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A Challenging Interaction of Chronic Kidney Disease With Other Metabolic Disorders

Paradoxes in Cardiometabolic Risk Factors

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Introduction. Controversial findings are reported on the risk of cardiovascular disease in chronic kidney disease (CKD). There are some interactions between CKD and other metabolic disorders including metabolic syndrome (MS) and obesity regarding coronary heart disease (CHD) outcomes.

Materials and Methods. A total of 2823 men and 3684 women aged 30 years and older, without cardiovascular disease, were followed for 10 years. Multivariable adjusted hazard ratio of CHD was estimated for those who developed CKD, MS or both by sex and body mass index levels below and above 27 kg/m^2. The interaction term of CKD and MS and also CKD-MS components were assessed in the Cox proportional hazard models as well.

Results. Chronic kidney disease without MS, showed a significant effect on CHD only in participants with low body mass index (hazard ratio, 2.06; 95% confidence interval, 1.28 to 3.31 in the men and hazard ratio, 2.56; 95% confidence interval, 1.04 to 6.31 in the women). The joint effect of CKD and MS decreased to one-third of their multiplicative effect in this subgroup, indicating a negative interaction between CKD, MS, and Obesity. The same interaction was observed between CKD and hypertension in both sexes and CKD and type 2 diabetes mellitus in the men.

Conclusions. Our results showed that CKD was an independent risk factor for CHD only in nonobese individuals; however, its risk was wiped out when joined to MS. Following the concept of "obesity paradox," the term of "risk factors paradox" also needs more attention.

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INTRODUCTION

Cardiovascular disease (CVD) is currently the leading cause of death worldwide, and current statistics show a universal 8% annual increase in the rate of coronary heart disease (CHD). It is therefore important to understand the true effect of the ever-increasing list of CVD risk factors, especially the more well-established ones. Two such risk factors are the metabolic syndrome (MS) and chronic kidney disease (CKD).[1-3]

Also known as insulin resistance syndrome, the MS encompasses several important CVD risk factors, including hyperglycemia, abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, and hypertension.[4] Chronic kidney disease is a globally increasing public health

concern and is closely linked to both MS and CVD; most common causes of CKD in the world today are obesity, diabetes, and hypertension,[5-7] all of which are components of the MS and risk factors for CVD. Conflicting evidence have been found for the role of CKD on CVD; some studies have shown that CKD is an independent risk factor for CVD,[8-13] while others have not.[14-16]

Furthermore, obesity paradox is a concern of interest in patients with CKD, which may modify the relationship of CKD with other metabolic disorders.[17-19] Understanding the interaction between CKD and MS, as well as components of MS, in different levels of body mass index (BMI) is therefore an important step in planning preventive strategies to deal with the rise in CVD. This study aims to study this interaction.

MATERIALS AND METHODS

Study Population

The Tehran Lipid and Glucose Study (TLGS) is a prospective population-based cohort study carried out on a representative population in district 13 of Tehran, the capital of Iran. The aim of the TLGS is determining the prevalence and incidence of noncommunicable diseases and their risk factors. The cross-sectional phase of the TLGS lasted from March 1999 to August 2001; the details of design and sampling method have been previously published.[20] Of the 15005 participants aged 3 years and greater at baseline, 5630 participants received education for lifestyle modification.[21] We selected all participants aged 30 years old and greater at baseline (n = 8071) and excluded those with a history of CVD or cancer (n = 483), and those with missing baseline data (n = 376) and missing follow-up data (n=705): the study population consisted of the remaining 6507 particiapants (2823 men and 3684 women) with a median follow-up of 10.1 years. The ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, approved the study protocol and informed written consent was obtained from each participant.

Clinical and Laboratory Measurements

At baseline, demographic data and medical, social, habitual, and family history were collected by a trained physician using a pretested questionnaire. Anthropometric measurements including weight, height, and waist circumference, as well as blood pressure were also measured based on the standard protocols. A fasting blood sample was taken from all participants and fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and creatinine levels were measured on the day of blood sampling. Two-hour post-challenge plasma glucose was measured in all except in diabetic patients. The details of laboratory measurements and data gathering have been published elsewhere.[21]

The primary outcome of the study was the first CHD event, defined as definite myocardial infarction (diagnosed by positive electrocardiography and biomarkers), probable myocardial infarction (positive electrocardiography plus cardiac symptoms or signs with missing biomarkers or positive electrocardiography plus equivocal biomarkers), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive electrocardiography findings with normal biomarkers) or angiographically proven CHD and CHD death.[22,23]

