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Do albuminuria and hs-CRP add to the International Diabetes Federation definition of the metabolic syndrome in predicting outcome?

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Abstract

Background. To investigate the added value of elevated urinary albumin excretion (UAE) and high high-sensitive C-reactive protein (hs-CRP) in predicting new-onset type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and chronic kidney disease (CKD) in addition to the present metabolic syndrome (MetS) defining criteria.

Methods. The PREVEND Study is a prospective population-based cohort study in the Netherlands, including 8592 participants. The MetS was defined according to the 2004 International Diabetes Federation criteria, elevated UAE as albuminuria $\geq$30 mg/24 h and high hs-CRP as $\geq$3 mg/L.

Results. At follow-up, subjects without MetS when compared to subjects with MetS had a lower incidence of T2DM, CVD as well as CKD (2.5 versus 15.5; 4.1 versus 10.3 and 5.8 versus 11.2%, all $P < 0.001$). In subjects with MetS, the incidence of all three outcomes was higher among subjects with elevated albuminuria versus subjects with normoalbuminuria (all $P < 0.01$). The incidence of all outcomes was also higher among subjects with high hs-CRP versus subjects without elevated hs-CRP but only significant for CKD ($P = 0.002$). Multivariate analysis including elevated UAE, hs-CRP and the variables defining the MetS showed that elevated albuminuria was independently associated with the risk for new-onset T2DM, CVD and CKD, whereas high hs-CRP was only independently associated with new-onset CVD and CKD.

Conclusion. Our data show that elevated UAE has added value to the present MetS defining variables in predicting new-onset T2DM, CVD and CKD, whereas hs-CRP adds to predicting new-onset CVD and CKD, but not T2DM.

Keywords: albuminuria; cardiovascular disease; chronic kidney disease; diabetes mellitus; metabolic syndrome

Introduction

Since the previous decades, there is great interest in the concept of the metabolic syndrome (MetS) and its association with new-onset type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1, 2]. In addition, the MetS has been identified as risk factor for the development of chronic kidney disease (CKD) [3].

The risk entailed by the MetS as a conglomeration of cardiovascular (CV) and metabolic risk factors is attributed to the simultaneous and complementary impact of its constituting factors [2, 3]. Microalbuminuria was initially one of the defining criteria for MetS [4], but was dropped as a criterion in subsequent definitions [5, 6]. This was done for reasons of practicality because urine collection was considered cumbersome. Furthermore, it was questioned whether elevated urinary albumin excretion (UAE) is a risk factor independent of the other variables defining the MetS.

Elevated UAE is indeed associated with various components of the MetS [1, 7, 8]. Elevated albuminuria has furthermore been identified as a predictor of T2DM, CVD as well as CKD [9–13]. Similarly, high-sensitive C-reactive protein (hs-CRP) has also been linked to the MetS defining factors [14–18] and is now acknowledged as a risk marker for new-onset CVD [11, 18, 19]. Albuminuria and hs-CRP are increasingly recognized as manifestations of systemic endothelial dysfunction and low-grade chronic vascular inflammation, respectively. The metabolic, CV and renal risks associated with albuminuria and hs-CRP may be independent of the traditional CV and metabolic risk factors, embedded in the International Diabetes Federation (IDF) definition of the MetS [13, 14].

In 2006, a consensus group of the IDF issued an updated definition of the MetS and also recommended further research into additional criteria that should be part of the definition of the MetS to improve its strength and validity in predicting outcomes [20]. The new recommended research areas included, among others, the potential role of elevated UAE and high hs-CRP [20]. We therefore investigated in a prospective observational cohort study, the added value of elevated UAE and/or high hs-CRP in predicting new-onset T2DM, CVD and CKD in addition to the present MetS defining variables.

Materials and methods

This study was performed in subjects participating in the PREVEND Study (acronym for Prevention of Renal and Vascular End-stage Disease), a prospective population-based cohort study in Groningen, The Netherlands. This study is designed to evaluate the predictive value of microalbuminuria for renal and CV outcome. Details of the study have been reported previously [21, 22]. In brief, the subjects of the PREVEND study have been selected in 1997 from subjects of the general population in Groningen, aged 28–75 years: 40 856 subjects sent by mail a vial containing a portion of spot morning urine sample to a central laboratory and answered a brief questionnaire. Pregnancy and insulin usage were exclusion criteria. Of these subjects, all subjects with a urinary albumin concentration (UAC) $\geq$10 mg/L, and a random sample of subjects with a UAC $<$10 mg/L, were invited for further screening. In total, 8592 subjects participated in the first screening (1997–98), of which 6000 subjects had a UAC $>$10 mg/L in the spot morning urine sample and 2592 subjects a UAC $<$10 mg/L, therefore resulting in a cohort enriched for increased levels of UAC. This screening consisted of two outpatient clinic visits, at which baseline measurements were performed as described in the following paragraph. After a follow-up period of ~4 years (2001–03) and 2.5 years (2003–06), these subjects were invited for a second and third screening, which were completed by 6894 and 5862 subjects, respectively. The PREVEND study is approved by the local ethics committee and conducted in line with Helsinki declaration of research conduct in humans. All participants gave informed consent.

