Association of the metabolic syndrome with mortality and major adverse cardiac events: A large chronic kidney disease cohort

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Abstract. Pammer LM, Lamina C, Schultheiss UT, Kotsis F, Kollerits B et al. Association of the metabolic syndrome with mortality and major adverse cardiac events: A large chronic kidney disease cohort. J Intern Med. 2021; 290: 1219–1232.

Background. Metabolic syndrome with its key components insulin resistance, central obesity, dyslipidemia, and hypertension is associated with a high risk for cardiovascular events and all-cause mortality in the general population. However, evidence that these findings apply to patients with chronic kidney disease (CKD) with moderately reduced estimated glomerular filtration rate and/or albuminuria is limited.

Objectives. We aimed to investigate the association between metabolic syndrome and its components with all-cause mortality and cardiovascular outcomes in CKD patients.

Methods. Prospective observation of a cohort of 5110 CKD patients from the German Chronic Kidney Disease study with 3284 (64.3%) of them having a metabolic syndrome at baseline.

Results. During the follow-up of 6.5 years, 605 patients died and 650 patients experienced major cardiovascular events. After extended data adjustment, patients with a metabolic syndrome had a higher risk for all-cause mortality (hazard ratio [HR] = 1.26, 95% confidence interval [CI]: 1.04–1.54) and cardiovascular events (HR = 1.48, 95% CI: 1.22–1.79). The risk increased steadily with a growing number of metabolic syndrome components (increased waist circumference, glucose, triglycerides, hypertension and decreased HDL cholesterol): HR per component = 1.09 (95% CI: 1.02–1.17) for all-cause mortality and 1.23 (95% CI: 1.15–1.32) for cardiovascular events. This resulted in hazard ratios between 1.50 and 2.50 in the case when four or five components are present. An analysis of individual components of metabolic syndrome showed that the glucose component led to the highest increase in risk for all-cause mortality (HR = 1.68, 95% CI: 1.38–2.03) and cardiovascular events (HR = 1.81, 95% CI: 1.51–2.18), followed by the HDL cholesterol and triglyceride components.

Conclusions. We observed a high prevalence of metabolic syndrome among patients with moderate CKD. Metabolic syndrome increases the risk for all-cause mortality and cardiovascular events. The glucose and lipid components seem to be the main drivers for the association with outcomes.

Keywords: cardiovascular disease, chronic kidney disease, metabolic syndrome, mortality, prospective cohort study
**Introduction**

Both metabolic syndrome [1] and chronic kidney disease (CKD) [2–4] are associated with an increased risk for cardiovascular disease. Although both conditions are common, only limited data are available on the association of metabolic syndrome with all-cause mortality and cardiovascular disease in patients with CKD with moderately reduced estimated glomerular filtration rate (eGFR) and/or albuminuria. In fact, whether metabolic syndrome adds further to cardiovascular risk beyond the risks associated with CKD is controversial [5].

In particular, studies on metabolic syndrome and mortality in CKD patients with moderately reduced eGFR and/or albuminuria are scarce. Navaneethan et al. analysed data from a large electronic health record-based CKD registry and did not find metabolic syndrome to be associated with all-cause mortality during a relatively short observation period of 2.3 years [6]. Other studies were either small, examined individual metabolic syndrome components and/or investigated a composite endpoint which included progression of CKD, end-stage kidney disease and death [7, 8]. Surprisingly, no large studies are available which prospectively investigated the association of metabolic syndrome with cardiovascular outcomes in patients with moderately severe CKD.

Importantly, some risk factors behave differently in patients with and without CKD and may even have an opposite impact in CKD patients compared to the general population. Due to this “reverse epidemiology”, extrapolations from the general population to patients with CKD need to be conducted with great caution [9]. Given the increasing importance of the metabolic syndrome for public health, we, therefore, aimed to investigate the associations of the metabolic syndrome and its components with all-cause mortality and cardiovascular events in a large and well-defined cohort of patients with moderately reduced eGFR and/or increased albuminuria.

**Methods**

**German Chronic Kidney Disease study**

The German Chronic Kidney Disease (GCKD) study is a prospective cohort study with ongoing follow-up investigations including 5217 Caucasian patients with CKD enrolled between the years 2010 and 2012. Design and details of the study have been published previously [10–12] and an extended description is given in the Supporting Information (extended methods description). Briefly, the study aimed to enroll patients with an eGFR 30–60 ml/min/1.73 m² (KDIGO stage G3, A1–3) or an eGFR >60 ml/min/1.73 m² in the presence of overt proteinuria (KDIGO stage G1–2, A3) under regular care by nephrologists. The study was approved by the ethics committees of all participating institutions and registered in the national registry for clinical studies (DRKS 00003971). All methods were carried out in accordance with approved guidelines and the Declaration of Helsinki. Written informed consent was obtained from each study participant. Data are collected and managed using Askimed (https://www.askimed.com) as a cloud-based web platform.

Patients are followed on a yearly basis by trained and certified personnel who collected data on hospitalizations, outcome events and medical history using a structured interview. Any hospital discharge reports are collected from the treating physicians and/or hospitals. Endpoints are continually adjudicated from these reports by an endpoint committee of trained medical doctors.

