

Original Paper

Metabolic Syndrome and Smoking Are Associated with Future Development of Advanced Chronic Kidney Disease in Older Adults

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Key Words

Metabolic syndrome · Chronic kidney disease · Smoking

Abstract

Introduction: Metabolic syndrome (MetS) and smoking have been identified as risk factors for chronic kidney disease (CKD) in cross-sectional studies in various age groups, but longitudinal data on progression of CKD in older adults are limited. Our objectives were to examine whether MetS and its components and smoking predict the onset of CKD stage 3b (CKD-3b) in older adults. **Methods:** A subset of participants of the Einstein Aging Study who were free of diabetes, dementia, and CKD-3b at enrollment were included in this analysis. CKD-3b was defined as an estimated glomerular filtration rate <45 ml/min/1.73 m². Cox proportional hazards models were used in these analyses. **Results:** In total, 413 ≥70-year-old individuals were eligible for this study. 65.4% were female and 26.6% were black. 22.3% of the participants had MetS at baseline, 4.4% were active smokers, and 6.1% developed CKD-3b over a mean of 4 years of follow-up. MetS and smoking independently predicted incident CKD in our fully adjusted model (hazard ratio 3.65, 95% CI 1.20–10.60, p = 0.022; hazard ratio 29.69, 95% CI 4.47–197.23, p = 0.000). **Conclusion:** MetS and smoking are associated with an increased incidence of CKD-3b. These risk factors are modifiable, easily identified and prevented through better health care practice and early diagnosis.

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Introduction

Chronic kidney disease (CKD) is subdivided into five stages that are linked to graded risks of adverse events [1]. Stages 1 [estimated glomerular filtration rate (eGFR) ≥ 90 ml/min/1.73 m²] and 2 (eGFR 60–89 ml/min/1.73 m²) are the least severe, showing mild kidney damage in stage 1 and a mild decrease in eGFR in stage 2. Stage 3 (eGFR 30–59 ml/min/1.73 m²) indicates moderately decreased eGFR and is sometimes divided into stage 3a (CKD-3a; mildly decreased eGFR, i.e. 45–60 ml/min/1.73 m²) and stage 3b (CKD-3b; moderately decreased eGFR, i.e. 30–45 ml/min/1.73 m²) because of its wide range [2]. CKD-3a and -3b are estimated to affect up to 25% of individuals above 70 years of age in the US [3]; however, complications, atherosclerotic events, hospitalizations, progression to end-stage renal disease (ESRD), and risk of death are more likely once eGFR decreases to 45 ml/min/1.73 m² or less, i.e. CKD-3b [4]. Stages 4 (eGFR 15–29 ml/min/1.73 m²) and 5 (eGFR < 15 ml/min/1.73 m²) indicate severe kidney damage and ESRD requiring dialysis support or kidney transplantation. The highest incidence rate of ESRD is in patients over 75 years of age [5, 6]. These categories, though somewhat arbitrary, provide a useful strategy system which facilitates diagnosis, management, and application of clinical guidelines [1].

The high prevalence of CKD is mainly attributed to diabetes and hypertension; it is also being linked to obesity. These are all factors that reflect underlying vascular and metabolic pathology and that are associated with older age groups and the metabolic syndrome (MetS) [7, 8]. MetS, which is a cluster of cardiovascular and metabolic risk factors, is thought to be a major risk factor for CKD, especially because of the associated vascular pathology and insulin resistance associated with the disease [9]. However, less remains known about the association of MetS with the progression of lower stages of CKD to CKD-3b in older adults.

Although there are some longitudinal studies that have investigated the association of MetS with incident CKD [9], they have used the typical cutoff of eGFR < 60 ml/min/1.73 m², which may be too general especially if applied to a heterogeneous elderly population. Furthermore, most prior studies investigating the association between CKD and MetS components have been cross-sectional [10–12]. In addition, these studies provide results for one or two racial/ethnic groups: Chen et al. [13], Hou et al. [10], and Zhang et al. [11] included only Asians; Kurella et al. [9] had a black and white sample. Also, most studies do not encompass the older-age groups: Kurella et al. [9] only had middle-aged individuals between the ages of 45 and 64 years, and Kaseda et al. [12] only had children between the ages of 1 and 18 years. Thus, most studies do not provide much evidence on how these associations affect an older cohort and much less on how these may be applicable to older-age multiethnic populations.