Exposure measurements

At all screening rounds, subjects visited an outpatient clinic twice within a period of 6 weeks, at which data regarding risk factors and outcomes were collected. Anthropometric measurements were performed (including weight, height and waist circumferences) and subjects completed a questionnaire on demographics, CV and renal disease history, smoking and use of medications for hypertension, diabetes and dyslipidaemia. Information on drug use was obtained by the questionnaire data and linked to information collected from community pharmacies. Blood pressure measurements were performed every minute during 10 min with automatic Dinamap XL Model 9300 series device (Johnson–Johnson Medical, Tampa, FL). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the mean of the last two blood pressure measurements of the two visits. Fasting blood samples were taken for measurements of serum cholesterol, triglycerides, hs-CRP and creatinine and plasma glucose and insulin levels. In case subjects arrived at the clinic in a non-fasting condition, subjects were asked to return another day in a fasting condition to take fasting blood samples. However, this was not feasible in a number of subjects, of whom non-fasting blood samples were taken. Subjects were asked to collect two 24-h urines in the week before their second visit to the outpatient clinic. The subjects received oral and written instructions on how to collect a 24-h urine and to postpone collection in event of fever, urinary tract infection, menstruation or heavy exercise. UAE is given as the mean of the two 24-h urine excretions. Elevated UAE was defined as a UAE of $\geq$30 mg/24 h. Glomerular filtration rate was estimated by the use of four-variable Modification of Diet in Renal Disease formula [23].

Laboratory methods

The biochemical measurement of plasma glucose, serum creatinine and lipid profile was performed using standard methods with the use of Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY) and a commercially available assay for high-density lipoprotein (HDL) cholesterol (Abbott Inc., Abbott Park, IL). Plasma insulin was determined on an Axsym analyser (Abbott, Amstelveen, The Netherlands) and hs-CRP by immunonephelometry (BNII; Dade Behring Diagnostic, Marburg, Germany). UAC was determined by immunonephelometry with a threshold of 2.3 mg/L and intra-assay and inter-assay coefficients of variation of 2.2 and 2.6%, respectively (BN™II; Dade Behring Diagnostic).

Definitions

The MetS was defined according to the IDF consensus group 2004 criteria, which were updated in 2006 [20]. In these criteria, central (abdominal) obesity was defined as a waist circumference of $\geq$94 cm in men and $\geq$80cm in women or body mass index $>$30 kg/m^2; and is essential plus any two of the following to define the MetS: serum triglycerides $>$1.7 mmol/L or treatment for this lipid abnormality; HDL cholesterol $<$1.03 mmol/L in men, $<$1.29 mmol/L in women or treatment for this lipid abnormality; blood pressure $\geq$130/85 mmHg or treatment for hypertension; fasting plasma glucose $\geq$5.6 mmol/L or previously diagnosed T2DM. Elevated UAE or in short 'elevated albuminuria' was defined as a UAE $\geq$30 mg/24 h and high hs-CRP as a hs-CRP $\geq$3 mg/L, in accordance with prevailing guidelines [20, 24].

Outcomes

Three outcome measures were investigated in this study, new-onset T2DM, CVD and CKD. New-onset T2DM was defined according to the American Diabetes Association criteria as a fasting plasma glucose level of $\geq$7mmol/L or non-fasting glucose level of $>$11.1 mmol/L at the second or third screening round or the start of oral anti-diabetic drugs during follow-up [25]. New-onset CVD was defined as the occurrence during follow-up of an acute myocardial infarction (ICD code 410), acute and subacute ischaemic heart disease (411), subarachnoid and intracerebral haemorrhages (430), occlusions of the precerebral (433) or intracerebral arteries (434), coronary artery bypass graft or percutaneous transluminal angioplasty and other vascular interventions as bypass grafting of the aorta or peripheral vessels. During follow-up, information on CVD morbidity and mortality was obtained until 31 December 2005. Mortality data were obtained from the Dutch Central Bureau of Statistics, a registry for all deaths in the Netherlands. Data on morbidity were obtained from PRISMANT, a registry that collects in The Netherlands information on hospitalization discharge diagnoses on the basis of the ICD-10 coding [26]. Survival time was defined as the period from the date of urine collection of each participant to the date of the first CVD event or 31 December 2005. People who moved to an unknown destination were lost to follow-up and were censored from that time on. New-onset CKD was defined as an estimated glomerular filtration rate (eGFR) of $<$60 mL/min/1.73m^2 at the second or third screening round [23].

Statistical analyses

All analyses were performed with the statistical package SPSS 16.0 (SPSS, Chicago, IL). Baseline characteristics were calculated for subjects without and with the MetS separately (Table 1). Continuous data are reported as mean and SD or median and interquartile range in case of skewed distribution. Categorical data are described as proportions or percentages. Differences between groups were tested by an independent *t*-test or by a Mann–Whitney test in case of skewed distribution. Differences in proportions between groups were tested with a chi-square test. The level of significance was determined at a P-value $<$0.05, two-tailed.