**Definition of metabolic syndrome**

The five metabolic syndrome components are defined as binary variables [13]: (1) waist circumference \(\geq 102 \text{ cm} \) in men and \(\geq 88 \text{ cm} \) in women, (2) fasting triglycerides \(\geq 150 \text{ mg/dl} \) (1.69 mmol/L) or \(\geq 175 \text{ mg/dl} \) (1.98 mmol/L) for non-fasting patients and/or drug treatment for elevated triglycerides, (3) serum HDL cholesterol \(<40 \text{ mg/dl} \) (1.03 mmol/L) in males and \(<50 \text{ mg/dl} \) (1.29 mmol/L) in females and/or drug treatment for reduced HDL cholesterol, (4) systolic blood pressure \(\geq 130 \text{ mm Hg} \) and/or diastolic blood pressure \(\geq 85 \text{ mm Hg} \) and/or antihypertensive drug treatment, (5) fasting glucose \(\geq 100 \text{ mg/dl} \) (5.55 mmol/L) or glycosylated haemoglobin HbA1c \(>42 \text{ mmol/mol} (6\%) \) and/or drug treatment for elevated glucose. The presence of at least three out of these five components constitutes a diagnosis of metabolic syndrome. As study participants were not necessarily fasting at the time of blood collection, we set the threshold for the triglyceride component at 175 mg/dl [14].
Definition of clinical endpoints

The endpoints considered in the present analysis refer to the first 6.5 years of follow-up. Censoring was performed either at death or the study’s end. All-cause mortality was defined as the primary endpoint. Specific causes of death and major cardiovascular events were considered secondary endpoints. Death from cardiovascular causes comprised myocardial infarction, coronary heart disease, sudden cardiac death, congestive heart failure, pulmonary embolism, cardiac valve disease and ischaemic stroke. Major adverse cardiovascular events (MACE) were either defined as 3-point MACE including death from cardiovascular causes, such as myocardial infarction, coronary heart disease, sudden cardiac death and ischaemic stroke as well as acute non-fatal myocardial infarction (STEMI and NSTEMI), non-fatal stroke, or as 4-point MACE additionally including fatal peripheral ischaemia, amputation due to peripheral vascular disease and surgical or percutaneous revascularization due to peripheral vascular disease. The prospectively collected endpoints considered in the present analysis refer to the first 6.5 years of follow-up, data export 9 March 2020.

Statistical methods

Mean ± SD for all variables was calculated. For variables with a skewed or non-normal distribution, median, 25th and 75th percentile were provided additionally. Group differences were tested using Kruskal–Wallis tests for continuous variables and Pearson’s chi-square test for categorical variables. Kaplan–Meier curves were constructed to check for differences in survival, testing for significance with log-rank tests. We performed the following three main time to first event Cox models: model 1 adjusted for age and sex, model 2 additionally for eGFR and urine albumin–creatinine ratio (UACR) and model 3 additionally for prevalent CVD, smoking status and LDL cholesterol. Model 4 was performed as sensitivity analysis including high-sensitivity C-reactive protein (hs-CRP) as the further variable.

Variables with a skewed or non-normal distribution were transformed using natural logarithm (LDL cholesterol, UACR, hs-CRP). Proportional hazard assumptions were tested using Schoenfeld residuals and fulfilled. To account for competing risks cumulative incidence curves and competing risk models were calculated for the endpoints (3-point MACE and 4-point MACE) and the different causes of death. For cause-specific endpoints, patients were censored when the death occurred by any other cause. In addition, associations with these cause-specific endpoints were examined using competing-risks survival regression, considering all deaths from other causes as competing events. Therefore, both cause-specific hazard ratios (HRs) and subdivision HRs are reported. For competing risk analyses, identical adjustments were used.

Data were analyzed using R 4.0.2 (https://www.r-project.org). Details on the various packages are provided in the Supporting Information. Statistical significance was set at \( \alpha = 0.05 \).

Results

Baseline characteristics of the study population

Table 1 shows the baseline characteristics of the 5110 patients available for analysis. The most prevalent metabolic syndrome component was the blood pressure component defined as systolic blood pressure \( \geq 130 \) mm Hg and/or diastolic blood pressure \( \geq 85 \) mm Hg and/or antihypertensive drug treatment in 97.8% of the patients. This was followed by the waist circumference component defined as waist circumference \( \geq 102 \) cm in men and \( \geq 88 \) cm in women in 67.6% of the patients. The glucose component defined as fasting glucose \( \geq 100 \) mg/dl or glycosylated haemoglobin Hba1c \( > 6 \) % and/or drug treatment for elevated glucose was present in 51.3% of the patients. Elevated fasting triglycerides \( \geq 150 \) mg/dl or \( \geq 175 \) mg/dl for non-fasting patients and/or drug treatment for elevated triglycerides were present in 49.6% of the patients and decreased HDL cholesterol \( < 40 \) mg/dl in males and \( < 50 \) mg/dl in females and/or drug treatment for reduced HDL cholesterol were present in 36.3%. At least three components had to be present to fulfil the definition of a metabolic syndrome which was the case in 3284 (64.3%) of all patients. When we compared patients with and without metabolic syndrome, we observed notable differences in age, sex, BMI, lipids, Hba1c, hs-CRP and the prevalence of diabetes and prevalent CVD (Table 1).

