm$ 9	1.01 (0.99–1.03)	0.18
M/I (mg·min <sup>-1</sup> ·kg <sup>-1</sup> /100 mU/liter)	5.2 $\pm$ 2.5	0.84 (0.70–1.02)	0.074
Intact proinsulin (pmol/liter)	8.0 $\pm$ 8.2	1.25 (1.05–1.49)	0.011
32–33 split proinsulin (pmol/liter)	10.3 $\pm$ 11.7	1.21 (1.01–1.45)	0.037
Specific insulin (pmol/liter)	49.6 $\pm$ 35.3	1.05 (0.87–1.26)	0.61
Fasting plasma glucose (mmol/liter)	5.7 $\pm$ 1.4	1.22 (1.06–1.41)	0.006
BMI (kg/m <sup>2</sup> )	26.0 $\pm$ 3.2	1.06 (0.89–1.27)	0.51
Waist circumference (cm)	94.3 $\pm$ 9.4	1.05 (0.87–1.27)	0.59
Smoking (%)	20.7	1.41 (0.93–2.16)	0.11

Data are arithmetic mean  $\pm$  SD. HR from Cox's proportional hazards regression were applied to variables standardized to 1 SD (except smoking) and adjusted for age at entry. The *P* values were not corrected for multiple testing because we found this correction too conservative (*i.e.* the level of significance would be as low as 0.004). However, we acknowledge that the lack of correction increases the possibility of type 1 errors.

in adiponectin was associated with a 23% reduced risk for CHD ( $P = 0.005$ ; Table 2). Figure 1 shows the Kaplan-Meier survival curves for incident CHD from baseline in the two groups defined by a baseline adiponectin level below or above the median (9.55 mg/liter). The risk for CHD during follow-up was most pronounced in the group with low adiponectin levels ( $P = 0.03$  for difference).

Multivariable regression analyses modeling of the relation between adiponectin and the development of CHD are presented in Table 3. Adiponectin levels adjusted for classical risk factors such as systolic BP, total and HDL cholesterol, smoking, and BMI did not abolish the observed association between adiponectin and CHD (model 1). Similar results were obtained when adjusting adiponectin levels for waist circumference instead of BMI. Of note, in models where the association between adiponectin and CHD was adjusted for M/I (model 2) or intact proinsulin (model 3), the association between adiponectin and CHD remained significant. No significant interactions were observed between the predictors presented in Table 3 (all  $P$  values between 0.15 and 0.99).

### Discussion

The present study is the first of its kind to examine the relationship between adiponectin, indices of insulin sensitivity, and the risk for development of CHD in a population-based cohort. In the cross-sectional analysis, serum adiponectin was associated with a lowered risk for CHD, and this relationship remained significant when adjusting for conventional risk factors (systolic BP, total cholesterol, and smoking), whereas it was abolished when estimates of insulin sensitivity, intact proinsulin, BMI or waist circumference, and HDL cholesterol were taken into account. However, the longitudinal analysis clearly showed an association between low serum levels of adiponectin at baseline and an increased risk for CHD during the 10 yr of follow-up, and importantly, this relationship remained significant after adjustment for various CHD risk factors. Thus, this study provides strong evidence that low circulating levels of adiponectin constitute an independent risk factor for CHD. For the

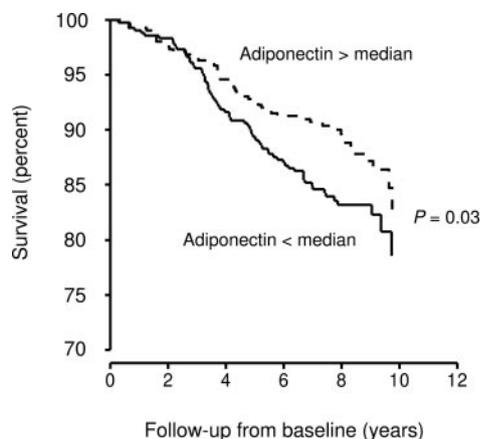


FIG. 1. Kaplan-Meier survival curves for incident CHD during 10.4 yr of follow-up in groups defined by baseline serum adiponectin levels below (solid line) or above (broken line) the median. The risk for CHD was most pronounced in the group with adiponectin levels below the median ( $P = 0.03$  for difference).

TABLE 3. Longitudinal study: multiple HR for CHD ( $n = 116$ ) over the 10.4-yr follow-up period

	HR (95% CI)	$P$ value
Model 1		
Adiponectin	0.81 (0.66–0.99)	0.041
Systolic BP	1.26 (1.05–1.52)	0.012
Serum total cholesterol	1.24 (1.02–1.50)	0.027
Serum HDL cholesterol	0.72 (0.58–0.89)	0.003
Smoking	1.39 (0.91–2.14)	0.13
BMI	0.89 (0.72–1.09)	0.25
Model 2		
Adiponectin	0.80 (0.64–0.98)	0.035
M/I	0.91 (0.73–1.12)	0.361
Model 3		
Adiponectin	0.81 (0.67–0.99)	0.038
Intact proinsulin	1.18 (0.97–1.42)	0.092

Adjustments were made for conventional risk factors and for insulin sensitivity (M/I), intact proinsulin, BMI, and waist. Multiple HR with 95% CI from Cox's proportional hazards regression were applied to variables standardized to 1 SD (except smoking) and adjusted for age at entry.

variables of secondary interest in the present study, the results should as always be interpreted with some precaution.