Our aim in this study was to determine if MetS and its components are predictors of incident CKD-3b in community-dwelling older adults. We also wanted to explore two biomarkers (inflammation and insulin resistance) and two lifestyle factors (past and current smoking and monthly alcohol consumption) that may be in the causal pathway in order to determine if they attenuate any associations between MetS and CKD. Based on our previous cross-sectional work, we hypothesized that MetS will be a stronger predictor of incident CKD-3b than any of its individual components. We also hypothesized that insulin resistance and smoking mediate the association between MetS and CKD due to their vascular associations.

Methods

This study is based on data from individuals enrolled in the Einstein Aging Study (EAS). The EAS is an ongoing longitudinal study that enrolls community-dwelling English-speaking residents of the Bronx county in New York who are 70 years or older. Between 1993 and 2004, participants were systematically recruited from the Health Care Financing Administration/Centers for Medicaid and Medicare Services rosters for

Medicare-eligible persons who were 70 years or older; from 2004 onwards, the study has been recruiting participants from New York City Board of Elections voter registration lists. Participants are excluded if they have visual and/or auditory impairments that interfere with neuropsychological testing, psychiatric symptomatology that interferes with test completion, or a nonambulatory status [14]. The study protocol was approved by the local institutional review board. The EAS began measuring serum creatinine in 2004. The present analysis is based on individuals who did not have CKD-3b as determined by eGFR levels, diabetes, or dementia at the time of their initial creatinine measure. Participants with missing data on any of these variables were also excluded from the study.

Definitions

CKD-3b. We estimated eGFR in ml/min/1.73 m² using the Modification of Diet in Renal Disease formula [15]. This eGFR formula has been recommended for use in older populations [16]. Our outcome was CKD-3b, i.e. eGFR <45 and >30 ml/min/1.73 m².

Metabolic Syndrome. We defined MetS as 3 or more of the following criteria, according to the revised criteria from the National Cholesterol Education Program Adult Treatment Panel III [17]:

- 1 elevated waist circumference (≥ 102 cm in men and ≥ 88 cm in women);
- 2 elevated triglycerides (≥ 150 mg/dl);
- 3 reduced high-density lipoprotein cholesterol (<40 mg/dl in men and <50 mg/dl in women);
- 4 high blood pressure (systolic ≥ 130 or diastolic ≥ 85 mm Hg or the use of antihypertensive medications), and
- 5 elevated fasting glucose (≥ 100 mg/dl).

Inflammation. High-sensitivity C-reactive protein (hsCRP; mg/l) was used to assess inflammation. We used this as a continuous variable, with values log transformed to reduce skewness.

Homeostasis Model Assessment Insulin Resistance. Insulin resistance was defined using the homeostasis model assessment insulin resistance (HOMA-IR) equation: fasting plasma insulin (mU/l) \times fasting plasma glucose (mmol/l)/22.5 [18]. Values were log transformed to reduce skewness.

Diabetes. A history of diabetes was defined as a present fasting glucose of 126 mg/dl and/or if the participant was currently on diabetes medications and/or if the participant replied yes during the clinical interview to the question: ‘Did a doctor ever tell you that you have diabetes?’

Smoking Status. This was defined as either: never smoked, past smoker, or current smoker. This was acquired from the clinical interview.

Alcohol Intake. This was based on the cumulative number of alcoholic drinks per month, which included hard liquor, wine, and beer. We treated alcohol intake as a continuous variable.

Statistical Analysis

We used independent sample t tests to examine differences between groups for continuous variables; we used χ^2 tests for categorical variables. To describe baseline demographic and clinical differences between participants with and without MetS, means and standard deviations or numbers and percentages are presented. Cox proportional hazards regression models were used to determine the adjusted hazard ratio (HR) of CKD-3b for participants with (1) MetS and (2) individual components of MetS. HRs were initially adjusted for age, gender, race, and education. In subsequent models, we additionally adjusted for alcohol intake, smoking status, HOMA-IR, and hsCRP.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 22.0, SPSS Inc., Chicago, Ill., USA).

Results

The eligible sample included 413 participants, 65.4% of whom were female and 26.6% of whom were black. 22.3% met criteria for MetS at the first visit when creatinine was measured (n = 92). Table 1 shows the sample characteristics for those with and without MetS. Those with MetS had lower baseline eGFR and had higher values of HOMA-IR and hsCRP. Over a period spanning 1–9 years (mean follow-up 3.98 years), 6.1% (n = 25) of the cohort developed CKD-3b.

