Associations of Adiponectin Levels With Incident Impaired Glucose Metabolism and Type 2 Diabetes in Older Men and Women

The Hoorn Study

Marieke B. Snijder, PhD[1,2]
Robert J. Heine, MD, PhD[2]
Jacob C. Seidell, PhD[1,2]
Lex M. Bouter, PhD[2]
Coen D.A. Stehouwer, MD, PhD[3]
Giel Nijpels, MD, PhD[2]
Tohru Funahashi, PhD[4]
Yuji Matsuzawa, MD, PhD[4]
Iichiro Shimomura, MD, PhD[4]
Jacqueline M. Dekker, PhD[2]

OBJECTIVE — Adiponectin is an adipose tissue–derived protein. Low levels are associated with obesity, insulin resistance, and type 2 diabetes. Our objective was to investigate the prospective association between adiponectin levels and the 6.4-year risk of type 2 diabetes and of impaired glucose metabolism (IGM).

RESEARCH DESIGN AND METHODS — The Hoorn Study is a cohort study among Caucasians, aged 50–75 years. BMI, waist-to-hip ratio (WHR), fasting glucose, 2-h glucose, triglycerides, HDL cholesterol, LDL cholesterol, alanine aminotransferase, leptin, and adiponectin were measured at baseline. Lifestyle (alcohol intake, smoking, and physical activity) was assessed by questionnaires. After a mean follow-up of 6.4 years, glucose tolerance was assessed by a 75-g oral glucose tolerance test. Analyses were performed in 1,264 subjects (584 men and 680 women) without type 2 diabetes at baseline. For analyses of incident IGM, 239 subjects with IGM at baseline and/or type 2 diabetes at follow-up were excluded.

RESULTS — Age- and lifestyle-adjusted odds ratios and 95% CIs comparing highest with lowest adiponectin quartile were 0.52 (0.23–1.18) in men and 0.15 (0.06–0.39) in women for type 2 diabetes and 0.90 (0.51–1.61) and 0.28 (0.16–0.48) for IGM, respectively. The risks were only slightly reduced after adjustment for WHR and leptin as markers of (abdominal) adiposity. Adjustment for baseline fasting and postload glucose levels (potential mediators) substantially diminished these inverse associations with type 2 diabetes (0.79 [0.32–1.91] and 0.62 [0.21–1.81]) and with IGM (1.20 [0.61–2.35] and 0.48 [0.26–0.90]), respectively.

CONCLUSIONS — A high adiponectin level was strongly associated with a lower risk of IGM and type 2 diabetes, particularly in women. These results suggest that adiponectin is involved in the pathophysiology linking obesity to type 2 diabetes.

Diabetes Care 29:2498–2503, 2006

The pathophysiology linking obesity to type 2 diabetes is not completely understood, but adipokines are thought to be involved (1). Adiponectin is a recently discovered protein that seems to be exclusively secreted by adipocytes and is the most abundant adipose tissue–derived protein (2,3). In contrast to other adipokines (such as leptin and interleukin-6) that are often elevated in obese subjects, adiponectin is reduced (3–6).

In animal studies, adiponectin has been shown to have insulin-sensitizing properties. Adiponectin knockout mice are insulin resistant in a gene-dose fashion (7,8). Overexpression of adiponectin prevented diabetes in transgenic mice (9), and administration of adiponectin reversed insulin resistance in various mouse models of obesity and diabetes (10). Adiponectin increased insulin action via effects on hepatic glucose production and by increasing fat oxidation and lowering circulating free fatty acids (10–13).

In humans, several cross-sectional studies showed that adiponectin correlates negatively with measures of insulin resistance and type 2 diabetes, but cause or consequence cannot be distinguished. Results from a few prospective studies suggest that a low adiponectin level is predictive of insulin resistance or diabetes in Pima Indians (14), Asian Indians (15), and Japanese subjects (16,17). Some of these studies are rather small (14,15) or had a short follow-up period (15,17). To our knowledge, the only prospective study in Caucasians was a nested case-control study based on self-reported diabetes after a follow-up of 2–3 years (18). All of these previous prospective studies were performed in relatively young subjects.

