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and Coronary Heart Disease in Apparently Healthy Middle-Aged Men: Results  
From the 18-Year Follow-Up of a Large Cohort From Southern Germany**

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## CLINICAL RESEARCH

## Coronary Artery Disease

# Serum Concentrations of Adiponectin and Risk of Type 2 Diabetes Mellitus and Coronary Heart Disease in Apparently Healthy Middle-Aged Men

## Results From the 18-Year Follow-Up of a Large Cohort From Southern Germany

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<b>OBJECTIVES</b>	We sought to assess the association between serum concentrations of adiponectin and long-term risk of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) in initially healthy middle-aged men within the same representative population in Augsburg, southern Germany.
<b>BACKGROUND</b>	It has been postulated that high serum concentrations of adiponectin, an emerging biomarker that is linked to insulin resistance and endothelial dysfunction, may be protective against T2DM and CHD.
<b>METHODS</b>	Serum concentrations of adiponectin were determined in apparently healthy middle-aged men, sampled from the general population in 1984/1985 and followed until 2002. During this period, 115 of 887 men had a newly diagnosed T2DM, and 126 of 937 men suffered from a CHD event.
<b>RESULTS</b>	In a Cox model, after multivariable adjustment for cardiovascular risk factors, the hazard ratio of incident T2DM, comparing extreme tertiles of the adiponectin distribution, was 0.55 (95% confidence interval [CI], 0.35 to 0.89), and for incident CHD it was 0.62 (95% CI, 0.39 to 0.98). Further adjustment for high-density lipoprotein cholesterol (HDL-C) attenuated the association, which became formally non-significant. In joint analysis, men with low adiponectin and low HDL-C values showed a 2.63 times (95% CI, 1.66 to 4.15) increased incidence of T2DM and a 1.91 times (95% CI, 1.20 to 3.04) increased incidence of CHD after multivariable adjustment in comparison with men with high HDL-C and high adiponectin.
<b>CONCLUSIONS</b>	For patients with low HDL-C values, additional measurement of adiponectin may be helpful to identify individuals at very high risk for T2DM and CHD. (J Am Coll Cardiol 2006;48:1369–77) © 2006 by the American College of Cardiology Foundation

Endothelial dysfunction is considered to represent the initial step in atherogenesis and is seen before any morphologic changes in the arterial vessel wall. Experimental studies have shown that it is important for plaque initiation and progression, and that it plays a pivotal role during plaque fissuring or rupture, leading to an acute coronary syndrome (1). Clinically, endothelial dysfunction has been associated with future coronary heart disease (CHD) events in patients with atherosclerosis (2).

Insulin resistance represents the pathophysiological hallmark of type 2 diabetes mellitus (T2DM) and is highly prevalent in the population. Approximately one-third of the general population above the age of 50 years (3) and two-thirds of all patients with CHD are insulin resistant (4).

Adiponectin, a 244 amino acid collagen-like protein, a member of a new family of obesity-related hormones, the adipocytokines, which is produced solely by white adipose tissue, may be linked to both insulin resistance and endothelial dysfunction (5). Low concentrations of circulating adiponectin are associated with low high-density lipoprotein cholesterol (HDL-C), obesity, hypertension, and glucose intolerance, all features of the insulin resistance syndrome. On the other hand, low adiponectin levels are associated with reduced expression of nitric oxide, and increased expression of angiotensin II and cellular adhesion molecules from the endothelium (5).

The “common soil” hypothesis put forward by Stern (6) in 1995 suggests similar underlying pathomechanisms for atherosclerosis and T2DM. Thus, considering that adiponectin may represent a link between insulin resistance and endothelial dysfunction makes it an attractive candidate marker for further study in T2DM and atherosclerosis.

Indeed, 2 prospective studies, one using a case-control design (7), the other one based on a case-cohort within the ARIC (Atherosclerosis Risk In Communities) Study (8),

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**Abbreviations and Acronyms**

AMI	= acute myocardial infarction
Apo	= apolipoprotein
ARIC	= Atherosclerosis Risk In Communities Study
BMI	= body mass index
CHD	= coronary heart disease
CI	= confidence interval
CRP	= C-reactive protein
CV	= coefficient of variation
ELISA	= enzyme-linked immunosorbent assay
HDL-C	= high-density lipoprotein cholesterol
HPFU	= Health Professionals' Follow-Up study
HR	= hazard ratio
KORA	= KOoperative Gesundheitsforschung in der Region Augsburg
LPL	= lipoprotein lipase
Lp-PLA <sub>2</sub>	= lipoprotein-associated phospholipase A <sub>2</sub>
MI	= myocardial infarction
MONICA	= MONItoring of trends and determinants in CARdiovascular disease
RR	= relative risk
SMC	= smooth muscle cell
TC	= total cholesterol
T2DM	= type 2 diabetes mellitus

have reported a protective effect of high plasma adiponectin levels against T2DM.