Table 1. Baseline demographic characteristics of the study participants with and without MetS

	MetS		p value
	yes (n = 92)	no (n = 321)	
<i>Demographics</i>			
Age, years	78.1±4.3	79.1±5.2	0.114
Male	24 (26.1)	119 (37.1)	0.051
Non-Hispanic white	64 (69.6)	219 (68.2)	0.807
Education, years	14.0±2.7	14.4±3.3	0.356
Never smoked	43 (46.7)	154 (48.3)	0.964
Past smokers	45 (48.9)	151 (47.3)	
Current smokers	4 (4.3)	14 (4.4)	
Alcohol consumption	12 (14.0)	46 (15.1)	0.786
<i>Clinical characteristics</i>			
Baseline eGFR, ml/min/1.73 m ²	69.9±14.5	74.7±16.1	0.010
Waist circumference, cm	100.7±12.4	90.1±11.6	0.000
Triglycerides, mg/dl	169.3±79.8	92.3±35.9	0.000
HDL cholesterol, mg/dl	48.6±11.8	62.2±15.1	0.000
Systolic blood pressure, mm Hg	139.6±16.8	135.6±17.7	0.063
Diastolic blood pressure, mm Hg	77.6±8.8	77.7±8.6	0.933
Fasting glucose, mg/dl	98.9±12.8	88.9±8.7	0.000
hsCRP	4.1±4.5	3.2±5.5	0.242
HOMA-IR	7.6±7.7	3.7±3.2	0.000

Values are means ± SD or n (%). HDL = High-density lipoprotein.

In unadjusted Cox proportional hazards models, MetS was associated with an increased risk of incident CKD-3b (HR 2.63, 95% CI 1.19–5.82, $p = 0.017$). The association remained significant in models adjusted only for demographics (table 2; model 1: HR 3.24, 95% CI 1.42–7.40, $p = 0.005$). When results were further adjusted for smoking status and alcohol intake, and then also for hsCRP, the association between MetS and CKD-3b became stronger (model 2: HR 3.93, 95% CI 1.66–9.31, $p = 0.002$, and model 4: HR 5.31, 95% CI 2.10–13.44, $p < 0.001$). However, when we added HOMA-IR to model 3, it attenuated the MetS/incident CKD-3b association (model 3: HR 2.73, 95% CI 0.98–7.62, $p = 0.056$). In the fully adjusted model, MetS was significantly predictive of incident CKD-3b (model 5: HR 3.65, 95% CI 1.20–10.60, $p = 0.022$).

When individual components of MetS were explored (table 3), elevated waist circumference was associated with incident CKD-3b in the models adjusting for demographics, lifestyle, and HOMA-IR (HR 3.21, 95% CI 1.06–9.77, $p = 0.040$) and hsCRP (HR 3.15, 95% CI 1.03–9.67, $p = 0.045$). There were no other MetS components that were associated with an increased risk of incident CKD-3b in the unadjusted, semi-adjusted, and fully adjusted models (table 3). However, current smoking status was significantly associated with incident CKD-3b in all models for both MetS and its individual components (tables 2, 3). None of the other covariates were significant.

Discussion

In this study, we explored the effect of MetS and its components on the prediction of incident CKD-3b. Our results showed that, overall, MetS independently predicted incident CKD-3b, but none of its individual components were significant predictors in the fully adjusted models. The results also showed that current smoking is a strong independent risk factor, but

Table 2. Nested Cox models predicting incident CKD-3b based on MetS with adjustments for demographics^a, lifestyle, and biomarkers of inflammation and insulin resistance

	Model 1: adjusted for demographics	Model 2: adjusted for model 1 and lifestyle	Model 3: adjusted for model 2 and HOMA-IR	Model 4: adjusted for model 2 and hsCRP	Model 5: adjusted for model 2, HOMA-IR, and hsCRP
MetS	<i>3.24 (1.42–7.40), 0.005</i>	<i>3.93 (1.66–9.31), 0.002</i>	2.73 (0.98–7.62), 0.056	<i>5.31 (2.10–13.44), 0.000</i>	<i>3.65 (1.20–10.60), 0.022</i>
Never smoked	–	ref.	ref.	ref.	ref.
Past smoker	–	1.46 (0.59–3.60), 0.418	1.21 (0.48–3.04), 0.682	1.44 (0.55–3.79), 0.454	1.20 (0.45–3.19), 0.713
Current smoker	–	<i>5.25 (1.04–26.56), 0.045</i>	<i>9.26 (1.78–48.13), 0.008</i>	<i>6.59 (1.25–34.70), 0.026</i>	<i>12.93 (2.37–70.58), 0.003</i>
Monthly alcohol	–	1.37 (0.31–6.14), 0.681	1.27 (0.28–5.76), 0.756	0.81 (0.10–6.06), 0.809	0.68 (0.09–5.47), 0.719
HOMA-IR	–	–	1.91 (0.39–9.46), 0.426	–	2.49 (0.48–13.06), 0.280
hsCRP	–	–	–	0.66 (0.26–1.67), 0.375	0.50 (0.19–1.34), 0.116