The objective of the present study was to investigate the association between adiponectin and subsequent 6.4-year incidence of abnormal glucose metabolism in a large population-based cohort of older men and women.

RESEARCH DESIGN AND METHODS

— The Hoorn Study is a population-based cohort study among 2,484 Caucasians (aged 50–75 years) that was performed in 1989–1991 and has been described previously (19). In 1996–1998, a follow-up examination took place. Of the 2,484 subjects, 150 subjects had died and 108 subjects had moved out

From the [1]Institute of Health Sciences, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; the [2]EMGO Institute, VU University Medical Center Amsterdam, Amsterdam, the Netherlands; [3]Internal Medicine, Academic Hospital Maastricht, Maastricht, the Netherlands; and [4]Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan.

Address correspondence and reprint requests to Marieke B. Snijder, PhD, Institute of Health Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, Netherlands. E-mail: marieke.snijder@falw.vu.nl.

Received for publication 10 May 2006 and accepted in revised form 4 August 2006.

Abbreviations: ALT, alanine aminotransferase; GFR, glomerular filtration rate; HMW, high molecular weight; IGM, impaired glucose metabolism; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0952

Table 1—*Baseline characteristics of men by quartiles of adiponectin*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}	P_{trend}*
n	145	151	143	145		
Adiponectin (μg/ml)	5.66 ± 0.89	7.92 ± 0.65	10.30 ± 0.77	20.41 ± 6.75	<0.001	<0.001
Age (years)	57.4 ± 5.9	59.7 ± 6.5	60.5 ± 7.2	62.4 ± 7.0	<0.001	—
Anthropometry						
BMI (kg/m^2)	26.6 ± 2.8	26.2 ± 2.4	26.1 ± 3.6	25.1 ± 2.5	<0.001	<0.001
Waist circumference (cm)	95.6 ± 8.4	94.7 ± 7.5	94.0 ± 9.0	91.9 ± 8.1	<0.001	<0.001
Hip circumference (cm)	101.1 ± 5.7	100.3 ± 4.7	100.1 ± 5.1	99.3 ± 5.0	0.002	0.003
WHR	0.94 ± 0.05	0.94 ± 0.05	0.93 ± 0.07	0.93 ± 0.06	0.004	<0.001
Metabolic variables						
Fasting glucose (mmol/l)	5.48 ± 0.50	5.54 ± 0.51	5.41 ± 0.48	5.40 ± 0.50	0.046	0.013
2-h glucose (mmol/l)	5.39 ± 1.63	5.35 ± 1.70	4.83 ± 1.48	5.03 ± 1.51	0.006	<0.001
LDL cholesterol (mmol/l)	4.44 ± 0.93	4.52 ± 1.03	4.46 ± 0.93	4.53 ± 0.95	0.583	0.575
HDL cholesterol (mmol/l)	1.16 ± 0.31	1.14 ± 0.25	1.18 ± 0.24	1.33 ± 0.36	<0.001	<0.001
Triglycerides (mmol/l)	1.4 (1.1–2.2)	1.5 (1.1–2.1)	1.4 (1.0–1.7)	1.2 (1.0–1.7)	<0.001	<0.001
Systolic blood pressure (mmHg)	133.8 ± 18.8	132.0 ± 16.7	130.3 ± 16.3	134.2 ± 18.6	0.951	0.025
Diastolic blood pressure (mmHg)	85.0 ± 9.2	83.1 ± 9.6	81.7 ± 8.7	82.4 ± 10.7	0.011	0.013
Leptin (μg/l)	3.29 (1.73–5.59)	3.51 (1.79–5.74)	3.13 (1.95–4.71)	2.43 (1.36–4.94)	0.002	0.001
ALT activity (units/l)	16.6 ± 10.9	14.2 ± 8.3	13.3 ± 6.2	11.9 ± 5.4	0.000	0.000
GFR (ml/min per 1.73 m^2)	74.7 ± 12.3	71.1 ± 10.0	70.9 ± 11.7	69.7 ± 12.7	0.001	0.668
Lifestyle factors						
Smoking (% yes)	31.7	39.7	40.6	32.4	0.881	0.696
Habitual physical activity (h/day)	2.8 (1.6–4.4)	2.9 (1.7–5.0)	3.0 (1.9–5.1)	3.1 (2.0–5.0)	0.217	0.878
Sports (% yes)	34.5	29.1	30.1	25.5	0.127	0.865
Alcohol (% yes)	90.3	87.1	84.2	85.8	0.199	0.601
Alcohol (g/day)						
0	9.7	12.9	15.8	14.2	0.199	0.601
<10	39.6	43.5	43.9	43.3	0.539	0.603
10–30	34.0	32.7	30.9	34.8	0.980	0.662
≥30	16.7	10.9	9.4	7.8	0.018	0.046