In addition, several cross-sectional, clinical studies have reported lower serum levels of adiponectin in patients with CHD (9–11) than in control subjects, and recently one prospective study by Pischon et al. (12) in U.S. health professionals for the first time has assessed the predictive value of adiponectin for future CHD events and found an inverse association in apparently healthy, non-diabetic subjects. However, a recent report from the Strong Heart Study (13) could not confirm this association.

Thus, we sought to assess the association between serum concentrations of adiponectin, and long-term risk of T2DM and CHD in initially healthy middle-aged men within the same representative population in Augsburg, southern Germany.

**METHODS**

**Study design, population, and follow-up.** The first population-based MONICA (MONItoring of trends and determinants in CARdiovascular disease Augsburg) survey 1984/1985 (S1) was used as the database. The MONICA project was part of the multinational World Health Organization MONICA project (14,15). Briefly, 4,022 individuals 25 to 64 years of age sampled at random from a study population of 282,279 inhabitants of a mixed urban/rural area participated in the S1 (response rate 79.3%). The present report is based on 1,074 men aged 45 to 64 years. Participants with missing values for adiponectin, or control variables, were excluded from the respective analyses leading to a sample of 976 subjects. For follow-up analyses, subjects with missing follow-up information or with prevalent

T2DM (n = 89) or with a previous myocardial infarction (MI) (n = 39) were excluded. Thus, for T2DM analysis, a total of 887 men had data on all variables studied; for CHD analysis, there were 937 men available.

In 2002, the vital status was assessed for all S1 participants. During the 18-year observation period, 331 of 1,074 men age 45 to 64 years at baseline had died. Incident T2DM was assessed by a questionnaire, which was then validated by collecting appropriate information from the treating physician or from medical chart review (16). Incident fatal or non-fatal acute MI (AMI) and sudden cardiac death were identified through the population-based MONICA/KORA (KOoperative Gesundheitsforschung in der Region Augsburg) coronary event registry that covers the same population (age range, 25 to 74 years) from which the survey participants had been sampled; follow-up times were censored at death or when participants reached the age of 75 years after which the register-based monitoring of coronary events ceases. The case finding and validation procedures of the clinical AMI diagnoses and the causes of death have been described in detail elsewhere (17). In brief, cases of non-fatal AMI were consecutively identified in up to 17 regional hospitals. The clinical diagnosis of AMI was validated according to MONICA criteria, and categorized in definite AMI, MONICA diagnosis (MD) 1, possible AMI (MD2), successfully resuscitated AMI without signs of definitive or possible AMI (MD3), or no acute AMI (MD4). The diagnostic criteria used for the present paper were acute chest pain lasting 20 min or longer, not relieved by rest or nitrates, electrocardiographic changes suggestive of an evolving MI (Q waves, non-Q waves in up to 4 electrocardiograms), and a subsequent increase in the concentration of at least 1 of 3 cardiac enzymes (creatinine phosphokinase, aspartate aminotransferase, and lactate dehydrogenase) to more than twice the upper limit of normal. For reasons of comparability, documented troponin values that have been collected since 2001 were not considered for the epidemiologic AMI diagnosis.

Coronary heart disease deaths were identified by checking all death certificate diagnoses suspect for CHD as the main cause of death and by contacting the last treating physician and/or coroner (response  $\geq 85\%$ ). According to MONICA diagnostic criteria for fatal cases before or within 24 h after hospitalization, witnessed symptoms or a positive history of CHD or the autopsy result (3.4% of the deceased) were used for the categorization in MD1, MD2, no MI, and unclassifiable deaths without signs of a cardiac or non-cardiac cause of death (MD9).

**Survey methods.** All participants completed a standardized questionnaire, including medical history, lifestyle, and drug history. Blood pressure, body height (m) and body weight (kg), body mass index (BMI, kg/m<sup>2</sup>), smoking behavior, history of diabetes, history of MI, and alcohol consumption (g/day) were determined as described elsewhere (16). Leisure-time physical activity was assessed on a 4-level graded scale for winter and summer (18). The number of

education years was calculated on the basis of the highest level of formal education completed.

**Laboratory procedures.** A non-fasting venous blood sample was collected from all participants while sitting. Samples for measurement of adiponectin and C-reactive protein (CRP) were stored at  $-70^{\circ}\text{C}$  until analysis. Serum levels of adiponectin ( $\mu\text{g/ml}$ ) were determined with a commercial enzyme-linked immunosorbent assay (ELISA) (R&D, Wiesbaden, Germany). The interassay coefficient of variation (CV) was 13.7%. Serum CRP concentrations ( $\text{mg/l}$ ) were measured using a high-sensitivity immunoradiometric assay (range, 0.05 to 10  $\text{mg/l}$ ) (16). The CV for repeated measurements was 12% over all ranges. Lipoprotein-associated phospholipase  $A_2$  (Lp-PLA $_2$ ) was determined with a commercial Lp-PLA $_2$ -ELISA kit (PLAC Test) supplied by diaDexus Inc. (South San Francisco, California). Total serum cholesterol (TC) and HDL-C were measured by routine enzymatic methods. Corresponding CVs were between 1% and 3% for TC and between 3% and 4% for HDL-C. The apolipoproteins (Apo)-B and -A-1 were analyzed by kinetic immunoturbidimetry on a Hitachi autoanalyzer, model 705. The intra-assay CVs for Apo-B were between 2.5% and 1.5%. The corresponding values for the interassay CVs were between 5.7% and 3.2%. Similar CVs were found for Apo-A-1. All analyses were run in a blinded fashion.

