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ORIGINAL ARTICLE

Differential association of adiponectin with cardiovascular risk markers in men and women? The KORA survey 2000

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Background: In men, high adiponectin concentrations were related to a lower risk of myocardial infarction, whereas no association with cardiovascular events was found in women.
Objective: To investigate sex differences in the associations of adiponectin with cardiovascular risk factors.
Design: Cross-sectional population-based KORA Survey 2000 in Southern Germany using the same study methods for cardiovascular risk factors as the former WHO MONICA project.
Participants: A total of 697 men and 657 women, aged 55–74 years. Glucose tolerance status was assessed by oral glucose tolerance tests.
Results: Adiponectin (geometric mean, interquartile range; μg/ml) levels were significantly higher in women (11.1; 8.5–14.9) than in men (7.1; 5.2–9.6) ($P<0.05$). In univariate analyses, HDL-cholesterol and age were significantly positively correlated with adiponectin in both sexes. Negative correlations were observed with BMI, waist circumference, fasting and postchallenge glucose, insulin, HOMA-IR, HbA1c, triglycerides, uric acid and CRP ($P<0.01$). In sex-specific multivariate regression, age and HDL-cholesterol were independently positively, and fasting insulin and 2-h glucose were negatively related to adiponectin in both sexes. Uric acid was significantly inversely related to adiponectin in women only (sex interaction: $P=0.02$). Exploratory sex-specific factor analysis of adiponectin and the core components of the metabolic syndrome yielded four similar factors. Adiponectin loaded negatively on the 'lipids' factor in both sexes.
Conclusion: The associations of adiponectin with cardiovascular risk factors showed a similar pattern in both sexes, except for uric acid. This small sex difference may not explain previous conflicting results on the association of adiponectin with cardiovascular events in men and women.
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Keywords: adiponectin; cardiovascular risk; epidemiology; insulin resistance; cholesterol

Introduction

Adiponectin has been suggested as a major factor linking the metabolic syndrome to its cardiovascular consequences, due to its anti-inflammatory and antiatherogenic properties, for example effects on endothelial-dependent vasodilatation, suppression of macrophage transformation to foam cells, and inhibition of vascular smooth muscle and endothelial cell proliferation and migration.[1] Adiponectin levels are decreased in obesity,[2] and in cross-sectional studies an inverse association has been found between adiponectin and prevalent coronary heart disease (CHD).[3–5] Adiponectin is not the only adipose-tissue-derived protein that shows altered circulating levels in obesity with implications for CHD risk. However, it is unique among adipokines since

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reduced levels in the circulation appear to be associated with obesity and CHD, but disease-related concentrations of other adipokines, such as leptin, interleukin-6 (IL-6) and IL-8 are elevated.[6–8] In addition, there is evidence for mutual inverse regulation of these adipokines on the cellular level since adiponectin has been reported to reduce the release of various cytokines, chemokines and inflammatory mediators from adipocytes,[9] whereas IL-6, tumor necrosis factor α (TNFα) and other adipokines decrease adiponectin expression in adipocytes.[10]

Beyond the cross-sectional data on adiponection and CHD, results of prospective studies have been conflicting so far.[11–14] Whereas in men aged 40–75 years (US Health Professionals Follow-up Study) high adiponectin concentrations were related to a lower risk of myocardial infarction both in all subjects and in type 2 diabetic patients,[12,13] no associations were found in American Indians,[11] and in elderly women aged 60–79 years from the British Women's Heart and Health Study.[14] Conflicting results have also been published for adiponectin and stroke. Whereas adiponectin levels showed an inverse relation with stroke severity on admission and 5-year survival in a clinic-based study,[15] no association was found between adiponectin and first-time stroke using data from population-based surveys in northern Sweden.[16]

Adiponectin levels are considerably higher in women than in men.[14] It has been speculated that the different study results for cardiovascular disease may be related to sex differences in the effects of adiponectin on cardiovascular risk factors.[14] Therefore, we analyzed whether there are sex differences in the associations of adiponectin concentrations with a variety of metabolic and other cardiovascular risk markers in a population-based sample. In particular, we evaluated the relations of adiponectin with the core components of the metabolic syndrome.

Methods

Study population

The KORA (Cooperative Health Research in the Region of Augsburg) Survey 2000 is a population-based cross-sectional study in Southern Germany in the same region and using the same methods as the previous WHO MONICA project.[17] Fasting oral glucose tolerance tests (OGTT) were performed after informed consent in participants without known diabetes. The study was approved by the Ethics Committee of the Bavarian Physician Chamber.