Data are means ± SD or median (interquartile range) unless otherwise indicated. *P_{trend} adjusted for age.

of Hoorn. Another 140 subjects were not invited because of logistic reasons. Of the remaining 2,086 subjects, 1,513 (72.5%) participated. At both examinations, an extensive physical examination and an oral glucose tolerance test were performed.

For the present analyses, from the baseline population (n = 2,484) we excluded subjects with missing baseline data (n = 184) and subjects who already had type 2 diabetes (either newly detected or previously diagnosed) at baseline (n = 224). From the remaining 2,076 subjects, 1,264 persons had follow-up data available on glucose tolerance status and were included for prospective analyses. Informed consent was obtained from all participants, and ethical approval was obtained from the Ethical Review Committee of the VU University Medical Center.

Adiponectin

Baseline adiponectin was determined in 2004 in spare plasma samples that had been stored at −80°C and had never been thawed before. Adiponectin was determined by a latex turbidometric immunoassay (Otsuka Pharmaceutical). The inter- and intra-assay coefficients of variation were <2.0 and <3.1%, respectively.

Glucose metabolism

Fasting glucose and 2-h postload glucose levels after a 75-g oral glucose tolerance test were measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany) at baseline and by the hexokinase method (Boehringer-Mannheim, Mannheim, Germany) at follow-up. Glucose levels were used to classify subjects according to the 1999 World Health Organization criteria into normal glucose metabolism, impaired glucose metabolism (IGM) (impaired fasting glucose and/or impaired glucose tolerance), or type 2 diabetes.

Additional measurements

Serum lipids and lipoproteins were determined by enzymatic techniques (Boehringer-Mannheim). Serum leptin concentrations (micrograms per liter) were determined by a radioimmunoassay. Serum alanine aminotransferase (ALT) enzyme activity was measured according to the method of the International Federation of Clinical Chemistry of 1985 and expressed as units per liter (20). The serum creatinine level was determined to calculate the glomerular filtration rate (GFR) by the Cockcroft-Gault formula in milliliters per minute per 1.73 m^2 body surface area. BMI (weight in kilograms divided by the square of height in meters) and waist-to-hip ratio (WHR) were calculated. Blood pressure (millimeters of mercury) was measured in duplicate by means of a random-zero sphygmomanometer (Hawksley-Gelma, Lancing, U.K.). Information on lifestyle factors was obtained by questionnaires. Habitual