Definitions

Type 2 diabetes mellitus was defined as a fasting plasma glucose of 7 mmol/L and higher ($\geq$ 126 mg/dL) or 2-hour post-challenge glocuse level of 11.1 mmol/L and higher ($\geq$ 200 mg/dL) or current use of glucose-lowering medications. Hypertension was defined as systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg and higher or current use of antihypertensive medications. Smoking was defined as current or past use of cigarettes or other smokes (water-pipes and pipes). Family history of premature CVD was defined as any prior diagnosis of CVD by a physician in male and female first-degree relatives under 55 and 65 years, respectively. Chronic kidney disease was considered as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, which was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[24,25]

Metabolic syndrome definition was based on the Report of the Iranian National Committee of Obesity.[26] According to this definition, at least 3 of the following was required: (1) elevated waist circumference to 95 cm and larger (men and women); (2) elevated triglyceride level to 150

mg/dL and higher (≥ 1.7 mmol/L), or medical treatment for elevated triglycerides; (3) reduced high-density lipoprotein cholesterol to lower than 40 mg/dL (1.0 mmol/L) in males and less than 50 mg/dL (1.3 mmol/L) in females; (4) elevated blood pressure, systolic blood pressure of 130 mm Hg or diastolic pressure of 85 mm Hg and higher or both, or antihypertensive medication; and (5) elevated fasting glucose of 100 mg/dL and higher or antidiabetic medication.

Research Design and Methods

At baseline, the participants were divided based on the presence or absence of CKD and MS into 4 groups: group 1, absence of both CKD and MS (control group); group 2, presence of CKD and absence of MS (CKD group); group 3, absence of CKD and presence of MS (MS group); and group 4, presence of both CKD and MS (CKD-MS group). Baseline characteristics are presented by these 4 groups in both sexes. The four groups were compared for baseline characteristics using the 1-way analysis of variance and the chi-square test for continuous and categorical variables, respectively. The groups were compared two by two considering correction for multicomparison.

Hazard ratios (HRs) were calculated for CKD, MS, and CKD-MS groups compared with the control group on incidence of CHD in crude, age-adjusted, and multivariable proportional hazards Cox regression models. Multivariable regression models were adjusted for variables that might confound the relationship between CHD and CKD-MS groups including age, education, smoking, total cholesterol, family history of cardiovascular diseases, educational intervention, and propensity score of follow-up. We also ran models including the interaction term of CKD and MS and calculated the significance of multiplicative interaction between CKD and MS adjusted for confounders. The interaction of CKD with components of MS was also calculated.

In this study, a propensity score was used for considering the differences between participants with and without follow-up data regarding their baseline variables. Propensity score estimates the probability of being lost-to-follow-up according to the baseline variables of any individual.[27] We reduced the selection bias, resulting from lost-to-follow up, by including the propensity score as a covariate in the model. We did the analysis in 2 levels of BMIs less than 27 kg/m^2 and 27 kg/m^2 and higher, as the median of BMI in our population was 27.12 kg/m^2. All analyses were carried out using the Stata (version 10.0, StataCorp LP, College Station, TX, USA). Results were presented as mean ± standard deviation for continuous variables and percentage for categorical variables. A *P* value less than .05 was considered significant.

RESULTS

Baseline characteristics are presented (Table 1). Generally, all baseline variables were significantly different among the 4 groups. The mean age was 48.4 years for the men and 46.7 years for the women; however, the CKD groups were older than those without CKD by more than 15 years.

A total of 545 first CHD events occurred in 3263.6 person-year of follow-up. The Figure shows the age-adjusted CHD event-free cumulative survival with regards to the CKD and MS groups; generally, the MS group had the lowest CHD-free survival. In a multivariate regression model, CKD (without MS) showed HRs of 2.06 (95% confidence interval [CI], 1.28 to 3.31) and 2.56 (95% CI, 1.04 to 6.31) for CHD events in the men and the women with a BMI lower than 27 kg/m^2, respectively; however, it did not show any significant effect on CHD in those with higher BMIs. On the other hand, MS (without CKD) had significant HRs in general; nevertheless, HRs for a BMI of 27 27 kg/m^2 and higher was less than the corresponding HRs for lower BMIs (Table 2).