The cumulative incidence of T2DM, CVD and CKD was calculated. Data are given in Figures 1–3. Logistic regression models were used to estimate relative risks for new-onset T2DM and CKD, and a Cox regression analysis to estimate the hazard rate for new-onset CVD. These relative risks and hazard rates were adjusted for age and sex (Tables 2–4). Furthermore, analyses were performed with multivariate models predicting new-onset T2DM, CKD and CVD, where, besides age and sex, all constituting factors of the MetS were entered as continuous variables (Table 5). For new-onset CKD, also baseline eGFR was added to the model. In case of skewed distribution, data were transformed to their natural logarithm to meet the prerequisites for multivariate regression analysis.

To investigate the robustness of our findings, sensitivity analyses were performed to correct for the enrichment of our cohort with subjects with higher levels of albuminuria that was introduced by the study design. This was done by repeating the analyses using complex sample analysis. Complex sample analysis is a statistical method which 'corrects' for the fact that the study population was not randomly selected (enrichment per design for subjects with a UAC $>$10 mg/L). Complex sample analysis adds weight to the subjects in such a manner that the results of analyses can be extended to the general population (aged 28–75 years).

Results

Baseline characteristics

Baseline characteristics of the study subjects are shown in Table 1 separately for those subjects with and without the MetS. The subjects with the MetS were on average older and more frequently males. As expected, they had higher baseline waist circumference, SBP, DBP, triglycerides and

Table 1. Baseline characteristics of the study population[a]

	MetS	
	No	Yes
N (%)	6534 (76)	2058 (24)
Age (years)	47.0 (12.3)	56.1 (11.5)
Caucasian, *N* (%)	6222 (95.2)	1990 (96.7)
Male, *N* (%)	3011 (46.1)	1280 (62.2)
Smoking, *N* (%)	2529 (38.8)	720 (35.1)
BMI (kg/m^2)	24.9 (3.5)	30.0 (4.0)
Plasma insulin (mU/L)	8.4 (6.5)	15.8 (11.3)
eGFR (mL/min/1.73m^2)	81.8 (14.4)	77.7 (15.0)
Waist circumference (cm)	84.3 (11.0)	102.0 (8.9)
WC ≥94 (M) or ≥80 cm (F), *N* (%)	2469 (37.8)	2053 (98.8)
SBP (mmHg)	124.7 (18.5)	143.0 (19.7)
DBP (mmHg)	72.3 (9.2)	79.6 (9.3)
BP ≥130/85 mmHg, *N* (%)	2126 (32.6)	1595 (77.5)
Use of BP lowering drugs, *N* (%)	609 (9.4)	745 (36.3)
sTriglycerides (mmol/L)	1.03 (0.78–1.38)	1.9 (1.4–2.6)
sTriglycerides >1.7 mmol/L, *N* (%)	779 (12.3)	1279 (62.5)
sHDL (mmol/L)	1.41 (0.39)	1.04 (0.27)
sHDL <1.03 (M), <1.29 mmol/L (F), *N* (%)	1537 (24.3)	1484 (72.6)
Use of lipid lowering drugs, *N* (%)	236 (3.6)	321 (15.6)
Plasma glucose (mmol/L)	4.7 (0.8)	5.6 (1.8)
Fasting glucose >7.0 mmol/L, *N* (%)	53 (0.8)	189 (9.3)
Use of glucose lowering medication, *N* (%)	37 (0.6)	119 (5.8)
hs-CRP (mg/L)	1.0 (0.5–2.5)	2.6 (1.3–4.8)
hs-CRP ≥3 mg/L, *N* (%)	1281 (19.6)	906 (44.0)
UAE (mg/24 h)	8.5 (6.0–14.4)	14.8 (8.3–34.9)
UAE ≥30 mg/24 h, *N* (%)	699 (10.7)	589 (28.6)

[a]Continuous values are given as mean (SD) or median (interquartile range) in case of skewed data distribution. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; s, serum.

glucose levels but lower HDL cholesterol and eGFR. Use of blood pressure, lipid and glucose lowering therapy was also more frequent in the subjects with the MetS. Baseline albuminuria and hs-CRP were significantly higher in subjects with the MetS.

New-onset T2DM

For the analysis on new-onset T2DM, data were used of the subjects who had completed at least one follow-up visit after the first screening round ($n = 6920$). Six thousand two hundred and sixteen subjects had fasting blood glucose levels measured at one or more follow-up visits, 704 subjects had data on non-fasting plasma glucose levels at follow-up and 71 subjects were excluded because data on glucose levels were lacking at baseline or during follow-up. Two hundred and twenty-three subjects who met the definition of diabetes at baseline were excluded, leaving 6626 subjects for this evaluation. Of these subjects, 348 (5.3%) developed T2DM over a mean follow-up period of 6.5 years. Figure 1 shows that the incidence of T2DM was only 2.5% in subjects without the MetS, whereas it was 15.5% in subjects with the MetS at baseline ($P < 0.001$). Stratifying the subjects with the MetS according to normo- and elevated UAE shows a significantly higher incidence of T2DM in subjects with the MetS and elevated UAE (20.5%) as compared to subjects with the MetS but with normal UAE (13.9%) ($P = 0.004$). Stratification of subjects with the MetS based on hs-CRP status shows a non-significant higher incidence of T2DM in subjects with the MetS and high hs-CRP (17.4%) as compared to subjects with the MetS and low hs-CRP (14.1%) ($P = 0.10$). Table 2 shows age- and sex-adjusted relative risks for new-onset T2DM. It shows that in subjects with central obesity, an increasing number of additional components defining the MetS is associated with a stepwise increased risk. This risk for new-onset T2DM is further increased if elevated UAE or high hs-CRP is present (Table 2).