Table 2—*Baseline characteristics of women by quartiles of adiponectin*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}	P_{trend}*
n	170	170	170	170		
Adiponectin (μg/ml)	8.48 ± 1.74	12.67 ± 1.03	16.60 ± 1.26	24.78 ± 5.72	<0.001	<0.001
Age (years)	59.1 ± 6.4	59.5 ± 6.7	60.2 ± 6.6	62.2 ± 7.2	<0.001	—
Anthropometry						
BMI (kg/m^2)	27.3 ± 3.3	26.8 ± 3.8	26.2 ± 3.3	25.7 ± 3.1	<0.001	<0.001
Waist circumference (cm)	88.5 ± 9.3	87.2 ± 10.4	85.4 ± 9.5	82.3 ± 9.0	<0.001	<0.001
Hip circumference (cm)	103.1 ± 6.9	103.6 ± 7.4	102.7 ± 6.4	102.3 ± 6.8	0.185	0.045
WHR	0.86 ± 0.07	0.84 ± 0.07	0.83 ± 0.07	0.80 ± 0.07	<0.001	<0.001
Metabolic variables						
Fasting glucose (mmol/l)	5.46 ± 0.50	5.32 ± 0.48	5.27 ± 0.54	5.13 ± 0.51	<0.001	<0.001
2 h glucose (mmol/l)	6.18 ± 1.72	5.42 ± 1.38	5.28 ± 1.44	5.07 ± 1.33	<0.001	<0.001
LDL cholesterol (mmol/l)	4.81 ± 1.19	4.60 ± 1.03	4.67 ± 1.07	4.51 ± 1.00	0.023	0.012
HDL cholesterol (mmol/l)	1.30 ± 0.32	1.46 ± 0.34	1.54 ± 0.32	1.66 ± 0.37	<0.001	<0.001
Triglycerides (mmol/l)	1.7 (1.2–2.2)	1.3 (1.0–1.7)	1.2 (0.9–1.5)	1.0 (0.8–1.3)	<0.001	<0.001
Systolic blood pressure (mmHg)	134.0 ± 20.9	132.2 ± 20.1	132.0 ± 20.5	130.0 ± 19.4	0.082	<0.001
Diastolic blood pressure (mmHg)	81.6 ± 10.0	80.7 ± 9.7	79.9 ± 9.7	78.9 ± 10.7	0.010	0.006
Leptin (μg/l)	16.44 (10.14–27.30)	12.13 (7.75–22.78)	14.82 (8.40–25.02)	10.86 (6.43–18.90)	<0.001	<0.001
ALT activity (units/l)	10.9 ± 4.9	10.4 ± 4.3	11.2 ± 6.6	10.3 ± 4.6	0.582	0.762
GFR (ml/min per 1.73 m^2)	73.1 ± 12.4	73.0 ± 12.0	70.6 ± 11.0	69.3 ± 10.6	0.001	0.149
Lifestyle factors						
Smoking (% yes)	35.7	27.8	27.1	16.5	<0.001	0.001
Habitual physical activity (h/day)	4.4 (3.3–6.0)	4.7 (3.3–6.3)	4.6 (3.4–5.9)	4.1 (3.0–5.7)	0.210	0.451
Sports (% yes)	28.4	33.5	39.4	38.8	0.024	0.004
Alcohol (% yes)	58.3	64.5	61.8	61.7	0.664	0.232
Alcohol (g/day)						
0	41.7	35.5	38.2	38.3	0.674	0.232
<10	37.5	43.8	44.1	46.1	0.126	0.079
10–30	18.5	18.3	10.0	14.4	0.097	0.242
≥30	2.4	2.4	7.6	1.2	0.771	0.506

Data are means ± SD or median (interquartile range) unless otherwise indicated. *P_{trend} adjusted for age.

physical activity (hours per day) included sports, bicycling, gardening, walking, odd jobs, and housekeeping. An additional variable was created that only included performing sports (yes/no).

Statistical analyses

Baseline characteristics are presented for men and women separately according to sex-specific quartiles of adiponectin. To test for trend over the adiponectin quartiles, linear (for continuous dependent variables) or logistic (for dichotomous dependent variables) regression analyses were performed, modeling the categorical variable of adiponectin quartiles as a continuous independent variable. Variables with a skewed distribution were log normal transformed for these analyses.

For prospective analyses, we first plotted the incidence density of type 2 diabetes (number of cases per person-years) against mean adiponectin within each sex-specific quartile of adiponectin. Logistic regression analyses were then performed to calculate the risk (odds ratios [ORs] with 95% CIs) of developing type 2 diabetes or developing IGM during a mean follow-up of 6.4 years. The lowest adiponectin quartile was the reference group. In separate analyses, the continuous adiponectin variable was used as independent variable. In this case, the OR was expressed per sex-specific SD of adiponectin. For the analyses on the incidence of IGM, subjects with IGM (n = 189) at baseline and/or with type 2 diabetes at follow-up (n = 118) were excluded (leaving 1,025 subjects for analyses). Effect modification by sex was examined by adding an interaction term (adiponectin quartiles × sex) to the regression models. Because there was significant interaction by sex (P = 0.051 for type 2 diabetes and P = 0.002 for IGM), the analyses were subsequently performed and reported separately for men and women. Further adjustments were made for age, sex, lifestyle factors, anthropometric variables, leptin, baseline fasting and postload glucose, lipids, ALT, and GFR by adding these variables to the regression models. All statistical analyses were performed using SPSS (version 11.0 for Windows; SPSS, Chicago, IL).