**Statistical analysis.** Means or proportions for baseline demographic and clinical characteristics were computed for men with and without incident coronary event as well as for men with and without incident T2DM. The distribution of adiponectin concentrations was markedly skewed and therefore log-transformed in analyses where normality was required. Differences between continuous variables were tested for statistical significance by means of *t* test; proportions were tested by chi-square test. We assessed associations among continuous variables with use of Pearson's correlation coefficient (R). Cox proportional hazards analysis was used to assess the independent risk for the incidence of T2DM or a first CHD event in tertiles of adiponectin. Tertile cut-points were 5.00 and 7.90  $\mu\text{g/ml}$  for  $n = 887$  (end point T2DM) and 4.98 and 7.79  $\mu\text{g/ml}$  for  $n = 937$  (end point CHD). Results are presented as hazard ratios (HR) together with their 95% confidence intervals (CIs). First, age-adjusted HRs were calculated. Results were then further adjusted for regular smoking (yes/no), BMI (continuous), physical activity (inactive/active), alcohol consumption (0 g/day, 0.1 to 39.9 g/day,  $\geq 40.0$  g/day), actual hypertension (blood pressure  $\geq 140/90$  mm Hg or on antihypertensive medication), and history of diabetes or MI. Finally, additional adjustments were carried out separately for TC (continuous), HDL-C (continuous). A test for trend was carried out by assigning median values to each tertile and including this variable in the Cox regression. To examine the joint effect of adiponectin and HDL-C on the development of T2DM and acute CHD events, combined HDL-C and adiponectin variables were created. For this

purpose, the lower tertile values of the 2 parameters were used as cut-points to define low and high groups. Tertile cut-points for HDL-C were 44.1 and 55.3  $\text{mg/dl}$  for  $n = 887$  (end point T2DM) and 43.7 and 55.3  $\text{mg/dl}$  for  $n = 937$  (end point CHD). Low HDL-C was defined as  $\leq 44.1$   $\text{mg/dl}$  for end point T2DM and as 43.7  $\text{mg/dl}$  for end point CHD. The same way, low adiponectin was defined as  $< 5.00$  and 4.98 ( $\mu\text{g/ml}$ ). Subjects were classified into 4 categories (low/low, low/high, high/low, and high/high). Those with high HDL-C and high adiponectin values were chosen as the reference group. Significance tests are 2-tailed, and *p* values  $< 0.05$  were considered as statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2, SAS Institute Inc., Cary, North Carolina).

## RESULTS

**Baseline characteristics.** During an average follow-up of 18 years, a total of 115 cases of incident T2DM in 887 men and 126 fatal and non-fatal CHD events, including sudden cardiac death, in 937 men occurred.

Men with prospectively identified incident T2DM compared with event-free subjects had a significantly higher BMI, had lower HDL-C, and a higher TC/HDL-C ratio. Men with an incident acute CHD event were significantly older, had higher TC, higher non-HDL-C, and a higher TC/HDL-C ratio, as well as higher Apo-B levels compared with subjects with no CHD event. Conversely, HDL-C and Apo-A1 were lower in the case group. Coronary heart disease cases also were more frequently smokers, were less frequently physically active, and had more frequently a history of diabetes. No significant differences were found for BMI, prevalence of actual hypertension (or systolic as well as diastolic blood pressures), alcohol consumption, and years of formal education. Concentrations of adiponectin were markedly lower in T2DM cases and CHD cases compared with non-cases (5.0  $\mu\text{g/ml}$  vs. 6.4  $\mu\text{g/ml}$ ,  $p < 0.001$  and 5.5  $\mu\text{g/ml}$  vs. 6.3  $\mu\text{g/ml}$ ,  $p = 0.011$ , respectively), whereas CRP was considerably higher in CHD cases compared with those free of an event during follow-up (2.2  $\text{mg/l}$  vs. 1.5  $\text{mg/l}$ ,  $p < 0.001$ ) but was not different between T2DM cases and non-cases (1.7  $\text{mg/l}$  vs. 1.5  $\text{mg/l}$ ,  $p = 0.22$ ) (Tables 1 and 2).