The results showed that CKD and MS had a significant negative interaction for CHD incidence in the men and women with a lower BMI level (HRs for CKD-MS interaction term, < 1.0; $P < .05$ in both sexes); however the interaction was not significant in those with a higher BMI (Table 3). To investigate the role of each MS component in this interaction, we tested the interaction between MS components and CKD separately, adjusted for other components (Supplementary Tables 1 to 5). These analyses showed that the most important negative interaction was between CKD with elevated fasting glucose (HR, 0.46; 95% CI, 0.21 to 1.01) in the men and with elevated blood pressure (HR, 0.19; 95% CI, 0.07 to 0.51) in the women with lower BMI level. We then checked the interaction of CKD with type 2 diabetes mellitus and hypertension

Table 1. Baseline Characteristics Study Population in 4 Groups of Patients With and Without Each or Both Chronic Kidney Disease (CKD) and Metabolic Syndrome (MS) by Sex*

Variables	All	Patient Groups			
		Control	CKD	MS	CKD and MS
Men					
Number of patients	2823	1488	209	899	227
Age, y	48.39 ± 13.18	44.21 ± 11.60[a]	63.79 ± 10.81[b]	47.85 ± 11.45[c]	63. 78 ± 8.98[d]
Education	1890 (67.0)	1097 (73.8)[a]	96 (45.9)[b]	605 (67.5)[c]	92 (40.5)[b,d]
Smoking	1288 (45.9)	715 (48.3)[a]	84 (40.4)[a,b]	395 (44.1)[a,b,c]	94 (41.8)[a,b,c,d]
Total cholesterol, mg/dL	209.96 ± 42.69	202.05 ± 41.02[a]	213.84 ± 38.39[b]	218.48 ± 42.81[b,c]	224.58 ± 45.97[d]
MS components					
Elevated waist circumference	970 (34.4)	185 (12.4)[a]	26 (12.4)[a,b]	600 (66.7)[c]	159 (70.0)[c,d]
Elevated triglyceride	1595 (56.5)	549 (36.9)[a]	52 (24.9)[b]	808 (89.9)[c]	186 (81.9)[d]
Reduced high-density lipoprotein	1824 (64.7)	800 (53.9)[a]	76 (36.4)[b]	771 (86.0)[c]	177 (78.3)[d]
Elevated blood pressure	1090 (38.8)	243 (16.4)[a]	99 (47.4)[b]	565 (63.1)[c]	183 (81.3)[d]
Elevated fasting glucose	786 (27.8)	155 (10.4)[a]	45 (21.5)[b]	448 (49.8)[c]	138 (60.8)[d]
Glomerular filtration rate, mL/min	73.09 ± 13.33	77.73 ± 10.60[a]	52.82 ± 7.19[b]	75.36 ± 10.20[c]	52.41 ± 6.87[b,d]
Coronary heart disease incident, per 1000 person-years	316 (11.2)	88 (5.9)	43 (20.6)	138 (15.4)	47 (20.7)
Women					
Number of patients	3684	1797	272	1108	507
Age, y	46.67 ± 11.76	40.68 ± 9.05[a]	56.42 ± 10.71[b]	47.68 ± 9.56[c]	60.49 ± 9.06[d]
Education	1823 (49.6)	1222 (68.0)[a]	73 (26.9)[b]	443 (40.20)[c]	85 (16.8)[d]
Smoking	250 (6.8)	114 (6.4)[a]	31 (11.5)[b]	60 (5.40)[a,c]	45 (8.9)[a,b,d]
Total cholesterol, mg/dL	221.75 ± 47.14	204.37 ± 39.67[a]	232.02 ± 45.74[b]	232.82 ± 46.87[b,c]	253.63 ± 47.39[d]
MS components					
Elevated waist circumference	1356 (37.0)	218 (12.2)[a]	56 (20.6)[b]	717 (64.80)[c]	365 (72.3)[d]
Elevated triglyceride	1925 (52.3)	451 (25.1)[a]	84 (30.9)[a,b]	954 (86.10)[c]	436 (86.0)[c,d]
Reduced high-density-lipoprotein	2741 (74.5)	1164 (64.8)[a]	134 (49.6)[b]	1010 (91.20)[c]	433 (85.4)[d]
Elevated blood pressure	1508 (41.1)	269 (15.0)[a]	93 (34.3)[b]	737 (66.80)[c]	409 (80.8)[d]
Elevated fasting glucose	1004 (27.3)	120 (6.7)[a]	33 (12.1)[b]	566 (51.10)[c]	285 (56.2)[c,d]
Glomerular filtration rate, mL/min	70.18 ± 12.72	76.15 ± 10.10[a]	53.87 ± 5.95[b]	72.48 ± 8.95[c]	52.74 ± 5.88[b,d]
Coronary heart disease events	229 (6.2)	36 (2.0)	18 (6.6)	95 (8.6)	80 (15.8)