New-onset CVD

For the analysis on new-onset CVD, data were used of the subjects who completed the first screening round ($n = 8592$). Subjects with CVD history at baseline were excluded ($n = 451$), leaving 8141 subjects for this evaluation. Of these subjects, 444 (5.5%) developed a CVD event over a mean follow-up period of 7.1 years. Figure 2 shows that the incidence of CVD was only 4.1% in subjects without the MetS, whereas it was 10.3% in subjects with the MetS at baseline ($P < 0.001$). Stratifying subjects with the MetS with respect to UAE status shows a significantly higher incidence of CVD in the subjects with the MetS and elevated UAE (15.6%) as compared to the subjects with the MetS but with normale UAE (8.3%) ($P < 0.001$). Stratification of subjects with the MetS based on hs-CRP status shows a non-significant higher incidence of CVD in subjects with the MetS and high hs-CRP (11.7%) as compared to subjects with the MetS and low CRP (9.3%) ($P = 0.09$). Table 3 shows age- and sex-adjusted hazard rates for new-onset CVD. It shows that in subjects with central obesity,

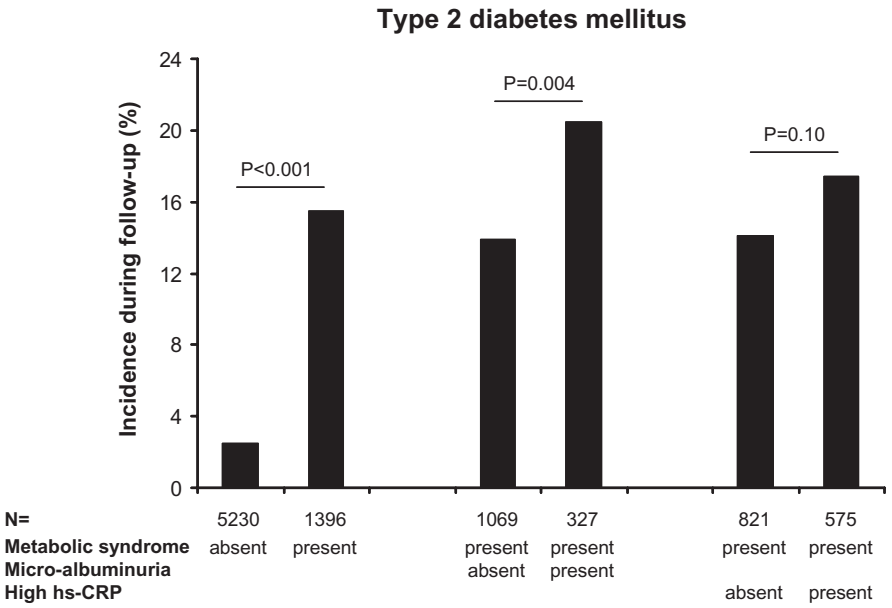

Fig. 1. Incidence of new-onset T2DM during 4.2 years of follow-up in the study population without the MetS, in those with the MetS and in those with the MetS subdivided according to absence/presence of microalbuminuria (albuminuria ≥30 mg/24 h) or absence/presence of high hs-CRP (≥3 mg/L).

Table 2. Relative risks with 95% confidence interval for new-onset T2DM, adjusted for age and sex[a]

	No central obesity	Central obesity plus other criteria of the MetS			
		0	1	2	≥3
Overall population					
N	4035	341	854	734	662
RR	1	1.0 (0.5–2.1)	1.6 (1.1–2.4)	4.0 (2.8–5.5)	9.0 (6.7–12.1)
Subgroups					
UAE <30 mg/24 h					
N		315	708	585	484
RR		0.8 (0.4–1.9)	1.4 (0.9–2.1)	3.7 (2.6–5.3)	8.5 (6.2–11.8)
UAE ≥30 mg/24 h					
N		26	146	149	178
RR		3.5 (0.8–15.1)	2.7 (1.4–5.2)	5.3 (3.2–9.0)	11.0 (7.2–16.7)
hs-CRP <3 mg/L					
N		266	592	434	387
RR		0.8 (0.3–1.9)	1.3 (0.8–2.1)	2.9 (1.9–4.5)	9.0 (6.4–12.6)
hs-CRP ≥3 mg/L					
N		75	262	300	275
RR		1.9 (0.6–6.2)	2.3 (1.3–4.0)	5.5 (3.7–8.2)	8.9 (6.1–12.9)

[a]*N*, number; RR, relative risk.

an increasing number of additional components defining the MetS is associated with a stepwise increased risk, with a steep increase in risk beyond three additional risk factors. The risk for new-onset CVD is increased if elevated UAE or high hs-CRP is present (Table 3).