**Correlations and associations between adiponectin and other risk factors ( $n = 976$ ).** The strongest positive correlation for adiponectin was seen with HDL-C ( $R = 0.39$ ,  $p < 0.001$ ) and Apo-A1 ( $R = 0.35$ ,  $p < 0.001$ ). It was further positively correlated with age ( $R = 0.17$ ,  $p < 0.001$ ). Adiponectin was negatively correlated with TC/HDL-C ( $R = -0.32$ ,  $p < 0.001$ ), Apo-B ( $R = -0.18$ ,  $p < 0.001$ ), and non-HDL-C ( $R = -0.16$ ,  $p < 0.001$ ). No correlation was seen with TC, CRP, Lp-PLA $_2$ , and plasma viscosity. Among demographic characteristics, a history of T2DM was associated with lower adiponectin levels ( $p = 0.015$ ), and there was a negative correlation with BMI ( $R = -0.19$ ,  $p < 0.001$ ) but not with smoking, actual hypertension (or

**Table 1.** Demographic and Clinical Characteristics for Men With and Without Incident T2DM During Follow-Up: MONICA/KORA Augsburg Cohort Study S1 1984 to 2002 (n = 887)

Characteristics	Total	T2DM Cases	T2DM Non-Cases	p Value
n	887	115	772	—
Age (yrs)*	54.1 (5.8)	54.4 (5.9)	54.1 (5.8)	0.645
Education (<12 yrs)†	74.2	80.9	73.2	0.079
Body mass index (kg/m <sup>2</sup> )*	27.6 (3.3)	29.1 (3.5)	27.3 (3.2)	<0.001
Actual hypertension†	47.2	49.6	46.9	0.592
Systolic BP (mm Hg)*	136.1 (17.6)	137.6 (15.5)	135.9 (17.9)	0.350
Diastolic BP (mm Hg)*	84.4 (11.0)	85.2 (10.3)	84.3 (11.1)	0.392
Low physical activity†	64.8	68.7	64.2	0.351
History of myocardial infarction†	3.6	5.2	3.4	0.321
Smoker†				0.162
Never smoker	25.7	20.9	26.4	
Former smoker	41.7	39.1	42.1	
Current smoker	32.6	40.0	31.5	
Alcohol intake†				0.061
0 g/day	12.9	13.0	12.8	
0.1–39.9 g/day	44.4	53.9	43.0	
≥40 g/day	42.7	33.0	44.2	
Total cholesterol (mg/dl)*	244.8 (44.8)	244.0 (43.4)	244.9 (45.1)	0.846
HDL cholesterol (mg/dl)*	51.5 (16.1)	43.6 (11.5)	52.6 (16.4)	<0.001
Total cholesterol/HDL ratio*	5.2 (2.0)	6.0 (2.4)	5.1 (1.9)	<0.001
Non-HDL cholesterol (mg/dl)*	193.3 (47.6)	200.4 (43.8)	192.3 (48.1)	0.087
Apolipoprotein A1 (mg/dl)*,‡	137.1 (21.7)	130.2 (19.5)	138.2 (21.8)	<0.001
Apolipoprotein B (mg/dl)*,§	90.6 (20.5)	93.7 (17.1)	90.2 (20.9)	0.050
Lp-PLA <sub>2</sub> (ng/ml)*	265.2 (83.5)	261.6 (78.9)	265.8 (84.2)	0.614
Plasma viscosity (mPa·s)*,	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	0.302
CRP (mg/l)¶	1.6 (0.7–3.6)	1.7 (0.8–4.2)	1.5 (0.7–3.5)	0.218
Adiponectin (μg/ml)¶¶	6.3 (4.4–9.1)	5.0 (3.5–7.8)	6.4 (4.6–9.2)	<0.001

\*Mean (SD), p value from *t* test; †percent, p value from chi-square test; ‡127 missing values; §26 missing values; ||31 missing values; ¶median (lower quartile – upper quartile), p value from Mann-Whitney *U* test.

BP = blood pressure; CRP = C-reactive protein; HDL = high-density lipoprotein; KORA = KOoperative Gesundheitsforschung in der Region Augsburg study; Lp-PLA<sub>2</sub> = lipoprotein-associated phospholipase A<sub>2</sub>; MONICA = MONItoring of trends and determinants in CArdiovascular disease study; T2DM = type 2 diabetes mellitus.

systolic/diastolic blood pressures), low physical activity, alcohol consumption, and education years. The geometric mean of adiponectin was not significantly different in subjects without or with prevalent MI (6.25 vs. 6.24 μg/ml, *p* = 0.95) (Table 3).

**Adiponectin and risk of incident T2DM and CHD.** Tables 4 and 5 show HRs of newly developed T2DM and incident CHD events across tertiles of adiponectin during 18 years of follow-up. In age-adjusted analyses, subjects in the top tertile compared with the bottom tertile had a significantly decreased risk for a new-onset T2DM (HR 0.44; 95% CI, 0.28 to 0.70, *p* for trend 0.0007) and incident CHD (HR 0.56; 95% CI, 0.36 to 0.87, *p* for trend 0.012). Further adjustment for BMI, smoking, physical activity, alcohol consumption, actual hypertension, history of MI (for end point T2DM), or history of diabetes mellitus (for end point CHD), and additionally for TC only slightly attenuated the associations, which, however, were still statistically significant. After introducing HDL-C in the model, the association became clearly non-significant for T2DM (HR 0.81; 95% CI, 0.50 to 1.33, *p* for trend of 0.40), as well as for CHD (HR 0.71; 95% CI, 0.44 to 1.13, *p* for trend 0.167). Additional adjustment for CRP, Lp-PLA<sub>2</sub> and plasma viscosity did not further alter the relationship (data not shown).

