Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 830–843

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Metabolic syndrome and its components are related to a higher risk for albuminuria and proteinuria: Evidence from a meta-analysis on 10,603,067 subjects from 57 studies

Elaheh Rashidbeygi [a], Maryam Safabakhsh [b], Saeideh Delshad aghdam [a], Shimels Hussien Mohammed [c], Shahab Alizadeh [b, *]

[a] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[b] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[c] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences-International Campus (TUMS-IC), Tehran, Iran

ARTICLE INFO

Article history:
Received 13 November 2018
Accepted 7 December 2018

Keywords:
Metabolic syndrome
Albuminuria
Proteinuria
Meta-analysis
CKD

ABSTRACT

Background & aim: Previous studies have explored the relation of metabolic syndrome (MetS), its components and the risk of albuminuria/proteinuria but their results are inconsistent. Then, we aimed to conduct a meta-analysis in order to resolve these controversies.
Method: PubMed and Scopus were systematically searched from their inception to 1 march 2018. Risk estimates and their 95% confidence intervals were extracted and pooled using the random-effects approach.
Result: A total of 57 studies, 44 studies on albuminuria and 13 studies on proteinuria, with a total sample size of 10,603,067 participants, were included in this meta-analysis. Overall, MetS was contributed to higher risks of proteinuria (OR = 2.08, 95%CI = 1.85–2.34) and albuminuria (OR = 1.92, 95%CI = 1.71–2.15), independent of diabetes status; although, this relationship was more noticeable in studies that used the WHO definition of MetS and in non-East Asian populations. Also, the relationship between MetS and proteinuria was sex independent, while, for albuminuria was significant only in men. MetS components such as obesity, impaired fasting glucose, elevated blood pressure and hypertriglyceridemia were associated with significant increases in proteinuria and albuminuria risk, while lower HDL-Cholesterol was only linked to greater risk of proteinuria. Moreover, the total impact of MetS on proteinuria was more remarkable than each component of the syndrome and an escalating dose-response association was found between the number of MetS components and albuminuria risk.
Conclusion: MetS and its components are potential risk factors for albuminuria and proteinuria.

1. Introduction

Proteinuria/albuminuria, as kidney damage indicators are associated with acceleration of end-stage renal disease (ESRD) progression; thus, early reduction in proteinuria/albuminuria can delay the progression of kidney disease [1,2]. Studies have shown that almost 1 in 10 adults in the United States have albuminuria [1–3]. prior studies have provided evidence that albuminuria is a risk factor for cardiovascular diseases, hypertension and lipid metabolism disorders [4]. Also, wide ranges of evidence supported that MetS and its components are metabolic determinants of CKD and its indicator, proteinuria/albuminuria [5,6].

The relation of MetS and its components to albuminuria and proteinuria have not been yet addressed as meta-analysis. Therefore, the present meta-analysis has been designed to assess the association between the MetS, its components and risk of albuminuria and proteinuria.

2. Methods

2.1. Data sources and search strategy

A systematic review and meta-analysis of studies was conducted

* Corresponding author.
E-mail address: sh_alizadeh@razi.tums.ac.ir (S. Alizadeh).

https://doi.org/10.1016/j.dsx.2018.12.006
1871-4021/

according to the PRISMA protocol [7]. A comprehensive literature search was performed to identify related studies in PubMed, Scopus, and Google scholar through March 2018 restricted to English language. The following key words were used for studies relevant to the study objectives: ("metabolic syndrome" OR "insulin resistance syndrome" OR "Metabolic Syndrome X" OR "syndrome X") AND ("proteinuria" OR "micro albuminuria" OR "macro albuminuria" OR "albuminuria"); for each keyword, Medical Subject Heading (MeSH) databases were used in PubMed. A manual search for additional relevant studies using references from retrieved articles was also performed.

2.2. Study's selection criteria

Studies were included in this meta-analysis if they fulfilled the following criteria; 1) study design was prospective cohort, cross-sectional or case control (observational studies); 2) studies investigating the association between MetS as exposure and proteinuria or albuminuria as the main outcome; 3) studies reporting the possibility of obtaining relative risk (or (OR) or hazard ratio (HR)) with 95% confidence intervals; 4) articles were published in English. Studies were excluded in this meta-analysis if they met the following criteria; 1) studies that were not observational in design; 2) non-original articles (reviews, editorials, or letters); 3) case reports, case series, molecular studies and animal studies; and 4) studies in a language other than English. All title and abstracts were screened independently by two reviewers for eligibility. If a consensus was reached, an article was excluded or selected for full-text screening. If a consensus was not reached, another reviewer was consulted regarding the disagreements.

2.3. Data extraction

After determining the qualified articles, the following data were extracted from the included papers: the first author's family name, country, journal details, year of publication, study design, participant characteristics including sample size, gender, age, race, health status, follow-up duration, definition used for MetS, definition used for proteinuria, risk estimates and their 95% CIs and variables adjusted for in multivariate analysis. When one study presented different adjustment variables, we collected data for the most adjusted model.

2.4. Quality assessment

The quality of studies was assessed according to the Newcastle–Ottawa Scale (NOS) for quality assessment of cohort and case–control studies [8] by two of the authors independently. A final score 7–9 was classified as high quality.

2.5. Statistical analysis

In order to examine the association of MetS and its components with the risk of proteinuria or albuminuria the study-specific maximally adjusted ORs, RRs or HRs were pooled. Heterogeneity among studies was evaluated with the Cochran Q test and I^2statistic [9]. I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity. The risk estimates were pooled using the random-effects model (DerSimonian–Laird approach) [10] because of anticipated statistical heterogeneity. To explore the potential source of heterogeneity, subgroup analyses were performed according to participant characteristics such as gender, and race, and study-properties such as study design and the definitions used for MetS. Moreover, sensitivity analysis was performed using a removed method by omitting studies which were based on crude estimates without adjustment for covariates and repeating the analysis. Publication bias was assessed by the Begg and Egger tests for funnel plot asymmetry [11,12]. All statistical tests for this meta-analysis were performed with STATA (version 13.0; Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

At the initial search, a total of 2654 studies were retrieved. The flow diagram demonstrating the process of screening and excluded studies with particular reasons in detail is shown in Fig. 1. At first, 52 articles were included through the eligibility process [5,6,13–61] and finally after crosscheck of the references of review articles and other databases search, 5 further studies were added [62–66]. Eventually a total of 57 studies comprising 44 studies with 46 data sets on albuminuria (30788 albuminuria cases) and 13 studies on proteinuria (210,848 proteinuria cases), with a total sample size of 10603067 participants, published between 2001 and 2018 were included. Among these articles, nine studies were prospective cohort (11189 cases, 112559 participants) [5,13–19,64] and 47 studies were cross-sectional reports (225396 cases, 10418139 participants) [6,20–63,65,66]. The quality assessment of studies showed acceptable methodological quality for all of 9 eligible cohort studies according to the criteria of the NOS with a total score ranging from 4 to 9. Table 1 summarizes the characteristics of the included studies.

3.2. Overall analysis of pooled data

The results of main and prespecified subgroup analyses as well as the heterogeneity test are shown in Table 2 and Table 3. Totally, after pooling all included studies, results presented that MetS approximately twofolded the risk of proteinoria (OR = 2.08, 95% CI = 1.85–2.34), while there was a significant heterogeneity across the studies (I2 = 79.9%, P < 0.001) (Fig. 2). Subgroup analysis was done in order to recognize the effect of different definitions of MetS on the pooled effect size. The pooled OR of proteinuria in studies that used the WHO definition of MetS (OR = 3.51, 95% CI = 1.47–8.42) was greater than the studies used the NCEP-ATP III (OR = 2.15, 95%CI = 1.85–2.50) or IDF (OR = 1.86, 95% CI = 1.70–2.04) definitions; although, this relationship was supported by all difinitions of the syndrome. Additionally, significant associations were found in both prospective cohort (OR = 2.02, 95% CI = 1.61–2.52) and cross-sectional (OR = 2.21, 95%CI = 1.78–2.73) studies. Besides, when the results analysed according to ethinicity, the risk of proteinuria associated with MetS in non-East Asian populations (OR = 1.87, 95%CI = 1.49–2.35) was lower than East-Asian populations (OR = 2.24, 95%CI = 1.88–2.66). The association between MetS and proteinuria was independent of diabetes status. It is noticable that men and women with MetS had a similar risk for proteinuria; although in both genders the risk increased (Table 2). When, in sesitivity analysis, the analysis was limited to studies that adjusted the risk estimate for potential confounders, the overall risk was similar to original estimate (OR = 2.08, 95% CI = 1.84–2.35).