Overall, 1653 (62%) subjects in the age group 55–74 years participated, including 131 subjects with known diabetes (self-reports or antidiabetic treatment). After further drop-outs, which were mainly subjects who were not able to attend the study center during morning hours ($n=168$) and excluding all subjects without fasting blood samples (including all with known diabetes), 697 men and 657 women remained for the present analysis.

Anthropometry and interviews

Body weight was measured in light clothing to the nearest 0.1 kg and height to the nearest 0.1 cm. Waist circumference was measured at the maximum abdominal girth to the nearest 0.1 cm. Blood pressure was measured in a sitting position three times at the right arm after 15 min rest using an automatic device (OMRON HEM 705-CP). The mean of the second and third measurement was used for analysis.

In a structured interview, subjects were asked to report the frequency and average duration of regular moderate and vigorous physical activity during leisure time in winter and summer using four categories. Less than 1 h activity per week in at least one season was defined as low physical activity. Alcohol intake was assessed for the previous workday and the previous week-end. Increased intake was defined as >40 g per day in men and >20 g per day in women. Regular smoking was defined as at least one cigarette per day on a regular basis.

Laboratory measurements

Serum adiponectin concentrations were determined using the radioimmunoassay from Linco Research (St Charles, MO, USA). Mean intra- und inter-assay variations were 5.5% (mean CV of duplicate measurements of 30 control sera) and 9.2% (mean CV of concentrations of two control sera tested in 16 assays), respectively. Blood glucose was assessed using a hexokinase method (Gluco-quant, Roche Diagnostics, Mannheim, Germany). HbA1c-values were determined using a turbidimetric immunologic assay (Tina-quant, Roche Diagnostics). Total cholesterol was measured by enzymatic methods (CHOD-PAP, Roche Diagnostics), high-density lipoprotein cholesterol (HDL-C) after precipitation with phosphotungstic acid/Mg^{2+} (Roche Diagnostics), and LDL-C after precipitation with dextran sulfate (Quantolip LDL, Immuno AG). Triglycerides were assessed with the Boehringer GPO-PAP assay. Insulin was measured using a microparticle enzyme immunoassay (MEIA, IMx Insulin, Abbott Laboratories, Wiesbaden, Germany). The insulin resistance score (HOMA-IR) was determined as fasting plasma glucose (mmol/l) $\times$ fasting serum insulin (mU/l)/22.5. EDTA plasma samples were stored at -80°C for analysis of inflammatory markers. Plasma CRP concentrations were measured using a latex enhanced nephelometric assay run on a BN II analyser (Dade Behring, Marburg, Germany) and fibrinogen using immunonephelometry.

Statistical analysis

The distributions of continuous variables were assessed for normality and the log transformations of skewed variables were used. Geometric means for all log-normal distributed continuous variables (adiponectin, fasting insulin, HOMA-IR, triglycerides, fibrinogen, CRP) were calculated and reported with 25th and 75th percentiles. Sex differences for continuous or dichotomous variables were assessed using

two-sample *t*-tests or χ^2 tests. Sex-specific Pearson correlation coefficients were used to evaluate the association of metabolic variables with log-transformed adiponectin concentrations. Sex-interactions in the associations of risk factors with adiponectin (log) were assessed in common linear regression models (both sexes combined) including age, the factor, sex (male sex = 1, female sex = 0), and a sex × factor interaction term (Wald tests of interaction terms). Then, sex-specific multivariate regression model were fitted including all variables that have been significantly related to adiponectin in univariate analyses (men or women). Tests for colinearity were performed. Colinearity was indicated by a variance inflation factor >5.0 or an condition index >30.0.[18] Furthermore, a sex-combined model was fitted including all significant sex × factor interaction terms.

Finally, sex-specific factor analysis (principal-factor solution) was used to further investigate the relationship of log adiponectin with the core components of the metabolic syndrome. The number of factors retained was based on screeplot analysis, retaining only factors above the break in the curve, and a proportion $>5\%$ of common variance explained.[19] Orthogonal varimax rotation was used to obtain a set of independent factors. The factor pattern was interpreted using factor loadings $\geqslant 0.3$. The percentage total variance and the cumulative total variance in the dataset explained by the factors were calculated. All analyses were performed using Stata Statistical Software: Release 9, StataCorp, College Station, TX, USA and SAS Version 9.1 for UNIX. The level of statistical significance was 5%.