Since the introduction of HDL-C strongly attenuated the association between adiponectin and CHD as well as with T2DM and it became non-significant, we looked closer into the relationship between adiponectin and HDL-C concerning the 2 end points. Estimating the T2DM and CHD incidence by person-years, it turned out that, for both end points the highest risk was seen in subjects belonging to the bottom tertiles of adiponectin and HDL-C (incidence per 1,000 person-years for T2DM was 20.3 and for CHD it was 14.6). The incidence was lowest in all subjects who were in the top tertile of HDL-C, independent of their adiponectin (incidence per 1,000 person-years between 2.5 and 3.9 for T2DM and between 1.2 and 6.9 for CHD). In subjects with high adiponectin, the incidence per 1,000 person-years was intermediate between 2.5 and 13.7 for T2DM and 6.9 and 8.0 for CHD in the 3 categories of HDL-C.

Finally, we looked at a potential joint relationship between HDL-C and adiponectin. Figure 1 shows that the combination of both low HDL-C and low adiponectin was associated with a statistically significantly increased risk for future CHD events (HR 1.91 [95% CI, 1.20 to 3.04]) and for incident T2DM (HR 2.63 [95% CI, 1.66 to 4.15]) compared with both markers not being low (referent) in the fully adjusted model.

**Table 2.** Demographic and Clinical Characteristics for Men With and Without Incident CHD During Follow-Up: MONICA/KORA Augsburg Cohort Study S1 1984 to 2002 (n = 937)

Characteristics	Total	CHD Cases	CHD Non-Cases	p Value
n	937	126	811	—
Age (yrs)*	54.1 (5.8)	55.7 (4.9)	53.9 (5.9)	<0.001
Education (<12 yrs)†	74.3	77.8	73.7	0.334
Body mass index (kg/m <sup>2</sup> )*	27.7 (3.3)	27.8 (3.3)	27.6 (3.3)	0.712
Actual hypertension†	48.6	57.1	47.2	0.038
Systolic BP (mm Hg)*	136.9 (17.8)	139.7 (15.8)	136.5 (18.0)	0.061
Diastolic BP (mm Hg)*	84.5 (11.3)	84.9 (10.8)	84.5 (11.3)	0.652
Low physical activity†	65.4	77.0	63.6	0.003
History of diabetes†	5.3	12.7	4.2	<0.001
Smoker†				<0.001
Never smoker	25.7	13.5	27.6	
Former smoker	40.8	34.9	41.7	
Current smoker	33.5	51.6	30.7	
Alcohol intake†				0.151
0 g/day	12.5	17.5	11.7	
0.1–39.9 g/day	44.9	39.7	45.7	
≥40 g/day	42.6	42.9	42.5	
Total cholesterol (mg/dl)*	245.0 (45.7)	257.0 (46.8)	243.1 (45.2)	0.002
HDL cholesterol (mg/dl)*	51.2 (16.1)	47.1 (15.0)	51.9 (16.2)	0.002
Total cholesterol/HDL ratio*	5.2 (2.1)	6.0 (2.4)	5.1 (2.0)	<0.001
Non-HDL cholesterol (mg/dl)*	193.8 (48.6)	209.9 (48.7)	191.3 (48.1)	<0.001
Apolipoprotein A1 (mg/dl)*,‡	137.1 (21.4)	133.5 (20.3)	137.6 (21.5)	0.047
Apolipoprotein B (mg/dl)*,§	90.9 (20.7)	98.1 (21.7)	89.7 (20.3)	<0.001
Lp-PLA <sub>2</sub> (ng/ml)*	266.5 (84.0)	285.2 (105.5)	263.6 (79.8)	0.029
Plasma viscosity (mPa·s)*,	1.28 (0.07)	1.30 (0.07)	1.27 (0.07)	<0.001
CRP (mg/l)¶	1.6 (0.7–3.8)	2.2 (1.1–5.7)	1.5 (0.7–3.4)	<0.001
Adiponectin (μg/ml)¶¶	6.2 (4.4–8.9)	5.5 (3.9–7.9)	6.3 (4.5–9.0)	0.011

\*Mean (SD), p value from *t* test; †percent, p value from chi-square test; ‡28 missing values; §27 missing values; ||31 missing values; ¶median (lower quartile – upper quartile), p value from Mann-Whitney *U* test.

CHD = coronary heart disease; other abbreviations as in Table 1.

## DISCUSSION

In this prospective cohort study, we assessed the relative risk (RR) for future T2DM and CHD events associated with reduced levels of adiponectin during an 18-year follow-up. Higher adiponectin levels were associated with considerably lower risk of about 45% to 55% for a first event. These associations were independent of a variety of potential confounders. Only the introduction of HDL-C in the models resulted in an appreciable attenuation of the association, which then became non-significant. Adiponectin was not correlated with several markers of inflammation measured in this cohort, like CRP, Lp-PLA<sub>2</sub>, and plasma viscosity. Finally, the present study showed an additive effect of HDL-C and adiponectin on risk prediction. In joint analyses, the highest risk for T2DM as well as acute coronary events was observed in men with low adiponectin in combination with low HDL-C.