The relationship between circulating adiponectin and CHD has been investigated by others. Rothenbacher *et al.* (13) observed a gradual reduction in the OR for CHD (minimum OR was 0.42) with increasing serum adiponectin levels in a cross-sectional case-control study comprising patients with angiographically confirmed stable CHD. However, after adjustment for HDL cholesterol, the predictive value of adiponectin became insignificant, for which reason the authors suggested the vasoprotective actions of adiponectin to be mediated in part by its beneficial effects on HDL cholesterol (13). Schulze *et al.* (14) came to a similar conclusion in a 5-yr follow-up study of men with type 2 diabetes mellitus, but they did not take the presence of diabetic nephropathy into account, and this may have biased the outcome (13). Findings in type 2 diabetic Pima and North American Indians have shown that circulating adiponectin increases with deteriorated kidney function and that albuminuria *per se* is associated with increased adiponectin levels even in the setting of a normal serum creatinine (12, 28). So far, two nested case control studies have been published. In males, Pischon *et al.* (15) reported that a doubling in plasma adiponectin was associated with an approximately 20–50% reduction in the risk for CHD after multivariable adjustment, which included lipids. However, Lawlor *et al.* (29) failed to confirm this relationship in females, a finding that made the authors speculate that the effect of adiponectin varied in males and females. Finally, low circulating levels of adiponectin have been suggested to be predictive of CHD in type 1 diabetic patients (30) and to predispose to progressive coronary artery calcification as estimated by computed tomography scan in nondiabetic subjects as well as patients with type 1 diabetes (16).

The variable results observed in the above mentioned studies are most likely explained by differences in study populations and follow-up periods as well as differences in the inclusion of variables that may affect the risk for CHD. Furthermore, because age is a major determinant of CHD, a standardized age at baseline is a major strength, but gener-

alization of results to other ages, different ethnic origin, and female sex cannot be done without reservation. Nevertheless, we believe that adiponectin plays a role in the development of CHD, at least in males. Our cross-sectional analysis showed that the OR for the predictive value of adiponectin for CHD was 0.84 without adjustment and 0.81 after adjustment for classical risk factors such as cholesterols, systolic BP, and smoking, whereas inclusion of indices of insulin sensitivity made the relationship insignificant. More importantly, however, in the 10-yr follow-up study, 1 SD increase in serum adiponectin reduced the risk for CHD by approximately 20%, depending on the model used (Table 3). Of note, this risk reduction was present even after adjustment for total and HDL cholesterol as well as insulin sensitivity as determined by the gold standard euglycemic insulin-clamp technique.

Insulin resistance (17) and hypoadiponectinemia have both been suggested to play a role in the development of CHD (5, 6, 17). However, it may be difficult to identify the isolated impact of insulin resistance *vs.* hypoadiponectinemia on the development of CHD, first because these two conditions show a bidirectional relationship and second because a cause-effect relationship has yet to be determined (6). For example, insulin down-regulates adiponectin mRNA levels in adipocytes *in vitro* (31) and suppresses the *in vivo* plasma levels of adiponectin (32); conversely, adiponectin sensitizes the body to insulin in experimental *in vivo* studies (6) and correlates with 2-h glucose levels after an oral glucose challenge (19). In the present study, we show for the first time in a longitudinal, population-based study cohort that low circulating levels of adiponectin independent of several indices of insulin sensitivity constitute a risk factor for development of CHD. This observation strongly suggests adiponectin to be involved with a causative role in the development of CHD and not only bystander to CHD. However, because this is a clinical epidemiological study, we cannot draw any conclusions on causality of the observed inverse association between low levels of adiponectin and the increased risk for CHD.

Numerous observations link low levels of adiponectin with undesirable conditions such as CHD, insulin resistance, and low-grade inflammation (6), and accordingly, one would expect high adiponectin levels to be advantageous and to reflect a more healthy condition. However, the association between health (in a broad sense) and adiponectin is not that simple. Thus, studies in patients with chronic heart failure have shown that elevated adiponectin levels independently of other risk factors are linked to an increased mortality (33), and in patients with type 1 diabetes, subjects with macroalbuminuria, who are at increased risk for CHD, have higher levels of adiponectin than patients without clinical signs of diabetic nephropathy (26, 34). Similarly, patients with chronic renal failure, who have a high mortality from cardiovascular disease, have 2.5-fold elevated adiponectin levels. However, in the latter condition, patients with low adiponectin levels had an even higher risk for cardiovascular events than those with high adiponectin levels, again stressing that adiponectin may be vasoprotective (35). The latter observation opens the possibility that elevated levels of adiponectin represent a beneficial counterregulatory mecha-

nism serving to protect the patient from the harmful effects of chronic heart or kidney failure.

We conclude that even after adjustment for known cardiovascular risk factors, elevated serum levels of adiponectin were associated with a lower risk of CHD in the prospective analysis. Furthermore, this association was independent of measurements associated with insulin resistance or obesity, suggesting an obesity-independent effect of adiponectin on atherosclerosis.

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