Regards to albuminuria, after pooling all eligible studies, the results suggested that the presence of MetS was associated with a significant increased in the risk of albuminuria (OR = 1.92, 95% CI = 1.71–2.15), with a remarkable heterogeneity (I^2 = 84.5%, P < 0.001). This relationship was significant for both micro-albuminuria and macroalbuminuria (Fig. 3) and was supported by all difinitions of the syndrome; howover, the risk conveyed by WHO criteria was highest. It was found a similar strength and direction of

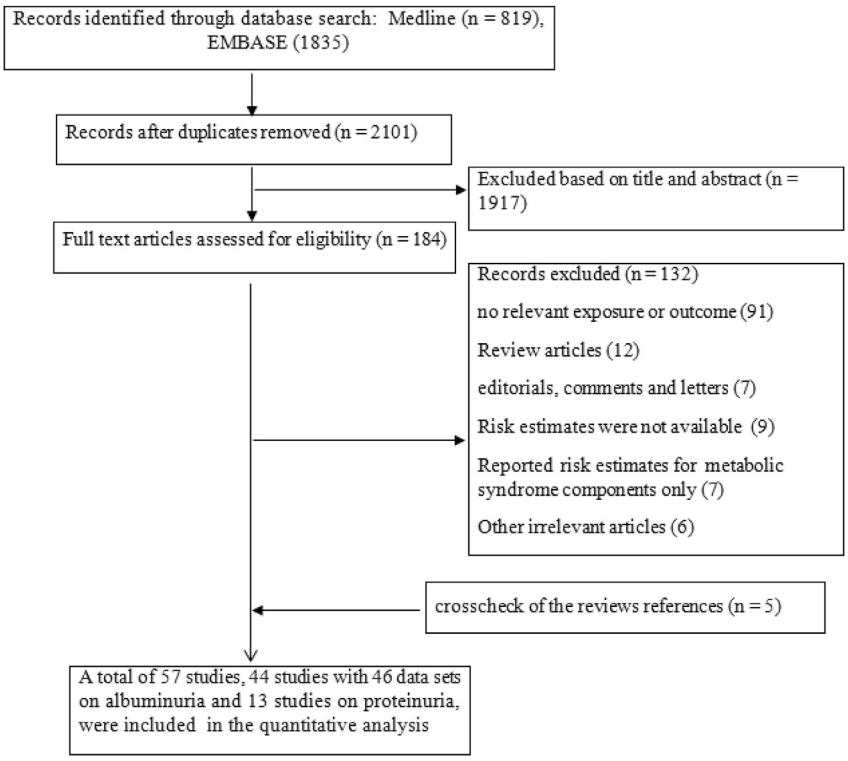

Fig. 1. Flow diagram of studies included in the meta-analysis.

this association in prospective cohort (OR = 1.68, 95% CI = 1.06–2.67) and cross-sectional (OR = 1.94, 95%CI = 1.74–2.17) studies. The risk of albominuria in non-East Asians populations with MetS (OR = 2.18, 95%CI = 1.80–2.64) was higher than that in East-Asian populations (OR = 1.62, 95%CI = 1.42–1.84). The relation of MetS to albuminuria was independent of diabetes status. The analysis stratified by sex revealed a significant association of MetS with albuminuria in men, but not in women. When analysis was limited to studies with adjusted results, the pooled estimate was similar to the overall risk (Table 3).

3.3. Increased blood glucose

After pooling all the studies, the results reported that, in comparison to subjects with normal fasting glucose, patients with impaired fasting glucose had a higher overall risk of proteinuria (OR = 2.05, 95% CI = 1.61–2.62). Due to a high heterogeneity among the studies (I2 = 81.2, P < 0.001), a random effect model was exerted. In the subgroup analysis by study design, a significant association between proteinuria and increased fasting glucose was observed in most of the subgroups, except for non-East Asians and non-diabetic subjects (Table 2).

Similarly, the overall relationship between albuminuria and impaired fasting glucose was significant (OR = 2.02, 95% CI = 1.68–2.41), but a high heterogeneity was observed among the studies (I2 = 82.8, P < 0.001). In all subgroups, this association was supported. After the elimination of studies that had not adjusted the risk estimate for none of the potential confounders, the overall risk also remained unchanged (OR = 1.93, 95%CI = 1.60–2.33) (Table 3).

3.4. Increased blood pressure

The result of pooled studies showed that subjects with elevated blood pressure, in comparison to subjects with normal blood pressure, had a higher overall risk of proteinuria (OR = 1.71, 95% CI = 1.39–2.12), with a high heterogeneity among the studies (I2 = 77.5, P < 0.001). In the subgroup analysis, a significant association between proteinuria and elevated blood pressure was observed in most of the subgroups (Table 2).

Likewise, the overall relationship between albuminuria and elevated blood pressure was significant (OR = 1.87, 95% CI = 1.53–2.28), although a high heterogeneity was observed among the studies (I2 = 95.1, P < 0.001). Despite most of subgroups that supported this association, this association was not significant in non-diabetic subjects (Table 3).

3.5. Increased TGs levels

Pooled analysis of 6 studies identified that the higher levels of triglycerides (TGs) were linked to greater risk of proteinuria (OR = 1.54, 95%CI = 1.19–1.99); although, the heterogeneity among the studies was significant (I2 = 94.7%, P<0.001). The association between increased TGs levels and proteinuria risk was supported by both cross-sectional and cohort studies and was independent of race (Table 2).

Moreover, meta-analysis of 20 studies revealed that patients with hypertriglyceridemia, compared with those without, are at 34% increased risk of albuminuria (OR = 1.34, 95%CI = 1.18–1.52), with a remarkable evidence of heterogeneity (I2 = 83.3%, P<0.001). The mentioned association was lower in cross sectional studies (OR = 1.27, 95%CI = 1.14–1.43) compared to cohort studies (OR = 3.21, 95%CI = 2.10–4.80) and was not modified by ethnicity. The relationship between increased TGs levels and albuminuria was a sex-dependent association. While, women with greater levels of TGs had 45% increased risk of albuminuria (OR = 1.45, 95% CI = 1.15–1.84), women had a non-significant increased risk. After excluding the studies with crude risk estimates, the association was

Table 1
Characteristics of studies included in the meta-analysis.

Study, year	Country	Population	Ethnicity	Study design	Male (%)	Age (range or mean ± SD)	Individuals with MetS	Albuminuria/ proteinuria cases	Study Sample Size	Definition of Metabolic Syndrome	Outcome	definition of outcome	Adjusted Variables in analyses
Isomaa et al.,2001	Finland	Diabetic	Non-East Asian	Case-control	62.3	60	85	21	167	WHO	Microalbuminuria	AER in overnight urine exceeded 20 μg/min or ACR 2/5 mg/mmol in males and 3/5 mg/mmol in females	NR
Hoehner et al.,2002	Native Americans	Non-diabetic	Non-East Asian	Cross-sectional	36.9	44/6 ± 13/4	69	142	934	≥3 criteria	Microalbuminuria	ACR of 30–299 mg/g	age, gender (total population only), BMI, education, smoking history, and family histories of diabetes and kidney disease
Palaniappan et al.,2003	USA	General population	Non-East Asian	Cross-sectional	49.5	20–80	1063	445	5659	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	age, sex, other components of MetS
Messerli et al.,2003	USA	Cardiovascular disease patients	Non-East Asian	Cross-sectional	64	45–64	NR	172	720	NCEP ATP-III	Albuminuria	ACR≥11 mg/g	Age, gender
Chen et al.,2004	USA	General population	Non-East Asian	Cross-sectional	50	44/79 ± 0/7	1173	353	6125	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	BMI, age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking
THORN et al.,2005	Finland	Diabetic	Non-East Asian	Cross-sectional	51	38.7 ± 0.4	944	709	2415	NCEP ATP-III	Albuminuria	AER >20 g/min or >30 mg/24 h	age, sex, smoking, and HBA1C
Bonnet et al.,2006	France	Non-diabetic	Non-East Asian	Prospective cohort	54.2	30–64	176	254	2738	NCEP-ATP III	Proteinuria	urinary albumin concentration of 20 mg/ or dipstick positive for proteinuria	age, use of angiotensin-converting enzyme inhibitors, smoking, and fibrinogen level
Hoy et al.,2006	Australia	General population	Non-East Asian	Cross-sectional	NR	≥18	523	NR	2019	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	Age, sex
Hoy et al.,2006	Australia	General population	Non-East Asian	Cross-sectional	NR	≥18	523	NR	2019	NCEP-ATP III	Albuminuria	ACR ≥3/4	Age, sex
Choi et al.,2006	South Korea	General population	East Asians	Cross-sectional	54.1	49	686	349	6588	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	age, BMI, ln(hsCRP), ln(HOMA), and smoking
Abdul-Ghani et al.,2006	Israel	Diabetic	Non-East Asian	Cross-sectional	58.4	53 ± 18	270	147	415	NCEP ATP-III	Microalbuminuria	urinary collection had > 20 mg microalbumin/24 h	age, gender, HbA1C, disease duration and blood pressure
Stengel et al.,2007	La Reunion island	Non-diabetic	Non-East Asian	Cross-sectional	40.86	30–69	NR	115	920	NCEP-ATP III	Proteinuria	Clinical proteinuria >200 mg/g creatinine	age, sex and geographical location
Tozawa et al.,2007	Japan	Non-diabetic	East Asians	Prospective cohort	63	47 ± 9	884	NR	6371	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	age, sex, current cigarette smoking and alcohol drinking habits
Hao et al.,2007	*Japan*	General population	East Asians	Cross-sectional	45.3	40–87	384	318	2321	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	Age, Gender
Lee et al.,2007	South Korea	Diabetic	East Asians	Cross-sectional	77.5	54	239	102	642	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	age, sex, smoking status, C-reactive protein, and HbA1c
Franciosi et al.,2007	Italy	Non-diabetic		Cross-sectional	51.4	62.6 ± 5.3	730	113	1919	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	NR