**Evidence for an association between adiponectin and T2DM from other studies.** To date, 2 prospective studies have reported a protective effect of high plasma adiponectin levels against T2DM. The first one was a small nested case-control study including 187 cases with incident T2DM and 376 control subjects of both genders within the population-based EPIC (European Prospective Investigation into Cancer and Nutrition) Potsdam cohort (7). In a model adjusted for age, gender, BMI, waist-to-hip ratio,

smoking, exercise, alcohol intake, education, and glycosylated hemoglobin A<sub>1c</sub>, across extreme quartiles, an odds ratio of 0.3 (95% CI, 0.2 to 0.7) was seen. However, adjustment for HDL-C was not considered in this analysis.

The other report was based on a case-cohort design from the ARIC study (8) including 581 subjects of both genders with incident T2DM and 572 non-cases. In multivariable analysis, adjusting for age, center, gender, race, family history of diabetes, hypertension, fasting glucose, insulin, waist-to-hip ratio, and additionally for an inflammation score but not for HDL-C, the HR was 0.58; 95% CI 0.34 to 0.99 across extreme quartiles. Thus, these data nicely compare with the results we found in our cohort study if adjustment for HDL-C is not considered.

**Evidence for an association between adiponectin and CHD from other studies.** Our data are in line with several cross-sectional clinical studies that have recently reported lower serum adiponectin levels in patients with CHD (9–11) than in control subjects. Kumada et al. (9) found a 2-fold increased risk for CHD associated with low adiponectin levels (<4 μg/ml) in 225 CHD patients and 225 blood donors. Furthermore, a strong inverse association between adiponectin concentrations and risk of CHD was observed among 312 patients with angiographically defined stable CHD and 479 healthy blood donors (10). The odds ratio for the presence of CHD after multivariate adjustment

**Table 3.** Unadjusted Associations and Correlations of Adiponectin (Log-Transformed) With Demographic and Clinical Characteristics for Men: MONICA/KORA Augsburg Cohort Study S1 1984 to 2002 (n = 976)

Characteristics	Association With Adiponectin	p Value
Age*	0.171	<0.001
Education†		
<12 yrs	6.32 (1.69)	0.243
≥12 yrs	6.05 (1.71)	
Body mass index*	-0.188	<0.001
Actual hypertension†		
No	6.29 (1.68)	0.664
Yes	6.21 (1.72)	
Systolic blood pressure*	0.013	0.676
Diastolic blood pressure*	-0.005	0.883
Low physical activity†		
No	6.05 (1.68)	0.196
Yes	6.36 (1.70)	
History of diabetes		
No	6.31 (1.69)	0.015
Yes	5.25 (1.73)	
History of MI		
No	6.25 (1.68)	0.949
Yes	6.24 (1.96)	
Smoker‡		0.316
Never smoker	6.27 (1.72)	
Former smoker	6.40 (1.66)	
Current smoker	6.04 (1.72)	
Alcohol intake†		0.555
0 g/day	6.20 (1.76)	
0.1–39.9 g/day	6.14 (1.71)	
≥40 g/day	6.38 (1.66)	
Total cholesterol*	-0.031	0.339
HDL cholesterol*	0.386	<0.001
Total cholesterol/HDL ratio*	-0.316	<0.001
Non-HDL cholesterol*	-0.156	<0.001
Apolipoprotein B*,‡	-0.176	<0.001
Apolipoprotein A1*,§	0.348	<0.001
Lp-PLA <sub>2</sub> *	0.046	0.156
Plasma viscosity*,	-0.036	0.264
CRP*	-0.028	0.377

\*Pearson correlation coefficient; †geometric mean (GSD) of adiponectin; ‡28 missing data; §29 missing data; ||34 missing data.

MI = myocardial infarction; other abbreviations as in Table 1.

for traditional cardiovascular risk factors was 0.52 (95% CI, 0.28 to 0.95, lowest vs. upper quintile), which, however, increased considerably and became non-significant after additional adjustment for HDL-C.

In the only prospective study in non-diabetic subjects published to date, of 18,225 male participants of the HPFU (Health Professionals' Follow-Up) Study, 266 men who subsequently developed CHD events (fatal and non-fatal MI) during a 6-year follow-up were compared with 532 event-free controls, matched for age, date of blood draw, and smoking status (12). The authors found a significantly reduced risk of subsequent AMI associated with higher levels of adiponectin in serum at baseline; notably, this association was also reduced after adjustment for covariates, but persisted after inclusion of lipids (LDL-C and HDL-C) in the model (RR, 0.56; 95% CI, 0.32 to 0.99). Further

**Table 4.** HRs for Incident Type 2 Diabetes Mellitus According to Baseline Levels of Adiponectin Estimated by Cox Proportional Hazard Models: MONICA/KORA Augsburg Cohort Study S1 1984 to 2002 (n = 887)