Results

Characteristics of study population

Adiponectin concentrations were significantly higher in women than in men as shown in Table 1 ($P<0.05$). This sex difference persisted after adjusting for age and BMI (linear regression: $P<0.05$). As expected, men showed a more unfavorable cardiovascular risk factor profile with respect to abdominal adiposity, fasting glucose, blood pressure, HDL-cholesterol, triglycerides, uric acid, regular smoking, alcohol intake and low physical activity than women ($P<0.05$), whereas women had significantly higher levels of total cholesterol, LDL-cholesterol and fibrinogen ($P<0.05$). No significant sex differences were found for BMI, postchallenge glucose, fasting insulin, insulin resistance (HOMA-IR), HbA1c and CRP concentrations.

Univariate associations

Sex-specific Pearson correlation coefficients for log-transformed adiponectin with the other variables are shown in Table 2. HDL-cholesterol and age were significantly positively correlated with adiponectin in both sexes. Negative correlations were observed with BMI, waist circumference, fasting and postchallenge glucose, insulin, HOMA-IR, HbA1c, triglycerides, uric acid, and CRP ($P<0.01$). Furthermore, in women but not in men, a significant negative correlation was found with LDL-cholesterol and with systolic and diastolic blood pressure. There were no statistically significant correlations with total cholesterol and fibrinogen in both sexes. Overall, the largest correlation coefficients were found for HDL-cholesterol and triglycerides.

Table 1 Characteristics of survey participants aged 55–74 years by sex: KORA Survey 2000, Augsburg, Germany

	Men (N = *697*)	*Women* (N = *657*)
Age (years)	64.1 (59–69)	63.9 (59–68)
BMI (kg/m^2)	28.2 (26–30)	28.6 (25–31)
Waist circumference (cm)	100.4 (94–107)*	90.4 (83–97)*
Adiponectin (μg/ml)[a]	7.1 (5.2–9.6)*	11.1 (8.5–14.9)*
Fasting glucose (mg/dl)	105.0 (95–111)*	99.2 (91–104)*
2-h Glucose (mg/dl)	127.6 (94–148)	123.9 (95–139)
Fasting insulin (mU/l)[a]	10.5 (6.9–14.7)	10.8 (7.2–14.4)
HOMA-IR[a]	2.7 (1.7–4.0)	2.6 (1.6–3.6)
HbA1c (%)	5.6 (5.4–5.8)	5.7 (5.4–5.9)
Cholesterol (mmol/l)	6.1 (5.3–6.9)*	6.4 (5.7–7.1)*
HDL-cholesterol (mmol/l)	1.4 (1.1–1.6)*	1.7 (1.4–1.9)*
LDL-cholesterol (mmol/l)	3.9 (3.2–4.6)*	4.0 (3.3–4.7)*
Triglycerides (mmol/l)[a]	1.4 (1.0–2.0)*	1.2 (0.9–1.7)*
Serum uric acid (mg/dl)	6.3 (5.4–7.2)*	4.9 (4.2–5.6)*
Systolic blood pressure (mmHg)	139.5 (126–151)*	130.8 (117–144)*
Diastolic blood pressure (mmHg)	81.9 (75–89)*	77.9 (71–85)*
Fibrinogen (g/l)[a]	2.8 (2.4–3.2)*	2.9 (2.6–3.3)*
C-reactive protein (mg/l)[a]	1.7 (0.8–3.4)	1.8 (0.9–3.5)
Regular smokers (%)	17.5*	10.4*
Increased alcohol intake (%)	20.5*	11.1*
Low physical activity (%)	59.5*	53.5*

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Data are means or geometric means. 25th and 75th percentiles or proportions *$P<0.05$ for sex difference.

Table 2 Sex-specific Pearson correlation coefficients of adiponectin with metabolic variables: KORA Survey 2000, Augsburg, Germany