Observed endpoints during prospective follow-up

During a follow-up of up to 6.5 years, 605 deaths (11.8% of the 5110 patients) were recorded and 473 patients experienced a 3-point MACE defined as a composite of death from cardiovascular causes including myocardial infarction, coronary heart
Table 1. Baseline characteristics of 5110 patients available for analysis by the presence or absence of metabolic syndrome

|                                | Total (N = 5110) | No metabolic syndrome (N = 1826) | Metabolic syndrome (N = 3284) | p-Value |
|--------------------------------|------------------|----------------------------------|------------------------------|---------|
| Age, years                     | 60.1 ± 12.0      | 56.0 ± 13.6                      | 62.3 ± 10.2                  | <0.001  |
| Sex (female)                   | 2050 (40.1%)     | 834 (45.6%)                      | 1216 (37.0%)                 | <0.001  |
| Body mass index (BMI; kg/m²)   | 29.8 ± 6.0       | 26.1 ± 4.5                       | 32.0 ± 5.7                   | <0.001  |
| Waist circumference (cm)       | 103.6 ± 15.8     | 92.2 ± 12.7                      | 110.1 ± 13.6                 | <0.001  |
| Current smokers                | 819 (16.1%)      | 311 (17.1%)                      | 508 (15.5%)                  | 0.15    |
| Statin use                     | 2442 (47.8%)     | 659 (36.1%)                      | 1783 (54.3%)                 | <0.001  |
| Metabolic syndrome components  |                  |                                  |                              |         |
| Triglyceride component         | 2518 (49.6%)     | 250 (13.7%)                      | 2268 (69.7%)                 | <0.001  |
| HDL cholesterol component      | 1845 (36.3%)     | 98 (5.4%)                        | 1747 (53.7%)                 | <0.001  |
| Blood pressure component       | 5000 (97.8%)     | 266 (14.7%)                      | 2334 (71.6%)                 | <0.001  |
| Glucose component              | 3392 (67.6%)     | 529 (29.5%)                      | 2863 (88.9%)                 | <0.001  |
| Total number of metabolic      | 3.0 ± 1.33 [2, 4]| 1.6 ± 0.52 [1, 2]                | 3.8 ± 0.84 [3, 4]            | <0.001  |
| Comorbidities at baseline      |                  |                                  |                              |         |
| Diabetes                       | 1842 (36.0%)     | 146 (8.0%)                       | 1696 (51.6%)                 | <0.001  |
| Hypertension                   | 4924 (96.3%)     | 1682 (92.0%)                     | 3242 (98.8%)                 | <0.001  |
| Systolic blood pressure (mm Hg)| 139.5 ± 20.4     | 137.1 ± 19.9                     | 140.8 ± 20.4                 | <0.001  |
| Diastolic blood pressure (mm Hg)| 79.3 ± 11.8   | 80.2 ± 11.3                      | 78.7 ± 12.0                  | <0.001  |
| Prevalent cardiovascular       | 1566 (30.6%)     | 360 (19.7%)                      | 1206 (36.7%)                 | <0.001  |
| Laboratory parameters          |                  |                                  |                              |         |
| eGFR-CKD-EPI (ml/min/1.73 m²)  | 49.4 ± 18.2      | 53.7 ± 20.2                      | 47 ± 16.5                    | <0.001  |
| Serum albumin (mg/L)           | 38.3 ± 4.4       | 38.7 ± 4.4                       | 38.2 ± 4.4                   | <0.001  |
| Urine albumin–creatinine ratio (UACR; mg/g) | 432 ± 96151 | 429 ± 92365 | 432 ± 98246 [9, 0.005] |
| Total cholesterol (mg/dl)      | 211 ± 53         | 215 ± 51                         | 209 ± 54                     | <0.001  |
| HDL cholesterol (mg/dl)        | 52.0 ± 18.1      | 63.1 ± 18.2                      | 45.6 ± 14.8                  | <0.001  |
| LDL cholesterol (mg/dl)        | 118 ± 44         | 125 ± 43                         | 114 ± 44                     | <0.001  |
| Triglycerides (mg/dl)          | 199 ± 128168     | 130 ± 63120                      | 238 ± 139207 [152, 0.001]   |
| Glycated haemoglobin (HbA1c; %)| 6.3 ± 1.06       | 5.8 ± 0.657                      | 6.6 ± 1.163 [5.9, 0.001]    |
| High-sensitivity C-reactive protein (hs-CRP; mg/L) | 4.8 ± 8.423 | 3.6 ± 9.215 | 5.4 ± 7.7282 [1.4, 0.001] |