New-onset CKD

For the analysis on new-onset CKD, data were used of the subjects who completed the first and at least one of the follow-up screening rounds ($n = 6920$). Subjects with known renal disease ($n = 47$) or who at baseline met the definition criteria for CKD ($n = 351$), had urinary sediment abnormalities ($n = 309$) or had missing data on eGFR at the first or at both follow-up screening rounds ($n = 54$) were excluded, leaving 6159 subjects for this evaluation. Of these subjects, 429 (7.0%) developed CKD over a mean follow-up period of 6.5 years. Figure 3 shows that the incidence of CKD was 5.8% in subjects without the MetS, whereas it was 11.2% in subjects with the MetS at baseline ($P < 0.001$). Stratifying subjects with the MetS with respect to UAE status shows a significantly higher incidence of CKD in the subjects with the MetS and elevated UAE (17.2% as compared to subjects with the MetS but with normoalbuminuria (9.3%) ($P < 0.001$). Stratification of subjects with the MetS based on hs-CRP status shows a significantly higher incidence of CKD in subjects with the MetS and high hs-CRP (14.3%) as compared to subjects with the MetS and low hs-CRP (8.9%) ($P = 0.002$). Table 4 shows age- and sex-adjusted relative risks for new-onset

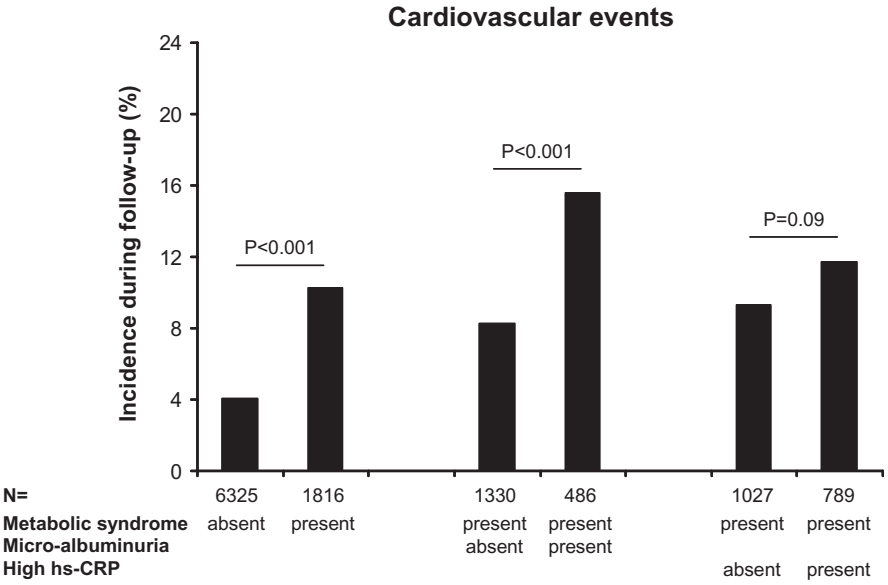

Fig. 2. Incidence of new-onset CVD during 7.1 years of follow-up in the study population without the MetS, in those with the MetS and in those with the MetS subdivided according to absence/presence of microalbuminuria (albuminuria ≥30 mg/24 h) or absence/presence of high hs-CRP (≥3 mg/L).

Table 3. Hazard rates with 95% confidence interval for new-onset CVD, adjusted for age and sex[a]

	No central obesity	Central obesity plus other criteria of the MetS			
		0	1	2	≥3
Overall population					
N	4873	421	1031	897	919
HR	1	0.4 (0.2–0.9)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.8 (1.4–2.2)
Subgroups					
UAE <30 mg/24 h					
N		382	851	707	623
HR		0.4 (0.2–0.9)	1.0 (0.7–1.3)	1.0 (0.8–1.4)	1.5 (1.1–2.0)
UAE ≥30 mg/24 h					
N		39	180	190	296
HR		1.0 (0.3–4.1)	1.5 (1.0–2.2)	1.2 (0.8–1.9)	2.2 (1.6–3.1)
hs-CRP <3 mg/L					
N		314	697	526	501
HR		0.1 (0.0–0.6)	0.9 (0.7–1.3)	1.0 (0.7–1.4)	1.5 (1.1–2.0)
hs-CRP ≥3 mg/L					
N		107	334	371	418
HR		1.6 (0.7–3.6)	1.4 (1.0–2.1)	1.2 (0.8–1.7)	2.1 (1.6–2.9)

[a]*N*, number; HR, hazard rate.

CKD. There is a stepwise increase in risk of CKD with an increasing number of MetS criteria that are met, with a major increment in risk at three additional risk factors or more. It shows that in subjects with central obesity, presence of elevated UAE increases the risk for CKD, whatever the number of other MetS defining criteria that is present. The presence of high hs-CRP is also associated with an increased risk for CKD, however, this association seems a little less strong than the association between UAE and CKD *de novo* (Table 4).