	Men		*Women*	
	R	P-*value*	R	P-*value*
Age	0.12	0.002	0.09	0.017
BMI	−0.16	<0.001	−0.14	<0.001
Waist circumference	−0.12	0.002	−0.17	<0.001
Fasting glucose	−0.20	<0.001	−0.19	<0.001
2-h Glucose	−0.26	<0.001	−0.26	<0.001
Fasting insulin	−0.24	<0.001	−0.25	<0.001
HOMA-IR	−0.26	<0.001	−0.26	<0.001
HbA1c	−0.20	<0.001	−0.18	<0.001
Cholesterol	0.04	0.328	0.004	0.928
HDL-cholesterol	0.30	<0.001	0.35	<0.001
LDL-cholesterol	−0.02	0.597	−0.09	0.018
Triglycerides	−0.27	<0.001	−0.27	<0.001
Uric acid	−0.13	<0.001	−0.25	<0.001
Systolic blood pressure	−0.04	0.337	−0.10	0.013
Diastolic blood pressure	−0.07	0.059	−0.09	0.023
Fibrinogen	−0.07	0.087	−0.05	0.189
C-reactive protein	−0.12	0.002	−0.16	<0.001

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Log-transformed: adiponectin, fasting insulin, HOMA-IR, triglycerides, fibrinogen, CRP, *P*-values for correlation coefficients.

Multivariate associations

In order to evaluate risk factors independently related to adiponectin in men or women, sex-specific multivariate regression models were fitted including all variables significantly related to log adiponectin in univariate analyses, adjusting for potential confounders (alcohol intake, current smoking and physical activity) (Table 3). Colinearity was excluded because the average VIF was 1.27 (range: 1.05–1.45) and the condition index less than 30.0 for the variables included in the final models. Age and HDL-cholesterol were independently positively, and fasting insulin and 2-h glucose were negatively related to adiponectin in both sex-specific models. Among confounders, physical activity was positively related to adiponectin in women only. Furthermore, serum uric acid was significantly inversely related to adiponectin in women but not in men. All results were essentially the same, when including HOMA-IR instead of fasting insulin and waist circumference instead of BMI into the models (data not shown).

Sex-differences in the associations of the various risk factors with adiponectin were assessed using sex × factor interaction terms included in age-adjusted linear regression models (men and women combined). Crude and adjusted models (age, BMI, HOMA-IR, smoking, alcohol, physical activity) were fitted (data not shown). Fasting and postchallenge glucose, HbA1c, fasting insulin, HOMA-IR, triglycerides and uric acid were inversely related to adiponectin, whereas a significant positive association was found with HDL-cholesterol ($P<0.001$). Except for uric acid, there was no indication for effect modification by sex for any risk factor. The inverse association of uric acid with adiponectin was stronger for women than men (adjusted model, interaction term: $P=0.02$).

Table 3 Sex-specific multivariate linear regression models for metabolic and other variables associated with adiponectin (μg/ml) (dependent variable): KORA Survey 2000

	Men		*Women*	
	ßeta	P-*value*	*ßeta*	P-*value*
Age (years)	0.163	<0.001	0.138	<0.001
BMI (kg/m^2)	0.009	0.838	0.098	0.026
2-h Glucose (mg/dl)	−0.183	<0.001	−0.185	<0.001
Fasting insulin (mU/l)	−0.137	0.002	−0.084	0.044
HDL-cholesterol (mmol/l)	0.196	<0.001	0.271	<0.001
Triglycerides (mmol/l)	−0.066	0.137	−0.064	0.125
Uric acid (mg/dl)	−0.036	0.353	−0.139	0.001
C-reactive protein (mg/l)	−0.043	0.268	−0.047	0.239
Diastolic blood pressure (mm Hg)	0.038	0.314	−0.048	0.190
Current smoking	−0.008	0.832	−0.069	0.055
Alcohol intake	0.017	0.635	0.038	0.291
Physical activity	0.059	0.105	0.095	0.008

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein. Log-transformed: adiponectin, fasting insulin, triglycerides, CRP, *P*-values for beta coefficients.

Factor analysis: adiponectin and the metabolic syndrome

Sex-specific factor analysis of adiponectin and the core components of the metabolic syndrome yielded four factors in both sexes, which explained 48.6% of variance in the data in men and 46.8% in women (Table 4). In men, factor 1 ('glucose') showed positive loadings (⩾0.3) for fasting and postchallenge glucose. Factor 2 ('blood pressure') had positive loadings for systolic and diastolic blood pressure. Factor 3 ('lipids') had a negative loading of HDL-cholesterol and loaded positive for triglycerides. Finally, factor 4 showed positive loadings for fasting insulin and waist circumference ('obesity-insulin'). Adiponectin loaded negatively on the 'lipids' factor only. In women, a similar four-factor solution was obtained. In addition, factor 3 ('lipids') showed a positive loading for waist circumference and insulin.