Values are HR (95% CI), p value. Italics indicate statistical significance. ^a Demographics include age, sex, race, and education.

Table 3. Nested Cox models predicting incident CKD-3b using the components of MetS with adjustments for demographics^a, lifestyle, and biomarkers for inflammation and insulin resistance

	Model 1: adjusted for demographics	Model 2: adjusted for model 1 and lifestyle	Model 3: adjusted for model 2 and HOMA-IR	Model 4: adjusted for model 2 and hsCRP	Model 5: adjusted for model 2, HOMA-IR, and hsCRP
Elevated triglycerides	1.99 (0.76–5.19), 0.162	2.49 (0.93–6.66), 0.069	2.38 (0.79–7.12), 0.122	2.48 (0.82–7.50), 0.109	2.01 (0.61–6.38), 0.244
Reduced HDL-C	1.53 (0.53–4.45), 0.436	1.33 (0.45–3.92), 0.601	1.65 (0.51–5.33), 0.401	1.66 (0.51–5.45), 0.402	1.49 (0.45–4.91), 0.517
Elevated fasting glucose	0.95 (0.34–2.69), 0.924	0.94 (0.33–2.67), 0.911	0.97 (0.33–2.92), 0.676	0.95 (0.32–2.83), 0.925	0.81 (0.25–2.62), 0.727
High blood pressure ^b	–	–	–	–	–
Elevated waist circumference	1.90 (0.74–4.89), 0.185	1.98 (0.76–5.17), 0.161	<i>3.21 (1.06–9.77), 0.040</i>	<i>3.15 (1.03–9.67), 0.045</i>	3.01 (0.97–9.26), 0.057
Never smoked	–	ref.	ref.	ref.	ref.
Past smoker	–	1.01 (0.39–2.60), 0.948	1.00 (0.39–2.57), 0.999	0.89 (0.31–2.45), 0.815	0.88 (0.32–2.43), 0.799
Current smoker	–	<i>27.68 (4.52–169.42), 0.000</i>	<i>25.63 (4.21–156.01), 0.000</i>	<i>32.76 (4.93–217.80), 0.000</i>	<i>29.69 (4.47–197.23), 0.000</i>
Monthly alcohol	–	1.18 (0.25–5.56), 0.832	1.15 (0.25–5.38), 0.861	0.60 (0.08–4.82), 0.631	0.58 (0.07–4.71), 0.613
HOMA-IR	–	–	1.81 (0.34–9.56), 0.484	–	2.11 (0.36–12.42), 0.411
hsCRP	–	–	–	0.57 (0.18–1.18), 0.331	0.55 (0.17–1.81), 0.329

Values are HR (95% CI), p value. Italics indicate statistical significance. HDL-C = High-density lipoprotein cholesterol. ^a Demographics include age, sex, race, and education. ^b High blood pressure was not included, because the high proportion of individuals with high blood pressure caused errors in the models.

alcohol consumption, insulin resistance, and hsCRP are not. The addition of HOMA-IR also attenuated the HR linking MetS to incident CKD-3b. These findings suggest that HOMA-IR shares predictive variance for CKD-3b onset with MetS.