Multivariate analyses

Multivariate analyses for the various outcomes with the MetS constituting factors entered as continuous variables are shown in Table 5. This table shows that with respect to new-onset T2DM waist circumference, triglycerides, HDL and serum glucose remained as significant predictors (Model 1). When albuminuria was added to this model, it significantly predicted the development of new-onset diabetes. hs-CRP was not found to be a significant predictor [Model 1 + C-reactive protein (CRP)]. Albuminuria remained significantly associated with the risk of new-onset T2DM even after adjustment for hs-CRP in the model (Model 1 + UAE + CRP). For new-onset CVD, it appeared that both albuminuria and hs-CRP were significant predictors, even when entered simultaneously into the model. For new-onset CKD, again albuminuria was a highly significant predictor, as was CRP. When albuminuria and CRP were entered in the same model, both

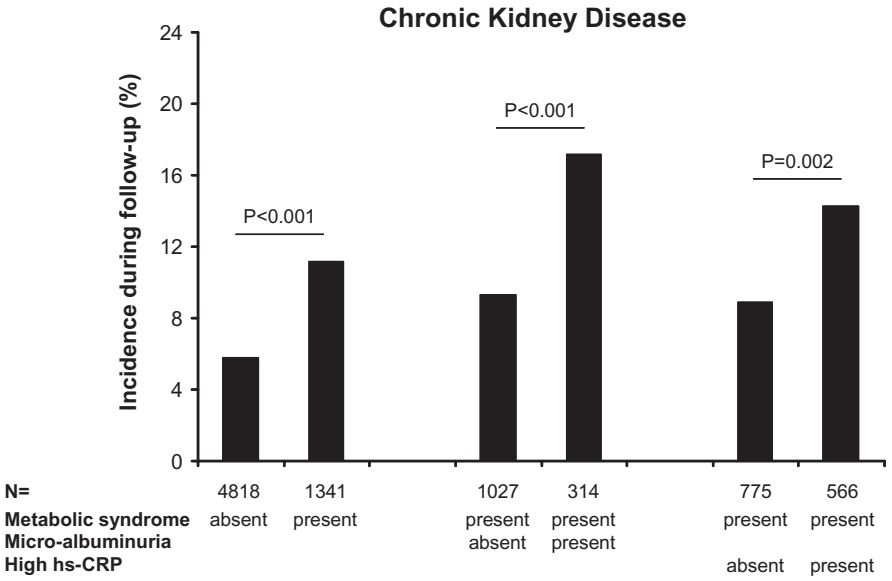

Fig. 3. Incidence of new-onset CKD during 4.2 years of follow-up in the study population without the MetS, in those with the MetS and in those with the MetS subdivided according to absence/presence of microalbuminuria (albuminuria ≥30 mg/24 h) or absence/presence of high hs-CRP (≥3 mg/L).

Table 4. Relative risks with 95% confidence interval for new-onset CKD, adjusted for age, sex and baseline eGFR[a]

	No central obesity	Central obesity plus other criteria of the MetS			
		0	1	2	≥3
Overall population					
N	3752	312	754	667	674
RR	1	0.8 (0.5–1.4)	0.9 (0.6–1.3)	1.1 (0.8–1.5)	1.6 (1.1–2.2)
Subgroups					
UAE <30 mg/24 h					
N		291	634	549	478
RR		0.8 (0.5–1.4)	0.8 (0.5–1.1)	0.9 (0.6–1.3)	1.4 (0.9–2.0)
UAE ≥30 mg/24 h					
N		21	120	118	196
RR		0.6 (0.1–5.3)	1.6 (0.9–3.0)	2.2 (1.2–4.1)	2.2 (1.4–3.7)
hs-CRP <3 mg/L					
N		245	525	396	379
RR		0.9 (0.5–1.5)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	1.3 (0.8–1.9)
hs-CRP ≥3 mg/L					
N		67	229	271	295
RR		0.6 (0.2–2.2)	1.1 (0.7–2.0)	1.7 (1.0–2.7)	1.9 (1.3–2.9)

[a]*N*, number; RR, relative risk.

remained significantly associated with new-onset CKD. Of note, univariately, all the components of the MetS were significantly associated with the risk of development of new-onset T2DM, CVD as well as CKD (data not shown).

Sensitivity analyses

To address the question whether elevated UAE is already associated with adverse outcomes in the microalbuminuric range (UAE 30–300 mg/24 h), analyses were repeated after exclusion of proteinuric subjects, being subjects with UAE >300 mg/24 h. Results of these analyses were similar to the above mentioned results, with only minor changes in risk estimates.

Furthermore, the multivariate models (Table 5) were repeated using urine albumin/creatinine ratio (ACR, mg/mmol) measured in a spot morning urine sample, instead of the average UAE of two 24-h urine collections. These data were available for 6937 subjects of the original PREVEND population ($n = 8592$). It appeared that for CVD and CKD, results of UAC were similar when compared to the use of UAE, and for the end point diabetes de novo, ACR was borderline significant in the full adjusted model [odds ratio (OR) = 1.14 per ln ACR, P = 0.07].

Lastly, to test whether the results of the present study apply to the general population and have not been biased by our study design (enrichment of the study population for increased levels of urine albumin concentration), complex sample analysis was performed. This rendered results that were essentially similar to our primary analyses.