Discussion

The associations of adiponectin concentrations with cardiovascular risk factors showed a largely comparable pattern in men und women aged 55–74 years, except for serum uric acid, which was independently positively related to adiponectin in women only. HDL-cholesterol showed the stron-

Table 4 Factor analysis of adiponectin and the core components of the metabolic syndrome in men and women aged 55–74 years adiponectin: KORA Survey 2000

	Factor 1 glucose	*Factor 2 blood pressure*	*Factor 3 lipids*	*Factor 4 obesity-insulin*
Men				
Log adiponectin	−0.22	−0.01	**−0.39**	−0.11
Waist circumference	0.21	0.12	0.11	**0.61**
Log fasting insulin	0.24	0.17	0.22	**0.62**
Fasting glucose	**0.74**	0.05	0.05	0.16
2-h Glucose	**0.76**	0.11	0.15	0.13
HDL-cholesterol	−0.14	−0.003	**−0.59**	−0.16
Log triglycerides	0.14	0.15	**0.58**	0.19
Systolic blood pressure	0.18	**0.76**	0.009	0.04
Diastolic blood pressure	0.04	**0.76**	0.08	0.07
Total variance (%)	0.15	0.14	0.10	0.11
Women				
Log adiponectin	−0.21	−0.07	**−0.45**	0.02
Waist circumference	0.29	0.07	**0.33**	**0.40**
Log fasting Insulin	0.29	0.12	**0.36**	**0.36**
Fasting glucose	**0.73**	0.10	0.10	0.09
2-h Glucose	**0.74**	0.16	0.15	0.05
HDL-cholesterol	−0.13	−0.02	**−0.61**	−0.13
Log triglycerides	0.22	0.15	**0.50**	0.12
Systolic blood pressure	0.16	**0.81**	0.05	0.04
Diastolic blood pressure	0.04	**0.81**	0.03	0.01
Total variance (%)	0.16	0.15	0.12	0.04

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein. Loadings ⩾0.30 in bold.

gest association with adiponectin in both sexes. Furthermore, higher age was related to increased adiponectin levels in both sexes, even after adjusting for obesity and the components of the metabolic syndrome. As expected, fasting insulin and hyperglycemia were inversely related to adiponectin concentrations in men and women, whereas no independent association was found for CRP. The small sex difference (uric acid) in the relationships between adiponectin and cardiovascular risk factors may not explain the conflicting results of prior prospective studies on its association with coronary heart disease.[11–14]

HDL-cholesterol and adiponectin

In line with previous studies in the present analysis the strongest association between adiponectin and the various components of the metabolic syndrome was found for HDL-cholesterol.[20] It has been shown in a previous cross-sectional study that adjustment for HDL-cholesterol largely attenuated the association between adiponectin and prevalent coronary heart disease.[5] Recently, an inverse association between adiponectin and hepatic lipase activity has been reported, independent of insulin resistance or inflammation.[21] Therefore, although the mechanism remains to be studied, adiponectin may have an independent elevating action on HDL-cholesterol, which may partly explain its antiatherogenic properties.[21] We found no sex differences for the adiponectin-HDL-cholesterol relation, despite significantly higher adiponectin and HDL-cholesterol concentrations in women than in men.

Sex hormones, age and adiponectin

Sex differences in adiponectin levels have already been found in children.[22] In boys a decline in adiponectin levels with the progression of puberty was observed, which was not found in girls, eventually leading to significantly lower adiponectin levels in boys compared to girls after completion of puberty.[22] Adiponectin levels are strongly related to serum androgen concentrations.[22] Androgens have been shown to decrease plasma adiponectin,[23] and testosterone replacement therapy reduced adiponectin levels.[24]

These findings may also partly explain the increasing adiponectin concentrations with higher age in the present study. Age was independently significantly related to adiponectin in our population, although the age range was rather limited (55–74 years). In a previous study with a broader age range, a similar age-dependency was observed.[25] Aging is associated with increasing insulin resistance and increased intra-abdominal fat accumulation, which would predict *lower* adiponectin concentrations in the elderly.[25] A decline of sex steroids in older individuals (testosterone, estrogen), which have been shown to inhibit adiponectin, could be partly responsible for higher adiponectin levels in the elderly.[23–25] Alternatively, a reduction in adiponectin clearance may contribute to the age-dependent increasing concentrations.[26] Recently, a decline in renal function with aging has been shown to be more closely related to adiponectin levels than sex hormones.[26] Overall, age-related changes need to be taken into account since they are potentially important confounders or effect modifiers when assessing the relation of adiponectin and coronary heart disease. Previous studies largely differed with respect to age and sex of the study populations, which hamper the comparability of results.[11–14]