	Tertiles of Adiponectin			p Value for Trend
	T1	T2	T3	
Median (μg/ml)	3.81	6.32	10.60	
IQR	3.05–4.45	5.64–7.07	9.05–13.20	
Number cases/ non-cases	57/241	31/263	27/268	
Model 1				
HR	1.00	0.50	0.44	0.0007
95% CI	Ref.	0.33–0.78	0.28–0.70	
Model 2				
HR	1.00	0.54	0.55	0.016
95% CI	Ref.	0.34–0.84	0.35–0.89	
Model 3				
HR	1.00	0.54	0.55	0.015
95% CI	Ref.	0.34–0.84	0.34–0.88	
Model 4				
HR	1.00	0.63	0.81	0.40
95% CI	Ref.	0.40–0.99	0.50–1.33	

Model 1: adjusted for age; Model 2: adjusted for age, smoking status, alcohol consumption, body mass index, physical activity, actual hypertension, and history of total cholesterol; Model 3: Model 2 and additional adjustment for total cholesterol; Model 4: Model 2 and additional adjustment for high-density lipoprotein cholesterol.

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; Ref = referent; other abbreviations as in Table 1.

adjustment for glycemic status and CRP did not appreciably affect the results.

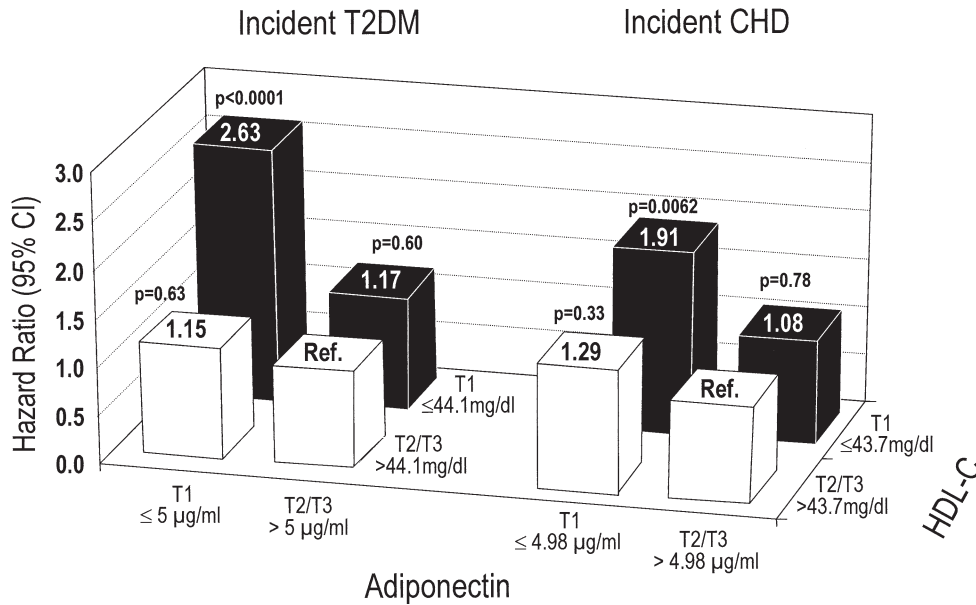
Low plasma adiponectin levels also predicted progression of coronary artery calcification, a marker of subclinical

**Table 5.** HRs for an Incident Coronary Heart Disease Event According to Baseline Levels of Adiponectin Estimated by Cox Proportional Hazard Models: MONICA/KORA Augsburg Cohort Study S1 1984 to 2002 (n = 937)

	Tertiles of Adiponectin			p Value for Trend
	T1	T2	T3	
Median (μg/ml)	3.80	6.23	10.40	
IQR	3.06–4.44	5.58–7.04	8.94–13.00	
Number cases/ non-cases	51/262	42/270	33/279	
Model 1				
HR	1.00	0.75	0.56	0.012
95% CI	Ref.	0.50–1.13	0.36–0.87	
Model 2				
HR	1.00	0.80	0.62	0.042
95% CI	Ref.	0.53–1.23	0.39–0.98	
Model 3				
HR	1.00	0.78	0.62	0.046
95% CI	Ref.	0.51–1.19	0.39–0.98	
Model 4				
HR	1.00	0.87	0.71	0.167
95% CI	Ref.	0.57–1.33	0.44–1.15	

Model 1: adjusted for age; Model 2: adjusted for age, smoking status, alcohol consumption, body mass index, physical activity, actual hypertension, and history of diabetes; Model 3: Model 2 and additional adjustment for total cholesterol; Model 4: Model 2 and additional adjustment for high-density lipoprotein cholesterol.

Abbreviations as in Table 4.



**Figure 1.** Hazard ratio (95% confidence interval [CI]) for incident type 2 diabetes mellitus (T2DM) and incident coronary heart disease (CHD) in men by subgroups of adiponectin and high-density lipoprotein cholesterol (HDL-C) tertile combinations. Ref = referent.

disease and a strong predictor of future CHD events in type 1 diabetic and non-diabetic subjects, independently of other cardiovascular risk factors (19). In addition, hypo-adiponectinemia was associated with ischemic cerebrovascular disease (20).