Table 5. Multivariate regression analysis for risk of new-onset T2DM, CVD and CKD[a]

	Model 1		Model 1 + UAE		Model 1 + CRP		Model 1 + UAE and CRP	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
T2DM								
Waist circumference	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	<0.001	1.02 (1.00–1.03)	<0.001
MAP	1.00 (1.00–1.02)	0.25	1.00 (0.99–1.02)	0.64	1.00 (1.00–1.02)	0.28	1.00 (0.99–1.02)	0.66
Ln(triglycerides)	1.57 (1.19–2.07)	0.001	1.55 (1.17–2.04)	0.002	1.57 (1.19–2.07)	0.001	1.55 (1.04–2.00)	0.002
HDL	0.43 (0.26–0.71)	0.001	0.45 (0.27–0.73)	0.001	0.45 (0.27–0.73)	0.001	0.46 (0.19–0.65)	0.002
Glucose	6.74 (5.51–8.24)	<0.001	6.72 (5.49–8.21)	<0.001	6.68 (5.46–8.17)	<0.001	6.67 (7.04–11.98)	<0.001
Ln(UAE)			1.20 (1.06–1.36)	0.005			1.19 (1.07–1.45)	0.008
Ln(CRP)					1.09 (0.96–1.23)	0.20	1.06 (0.94–1.26)	0.34
CVD								
	Model 1		Model 1 + UAE		Model 1 + CRP		Model 1 + UAE and CRP	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Waist circumference	1.00 (0.99–1.01)	0.77	1.00 (0.99–1.01)	0.98	1.00 (0.99–1.00)	0.38	1.00 (0.99–1.00)	0.27
MAP	1.03 (1.02–1.04)	<0.001	1.02 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Ln(triglycerides)	1.24 (1.00–1.55)	0.05	1.23 (0.99–1.52)	0.07	1.25 (1.00–1.56)	0.05	1.24 (0.99–1.54)	0.06
HDL	0.59 (0.41–0.84)	0.003	0.59 (0.42–0.84)	0.003	0.69 (0.49–0.98)	0.04	0.69 (0.49–0.98)	0.04
Glucose	1.01 (0.95–1.08)	0.70	1.00 (0.94–1.06)	0.88	1.00 (0.94–1.06)	0.96	0.99 (0.93–1.05)	0.65
Ln(UAE)			1.14 (1.05–1.24)	0.002			1.12 (1.03–1.22)	0.008
Ln(CRP)					1.36 (1.23–1.49)	<0.001	1.34 (1.22–1.48)	<0.001
CKD								
	Model 1		Model 1 + UAE		Model 1 + CRP		Model 1 + UAE and CRP	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Waist circumference	1.00 (0.98–1.01)	0.40	0.99 (0.98–1.00)	0.25	0.99 (0.98–1.00)	0.06	0.99 (0.98–1.00)	0.04
MAP	1.02 (1.01–1.03)	<0.001	1.02 (1.00–1.03)	0.002	1.02 (1.01–1.03)	<0.001	1.02 (1.00–1.03)	0.004
Ln(triglycerides)	0.99 (0.75–1.31)	0.96	0.97 (0.74–1.29)	0.85	0.97 (0.74–1.29)	0.84	0.96 (0.72–1.27)	0.75
HDL	0.94 (0.65–1.37)	0.75	0.92 (0.63–1.34)	0.67	1.02 (0.70–1.49)	0.92	0.99 (0.68–1.45)	0.97
Glucose	1.18 (1.08–1.28)	<0.001	1.14 (1.05–1.24)	0.003	1.16 (1.07–1.26)	<0.001	1.13 (1.04–1.23)	0.006
Ln(UAE)			1.38 (1.22–1.57)	<0.001			1.36 (1.20–1.54)	<0.001
Ln(CRP)					1.28 (1.14–1.44)	<0.001	1.25 (1.11–1.41)	<0.001

[a]All models are also adjusted for age, gender, and, for new-onset CKD, also for baseline eGFR.

Discussion

The present study examined the impact of adding UAE and hs-CRP to the criteria of the MetS as defined by the IDF in 2004 [20]. We showed that elevated UAE can make a clear distinction between subjects with the MetS at higher and lower risk for new-onset T2DM, CVD and CKD, which is already present in the microalbuminuric range. Importantly, in contrast to the variables that are currently used to define the MetS, albuminuria is the only variable that is significantly associated with all three outcomes. In contrast, hs-CRP was found to be significantly associated with new-onset CVD and CKD, but not with new-onset T2DM in our multivariate analyses.

The inclusion of albuminuria as part of the MetS, as done in this study, has been controversial. Initially, microalbuminuria was considered a component of the syndrome [1, 4], but later, it was decided to drop microalbuminuria as a defining criterion. This was done for reasons of practicality (collecting urine samples was thought to be cumbersome and less feasible) and because some authors questioned whether albuminuria is an independent risk factor by itself. It was argued that albuminuria is merely an integrated risk marker, reflecting the vascular damage induced by being overweight, high blood pressure, cholesterol and glucose, risk factors already embedded in the definition of the MetS. To date, it is still undecided whether the addition of albuminuria and hs-CRP will improve usefulness and predictive value of the MetS [20, 27]. It has been shown in studies linking the syndrome with high CVD risk, that even after adjustment for the other traditional risk factors, excess risk remained [13, 20]. This suggests that the addition of other criteria, e.g. albuminuria and high hs-CRP, to the current definition of the syndrome may improve its applicability and predictive ability.