(*continued on next page*)

Table 1 (*continued*)

Study, year	Country	Population	Ethnicity	Study design	Male (%)	Age (range or mean ± SD)	Individuals with MetS	Albuminuria/ proteinuria cases	Study Sample Size	Definition of Metabolic Syndrome	Outcome	definition of outcome	Adjusted Variables in analyses
			Non-East Asian										
BURANAKITJAROEN et al.,2007	Thailand	Hypertensive Patients	East Asians	Cross-sectional	34	58.0 ± 11.2	271	94	494	IDF	Microalbuminuria	negative Multistix test plus positive Microalbustix test	NR
Sumaili et al.,2008	Congo	General population	Non-East Asian	Cross-sectional	58.7	12–85	NR	516	3018	NCEP-ATP III	Proteinuria	presence of ≥1 + protein (equivalent to equal or more30 mg/dl)	age, gender, smoking, alcohol consumption, indigenous herbal remedies, birth weight knowledge
Iwasaki et al.,2008	Japan	Diabetic	East Asians	Cross-sectional	61.5	61	76	13	130	NCEP-ATP III	Proteinuria	UAE of 200 mg/min and serum creatinine 1/1 mg/dl	age, gender, duration of diabetes
Bianchi et al.,2008	Italy	Diabetic	Non-East Asian	Cross-sectional	58	62 ± 10	921	278	1314	NCEP-ATP III	Albuminuria	microalbuminuria (A/C < 25 mg/mmol if male, < 35 if female) or macroalbuminuria (A/C > 25/35 mg/mmol)	age and gender, MetS, diabetes duration, HbA1c, low-density lipoprotein (LDL), smoking and low estimated glomerular filtration rate (eGFR)
Lucove et al.,2008	USA	Non-diabetic	Non-East Asian	Prospective cohort	44	45–74	896	290	2386	NCEP-ATP III	Albuminuria	ACR >30 mg/g	age, sex, center, education, smoking
Hanai et al.,2008	Japan	Diabetic	East Asians	Cross-sectional	58	62 ± 12	592	300	1003	Japanese definition	Microalbuminuria	UACR of 30–300 mg/g	age, sex, presence of diabetic duration 10 years, presence of diabetic retinopathy, hemoglobin A1C, LDL cholesterol and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
Lee et al.,2008	Taiwan	Diabetic	East Asians	Cross-sectional	60.7	64 ± 1	271	119	446	NCEP ATP-III	Albuminuria	UAE>30 mg/g	age, gender and medications (including anti-platelet drugs, thiazolidinediones, statins and fibrates)
Nguyen et al.,2008	USA	General population	Non-East Asian	Cross-sectional	52.6	12–19	82	226	2515	NCEP ATP-III	Microalbuminuria	UACR of 30–300 mg/g	age, gender, race/ethnicity
Chiowanich et al.,2009	Thailand	Diabetic	East Asians	Cross-sectional	34.50	56.55	862	602	2231	NR	Microalbuminuria	UACR of 30–300 mg/g	NR
Anvari et al.,2009	Iran	Cardiovascular disease patients	Non-East Asian	Cross-sectional	66.7	58.93	211	109	531	NCEP ATP-III	Microalbuminuria	UACR of 30–300 mg/g	age, gender
Rodilla et al.,2009	Spain	hypertensive, nondiabetic	Non-East Asian	Cross-sectional	49	47/1 ± 10/2	202	88	429	NCEP ATP-III	Microalbuminuria	>30 mg/24 h	Age, sex
Aekplakorn et al.,2009	Thailand	Diabetic	East Asians	Cross-sectional	32.1	58/6 ± 11/1	891	1628	4162	NCEP ATP-III	Microalbuminuria	ACR ranged from 30 to 299 mg/mg creatinine	age, sex, duration of disease, triglyceride, LDL-C, low HDL-C, BMI, HbA1c, hypertension, smoking status and clinical setting (general hospital,

												community hospital and primary care center)
Aekplakorn et al.,2009	Thailand	Diabetic	East Asians	Cross-sectional	34.1	60/7 ± 10/2	185	326	4162	NCEP ATP-III	Microalbuminuria	UACR 300 mg/mg creatinine	age, sex, duration of disease, triglyceride, LDL-C categories, low HDL-C, BMI, HbA1c, hypertension, smoking status and clinical setting (general hospital, community hospital and primary care center)
Watanabe et al.,2010	Japan	General population	East Asians	Prospective cohort	34	59.0 ± 11.3	3679	2206	34,986	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	sex and age
Oda et al.,2010	Japan	General population	East Asians	Cross-sectional	63	53.17	485	325	3897	NCEP-ATP III	Proteinuria	NR	NR
Esteghamati et al.,2010	Iran	Diabetic	Non-East Asian	Cross-sectional	43	54.8 ± 9.6	645	237	800	IDF	Microalbuminuria	UACR of 30–300 mg/g	NR
Gojaseni et al.,2010	Thailand	nondiabetic hypertensive patients	East Asians	Cross-sectional	50.6	58.0 ± 11.6	231	93	559	IDF	Albuminuria	ACR was more than 17 mg/g creatinine in males and 25 mg/g creatinine in female as per standard guideline	NR
Ferraro et al.,2011	Italy	General population	Non-East Asian	Cross-sectional	48.2	65.1 ± 10	841	286	3757	NCEP-ATP III	Albuminuria	albumin-to-creatinine ratio (ACR)≥ 3/4 mg/mmol)	age, gender, BMI, smoking status, cardiovascular disease
Duran-Perez et al.,2011	Mexico	Diabetic	Non-East Asian	Retrospective cohort	45.2	35–65	181	221	400	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g	age, sex, adjusted for the other components of MetS
Sanad et al.,2011	Egypt	obese children	Non-East Asian	Cross-sectional	49	7 ± 2.4	23	22	150	NCEP ATP-III	Microalbuminuria	UACR of 30–300 mg/g	age, gender, BMI, MS and all of its different constituents
Leoncini et al.,2012	Italy	Hypertensive patients	Non-East Asian	Cross-sectional	54	62 ± 11	1725	758	2916	NCEP-ATP III	Microalbuminuria	mean UACR ≥2/5 mg/mmol in men and ≥3/5 mg/mmol in women	age, gender, BMI, serum uric acid, previous cardiovascular disease, active smoking, duration of hypertension >10 years, controlled blood pressure
Navaneethan et al.,2013	USA	CKD patients	Non-East Asian	Prospective cohort	46	71.06 ± 10.9	15,605	3482	25,868	IDF	Proteinuria	presence of ≥ +1 proteinuria in dipstick	age, sex, race, smoking, malignancy, congestive heart failure, cerebrovascular disease, coronary artery disease, chronic obstructive pulmonary disease, use of angiotensin-converting enzyme inhibitors angiotensin receptor blockers, LDL cholesterol, hemoglobin, albumin, and eGFR
Kim et al.,2013	South Korea	General population	East Asians	Cross-sectional	0.00	28.9 ± 5.5	540	104	10,385	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	age, smoking, BMI, systolic BP, pulse pressure, cholesterol, presence of metabolic syndrome and Egfr
Jiang et al.,2013	China				44.6	51.7 ± 11.1	1076	653	4191		Microalbuminuria	UACR of 30–300 mg/g	

(*continued on next page*)

Table 1 (*continued*)