Note: Values are provided as mean ± standard deviation and [25th, 50th (median) and 75th percentiles] or a number of patients, n (%). eGFR-CKD-EPI, estimated glomerular filtration rate calculated according to the CKD-EPI formula. p-Values are given for the comparison between patients with and without metabolic syndrome.
Table 2. Distribution of endpoints during the 6.5 years prospective follow-up stratified by the presence or absence of metabolic syndrome at baseline

| Endpoint                | Total N = 5110 (100%) | No metabolic syndrome N = 1826 (35.7%) | Metabolic syndrome N = 3284 (64.3%) | p-Value |
|-------------------------|-----------------------|----------------------------------------|------------------------------------|---------|
| All-cause mortality     | 605                   | 137                                    | 468                                | <0.001  |
| 3-Point MACE            | 473                   | 102                                    | 371                                | <0.001  |
| 4-Point MACE            | 649                   | 137                                    | 512                                | <0.001  |
| Main causes of death    |                       |                                        |                                     |         |
| Cardiovascular death    | 183                   | 28                                     | 155                                | <0.001  |
| Death due to cancer     | 90                    | 26                                     | 64                                 | 0.17    |
| Death due to infection  | 140                   | 26                                     | 114                                | <0.001  |
| Death due to other cause| 62                    | 26                                     | 42                                 | 0.57    |
| Death due to unknown cause | 130               | 37                                     | 93                                 | 0.08    |

Note: 3-Point MACE (Major Adverse Cardiovascular Events) includes death from cardiovascular causes including myocardial infarction, coronary heart disease, sudden cardiac death, and ischemic stroke as well as acute non-fatal myocardial infarction (STEMI and NSTEMI) and non-fatal stroke. 4-Point MACE comprised all endpoints included in 3-point MACE plus fatal peripheral ischemia, amputation due to peripheral vascular disease, and surgical or percutaneous revascularization due to peripheral vascular disease.

Presence of metabolic syndrome at baseline and risk for endpoints

Kaplan–Meier-curves were constructed for the outcomes of all-cause mortality, 3-point MACE and 4-point MACE, stratified by metabolic syndrome status (Fig. 1). Significant differences between the two groups for all three endpoints were observed, with higher endpoint-free survival rates for those without metabolic syndrome (all p-values of log-rank test <0.0001). Cox regression models with different degrees of adjustment for confounders are summarized in Table 3. In the age- and sex-adjusted model 1, the presence of a metabolic syndrome increased the probability to die of any cause during the observation period by 1.47-fold (95% confidence interval [CI]: 1.21–1.78, p < 0.0001). Estimates were slightly attenuated when adjusted for kidney function parameters (model 2) and by extended adjustment for current smoking, prevalent CVD at baseline and LDL cholesterol (model 3). Only when we additionally adjusted for hs-CRP in model 4, the association was no longer significant (Table 3).

The estimates for 3-point MACE and 4-point MACE were higher than that for all-cause mortality in the extended adjustment model 3: HR = 1.43 (95% CI: 1.14–1.79; p = 0.002) for 3-point MACE and HR = 1.48 (95% CI: 1.22–1.79; p = 0.0001) for 4-point MACE (Table 3). The associations remained significant even after further adjustment for hs-CRP in model 4 (Table 3).

In order to avoid potential overestimation of the HRs for 3-point MACE and 4-point MACE, we additionally performed a competing risk analysis. The corresponding cumulative incidence curves are provided in Fig. S1, and the results from the competing risk regression are provided in Table 3 (right columns). The subdivision hazard ratios remained almost unchanged and highly significant in all models.
**Fig. 1** Kaplan-Meier-curves and cumulative event tables for all-cause mortality, 3-point MACE and 4-point MACE. *p*-values were calculated using the log-rank test.
Table 3. Association of metabolic syndrome with all-cause mortality, 3-point MACE and 4-point MACE during the prospective follow-up of 6.5 years using Cox proportional hazards regression models with various adjustments for confounders. For 3-point MACE and 4-point MACE, both cause-specific hazard ratio (HR) and subdivision HR (SHR) are given.

|                    | HR     | 95% CI          | p-Value | SHR    | 95% CI          | p-Value |
|--------------------|--------|-----------------|---------|--------|-----------------|---------|
| **All-cause mortality** |        |                 |         |        |                 |         |
| Model 1            | 1.47   | [1.21–1.78]     | <0.0001 | –      | –               | –       |
| Model 2            | 1.37   | [1.13–1.67]     | 0.002   | –      | –               | –       |
| Model 3            | 1.26   | [1.04–1.54]     | 0.021   | –      | –               | –       |
| Model 4            | 1.11   | [0.91–1.35]     | 0.325   | –      | –               | –       |
| **3-Point MACE**   |        |                 |         |        |                 |         |
| Model 1            | 1.68   | [1.35–2.10]     | <0.0001 | 1.66   | [1.32–2.07]     | <0.0001 |
| Model 2            | 1.59   | [1.27–1.98]     | 0.0001  | 1.57   | [1.25–1.97]     | <0.0001 |
| Model 3            | 1.43   | [1.14–1.79]     | 0.002   | 1.42   | [1.13–1.78]     | 0.003   |
| Model 4            | 1.31   | [1.04–1.64]     | 0.020   | 1.32   | [1.05–1.66]     | 0.019   |
| **4-Point MACE**   |        |                 |         |        |                 |         |
| Model 1            | 1.74   | [1.44–2.10]     | <0.0001 | 1.72   | [1.42–2.08]     | <0.0001 |
| Model 2            | 1.67   | [1.38–2.02]     | 0.0001  | 1.66   | [1.37–2.01]     | <0.0001 |
| Model 3            | 1.48   | [1.22–1.79]     | 0.0001  | 1.47   | [1.21–1.78]     | 0.0001  |
| Model 4            | 1.36   | [1.12–1.65]     | 0.0022  | 1.36   | [1.12–1.66]     | 0.002   |