RESULTS — Baseline characteristics are shown in Table 1 (men) and Table 2 (women). At baseline, after adjustment for age, a low adiponectin level was strongly associated with unfavorable measures of anthropometric body composition and measures of glucose (except for HbA_{1c} in men) and lipid metabolism (except for LDL cholesterol in men). A low adiponectin level was also associated with high leptin levels and with high systolic and diastolic blood pressure. In women, smoking was associated with

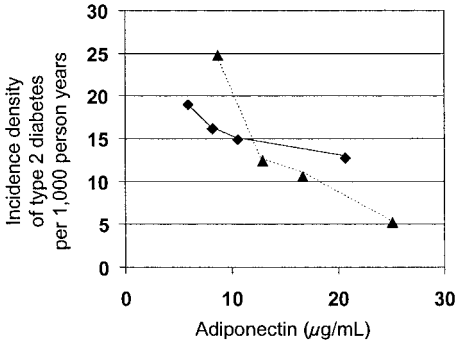

Figure 1—*Incidence density of type 2 diabetes within sex-specific adiponectin quartiles, after a mean follow-up of 6.4 years. ♦, men; ▲, women.*

lower adiponectin levels, and participating in sports was associated with higher adiponectin levels.

The mean follow-up duration was 6.4 ± 0.5 years for both sexes. Figure 1 shows the crude association between adiponectin levels and the incidence density of type 2 diabetes. High adiponectin levels were associated with a lower incidence of type 2 diabetes, and this association appeared stronger in women than in men. After adjustment for age and lifestyle, higher adiponectin levels at baseline were associated with a lower risk of development of type 2 diabetes, although not statistically significant in men (Table 3, model 1). Adjustment for leptin, as a marker for body fat, and WHR weakened the associations, particularly in women (model 2). Adjustment for waist and hip separately or for waist circumference alone instead of WHR or additional adjustment for BMI yielded similar results (not shown). Adjustment for glucose levels, particularly postload glucose, substantially weakened the associations (model 3). Additional adjustment for triglycerides also diminished the associations (model 4), whereas adjustment for LDL cholesterol did not (not shown). Adjustment for HDL cholesterol instead of triglycerides diminished the strength of the associations (ORs [95% CI] in quartile 2, 3, and 4 were 0.66 [0.29–1.52], 0.95 [0.40–2.25], and 0.75 [0.30–1.90] in men and 0.98 [0.44–2.19], 0.75 [0.31–1.80], and 0.71 [0.23–2.17] in women, respectively), but not if triglycerides were already entered into the model (data not shown). Adjustment for ALT or GFR (instead of triglycerides in model 4) did not change the associations (not shown). If only subjects with normal glucose tolerance were selected (subjects with IGM at baseline also excluded) the risk of development of diabetes associated with low adiponectin levels became stronger: the OR (95% CI) for the highest compared with the lowest adiponectin quartile was 0.45 (0.14–1.47) in men and 0.17 (0.03–0.83) in women, after adjustment for age, lifestyle, and WHR.

The association between adiponectin levels and the incidence of IGM (Table 4) had a pattern similar to that for the association with type 2 diabetes in women, but the association of a high adiponectin level with a lower risk of IGM was not observed in men. We also calculated the risk for the incidence of impaired fasting glucose and impaired glucose tolerance separately. After adjustment for age, lifestyle, and WHR, the ORs (95% CI) for highest compared with lowest adiponectin quartile were 1.15 (0.60–2.20) in men and 0.54 (0.28–1.03) in women for impaired fasting glucose and 0.92 (0.34–2.44) in men and 0.28 (0.12–0.68) in women for impaired glucose tolerance.

CONCLUSIONS — Our main finding is that a lower adiponectin level is associated with a higher risk of developing type 2 diabetes after a mean follow-up of 6.4 years in an elderly Caucasian population. This association was largely explained by fasting and postload glucose levels. In women with a normal glucose metabolism at baseline, a low adiponectin level was associated with an increased risk of developing IGM (pre-diabetic state), but this association was not observed in men. To our knowledge, our study is the first prospective cohort study in elderly Caucasian men and women.