Most recently, again based on data from the HPFU Study, Schulze et al. (21) prospectively looked into the relationship between adiponectin and CHD events in T2DM patients. The database comprised 745 men, age 46 to 81 years with confirmed T2DM who were followed for 5 years. Eighty-nine incident CHD cases were identified (19 MIs and 70 cases of coronary artery bypass surgery). In multivariate analyses, an inverse association was found with a 29% risk reduction for a doubling of adiponectin levels. However, inclusion of HDL-C into the model attenuated this association (RR, 0.78; 95% CI, 0.57 to 1.06), and it became non-significant. Thus, the authors concluded that the association between low adiponectin and CHD may be mediated, in part, by the effects of adiponectin on HDL cholesterol.

These data are in line with a report from the Strong Heart Study (13). From this group at particular risk of obesity and T2DM, 251 incident cases and 251 matched controls were identified. The mean BMI was 31 kg/m<sup>2</sup>, and there were 74% T2DM patients. Neither in unadjusted nor in adjusted analyses was adiponectin found to be associated with incident CHD in this cohort. Taking the latter 2 studies together, one may conclude that the relationship between adiponectin and CHD is less apparent in the presence of T2DM, and thus associations are likely to be different according to the prevalence of obesity and associated metabolic disorders.

#### Correlations between adiponectin and other risk factors.

All studies have consistently reported relationships between adiponectin and metabolic and lipid measures, the strongest correlation being present between adiponectin and HDL-C and Apo-A1, respectively ( $R = 0.30$  to  $0.45$ ) (10,22). Thus, the molecular mechanism of this relationship is of particular interest. In a recent study, von Eynatten et al. (22) reported data from 206 non-diabetic men and 110 patients with T2DM in whom they found an association between decreased post-heparin lipoprotein lipase (LPL) activity and low plasma adiponectin, independent of systemic inflammation and insulin resistance. Conversely, dramatically raised levels of LPL activity have been found with increased plasma adiponectin in an animal model (23). Thus, adiponectin may directly stimulate the expression of LPL, which then will result in increased HDL-C levels. In contrast with other studies (10,12,24), we did not see an inverse correlation between adiponectin and CRP in this study. Therefore, the associations of both molecules with T2DM and CHD may operate through different mechanisms.

**Potential prodiabetic and proatherosclerotic mechanisms of low adiponectin serum concentrations.** The mechanisms whereby adiponectin exerts its physiological actions are not entirely understood. Apart from its role as an insulin-sensitizing agent, and its implication in metabolic disorders, adiponectin might also be involved in the regulation of inflammatory processes that are contributing to atherosclerosis by, for instance, inhibiting the expression of adhesion molecules, and by preventing the attachment of monocytes to the endothelial surface via inhibition of nuclear factor-kappa-B signaling (5). Furthermore, through the inhibition of macrophage scavenger receptor A gene

expression, adiponectin reduces cholesterol ester accumulation and decreases oxidized low-density lipoprotein uptake, thereby diminishing the transformation of macrophages into foam cells (25), a crucial step in atherogenesis. Finally, smooth muscle cell (SMC) proliferation and migration is also suppressed by adiponectin (26).

Very recent data in adiponectin-deficient mice have shown a 2-fold increase in neointimal thickening and increased proliferation of vascular SMCs in arteries after mechanical injury (26,27). In addition, adiponectin knockout mice showed high levels of TNF-alpha mRNA in adipose tissue (28).

Thus, these data suggest an antidiabetic and antiatherogenic role of increased concentrations of adiponectin and that hypo adiponectinemia, in particular in combination with low HDL-C, therefore might be associated with a strongly increased risk of T2DM and atherosclerotic disease. The effects of both, low adiponectin and low HDL-C on endothelial dysfunction, and their enhancement of an inflammatory response may represent 2 plausible arguments for their additive effect on risk (1,5).

**Study strengths and limitations.** The present study has several strengths and limitations. We used a complete cohort of men, drawn randomly from the general population in southern Germany, and analyzed the association between hypo adiponectinemia and risk of T2DM and CHD simultaneously considering HDL-C in the same population. We used only hard coronary end points in our analysis, whereas in other studies either revascularization procedures or stroke were included in addition to fatal and non-fatal MI. The considerably longer follow-up of 18 years extends the observations reported from these other studies regarding the time frame within which adiponectin might be a useful predictor.

**Conclusions.** Despite its relatively small sample size, our study provides evidence for an inverse association between serum concentrations of adiponectin and subsequent risk of T2DM and CHD in apparently healthy middle-aged men from the same representative, general population. Individuals with low adiponectin values combined with low HDL-C open a new field of pathophysiological research for a better understanding of the underlying mechanisms within the pathway to incident T2DM and CHD. Public health relevance is given, because, among the middle-aged Augsburg population, more than 20% of men were affected by this specific disorder. Therefore, additional measurement of adiponectin in individuals with low HDL-C could help to identify a highly prevalent subgroup at increased risk for T2DM and CHD.

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**Serum Concentrations of Adiponectin and Risk of Type 2 Diabetes Mellitus and Coronary Heart Disease in Apparently Healthy Middle-Aged Men: Results From the 18-Year Follow-Up of a Large Cohort From Southern Germany**

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