The results on the association between MetS and incident CKD have extended previous findings to a more specific stage of the CKD process in a multiethnic cohort of older adults. Previous cross-sectional and longitudinal studies have shown associations between MetS and prevalent/incident CKD-3a in various populations and age groups [9, 13, 19, 20]. Research on 6,215 participants 20 years and older in the National Health and Nutrition Examination Survey (NHANES III) showed that individuals with MetS had 2.60 higher odds (95% CI 1.68–4.03) of prevalent CKD than those without [13]. Similarly, in the EAS [unpubl. data], 616 participants over the age of 70 years showed odds of CKD of up to 1.83 (95% CI 1.16–2.88) in the presence of MetS. In a national survey of adults in China [19], 15,160 Chinese adults between 35 and 74 years of age also showed that individuals with MetS had higher odds of CKD (odds ratio 1.64, 95% CI 1.16–2.32) when compared with those who did not have MetS. These studies were all cross-sectional and employed CKD-3a to study their associations. However, prospective studies have also found similar results. Kurella et al. [9] showed an HR of 1.24 (95% CI 1.01–1.51) of incident CKD among individuals with MetS in 10,096 45- to 64-year-old nondiabetic participants in the Atherosclerosis Risk in Communities Study after a 9-year follow-up. Lucove et al. [21] also found similar results in 4,549 participants from the

Strong Heart Study aged 45–74 years, where the HR of incident CKD in MetS was 1.3 (95% CI 1.1–1.6). Again, both studies examined CKD at the <60 ml/min/ 1.73 m² eGFR cutoff.

In our study, we also found that current smoking was a stronger risk factor than MetS or any other predictor. Over the last decade, the consequences of smoking have been deemed severe, affecting the progression of CKD and related cardiovascular disease (CVD) factors (for a review, see Orth and Hallan [22]). Current smoking has in fact been associated with the incidence of CKD-3a in >40 -year-olds [23] and in elderly Western and Asian populations [24, 25]; it has been associated with a higher risk of progression of CKD in proportion to the number of cigarettes smoked per day, with more cigarettes being associated with higher risk [26]; and it has been associated with CKD and ESRD death as well as with death due to CVD in older adults with CKD-3a [23]. Our study extended past research results to older age groups and to smoking risk factors associated with incident CKD-3b.

In summary, studies on CKD typically use the 60 ml/min/ 1.73 m² cutoff to find predictors of incident CKD [15–17]. By strictly studying the onset of CKD-3b, we explored a more precise perimeter that may identify more rigorously associated predictors that are indicative of a more severe CKD substage. Although our results may still be applicable to the more general stage 3 (both a and b), it is important to be aware of the risk predictors may pose and their severity as the disease progresses. Modifiable risk factors, such as smoking and being overweight, can be targeted in prior stages before they potentially, and most likely, lead to worsening of the conditions, as results have shown in previous studies. Our results suggest that progression to more pronounced CKD stages may be more strongly linked to some lifestyle factors than previously thought, especially since waist circumference and current smoking status reflect lifestyle choices which subsequently lead to vascular and metabolic complications. Although a causal role between smoking and CKD has been suggested [26], the causal explanation of the direct effects of smoking on kidney function is unclear. Studies have shown links to increased microalbuminuria, proteinuria, and serum creatinine in both healthy individuals and diabetic and hypertensive smokers [26]. Several potential mechanisms have also been discussed, which include hemodynamic changes, increases in blood pressure, and alterations in endothelial function [22].

Recent reports have called for more studies to identify clinical characteristics that predict CKD progression and to establish risk factors of different patient subgroups [3]. Our results suggest that CVD lifestyle prevention measures such as regulating body weight through diet and exercise and avoiding smoking are also linked to the prevention of CKD. Given the high prevalence of hypertension, diabetes, and CVD, especially in older adults, and the association with MetS, public health care may need to start including CKD as a central issue in their preventative measures.

This study's strengths include a large multiethnic sample free of CKD-3b at baseline, a long follow-up period, a very specific stage of CKD, and a very specific age group. The number of current smokers in our study was relatively low [4 (4.3%) in the MetS group and 14 (4.4%) in the non-MetS group]. Although, in this study, we only observed individuals who progressed to CKD-3b, this is a very vulnerable group that is more prone to complications, hospitalization, and death. Our findings together with those by others [4] support efforts to refine the National Kidney Foundation CKD staging system.

In conclusion, the results of this study illustrate that MetS as a single entity is a stronger independent risk factor than any of its components and should be considered as a whole when working with CKD risk factors. This study also demonstrated the strong independent predictive risk of current smoking in relation to incident CKD-3b. Lastly, the results also show that elevated waist circumference is a risk factor. The time-to-event models in this study suggest the importance of long-term prevention, especially because these risk factors are, to some extent, modifiable.

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Disclosure Statement

All authors declare that there are no financial, personal, or other potential conflicts of interest.

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