Note: HR: hazard ratios derived from Cox models; SHR: subdivision HR derived from competing for risk regression. Model 1: adjusted for sex and age; Model 2: Model 1 + eGFR, log(urine albumin–creatinine ratio); Model 3: Model 2 + current smoking, prevalent cardiovascular disease, log(LDL cholesterol); Model 4: Model 3 + log(hs-CRP). For definitions of 3-point MACE and 4-point MACE, see footnotes of Table 2.

We furthermore investigated whether the metabolic syndrome is a predictor for each of the main causes of death. This was the case for cardiovascular death and death due to infections but not for death due to cancer or death due to other causes (Fig. S2 and Table S1).

**Number of metabolic syndrome components and risk for endpoints**

In the next step, we investigated whether the total number of metabolic syndrome components in each individual has an influence on outcomes. Due to the high frequency of the blood pressure component (97.8%), at least one metabolic syndrome component was fulfilled by close to all patients. Therefore, patients who had either none or one component were combined and used as the reference group. Figure 2 shows a linear increase of HRs for each additional metabolic syndrome component reaching significance at three components for all-cause mortality and 4-point MACE. For 3-point MACE, significance was reached with four components (Fig. 2 and Table S2).

Since the risk increase for each additional component was rather linear (especially for 3-point MACE and 4-point MACE, Fig. 2), we also used the number of components as a linear predictor. When data were adjusted for age, sex, eGFR, UACR, current smoking, prevalent CVD and LDL cholesterol (model 3 in Table 4), the risk for all-cause mortality, 3-point MACE and 4-point MACE increased significantly per component by 9%, 24% and 23%, respectively. Additional adjustment for hs-CRP weakened the association only for all-cause mortality (model 4 in Table 4).

**Associations of individual metabolic syndrome components and risk of endpoints**

To elucidate how strongly each component contributes to the risk for reaching an endpoint, individual models for each of the components were calculated (Fig. 3 and Table S3). The glucose component consistently conferred higher risk for all endpoints (HR = 1.68 for all-cause mortality, HR = 1.73 for 3-point MACE and HR = 1.81 for 4-point MACE). Additionally, for both 3-point MACE and 4-point MACE, HDL cholesterol, waist circumference, and triglyceride components were associated with increased risk. For all-cause mortality, high triglyceride concentrations...
were associated with lower risk (HR = 0.82, p = 0.019).

Results only slightly changed when all components were included in one model simultaneously, thereby also adjusting all components for each other (see Fig. S3 and Table S4).

**Fig. 2.** Forest plots of hazard ratios for all-cause mortality, 3-point MACE, and 4-point MACE, grouping by the sum of metabolic syndrome components. All models are adjusted for sex, age, estimated glomerular filtration rate (eGFR), log(urine albumin–creatinine ratio), smoking status, log(LDL cholesterol) and prevalent cardiovascular disease.

**Table 4.** Association of the number of metabolic syndrome components (HR refers to increase by one additional component) with all-cause mortality, 3-point MACE and 4-point MACE during the prospective follow-up period using Cox proportional hazards regression models with various adjustments for confounders. For 3-point MACE and 4-point MACE, both cause-specific hazard ratio (HR) and subdivision HR (SHR) are given.

|                | HR   | 95% CI     | p-Value | SHR  | 95% CI     | p-Value |
|----------------|------|------------|---------|------|------------|---------|
| **All-cause mortality** |      |            |         |      |            |         |
| Model 1        | 1.18 | [1.10,1.26]| <.0001  | –    | –          | –       |
| Model 2        | 1.14 | [1.07,1.22]| <.0001  | –    | –          | –       |
| Model 3        | 1.09 | [1.02,1.17]| 0.011   | –    | –          | –       |
| Model 4        | 1.04 | [0.98,1.12]| 0.189   | –    | –          | –       |
| **3-Point MACE** |      |            |         |      |            |         |
| Model 1        | 1.32 | [1.22,1.42]| <.0001  | 1.31 | [1.21,1.42]| <.0001  |
| Model 2        | 1.29 | [1.19,1.40]| <.0001  | 1.29 | [1.19,1.40]| <.0001  |
| Model 3        | 1.24 | [1.15,1.35]| <.0001  | 1.24 | [1.14,1.35]| <.0001  |
| Model 4        | 1.21 | [1.11,1.31]| <.0001  | 1.22 | [1.12,1.33]| <.0001  |
| **4-Point MACE** |      |            |         |      |            |         |
| Model 1        | 1.31 | [1.23,1.40]| <.0001  | 1.31 | [1.23,1.40]| <.0001  |
| Model 2        | 1.30 | [1.21,1.38]| <.0001  | 1.30 | [1.21,1.39]| <.0001  |
| Model 3        | 1.23 | [1.15,1.32]| <.0001  | 1.23 | [1.15,1.32]| <.0001  |
| Model 4        | 1.20 | [1.12,1.28]| <.0001  | 1.20 | [1.12,1.29]| <.0001  |