Baseline adiponectin independently predicted subsequent type 2 diabetes during 6.4 years of follow-up in our population. Together with the observation that weight reduction affected adiponectin (5), but that adiponectin did not predict weight change (17), our results support the hypothesis that adiponectin may play an important role in the pathogenesis of abnormal glucose metabolism. It is suggested that, possibly as a result of a low adiponectin level, liver fat accumulation plays a key role in the development of metabolic disturbances (21). However, ALT, which is used as a marker of liver fat accumulation, was inversely associated with adiponectin in men but not in women. Additional analyses revealed that an inverse association between ALT and adiponectin existed in the entire population of women, but it disappeared once

Table 3—*Risk of developing type 2 diabetes in 6.4 years associated with adiponectin*

	Adiponectin				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Continuous, per SD
Men					
Cases (%)	12.4 (18/145)	10.6 (16/151)	9.8 (14/143)	8.3 (12/145)	10.3 (60/584)
Model 1	1.0	0.77 (0.37–1.61)	0.67 (0.31–1.46)	0.52 (0.23–1.18)	0.83 (0.62–1.12)
Model 2	1.0	0.79 (0.38–1.67)	0.71 (0.33–1.55)	0.61 (0.27–1.40)	0.89 (0.66–1.20)
Model 3	1.0	0.66 (0.29–1.52)	0.96 (0.41–2.27)	0.79 (0.32–1.91)	1.01 (0.74–1.39)
Model 4	1.0	0.67 (0.29–1.54)	0.98 (0.41–2.33)	0.80 (0.33–1.95)	1.02 (0.75–1.40)
Women					
Cases (%)	15.8 (27/170)	8.2 (14/170)	7.2 (11/170)	3.5 (6/170)	8.5 (58/680)
Model 1	1.0	0.48 (0.24–0.97)	0.37 (0.18–0.97)	0.15 (0.06–0.39)	0.42 (0.28–0.62)
Model 2	1.0	0.58 (0.28–1.20)	0.47 (0.22–1.01)	0.27 (0.10–0.73)	0.55 (0.36–0.83)
Model 3	1.0	0.91 (0.41–2.00)	0.68 (0.29–1.61)	0.62 (0.21–1.81)	0.78 (0.52–1.18)
Model 4	1.0	0.97 (0.43–2.17)	0.75 (0.31–1.80)	0.69 (0.23–2.07)	0.82 (0.54–1.26)

Data are OR (95% CI) unless otherwise indicated. Model 1: adjusted for age and lifestyle (smoking and sports). Model 2: model 1 plus adjusted for leptin (log normal transformed) and WHR. Model 3: model 2 plus adjusted for fasting and postload glucose. Model 4: model 3 plus adjusted for triglycerides (log normal transformed).

Table 4—*Risk of developing IGM in 6.4 years associated with adiponectin (excluding subjects who already had IGM at baseline or developed type 2 diabetes at follow-up)*

	Adiponectin				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Continuous, per SD
Men					
Cases (%)	32.4 (35/108)	36.5 (42/115)	29.9 (35/117)	34.4 (41/119)	33.3 (153/459)
Model 1	1.0	1.08 (0.62–1.90)	0.80 (0.45–1.43)	0.90 (0.51–1.61)	0.93 (0.76–1.14)
Model 2	1.0	1.15 (0.65–2.03)	0.89 (0.49–1.60)	1.11 (0.61–2.02)	0.99 (0.80–1.22)
Model 3	1.0	1.06 (0.56–2.01)	1.06 (0.54–2.07)	1.20 (0.61–2.35)	1.01 (0.79–1.28)
Model 4	1.0	1.05 (0.55–2.00)	1.11 (0.57–2.16)	1.25 (0.63–2.46)	1.03 (0.81–1.31)
Women					
Cases (%)	45 (54/120)	27.8 (40/144)	27.1 (39/144)	20.9 (33/158)	29.3 (166/566)
Model 1	1.0	0.45 (0.27–0.76)	0.44 (0.26–0.74)	0.28 (0.16–0.48)	0.68 (0.54–0.84)
Model 2	1.0	0.49 (0.29–0.83)	0.50 (0.30–0.86)	0.36 (0.20–0.65)	0.76 (0.60–0.96)
Model 3	1.0	0.57 (0.32–1.01)	0.64 (0.36–1.14)	0.48 (0.26–0.90)	0.82 (0.65–1.03)
Model 4	1.0	0.63 (0.36–1.13)	0.79 (0.43–1.44)	0.62 (0.32–1.18)	0.91 (0.73–1.15)