Uric acid and adiponectin

The only sex difference we found was with respect to uric acid, which was significantly related to adiponectin in women only after adjusting for obesity and the other metabolic parameters. Serum uric acid is closely related to obesity, in particular, abdominal adiposity and the various components of the metabolic syndrome, including hypertension and dyslipidemia.[27] These associations may also inversely link uric acid concentrations to adiponectin levels. Already in children, uric acid was inversely associated with adiponectin levels independently of BMI.[22] Recent experimental and animal study findings have suggested that uric acid may contribute to endothelial dysfunction, for example by impairing nitric oxide production.[28,29] Hypoadiponectinemia is also closely linked to endothelial dysfunction, which could be related to oxidative stress.[30,31] Adipose cells are highly sensitive to oxidative stress with subsequent decreased adiponectin secretion.[31] It has been suggested that in a prooxidative environmental milieu the original antioxidant properties of uric acid paradoxically become prooxidant, thus contributing to oxidative stress.[32] This may be a pathway linking uric acid to low adiponectin concentrations independent of obesity.

Blood pressure, acute-phase proteins and adiponectin

Similar to another cross-sectional study no significant association of adiponectin with fibrinogen was found in the present analysis.[5] A significant correlation of adiponectin with systolic and diastolic blood pressure was found in women only in the KORA data, which did not persist after adjusting for the other risk factors. Furthermore, although an inverse correlation was observed with CRP in univariate analysis, the association did also not persist in multivariate models adjusting for obesity and the metabolic parameters. The absence of an independent association with this inflammatory mediator may appear unexpected considering the evidence from *in vitro* studies that adiponectin exhibits anti-inflammatory properties.[9,33–36] As these experiments were carried out using recombinant low-molecular weight adiponectin without multimerization sites, results might however not be comparable with human endogenous adiponectin which consists to a considerable extent of middle- and high molecular weight (HMW) forms.[37] In contrast to the association with CRP, the association between

adiponectin and HDL-cholesterol was not affected by the inclusion of the covariates. Thus, if the link between adiponectin and coronary heart disease could be confirmed in future studies, this may be largely due to its correlation with HDL-cholesterol levels and probably to a lesser extent due to potential anti-inflammatory activities.

Factor analysis: adiponectin and the metabolic syndroms
Factor analysis is a multivariate correlation technique with the aim to reduce a larger number of intercorrelated variables to a smaller set of underlying independent factors.[19] Most factor analyses of the metabolic syndrome in different populations have identified between three to four distinct factors including obesity, dyslipidemia, hyperglycemia and hypertension.[38,39] In the present study based on an elderly Caucasian population, the exploratory analysis emerged four separate factors (glucose, blood pressure, lipids, obesity-insulin). Adiponectin loaded negatively on the third factor in both sexes, which included HDL-cholesterol (negative), triglycerides (positive), waist circumference and fasting insulin (positive loading in women only). This finding is in line with two previous factor analyses from different ethnic populations (Native Canadians, Indians).[19,40] In these analyses, two (Indians) and three (Native Canadians) factors has been shown with adiponectin loading with the lipids factors.[19,40] Adiponectin clustered with HDL-cholesterol (positive correlation) and triglycerides (inverse correlation), In particular, the positive association with HDL-cholesterol may explain the anti-atherogenetic properties of adiponectin, which may reflect the insulin-sensitizing effects of adiponectin.[40] It is noteworthy, that adiponectin also clustered together with fasting insulin and waist circumference in women in the present study.

Study limitations
A limitation of the present study is that we were not able to distinguish adiponectin low and high molecular forms, which are difficult to measure. Women have increased high molecular forms compared to men, whereas no sex differences were found for middle and low multimer concentrations,[41] indicating that testosterone may selectively reduce the HMW forms. In particular, HMW forms are related to HDL-cholesterol.[42] Furthermore, cross-sectional data like the present study are limited due to the potential of reverse causality. Thus, future prospective analyses on the relation of adiponectin with coronary heart disease should take the adiponectin oligomer composition into account.

Conclusions

The associations of adiponectin with metabolic risk factors showed a largely similar pattern in men and women aged 55–74 years, except for uric acid, which was independently related to adiponectin in women only, even after adjusting for obesity and insulin resistance. This difference may not explain conflicting results of prior studies on the association of adiponectin with CHD.

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