Note: HR: Hazard ratios derived from Cox models; SHR: subdivision HR, derived from competing risk regression.
Model 1: adjusted for sex and age; Model 2: Model 1 + eGFR, log(urine albumin–creatinine ratio); Model 3: Model 2 + current smoking, prevalent cardiovascular disease, log(LDL cholesterol); Model 4: Model 3 + log(hs-CRP).
For definitions of 3-point MACE and 4-point MACE, see footnotes of Table 2.

Combinations of metabolic syndrome components and risk of endpoints

Finally, we investigated which combinations of metabolic syndrome components were most frequent and whether any of these combinations were associated with a markedly different increase of
**Table 5.** Frequency of combinations of metabolic syndrome components and associations with main outcomes. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) are given for each combination in comparison to the combination with the lowest risk (except the binned group), separately for the patients with three and four metabolic syndrome components, respectively.

| BP       | Glucose | Waist | TG   | HDL | n   | All-cause mortality | 3-Point MACE | 4-Point MACE |
|----------|---------|-------|------|-----|-----|---------------------|--------------|--------------|
|          |         |       |      |     |     | HR (95% CI)          | HR (95% CI)  | HR (95% CI)  |
| Patients with three metabolic syndrome components present (N = 1394) | | | | | | | | |
| BP       | Glucose | Waist | –    | –   | 590 | 1.70 (1.06–2.74)    | 1.58 (0.65–3.82) | 2.07 (0.93–4.60) |
| BP       | –       | Waist | TG   | –   | 322 | 1.00                | 1.21 (0.47–3.12) | 1.38 (0.59–3.22) |
| BP       | –       | Waist | –    | HDL | 129 | 1.42 (0.70–2.90)    | 1.68 (0.60–4.67) | 1.74 (0.68–4.47) |
| BP       | –       | –     | TG   | HDL | 114 | 1.03 (0.45–2.35)    | 1.00          |              |
| BP       | Glucose | –     | TG   | –   | 108 | 1.37 (0.69–2.75)    | 2.08 (0.77–5.60) | 2.54 (1.06–6.10) |
| Binned remaining rarer combinations | | | | | 131 | 1.89 (1.00–3.58)    | 1.29 (0.44–3.81) | 1.72 (0.68–4.37) |
| Patients with four metabolic syndrome components present (N = 1153) | | | | | | | | |
| BP       | Glucose | Waist | TG   | –   | 462 | 1.70 (1.03–2.82)    | 1.57 (0.96–2.56) | 1.39 (0.91–2.11) |
| BP       | –       | Waist | TG   | HDL | 333 | 1.00                | 1.00          | 1.00         |
| BP       | Glucose | Waist | –    | HDL | 219 | 3.22 (1.91–5.40)    | 1.86 (1.06–3.24) | 1.64 (1.02–2.62) |
| BP       | Glucose | –     | TG   | HDL | 96  | 1.94 (1.01–3.74)    | 1.67 (0.85–3.26) | 1.43 (0.80–2.55) |
| Binned remaining rarer combinations | | | | | 43  | 0.57 (0.13–2.47)    | 0.57 (0.13–2.46) | 0.36 (0.09–1.53) |

*Note:* Hazard ratios derived from Cox models adjusted for sex, age, eGFR, log(urine albumin–creatinine ratio), current smoking, prevalent cardiovascular disease and log(LDL cholesterol).

Metabolic syndrome components: BP, high blood pressure; glucose, high glucose; waist, high waist circumference; TG, high triglycerides; HDL, low HDL cholesterol.

risk in individuals with the same number of components (Table 5). In the 1394 patients with exactly three components, the most common combination included blood pressure, glucose and waist (n = 590), followed by blood pressure, waist and triglycerides (n = 322) and blood pressure, waist and HDL (n = 129). The combination of components with blood pressure, glucose and waist showed the highest risk for all-cause mortality. For 4-point MACE, it was blood pressure, glucose and triglycerides. Triglycerides or HDL in any other combinations did not seem to drive the risk for those with three components. In the 1153 patients with exactly four components, the most frequent
combination contained blood pressure, glucose, waist, and triglycerides ($n = 462$), followed by blood pressure, waist, triglycerides and HDL ($n = 333$) and blood pressure, glucose, waist, and HDL cholesterol. In the groups with four components, the glucose component was always included when the risk for outcomes was increased. However, waist and HDL contributed to the increase in risk (Table 5).

Discussion
This prospective observational study provides evidence that the presence of a metabolic syndrome in CKD patients with moderately reduced eGFR and/or increased albuminuria is independently associated with increased all-cause mortality and more cardiovascular endpoints during an observation period of 6.5 years. The association became stronger with an increasing number of metabolic syndrome components. Especially the glucose component drives the association followed by the lipid and waist circumference component. These associations were stronger for cardiovascular outcomes than that for all-cause mortality.