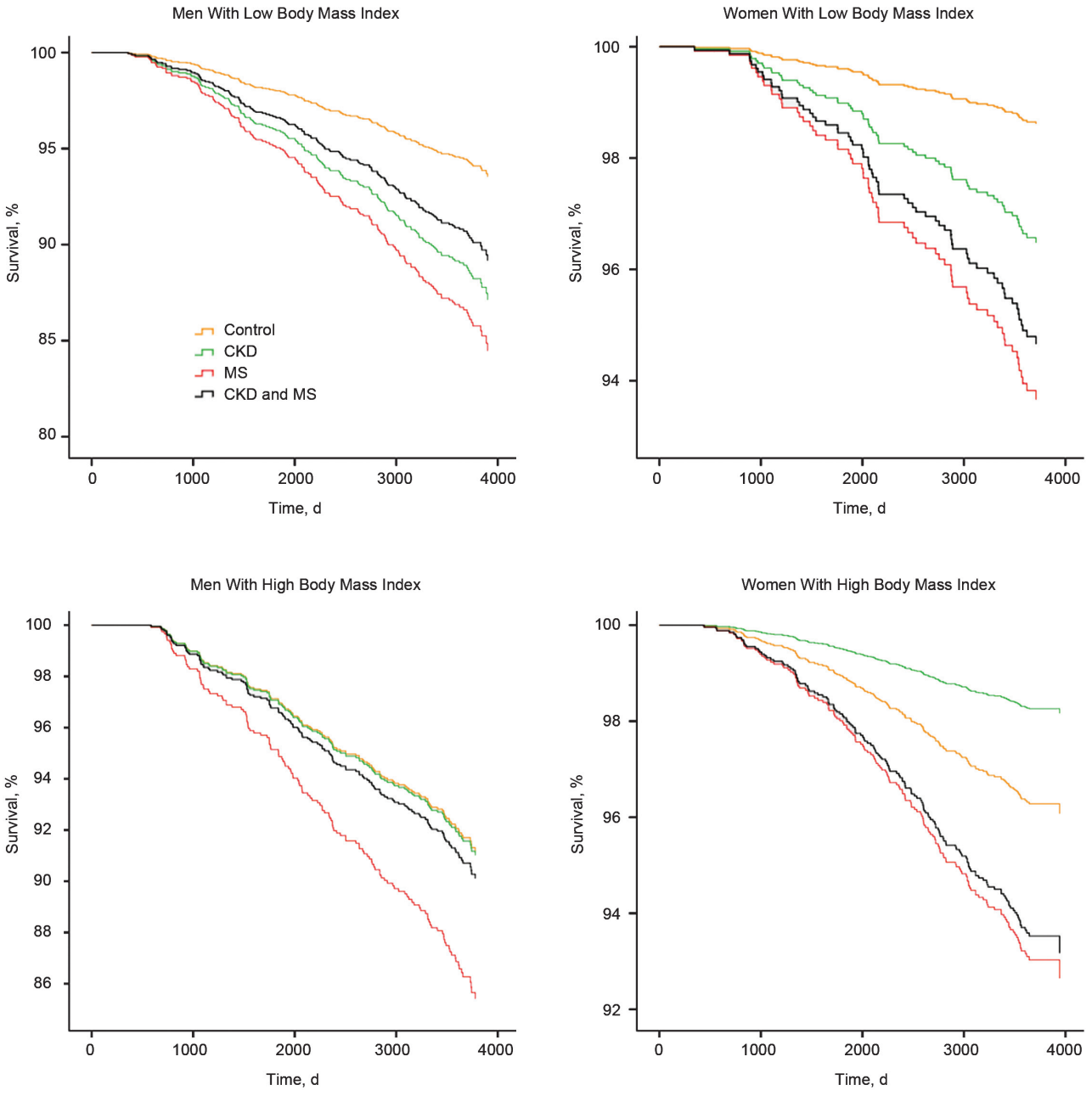
*Data are shown as mean ± standard deviation or frequency (percentage). The same small letters shows different between groups.

in those with lower BMI levels and found that CKD had a significant interaction with type 2 diabetes mellitus (HR, 0.31; 95% CI, 0.13 to 0.72) in the men and those with hypertension in both sexes (HR, 0.33; 95% CI, 0.15 to 0.72 and HR, 0.11; 95% CI, 0.04 to 0.30 in the men and the women, respectively; Table 4).