Study, year	Country	Population	Ethnicity	Study design	Male (%)	Age (range or mean ± SD)	Individuals with MetS	Albuminuria/ proteinuria cases	Study Sample Size	Definition of Metabolic Syndrome	Outcome	definition of outcome	Adjusted Variables in analyses
		General population	East Asians	Cross-sectional						Chinese Diabetes Society criteria			age, sex, smoking status, alcohol use, education level, history of cardiovascular disease or stroke and CRP, other components of MetS
Chen et al.,2013	Taiwan	Occupational drivers	East Asians	Cross-sectional	96.8	46.5 ± 9.4	190	53	441	NCEP-ATP III	Albuminuria	UACR >30 mg/g creatinine	age, sex, a history of diabetes mellitus, and gout, betel nut chewing, exercise, and albuminuria
Gutiérrez-Repiso et al.,2013	Spain	General population	Non-East Asian	Cross-sectional	42.9	50 ± 17	NR	388	5072	NCEP-ATP III	Albuminuria	UACR >30	age and sex
Kang et al.,2014	South Korea	Non-diabetic	East Asians	Cross-sectional	56.18	46.86 ± 13.8	2,281,675	202,928	10253085	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	age, sex
Chen et al.,2014	China	General population	East Asians	Cross-sectional	39.2	44.5 ± 13.5	10075	7450	38,203	IDF	Albuminuria	UACR of 30–300 mg/g	age, sex, cardiovascular disease (CVD) and diabetes mellitus family history
Huang et al.,2014	Taiwan	Relatives of Hemodialysis Patients	East Asians	Case-control	47	39.65	40	80	540	NCEP-ATP III	Albuminuria	UACR >30	NR
Nishikawa et al.,2015	Japan	Non-Obese workers	East Asians	Prospective cohort	85.8	18–69	2867	905	23,894	NCEP-ATP III	Proteinuria	dipstick proteinuria ≥ +1	age, sex, smoking status, alcohol consumption, exercise habits, walking time in commutation, type of work and occupational exposure
Nand et al.,2015	India	Hospital-based	Non-East Asian	Case-control	49.6	62.07 ± 10.68	*150*	63	*300*	NCEP-ATP III	Microalbuminuria	UACR of 30–300 mg/g in females and 20–200 mg/g in males	NR
Lee et al.,2015	South Korea	General population	East Asians	Cross-sectional	42.6	48.9 ± 5	2664	514	8497	joint harmonized assessment	Microalbuminuria	UACR of 30–300 mg/g	age, smoking status, alcohol consumption, physical inactivity, and education level
Hong et al.,2015	China	General population	East Asians	Cross-sectional	41.9	50 ± 15	11138	3187	41,131	NCEP-ATP III	Albuminuria	UACR >30 mg/g creatinine	age, sex, hypertension and diabetes, cardiovascular disease, former kidney disease and nephrotoxic drugs, hyperuricaemia, smoking, alcohol, regular exercise, and income
Ryoo et al.,2015	South Korea	General population	East Asians	Prospective cohort	100	53/2 ± 10/4	364	91	1649	IDF	Microalbuminuria	UACR of 30–300 mg/g	age, LDL-cholesterol, eGFR, GGT and HOMA-IR, recent smoking status, regular exercise, alcohol intake, diabetes mellitus and hypertension
Sipahioglu et al.,2015	Turkey	CKD disease patients	Non-East Asian	Cross-sectional	63.5	39/3 ± 11	78	65	170	NCEP ATP-III	Microalbuminuria	UACR >30 mg/g creatinine	age, sex, time after transplantation, use of angiotensin converting enzyme inhibitors, angiotensin receptor antagonist, and mTOR inhibitors

Billow et al.,2015	India	Diabetic	Non-East Asian	Cross-sectional	25.2	>18	100	81	451	joint harmonized assessment	Albuminuria	Microalbuminuria was defined as UAE of 30 −299 μg/mg of creatinine, while macroalbuminuria was diagnosed if the UAE was >300μg/mg of creatinine or if the 24 h protein excretion was >500 mg	age & duration of diabetes, gender, BMI, HbA1c
Greenberg et al.,2016	Israel	Apparently healthy individuals	Non-East Asian	Cross-sectional	66.8	44.0 ± 9.9	315	394	2027	joint harmonized assessment	Microalbuminuria	ACR values above 3 mg/g	age, sex, heart rate, diastolic and systolic blood pressures, metabolic equivalents, high-sensitivity C-reactive protein, white blood cell count, glomerular filtration rate
Li et al.,2016	China	Aged population	East Asians	Cross-sectional	39.4	55−98	199	273	674	Chinese Diabetes Society criteria	Microalbuminuria	UACR ≥3mg/mmoL	Age- and gender
Chen et al.,2017	China	General population	East Asians	Cross-sectional	71.7	48.7 ± 14.3	9683	NR	26,601	NCEP ATP-III	Proteinuria	urine protein ≥1+	age, gender, cigarette smoking, Alcohol drinking, UA and all the other components of MetS
Cho et al.,2017	Korea	Non-diabetic	East Asians	Cross-sectional	57	10−19	38	59	1976	IDF	Microalbuminuria	UACR of 30 mg/g and <300 mg/g	age and sex
Viazzi et al.,2017	Italy	Diabetic	Non-East Asian	Prospective cohort	56.4	63 ± 10	8408	3740	14,267	NCEP ATP-III	Albuminuria	If urinary albumin concentration was >30 mg/l, or if urinary albumin excretion rate was >20 μg/min, or if UACR was >2/5 mg/mmol in men and >3/5 mg/mmol in women/	NR
Raikou et al.,2018	Greece	Hospital-based	Non-East Asian	Cross-sectional	51.6	69.4 ± 14.6	120	98	149	IDF	Albuminuria	ACR > 30 mg/gr	age, gender, smoking, alcohol intake, physical activity and the presence of diabetes

BMI: body mass index, AER: albumin excretion rate, UACR: urine albumin-to-creatinine ratio, UAE: Urinary albumin excretion.

Table 2
Main analyses and prespecified subgroup analyses for proteinuria risk in relation to the presence of metabolic syndrome, its individual components, and number of metabolic syndrome components.

Risk factor	Subgroup	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95%CI	I^2 (%)	P	t	P
Metabolic syndrome	Overall	13	2.08	1.85–2.34	79.9	<0.001	1.66	0.125
	NCEP-ATP III criteria	12	2.15	1.85–2.50	81.5	<0.001		
	IDF criteria	3	1.86	1.70–2.04	0.0	0.595		
	WHO criteria	2	3.51	1.47–8.42	24.8	0.249		
	Prospective cohorts	5	2.02	1.61–2.52	89.0	<0.001		
	Cross-sectionals	8	2.21	1.78–2.73	65.9	0.005		
	East-Asians	8	2.24	1.88–2.66	86.4	<0.001		
	Non East-Asians	5	1.87	1.49–2.35	49.7	0.093		
	Males	3	1.95	1.55–2.45	34.0	0.220		
	Females	3	1.95	1.46–2.61	26.1	0.258		
	General population	6	2.12	1.67–2.69	71.8	0.003		
	Diabetics	1	9.49	1.12–80.11	–	–		
	Nondiabetics	4	1.90	1.68–2.14	15.7	0.313		
	Adjusted	12	2.08	1.84–2.35	81.5	<0.001		
	Non-adjusted	1	2.20	1.19–3.21	–	–		
Increased fasting glucose	Overall	6	2.05	1.61–2.62	81.2	<0.001	0.90	0.417
	Prospective cohorts	2	1.93	1.54–2.42	81.5	0.020		
	Cross-sectionals	4	2.41	1.35–4.32	85.9	<0.001		
	East-Asians	4	2.26	1.73–2.95	84.4	<0.001		
	Non East-Asians	2	1.36	0.95–1.95	5.5	0.304		
	General population	4	2.06	1.45–2.91	86.1	<0.001		
	Nondiabetics	1	2.70	0.70–10.70	–	–		
	Non-Obese workers	1	2.18	1.87–2.55	–	–		
Elevated blood pressure	Overall	7	1.71	1.39–2.12	77.5	<0.001	1.21	0.279
	Prospective cohorts	2	1.62	1.50–1.74	0.0	0.517		
	Cross-sectionals	5	2.31	1.31–4.06	84.6	<0.001		
	East-Asians	5	1.83	1.50–2.23	71.8	<0.001		
	Non East-Asians	2	1.49	0.61–3.67	66.1	0.086		
	General population	4	1.72	1.24–2.38	86.5	<0.001		
	Diabetics	1	7.44	1.15–48.21	–	–		
	Nondiabetics	1	2.80	1.00–8.50	–	–		
	Non-Obese workers	1	1.68	1.46–1.93	–	–		
Increased triglycerides	Overall	6	1.54	1.19–1.99	94.7	<0.001	5.32	0.006
	Prospective cohorts	1	1.34	1.20–1.51	37.8	0.205		
	Cross-sectionals	1	2.03	1.18–3.50	94.1	<0.001		
	East-Asians	5	1.48	1.14–1.92	95.6	<0.001		
	Non East-Asians	1	3.60	1.07–12.09	–	–		
	General population	3	2	1.21–3.31	92.9	<0.001		
	Diabetics	1	0.99	0.97–1.01	–	–		
	Nondiabetics	1	3.60	1.10–12.40	–	–		
	Non-Obese workers	1	1.44	1.24–1.66	–	–		
Obesity	Overall	7	1.72	1.27–2.34	96.0	<0.001	1.71	0.147
	Prospective cohorts	3	1.68	1.55–1.81	0.0	0.494		
	Cross-sectionals	4	1.82	1.05–3.15	93.6	<0.001		
	East-Asians	5	1.63	1.16–2.28	97.2	<0.001		
	Non East-Asians	2	2.11	1.41–3.15	0.0	0.567		
	General population	3	2.06	1.07–3.96	96.0	<0.001		
	Diabetics	1	1.02	0.96–1.07	–	–		
	Nondiabetics	2	2.11	1.41–3.15	0.0	0.567		
	Non-Obese workers	1	1.75	1.52–2.02	–	–		
Reduced HDL-cholesterol								
	Overall	6	1.32	1.04–1.68	88.3	<0.001	2.66	0.057
	Prospective cohorts	1	1.19	1.07–1.32	0.0	1.00		
	Cross-sectionals	4	1.78	0.89–3.58	90.6	<0.001		
	East-Asians	5	1.27	1.00–1.62	89.9	<0.001		
	Non East-Asians	1	2.80	0.90–8.71	–	–		
	General population	3	1.74	0.88–3.47	90.7	<0.001		
	Diabetics	1	0.96	0.91–1.02	–	–		
	Nondiabetics	1	2.80	0.90–8.71	–	–		
	Non-Obese workers	1	1.19	0.98–1.44	–	–		