Our findings might have been expected from investigations in the general population [1, 15–17], while studies investigating metabolic syndrome in patients with moderate CKD are surprisingly sparse [6, 7, 18]. The largest study to date by Navaneethan et al. [6] is an electronic health record-based CKD registry with 43,546 patients in stages 3 and 4. Metabolic syndrome data were available from 25,868 (59%) patients with a mean follow-up period of 2.3 years. They observed an association of metabolic syndrome with progression to end-stage kidney disease but no association with all-cause mortality [6]. A further study, the African-American Study of Kidney Disease and Hypertension in 842 hypertensive individuals with CKD found no association of metabolic syndrome with a composite endpoint of progression of CKD and death without giving detailed data for each of the outcomes [7]. Interestingly, no sufficiently powered prospective studies investigated the association of metabolic syndrome with cardiovascular outcomes in non-dialyzed CKD patients. This is worrisome since it is generally claimed that metabolic syndrome is associated with cardiovascular endpoints in CKD patients, a conclusion extrapolated from the general population not backed up by data.

One of the explanations for the lack of studies might be that most definitions of a metabolic syndrome require blood collection in a fasting state. This is not easy to accomplish in a standardized way especially when many recruitment centres are involved and the rate of patients with diabetes is high. However, many studies in non-CKD populations faced the same problem and used surrogate parameters such as substituting HbA1c for fasting glucose, a higher threshold for non-fasting triglycerides or BMI for waist circumference measurements. Since GCKD study participants were not necessarily fasting, we had to use a threshold for triglyceride concentrations of 175 mg/dl instead of 150 mg/dl as recommended by a recent consensus statement [14].

More studies are available in CKD patients that investigated associations of single metabolic syndrome components with outcomes. For example, impaired glucose metabolism is a well-known risk factor for cardiovascular disease and all-cause mortality in the general population [19–21]. In the GCKD study, the glucose component showed the strongest association with both, all-cause mortality and cardiovascular disease, independent of the other metabolic syndrome components. This is in line with data from Neves et al. [22] who investigated 3701 CKD patients with normoglycaemia, prediabetes, and diabetes. Patients with pre-diabetes had a higher risk of a composite cardiovascular outcome and a trend towards higher risk for all-cause mortality. Participants with diabetes had increased risk for both outcomes when compared to normoglycaemic patients.

A recent systematic review and meta-analysis using BMI as a measure of obesity in CKD stage G3–5 patients [23] found only five studies including 10,443 patients for all-cause mortality and two studies including 2101 patients for cardiovascular mortality. There was a minuscule association of BMI with all-cause mortality and no association with cardiovascular mortality. The authors concluded that the number of studies were not enough to reach definite conclusions. Data from the REGARDS study with 5805 patients with CKD stages 1–4 and with a median follow-up of 4 years described a graded and increased mortality risk across increasing waist circumference categories after adjustment for BMI and other covariates [24].

In our study, elevated triglyceride concentrations were associated with a lower risk for all-cause
mortality which even remained significant when adjusted for other metabolic syndrome components as well as other risk factors. For the cardiovascular endpoints, this trend reversed but lost significance as soon as we adjusted also for the other metabolic syndrome components. The protective association of triglycerides seems to be counterintuitive in light of its association in the general population, where elevated triglycerides are a well-known cardiovascular risk factor [25, 26]. A recent study by Soohoo et al. [27] in over two million patients from the United States Veterans Affairs databases showed that the risk increase conferred by triglyceride levels is increasingly attenuated with declining kidney function which might be related to an increasing prevalence of inflammation and malnutrition. The risk for all-cause mortality was significantly increased for triglyceride levels <80mg/dl in all groups of CKD and non-CKD patients. For levels ≥240mg/dl, risk for all-cause mortality was increased for all groups except for those with end-stage kidney disease, suggesting a possibly U-shaped relationship between triglycerides and all-cause mortality in kidney patients. Lee et al. [28] studied CKD patients with diabetes and no prevalent CVD at baseline and found lower TG/HDL cholesterol ratios to be associated with decreased risk for all-cause mortality and major cardiac adverse events.

The pathways that lead to cardiovascular disease in either metabolic syndrome or chronic kidney disease may have common endpoints. Changes in cardiac structure occur in both metabolic syndrome [29] and CKD [30]. Similarly, vascular endothelial dysfunction is present in both metabolic syndrome [31] and CKD [32]. This could explain why our analyses showed the additive risk for those patients who have both disorders.