DISCUSSIONS

With the CVD pandemic now upon us, besides the growing population of older patients, the presence of concomitant metabolic conditions such as CKD, MS, type 2 diabetes, and hypertension is an area of growing concern. Current literature recognizes all of the conditions mentioned as independent risk factors for CHD,[3-13] but there is less evidence regarding the simultaneous effect of these comorbidities. The present study confirms that CKD is an independent risk factor for CHD incidence in nonobese men and women; however, this effect was not sustained among obese subjects (BMI ≥ 27 kg/m^2). Additionally, although the presence of MS was also confirmed as an independent risk factor for CHD, this risk was about 1.5- to 2.0-fold in nonobese compared to obese individuals. Interestingly, the risk associated with CKD in nonobese individuals disappeared in those with MS, implying that the presence of MS may be protective against CHD in this specific population.

Some of our findings are mirrored in a number of studies looking at survival and CVD events in established at-risk populations, such as those with CKD, on dialysis, and with heart failure,[17,28-30] which are the basis for the term "obesity paradox." However, concerning the negative interaction between CKD and MS and also CKD with hypertension and diabetes in nonobese patients,



Age-adjusted coronary heart disease (CHD) event-free cumulative survival of 4 groups of patients with and without each or both chronic kidney disease (CKD) and metabolic syndrome (MS) by the body mass index level.

our finding seems to confirm the presence of a "risk factor paradox"; the point that some of the components of MS, namely obesity, dyslipidemia, and hypertension, have previously been reported to paradoxically affect outcome in similar high-risk populations.[31] The meaning of these findings is that the risk associated with the presence of both CKD and MS was not only noncumulative, but also significantly reversed. These results are contrary to Agarwal and colleagues' results which indicated an additive interaction between CKD and MS for incident cardiovascular events[32]; however, they did not do the analysis by sex and obesity as we did.

The term "reverse epidemiology" has been coined to address such situations in which well-known risk factors are paradoxically associated with better outcome in subjects suffering chronic diseases.[33,34] This phenomenon has been a subject

Table 2. Cox Regression Models for Coronary Heart Disease Events by Body Mass Index and Sex*

Factor and Model	Hazard ratio (95% Confidence Interval) for Patient Groups			
	Control	CKD	MS	CKD and MS
Low body mass index				
Men				
Crude	1 (reference)	4.60 (3.06 to 6.89)	3.02 (2.09 to 4.38)	4.13 (2.43 to 7.04)
Age adjusted	1 (reference)	2.07 (1.30 to 3.28)	2.47 (1.70 to 3.60)	1.80 (1.01 to 3.20)
Multivariable adjusted†	1 (reference)	2.06 (1.28 to 3.31)	2.52 (1.71 to 3.73)	1.71 (0.95 to 3.09)
Women				
Crude	1 (reference)	7.65 (3.65 to 16.05)	7.85 (4.04 to 15.25)	14.31 (7.36 to 27.83)
Age adjusted	1 (reference)	2.76 (1.18 to 6.47)	4.67 (2.33 to 9.36)	4.21 (1.85 to 9.59)
Multivariable adjusted†	1 (reference)	2.56 (1.04 to 6.31)	4.68 (2.20 to 9.95)	3.93 (1.62 to 9.52)
High body mass index	1 (reference)			
Men				
Crude	1 (reference)	2.66 (1.13 to 6.25)	2.43 (1.51 to 3.90)	3.86 (2.21 to 6.74)
Age adjusted	1 (reference)	1.10 (0.45 to 2.68)	1.93 (1.19 to 3.12)	1.36 (0.73 to 2.53)
Multivariable adjusted†	1 (reference)	1.02 (0.41 to 2.50)	1.70 (1.05 to 2.78)	1.13 (0.60 to 2.13)
Women				
Crude	1 (reference)	1.16 (0.40 to 3.36)	3.05 (1.89 to 4.91)	6.25 (3.82 to 10.22)
Age adjusted	1 (reference)	0.50 (0.17 to 1.49)	2.09 (1.28 to 3.40)	2.04 (1.16 to 3.58)
Multivariable adjusted†	1 (reference)	0.46 (0.16 to 1.37)	1.90 (1.16 to 3.13)	1.76 (1.00 to 3.10)

*CKD indicates chronic kideny disease and MS, metabolic syndrome.
†Adjustment for age, education, smoking, high total colostrol, family history of cardiovascular disease, intervention, and propensity score of follow-up.