not changed remarkably (Table 3).

3.6. Obesity

The criteria used for obesity was different in the included studies, in 5 studies the assessment was based on waist circumference [5,14,20,21,40] and in 2 of them was based on body mass index (BMI) [15,36]. There was a significant direct association between overall obesity, either defined by BMI or waist circumference, and proteinuria risk (OR = 1.72, 95%CI = 1.27–2.34); although, in the stratified analysis, this relationship was observed only for central obesity (OR = 2.06, 95%CI = 1.36–3.10), not for general obesity (OR = 1.28, 95%CI = 0.69–2.38). The analysis revealed that the relation of obesity to proteinuria in all of the

Table 3
Main analyses and prespecified subgroup analyses for albuminuria risk in relation to the presence of metabolic syndrome, its individual components, and number of metabolic syndrome components.

Risk factor	Subgroup	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95%CI	I^2 (%)	P	t	P
Metabolic syndrome	Overall	44	1.92	1.71–2.15	84.5	<0.001	- 0.17	0.863
	NCEP-ATP III criteria	29	1.88	1.63–2.17	85.3	<0.001		
	IDF criteria	9	1.78	1.43–2.22	79.9	<0.001		
	Chinese diabetes society criteria	3	1.60	1.19–2.14	84.2	0.002		
	Joint harmonized assessment	3	1.92	2.08–4.09	55.1	0.108		
	WHO criteria	2	3.35	2.32–4.83	0.0	0.730		
	Prospective cohorts	4	1.68	1.06–2.67	90.1	<0.001		
	Cross-sectionals	41	1.94	1.74–2.17	80.8	<0.001		
	East-Asians	19	1.62	1.42–1.84	80.4	<0.001		
	Non East-Asians	26	2.18	1.80–2.64	86.2	<0.001		
	Males	4	2.27	1.21–4.26	84.9	<0.001		
	Females	4	1.65	0.99–2.74	82.0	0.001		
	General population	13	1.93	1.65–2.25	82.5	<0.001		
	Diabetics	14	2	1.52–2.64	91.9	<0.001		
	Nondiabetics	6	1.74	1.33–2.28	42.4	<0.122		
	Adjusted	36	1.99	1.77–2.23	0.81	<0.001		
	Non-adjusted	9	1.63	1.23–2.18	82.8	<0.001		
Increased fasting glucose	Overall	20	2.02	1.68–2.41	82.8	<0.001	0.35	0.732
	Cross-sectionals	19	2.02	1.68–2.41	82.8	<0.001		
	East-Asians	9	1.79	1.41–2.28	86.3	<0.001		
	Non East-Asians	10	2.29	1.93–2.72	36.0	0.120		
	Males	4	2.08	1.64–2.63	0.0	0.858		
	Females	4	2.22	1.76–2.79	0.0	0.403		
	General population	10	1.89	1.51–2.37	88.3	<0.001		
	Nondiabetics	4	1.57	1.21–2.04	0.0	0.986		
	Adjusted	15	1.93	1.60–2.33	83.8	<0.001		
	Non-adjusted	4	2.77	1.37–5.62	79.7	0.002		
Elevated blood pressure	Overall	26	1.87	1.53–2.28	95.1	<0.001	1.29	0.215
	Prospective cohorts	1	1.86	0.61–1.22	–	–		
	Cross-sectionals	25	1.94	1.58–2.39	95.2	<0.001		
	East-Asians	13	1.84	1.57–2.17	76.9	<0.001		
	Non East-Asians	13	1.88	1.33–2.68	93.0	<0.001		
	Males	5	1.82	1.14–2.89	78.7	0.001		
	Females	5	2.13	1.33–3.43	86.2	<0.001		
	General population	10	2.21	1.82–2.67	85.7	<0.001		
	Diabetics	7	1.34	1.04–1.72	79.6	<0.001		
	Nondiabetics	3	1.73	0.99–3.04	35.0	0.215		
	Adjusted	20	1.87	1.49–2.36	96.0	<0.001		
	Non-adjusted	6	1.81	1.24–2.65	60.4	0.027		
Increased triglycerides	Overall	20	1.34	1.18–1.52	83.3	<0.001	- 1.35	0.227
	Prospective cohorts	1	3.21	2.10–4.80	–	–		
	Cross-sectionals	19	1.27	1.14–1.43	78.3	0.001		
	East-Asians	9	1.25	1.09–1.43	54.7	0.024		
	Non East-Asians	11	1.47	1.11–1.94	85.5	<0.001		
	Males	4	1.46	0.96–2.23	51.6	0.102		
	Females	4	1.45	1.15–1.84	0.0	0.543		
	General population	9	1.32	1.15–1.51	62.8	0.006		
	Diabetics	4	1.46	0.83–2.58	90.7	<0.001		
	Nondiabetics	3	1.18	0.84–1.64	0.0	0.407		
	Adjusted	18	1.30	1.15–1.48	83.1	<0.001		
	Non-adjusted	2	1.88	1.01–3.51	64.8	0.092		
Obesity	Overall	22	1.28	1.14–1.44	86.3	<0.001	3.12	0.007
	Prospective cohorts	1	0.76	0.52–1.10	–	–		
	Cross-sectionals	21	1.32	1.16–1.48	86.8	<0.001		
	East-Asians	10	1.37	1.17–1.60	81.0	<0.001		
	Non East-Asians	12	1.19	0.99–1.41	64.2	0.001		
	Males	3	1.88	1.31–2.69	29.7	0.241		
	Females	3	1.17	0.55–2.52	90.9	<0.001		
	General population	10	1.26	1.08–1.47	82.0	<0.001		
	Diabetics	6	1.29	0.91–1.82	82.1	<0.001		
	Nondiabetics	2	1.48	1.06–2.07	0.0	0.664		
	Adjusted	18	1.25	1.11–1.42	88.3	<0.001		
	Non-adjusted	4	1.53	1.15–2.02	0.0	0.936		
Reduced HDL-cholesterol	Overall	21	1.23	1.00–1.52	97.4	<0.001	1.22	0.238
	Prospective cohorts	1	1.19	0.76–1.79	–	–		
	Cross-sectionals	20	1.24	1.00–1.53	97.6	<0.001		
	East-Asians	10	1.17	0.96–1.42	69.4	0.001		
	Non East-Asians	11	1.31	0.94–1.83	98.6	<0.001		
	Males	4	1.38	0.99–1.92	24.3	0.266		
	Females	4	1.27	0.79–2.04	62.2	0.048		

(*continued on next page*)

Table 3 (*continued*)