Several studies have shown that the MetS predicts future diabetes [20, 28, 29]. In our study the risk was indeed higher in subjects with the MetS than in those without, and it is also clear that the highest risk was seen in those subjects with the MetS and elevated UAE as well as in those with the MetS and elevated levels of hs-CRP. Although microalbuminuria is often regarded as being merely a complication of T2DM, some recent studies suggest that it can also precede it [10, 11]. In line with these findings, the present study found that elevated 24-h UAE predicted the development of T2DM. In addition, we found that this predictive value of albuminuria was independent of age, sex and the traditional components of the MetS. In contrast, although in our study high hs-CRP univariately indicated a worse prognosis with respect to new-onset T2DM, we found that the level of hs-CRP was not statistically significant associated with this outcome in a multivariate model.

A number of epidemiological studies have shown that both albuminuria and high hs-CRP are strong and independent risk factors for CVD in patients with hypertension and diabetes as well as in the general population [30–36]. The increase in risk conferred by presence of elevated

albuminuria exceeds in some studies that conferred by hypertension or hyperlipidaemia. Data from the DECODE study, for instance, showed that microalbuminuria was the strongest risk factor for CVD death when compared to obesity, hypertension and dyslipidaemia [37]. In the present study, mean arterial blood pressure (MAP), UAE and CRP are the most significant risk factors in the multivariate model predicting CV outcome, as shown in Table 5. When using standardized variables in a multivariate model, the OR of CRP per SD is highest (OR = 1.39 per s.d.) and comparable to that of MAP.

Recent studies have linked the MetS with the risk of development of CKD [3, 38]. We extended these findings by showing a graded and significant increase in the risk of CKD with an increasing number of criteria that define the MetS being positive. Furthermore, we found that for each number of criteria being positive, the presence of elevated UAE was associated with a higher risk for CKD and that albuminuria was independently associated with the incidence of new-onset CKD. The same holds true for hs-CRP.

What may be the consequences of our findings? This study provides further arguments to add UAE, and possibly high hs-CRP, as criteria to the present definition of the MetS since albuminuria and high hs-CRP independently predicted various outcomes that are associated with the MetS (new-onset T2DM, CVD and CKD). Given the high prevalence of patients with the MetS in the population and its devastating consequences, we need to be more effective in identifying individuals at risk for T2DM, CVD and CKD in whom preventive measures should be started. Urinary albumin is a cheap, non-invasive and easily assessable risk marker and its measurement does not even require a visit to a physician or health centre. For instance, in the PREVEND study, a vial containing a sample of a spot morning void urine was collected at home and sent by post to a central laboratory. In a sensitivity analysis, it was shown that urine ACR measured in a spot urine void is as strongly associated with the outcome of CVD and CKD de novo as is 24-h UAE and for diabetes mellitus de novo nearly as strong.

Similarly, compared to several other biomarkers that reflect biological aspects of inflammation and insulin resistance, hs-CRP measurement is inexpensive to measure, well standardized, widely available, and has a reasonably low intra-subject variation coefficient, similar to that of cholesterol [39]. Given the consistency of prognostic data for UAE and hs-CRP, and the practicality of the use of these biomarkers in outpatient clinical settings, we believe the time has come for a careful consideration of adding these variables as new criteria to define the MetS. However, given our data, it seems more promising to add albuminuria than high hs-CRP.

As stated, a consensus group of the IDF issued in 2006 an updated definition of the MetS and also recommended further research into additional criteria for the definition of the MetS to improve its strength and validity in predicting outcomes [20]. We chose to study the value of adding albuminuria and CRP because these were mentioned as recommended research areas. Our Table 1 suggests that also other patient characteristics may have value as defining criterion. Of note, more recently a report was issued by a WHO expert consultation [40] that questioned among others the relevance of the MetS as a diagnostic and prognostic tool, and whether the predictive value of the MetS is more than the predictive value of the sum of the individual components defining the MetS. In that respect, it is interesting that, as illustrated in Tables 2–4, the main component of the IDF definition, being central obesity, is not associated with increased risk of the adverse outcomes on its own. However, when other components of the MetS are added, obesity becomes a significant risk factor for at least two adverse outcomes, being diabetes mellitus de novo and CKD (Table 5). Therefore, it seems that although obesity is a central component of the MetS, it is not just a risk factor on its own but does contribute to increased risk of adverse outcomes when it is a part of the MetS.

This study has several strengths. Firstly, our study comprises a large cohort of community dwelling participants, with extensive information on risk factors, medication use and various outcome measures. These data were collected prospectively, thereby minimizing selection and/or recall bias. To our knowledge, no study has yet investigated the added predictive value of microalbuminuria as well as high hs-CRP in one study nor taken into account all three outcome measures that have been associated with the MetS. Secondly, we measured albuminuria using 24-h urine collections, which is considered the gold standard for assessing albuminuria. A limitation is that our study population consists predominantly of Caucasians. Whether our results hold true for other populations needs therefore additional study.

In conclusion, this population-based study adds to literature by investigating the impact of adding UAE and high hs-CRP to the current definition of the MetS in predicting diabetes mellitus type 2 de novo, CKD de novo and CVD outcome. We showed that albuminuria can make a distinction between subjects with the MetS at higher and lower risk for new-onset T2DM, CVD and CKD. In contrast to the variables that are currently used to define the MetS, albuminuria is the only variable that was significantly associated with new-onset T2DM, CVD as well as CKD. hs-CRP was found to be significantly associated with new-onset CVD and CKD, but not with new-onset T2DM. Taken together, our data suggest that UAE should be added to the present criteria defining the MetS.

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