Table 3. Cox Regression Models for Coronary Heart Disease Events Including Interaction of Chronic Kidney Disease (CKD) with Metabolic Syndrome (MS) by Body Mass Index and Sex*

Factor	Men		Women	
	Hazard ratio (95% Confidence Interval)	*P*	Hazard ratio (95% Confidence Interval)	*P*
Low body mass index				
CKD	2.06 (1.28 to 3.31)	.003	2.56 (1.04 to 6.31)	.04
MS	2.52 (1.71 to 3.73)	< .001	4.68 (2.20 to 9.95)	< .001
CKD × MS	0.33 (0.16 to 0.66)	.002	0.33 (0.12 to 0.90)	.03
High body mass index				
CKD	1.02 (0.41 to 2.50)	.97	0.46 (0.16 to 1.37)	.17
MS	1.70 (1.05 to 2.78)	.03	1.90 (1.16 to 3.13)	.01
CKD × MS	0.65 (0.25 to 1.69)	.38	2.00 (0.65 to 6.15)	.23

*Adjustment for age, education, smoking, high total colostrol, family history of cardiovascular disease, intervention, and propensity score of follow-up.

Table 4. Cox Regression Models for Coronary Heart Disease Events Including Interaction of Chronic Kidney Disease (CKD) with Diabetes Mellitus and Hypertension by Sex*

Factor	Men		Women	
	Hazard ratio (95% Confidence Interval)	*P*	Hazard ratio (95% Confidence Interval)	*P*
Diabetes				
CKD	1.72 (1.12 to 2.64)	.01	1.62 (0.72 to 3.67)	.24
Diabetes	2.72 (1.69 to 4.38)	< .001	5.88 (2.85 to 12.14)	< .001
CKD × diabetes	0.31 (0.13 to 0.72)	.007	0.82 (0.30 to 2.20)	.69
Hypertension				
CKD	1.69 (1.07 to 2.66)	.02	3.08 (1.47 to 6.49)	.003
Diabetes	3.69 (2.25 to 6.05)	< .001	7.18 (3.48 to 14.80)	< .001
CKD × hypertension	0.33 (0.15 to 0.72)	.005	0.11 (0.04 to 0.30)	< .001

*Adjustment for age, education, smoking, high total colostrol, family history of cardiovascular disease, intervention, and propensity score of follow-up.

of debate among scientists since its introduction,[35] and while some describe it as a misleading and non-existent entity as it is currently described,[36] there are numerous reports of such observations among subjects with chronic diseases and especially wasting conditions.[31,37]

When trying to explain similar reverse epidemiology findings, other scientists have described the role of the "malnutrition-inflammation complex" in such conditions.[38,39] The main concept behind this theory is that the reason for this reverse epidemiology is not the beneficial effect of overnutrition and its markers, but the greater detrimental effect associates with undernutrition and its markers. Thus, while hypercholesterolemia, hypertension, and even diabetes are recognized CHD risk factors, in a population of patients suffering from a potentially wasting condition, these same factors are indicative of a better chance for survival. The fact that the negative interaction between CKD and MS was only observed in the nonobese group in our study supports this hypothesis.

The complexity of concomitant comorbidities requires great attention for identifying true risk factors. The points described here are observations of an association not causation, as is the limit of similarly designed studies. Another important limitation is the effect of confounding factors that we may have overlooked, such as inflammatory factors. Future studies can be designed to address these issues and shed further light on this topic.

CONCLUSIONS

Our results showed that CKD is an independent risk factor for CHD only in nonobese individuals; however, its risk was wiped out when joined to MS. Following the new concept of "obesity paradox" the term of "risk factors paradox" also needs more attention to explain findings like the 3-dimensional negative interaction among CKD, MS, and obesity found in the current study. Although these disorders may have some common pathological basis, there is insufficient knowledge of the underlying relationship among them and CVD.

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CONFLICT OF INTEREST

None declared.

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