Risk factor	Subgroup	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95%CI	I^2 (%)	P	t	P
	General population	9	1.24	1.04–1.47	71.0	<0.001		
	Diabetics	4	1.06	0.89–1.26	26.1	0.255		
	Nondiabetics	3	1.07	0.59–1.96	46.3	0.155		
	Adjusted	19	1.21	1.50–0.97	97.7	<0.001		
	Non-adjusted	2	1.54	1.04–2.27	0.0	0.543		
1 component	Overall	10	1.63	1.33–1.99	33.7	0.138	–	–
2 components	Overall	12	1.95	1.40–2.70	78.4	<0.001	–	–
3 components	Overall	11	2.98	2.26–3.91	72.8	<0.001	–	–
4 components	Overall	8	3.49	2.33–5.22	76.7	0.001	–	–
5 components	Overall	8	6.16	3.41–11.12	84.2	<0.001	–	–

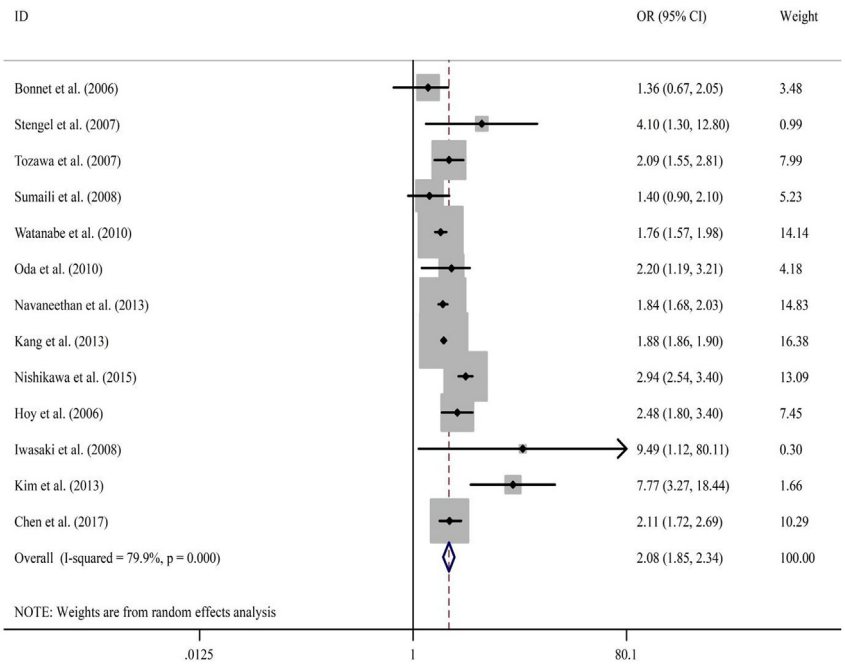

Fig. 2. Forest plot showing the overall association between metabolic syndrom and risk of protienoria.

subgroups were significant except for diabetics subgroup, which was based on only 1 study (Table 2).

Similar to proteinuria, there was a significant direct association between overall obesity, either defined by BMI or waist circumference, and proteinuria risk (OR = 1.28, 95%CI = 1.14–1.44); however, in the stratified analysis, this relationship was found to be significant only for central obesity (OR = 1.35, 95%CI = 1.18–1.55), not general obesity (OR = 1.03, 95%CI = 0.77–1.36). The association of obesity with albuminuria was found to be race and gender dependent; while East-Asians and men had a significant increased risk for albuminuria, no such relationships was detected for non-East-Asians and women. In the sensitivity analysis, after excluding the studies with crude risk estimates, the association was not changed remarkably (Table 3).

3.7. Reduced HDL-cholesterol

For HDL-cholesterol, the analysis confirmed that lower levels of HDL-cholesterol significantly enhanced the risk of proteinuria (OR = 1.32, 95%CI = 1.04–1.68), with a high heterogeneity among studies (I2 = 88.3%, P<0.001). Nevertheless, this relationship was not supported in the stratified analyses (Table 2).

Pooled analysis revealed no significant association between the lower levels of HDL-cholesterol and the risk of albuminuria (OR = 1.23, 95%CI = 1.00–1.52). All subgroups analyses supported this finding except for studies on general population (OR = 1.24, 95%CI = 1.04–1.47) and studies with crude risk estimates (OR = 1.54, 95%CI = 1.04–2.27), which revealed a significant relationship between reduced HDL-cholesterol levels and albuminuria risk (Table 3).

3.8. The comparison of the overall risk of proteinuria and albuminuria associated with the MetS, its individual components and the number of MetS components

As it was mentioned, there was a significant association between MetS and all of its five components with the risk of proteinuria. Among components, increased fasting glucose, obesity and elevated blood pressure were the most important risk factors for proteinuria, respectively. The overall risk estimates of each component of the MetS were lower than that obtained for the full syndrome in the same studies. For albuminuria, MetS and its components, with the exception of reduced HDL-cholesterol, were found to be significant predictors of the disease risk. Among the

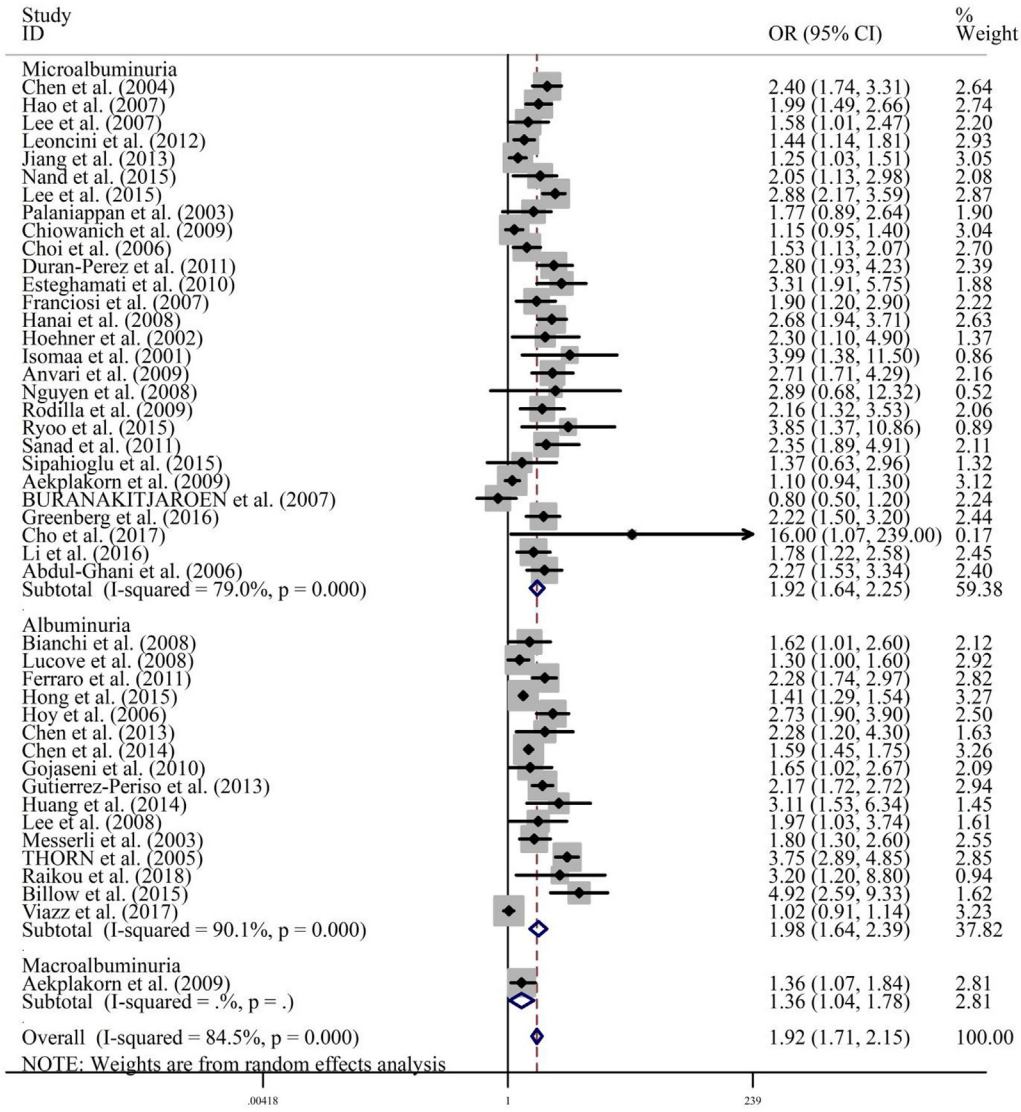

Fig. 3. Forest plot showing the overall and subgroup analysis by albominoria type on the association between metabolic syndrome and risk of albomnoria.

components of the syndrome, increased fasting glucose and elevated blood pressure, respectively, were recognized as the most potential risk factors for albuminuria; even odds of albuminuria associated with increased fasting glucose was higher than that obtained for MetS. Moreover, an escalating dose response relationship was found between the number of MetS components and albuminuria risk (Table 3 and Fig. 4).