**Pathophysiological consideration**

The underlying mechanisms for the association of metabolic syndrome with outcomes are not fully elucidated. They might include misguided immune system activity [33], dysregulation of haemostasis [34] and excess intra-abdominal fat [35]. Excess visceral adipose tissue might trigger a cascade of metabolic changes, leading to changes in insulin, leptin and adiponectin signalling [36]. Besides metabolic activity, visceral adipose tissue has a higher relative percentage of inflammatory cells and produces pro-inflammatory cytokines. Therefore, systemic, vascular and endothelial inflammation due to metabolic syndrome may account for some of the risk increases. When we modelled the association between metabolic syndrome and outcomes we started with a simple age- and sex-adjusted model 1 followed by additional adjustment for the main kidney function parameters eGFR and UACR in model 2 and finally adjusted for major cardiovascular risk factors not yet included in the metabolic syndrome definition (i.e. prevalent CVD, smoking and LDL cholesterol) in model 3. The associations with all endpoints were slightly attenuated but still remained significant. This was also the case for both MACE definitions when we additionally adjusted for hs-CRP as a measure of systemic inflammation. For all-cause mortality, however, the association was no longer significant. It might be discussed controversially whether an adjustment for hs-CRP is appropriate. Some might argue that elevated CRP levels, as well as pro-inflammatory cytokines, are a consequence rather than a cause of the metabolic syndrome. The expansion of adipose tissue results in further insulin resistance by disruption of insulin signalling with further metabolic derangements [37]. It is likely a complex vicious cycle further escalating with decreasing kidney function.

A joint statement from the American Diabetes Association and the European Association for the Study of Diabetes has raised several critical questions on the imprecise definition of the metabolic syndrome, the lack of certainty regarding the pathogenesis and its value as a marker for CVD risk [38]. A dichotomized variable such as the presence of a metabolic syndrome likely mirrors the heterogeneous pathogenesis of the disease inadequately. This statement questioned whether the metabolic syndrome on its own conveys greater information than the sum of its component risk factors [38]. This was one of the reasons why we analysed our data on a per-component basis to see whether the sum of the components may better reflect the risk of certain outcomes. We showed that there was a linear increase in risk with the number of metabolic syndrome components which resulted in HRs between 1.50 and 2.50 in case of four to five components present, a lot higher than considering a binary variable with HRs between 1.26 and 1.48 (model 3) for various outcomes. Furthermore, the extent of the association for each of the components with various outcomes was also explored. The weight of the glucose component is significantly attenuated with declining kidney function.

 studying with decreasing kidney function.
whether there was a markedly different risk for outcomes among combinations of metabolic syndrome components. However, these latter analyses were not fully conclusive but supported the impression that the glucose component may carry the greatest weight for adequate risk estimation (Table 5).

Clinical implications
We found an association between the binary condition of a metabolic syndrome with outcomes. As an umbrella term, it may ease communication between physicians and their patients. However, it may not reflect the entire information behind this label. The finding of a graded association between the number of metabolic syndrome components and the outcomes as described in the general population [39] is an easily transmittable information to the patient (the higher the number the higher the danger). This could be a motivating factor for the individual patient in the sense that each metabolic syndrome component successfully avoided might decrease the risk for a cardiovascular endpoint or premature death. Hence not all metabolic syndromes are created equally and individual analysis of each of the metabolic syndrome components should guide the search to find the most promising target for therapeutic intervention on a case-by-case basis. In this context, it may be worth considering that the association between the single components of a metabolic syndrome with outcomes might be far more pronounced than estimated by epidemiological studies: these studies count the singular components as a metabolic component to be present even if successfully treated (e.g. lipids, blood pressure or blood glucose) and thereby underestimate the risk for those who are not successfully treated yet.

In terms of prioritizing therapeutic approaches, targeting the glucose component including insulin resistance might be the most promising therapeutic approach. A combination of drug treatment with lifestyle changes (physical activity and diet) will also have an influence on other metabolic syndrome components including lipids, central obesity and increased blood pressure. One should not be misguided by the observation that the blood pressure component was not predictive for any of the outcomes. This can be explained by the simple fact that the increased blood pressure component was present in 97.8% of all patients. Thus, it may have contributed to the pathogenesis of the clinical endpoints, even if it did not contribute to the risk discrimination in our models.

Since more than 71.6% of our patients with metabolic syndrome were diagnosed by fulfilling the glucose component but only 51.6% of these patients had a documented diagnosis of diabetes, the question arises whether the diagnosis of a metabolic syndrome may provide earlier identification of high-risk patients than is the case if only single component was diagnosed. Furthermore, distinct components of the syndrome such as waist circumference, low HDL cholesterol or hypertriglyceridemia are often missed when the screening, diagnosis, and management of dyslipidaemia is mostly centred around measuring LDL concentration as the primary lipid analysis method [40].

Strengths and limitations of the study
Strengths of the study include the large sample size of a well-defined homogeneous study population with a median follow-up of 6.5 years with a very low loss to follow-up. Limitations include that blood was not necessarily drawn in a fasting state. We, therefore, had to use HbA1c instead of fasting glucose for the estimation of the glucose component which, however, has the advantage that it does not simply reflect a single measurement of glucose. For triglycerides, we used a threshold of 175 mg/dl instead of 150 mg/dl to define the triglyceride component. A further limitation was that the study population was restricted to Caucasian ethnicities and thus the findings are not generalizable to other ethnicities.

Conclusions
This study demonstrates a strong association between metabolic syndrome and cardiovascular disease as well as an increased risk for mortality in patients with moderately severe CKD, which up to now has only been anticipated from data in the general population.

Conflict of interest
The authors have no conflict of interest to declare.

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Appendix

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Supporting Information

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