Data are OR (95% CI) unless otherwise indicated. Model 1: adjusted for age and lifestyle (smoking and sports). Model 2: model 1 plus adjusted for leptin (log normal transformed) and WHR. Model 3: model 2 plus adjusted for fasting and postload glucose. Model 4: model 3 plus adjusted for triglycerides (log normal transformed).

women with type 2 diabetes were excluded. An association of ALT with incident type 2 diabetes was previously found in the Hoorn Study (which also disappeared after additional adjustment for baseline glucose levels); however, a possible difference between men and women was not evaluated (22). Our results suggest that the association between adiponectin and incident type 2 diabetes was not explained by ALT.

Adjustment for glucose (particularly postload glucose) and triglycerides substantially reduced the associations between adiponectin and incident type 2 diabetes. This could suggest that the associations are (partly) mediated by these factors, confirming the hypothesis of adiponectin contributing to type 2 diabetes risk through effects on (hepatic) insulin resistance. Previous prospective studies found associations between adiponectin and type 2 diabetes, even independent of fasting glucose levels. It is likely, however, that this is caused by residual effects of postload glucose and triglycerides, which were usually not measured.

There are still unexplained phenomena concerning adiponectin metabolism. The association between adiponectin and type 2 diabetes was stronger in women than in men. Because of differences in design among studies, it is difficult to compare the absolute strength of the association, but a sex difference has previously been shown in younger adults (18), with stronger associations also being shown in women. Other prospective studies on adiponectin and type 2 diabetes did not report on possible differences between men and women (14–17). It is remarkable that, despite their higher body fat percentage, women appear to have higher adiponectin levels than men. Previously, this difference could not be explained by differences in fat distribution (6). Another counterintuitive observation is that adiponectin is positively associated with age. This has also been shown in many other studies in which the association between adiponectin and age was reported (e.g., the study by Cnop et al. [6] and the Funagata Study [16]) but so far has received little attention. So, despite the increase in body fat with aging and the accompanying increased cardiovascular risk, adiponectin levels also increase. These observations emphasize that the mechanisms that underlie the association between adiponectin and disturbed glucose metabolism are poorly understood. Recent work has shown that adiponectin exists in different isoforms, low–molecular weight and high–molecular weight (HMW) complexes (2). Diabetic patients had a significantly decreased HMW-to-total adiponectin ratio (23), and HMW adiponectin correlated better with glucose tolerance than total adiponectin in Indo-Asian males (24). Also, a relatively larger increase in HMW adiponectin after weight reduction has been shown (25). These findings indicate that the HMW adiponectin complex is possibly the active form of this protein. Women have more HMW adiponectin than men (23), which may partly explain the differences that we have found between men and women.

A limitation of the present study may be that we had no repeated measurement of adiponectin at the follow-up examination. Adiponectin levels may have changed considerably after >6 years. Despite the long follow-up duration, however, we were still able to find an association indicating that the relation is very strong. In addition, participants in the follow-up examination were healthier at baseline than the nonparticipants (26). This may have led to an underestimation of the true incidence of type 2 diabetes and consequently to an underestimation of the associations with adiponectin.

In summary, our findings strongly support the hypothesis that adiponectin may play an important role in the pathogenesis of abnormal glucose metabolism. However, further investigation of the underlying mechanisms, focusing on adiponectin isomer distribution, is needed to elucidate the associations of adiponectin with sex and age.

Acknowledgments— The Hoorn Study has been made possible by Vrije Universiteit Amsterdam, the VU University Medical Center, the Dutch Diabetes Research Foundation, the Dutch Organization for Scientific Research, the Netherlands Heart Foundation, and the Health Research and Development Council of the Netherlands.

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