3.9. Evaluation of publication bias

In most of associations, funnel plot and Egger's tests didn't show any significant publication bias, but in the overall analyses only in the studies that investigated the association between obesity and risk of albuminuria ($t = 3.12$, $p = 0.007$) and increased TGs levels and risk of proteinuria ($t = 5.32$, $p = 0.006$) possible publication bias based on Egger's linear regression test was observed (Tables 2 and 3).

4. Discussion

Previously, several studies examined the role of MetS and its components in the risk of proteinuria/albuminuria; however the available evidence is inconsistent. To the best of our knowledge, the present study is the first meta-analysis attempting to comprehensively analyze the association between MetS and its components to the risk of proteinuria/albuminuria to resolve these inconsistencies. The results manifested that regardless of diabetes status, study type and ethnicity, the presence of MetS identified by the different criteria, is associated with greater albuminuria and proteinuria risk. MetS was found to be a significant predictor of both micro and macro albuminuria. In addition, all single components of MetS were related to a significant increase in albuminuria risk and their coexistence resulted in an escalating dose-response association. Except for reduced HDL-cholesterol levels, all components of MetS were significantly associated with albuminuria.

Albuminuria and proteinuria are the early warning signs of chronic kidney disease [61]. Following change in glomerular permeability or inadequate tubular reabsorption of the filtered proteins, glomerular filtration of plasma proteins is elevated and causes the proteinuria [67]. The association between albuminuria/proteinuria with obesity, particularly central obesity, was found in recent studies [68–70]. The present meta-analysis identified that fat distribution has a critical role in albuminuria/proteinuria, as abdominal, not general obesity was a risk factor for these

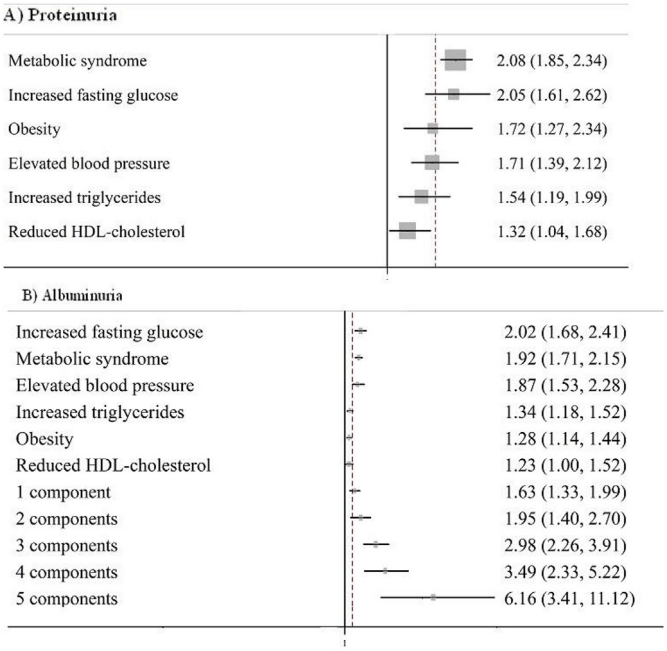

Fig. 4. The comparison of the overall risk of proteinuria (A) and albuminuria (B) associated with the MetS, its individual components and the number of MetS components.

conditions [71]. Mechanistically, greater glucagon levels, glomerular hyperfiltration, and obesity-related inflammation, which in turn, results in insulin resistance, are some of the probable mechanisms underlying the association between obesity and proteinuria [68]. Insulin resistance and inflammation are associated with endothelial dysfunction, reduced synthesis of endothelial nitric oxide, and worsening of renal hemodynamic function, which led to hypertension, podocytes injury, and consequently proteinuria/albuminuria [60]. Also, insulin resistance is associated with overproduction of low-density lipoprotein (LDL)-cholesterol, hypertriglyceridemia, sodium retention, activation of sympathetic nervous system, reduction of Na+, K + -ATPase activity and increase in GFR, which may led to impaired mitochondrial function and kidney cell damage [60,72]. Elevated blood pressure and hyperglycemia are associated with increased risk of renal insufficiency through the inflammation, vascular endothelial dysfunction, increased oxidative stress and advanced glycation end products (AGE) [18]. Furthermore, the MetS components especially dyslipidemia, probably induces kidney damage by increasing of glomerulosclerosis [36].

Large pooled sample size and detailed subgroup analysis were the chief strength of the present study. Additionally, this meta-analysis compared the magnitude of the risk of albuminuria/proteinuria conveyed by MetS, each component of MetS separately, and the number of MetS components, which might be helpful for adopting the best approach for identifying people at risk of early kidney damage, and thus, prevention of CKD and ESRD incidence. However, similar to other meta-analyses, our study has several limitations. First, the present meta-analysis has focused only on papers published in English; the ones that reported in other languages may affect the present results; although publication bias was not significant in most analyses. Second, the presence of heterogeneity in the pooled results limited the interpretation of our findings. In the stratified analysis the sources of heterogeneity for proteinuria were found to be various definitions of MetS, race, sex and background disease. Besides, in albuminuria analyses, different definitions of MetS and underlying disease were the sources of heterogeneity. Third, what also is important to be considered is that the majority of included studies in this meta-analysis were cross-sectional in design, which are more prone to selection and recall bias than a cohort studies.

In conclusion, the present meta-analysis showed that there was a noticeable association between MetS, its components and the risk of proteinuria/albuminuria, while reduced HDL-cholesterol had no significant relationship albuminuria. Among individual components of the syndrome, most predictor factors for development of albuminuria were hyperglycemia and hypertension, while hyperglycemia and obesity were more essential risk factors for proteinuria. Therefore, early detection, management and ultimately prevention of MetS and its single traits should become an important approach for prevention of albuminuria/proteinuria and subsequently CKD progression.

Conflicts of interest

The authors declared no conflicts of interest.

Sources of support

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.12.006.

References

[1] Ninomiya T, et al. Proteinuria and stroke: a meta-analysis of cohort studies. Am J Kidney Dis 2009;53(3):417–25.
[2] Leong A, et al. Long-term intra-individual variability of albuminuria in type 2 diabetes mellitus: implications for categorization of albumin excretion rate. BMC Nephrol 2017;18(1):355.
[3] van der Velde M, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011;79(12):1341–52.
[4] Sun K, et al. Fatty liver index, albuminuria and the association with chronic kidney disease: a population-based study in China. BMJ Open 2018;8(1). e019097.
[5] Bonnet F, et al. Waist circumference and the metabolic syndrome predict the development of elevated albuminuria in non-diabetic subjects: the DESIR Study. J Hypertens 2006;24(6):1157–63.
[6] Choi HS, Ryu SH, Lee KB. The relationship of microalbuminuria with metabolic syndrome. Nephron Clin Pract 2006;104(2). c85–93.
[7] Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7). e1000097.
[8] Wells G, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
[9] Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[10] DerSimonian R, Laird N. Meta-analysis in clinical trials control clin trials 7: 177–188. 1986. Find this article online.
[11] Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[12] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics; 1994. p. 1088–101.
[13] Tozawa M, et al. Metabolic syndrome and risk of developing chronic kidney disease in Japanese adults. Hypertens Res 2007;30(10):937–43.
[14] Watanabe H, et al. Metabolic syndrome and risk of development of chronic kidney disease: the Niigata preventive medicine study. Diabetes Metab Res Rev 2010;26(1):26–32.
[15] Nishikawa K, et al. Risk of chronic kidney disease in non-obese individuals with clustering of metabolic factors: a longitudinal study. Intern Med 2015;54(4):375–82.
[16] Ryoo JH, et al. Clinical associations between metabolic syndrome and the development of microalbuminuria in Korean men. Diabetes Res Clin Pract 2015;107(3):407–14.
[17] Lucove J, et al. Metabolic syndrome and the development of CKD in American Indians: the strong heart study. Am J Kidney Dis 2008;51(1):21–8.
[18] Viazzi F, et al. Metabolic syndrome, serum uric acid and renal risk in patients

with T2D. PLoS One 2017;12(4). e0176058.
[19] Duran-Perez EG, et al. Treatment of metabolic syndrome slows progression of diabetic nephropathy. Metab Syndrome Relat Disord 2011;9(6):483–9.
[20] Iwasaki T, et al. Neither the presence of metabolic syndrome as defined by the IDF guideline nor an increased waist circumference increased the risk of microvascular or macrovascular complications in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2008;79(3):427–32.
[21] Kim JK, et al. High pulse pressure and metabolic syndrome are associated with proteinuria in young adult women. BMC Nephrol 2013;14:45.
[22] Buranakitjaroen P, Phoojaroenchanachai M, Saravich S. Microalbuminuria in Thai essential hypertensive patients. J Int Med Res 2007;35(6):836–47.
[23] Lee JE, et al. Association of metabolic syndrome with microalbuminuria in non-hypertensive type 2 diabetic patients. Nephron Clin Pract 2007;106(3). c98–103.
[24] Hao Z, et al. The association between microalbuminuria and metabolic syndrome in the general population in Japan: the Takahata study. Intern Med 2007;46(7):341–6.
[25] Hanai K, Babazono T, Iwamoto Y. Renal manifestations of metabolic syndrome in type 2 diabetes. Diabetes Res Clin Pract 2008;79(2):318–24.
[26] Chiowanich P, et al. Prevalence and risk factors of microalbuminuria in patient with diabetic mellitus at northern part referral hospital in Thailand. Diabetes and Metabolic Syndrome: Clin Res Rev 2009;3(3):152–4.
[27] Aekplakorn W, Srivanichakorn S, Sangwatanaroj S. Microalbuminuria and metabolic risk factors in patients with type 2 diabetes in primary care setting in Thailand. Diabetes Res Clin Pract 2009;84(1):92–8.
[28] Gojaseni P, et al. Prevalence and risk factors of microalbuminuria in Thai nondiabetic hypertensive patients. Vasc Health Risk Manag 2010;6:157–65.
[29] Chen SC, et al. Association of metabolic syndrome and albuminuria with cardiovascular risk in occupational drivers. Int J Mol Sci 2013;14(11): 21997–2010.
[30] Jiang L, et al. Metabolic syndrome, C-reactive protein and microalbuminuria in a rural Chinese population: a cross-sectional study. BMC Nephrol 2013;14: 118.
[31] Huang JC, et al. Association of relatives of hemodialysis patients with metabolic syndrome, albuminuria and Framingham Risk Score. PLoS One 2014;9(5). e96362.
[32] Chen F, et al. Albuminuria: prevalence, associated risk factors and relationship with cardiovascular disease. J Diabetes Investig 2014;5(4):464–71.
[33] Hong D, et al. Metabolic syndrome without diabetes or hypertension still necessitates early screening for chronic kidney disease: information from a Chinese national cross-sectional study. PLoS One 2015;10(7).
[34] Li XH, et al. Association of microalbuminuria with metabolic syndrome among aged population. BioMed Res Int 2016;2016:9241278.
[35] Cho H, Kim JH. Prevalence of microalbuminuria and its associated cardiometabolic risk factors in Korean youth: data from the Korea National Health and Nutrition Examination Survey. PLoS One 2017;12(6). e0178716.
[36] Chen J, et al. Association between metabolic syndrome and chronic kidney disease in a Chinese urban population. Clin Chim Acta 2017;470:103–8.
[37] Isomaa B, et al. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. Diabetologia 2001;44(9):1148–54.
[38] Nand N, et al. Evaluation of renal functions in patients having metabolic syndrome in Asian Indian cohort. J Indian Acad Clin Med 2015;16(1):33–8.
[39] Hoy WE, et al. Renal disease, the metabolic syndrome, and cardiovascular disease. Ethn Dis 2006;16(2 Suppl 2). S2-46-51.
[40] Stengel B, et al. High prevalence of chronic kidney disease in La Réunion island and its association with the metabolic syndrome in the non-diabetic population: La Réunion Diabetes (REDIA) Study. Diabetes Metab 2007;33(6): 444–52.
[41] Messerli AW, et al. Relation of albumin/creatinine ratio to C-reactive protein and to the metabolic syndrome. Am J Cardiol 2003;92(5):610–2.
[42] Sumaili EK, et al. Screening for proteinuria and chronic kidney disease risk factors in Kinshasa: a world kidney day 2007 study. Nephron Clin Pract 2008;110(4):c220–8.
[43] Hoehner CM, et al. Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. J Am Soc Nephrol 2002;13(6):1626–34.
[44] Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANES III. Am J Hypertens 2003;16(11 Pt 1):952–8.
[45] Chen J, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med 2004;140(3):167–74.
[46] Thorn LM, et al. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28(8):2019–24.
[47] Abdul-Ghani M, et al. Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome. Isr Med Assoc J 2006;8(6):378–82.
[48] Franciosi M, et al. Identifying patients at risk for microalbuminuria via interaction of the components of the metabolic syndrome: a cross-sectional analytic study. Clin J Am Soc Nephrol 2007;2(5):984–91.
[49] Bianchi C, et al. The metabolic syndrome is related to albuminuria in Type 2 diabetes. Diabet Med 2008;25(12):1412–8.
[50] Nguyen S, et al. Being overweight modifies the association between cardiovascular risk factors and microalbuminuria in adolescents. Pediatrics 2008;121(1):37–45.
[51] Rodilla E, et al. Association between serum uric acid, metabolic syndrome and microalbuminuria in previously untreated essential hypertensive patients. Med Clínica 2009;132(1):1–6.
[52] Anvari MS, et al. Potential link of microalbuminuria with metabolic syndrome in patients undergoing coronary angiography. Arch Med Res 2009;40(5): 399–405.
[53] Sanad M, Gharib A. Evaluation of microalbuminuria in obese children and its relation to metabolic syndrome. Pediatr Nephrol 2011;26(12):2193–9.
[54] Esteghamati A, et al. Metabolic syndrome is independently associated with microalbuminuria in type 2 diabetes. Acta Diabetol 2010;47(2):125–30.
[55] Ferraro PM, et al. Metabolic syndrome, cardiovascular disease, and risk for chronic kidney disease in an Italian cohort: analysis of the INCIPE study. Metab Syndrome Relat Disord 2011;9(5):381–8.
[56] Gutiérrez-Repiso C, et al. Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study. Clin Sci 2013;124(4): 269–77.
[57] Sipahioglu MH, et al. Relationships between metabolic syndrome, microalbuminuria, and C-reactive protein in Turkish kidney transplant recipients. Transplant Proc 2015;47(5):1408–12.
[58] Billow A, et al. Prevalence and clinical profile of metabolic syndrome among type 1 diabetes mellitus patients in southern India. J Diabetes Complicat 2015;29(5):659–64.
[59] Greenberg S, et al. Exercise-induced albuminuria is related to metabolic syndrome. Am J Physiol Renal Physiol 2016;310(11):F1192–6.
[60] Raikou VD, Gavriil S. Metabolic syndrome and chronic renal disease. Diseases 2018;6(1):12.
[61] Lee IT, et al. Aggravation of albuminuria by metabolic syndrome in type 2 diabetic Asian subjects. Diabetes Res Clin Pract 2008;81(3):345–50.
[62] Kang YU, et al. Metabolic syndrome and chronic kidney disease in an adult Korean population: results from the Korean National Health Screening. PLoS One 2014;9(5). e93795.
[63] Lee HO, et al. Association between metabolic syndrome and microalbuminuria in Korean adults. Korean J Fam Med 2015;36(2):60–71.
[64] Navaneethan SD, et al. Metabolic syndrome, ESRD, and death in CKD. Clin J Am Soc Nephrol 2013;8(6):945–52.
[65] Oda E, Kawai R. Low-density lipoprotein (LDL) cholesterol is cross-sectionally associated with preclinical chronic kidney disease (CKD) in Japanese men. Intern Med 2010;49(8):713–9.
[66] Leoncini G, et al. Metabolic syndrome and chronic kidney disease in high-risk Italian hypertensive patients: the I-DEMAND study. J Nephrol 2012;25(1): 63–74.
[67] El-Bassossy HM, Shaltout HA. Allopurinol alleviates hypertension and proteinuria in high fructose, high salt and high fat induced model of metabolic syndrome. Transl Res 2015;165(5):621–30.
[68] Kashif W, et al. Proteinuria: how to evaluate an important finding. Cleve Clin J Med 2003;70(6):535–7.
[69] Mulyadi L, et al. Body fat distribution and total body fat as risk factors for microalbuminuria in the obese. Ann Nutr Metabol 2001;45(2):67–71.
[70] Basdevant A, et al. Microalbuminuria and body fat distribution in obese subjects. Int J Obes Relat Metab Disord: journal of the International Association for the Study of Obesity 1994;18(12):806–11.
[71] Basdevant A, et al. Microalbuminuria and body fat distribution in obese subjects. Int J Obes Relat Metab Disord : journal of the International Association for the Study of Obesity 1994;18(12):806–11.
[72] Gluba A, et al. Metabolic syndrome and renal disease. Int J Cardiol 2013;164(2):141–50.