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Usefulness of Microalbuminuria vs. the Metabolic Syndrome as a Predictor of Cardiovascular Disease in Women and Men > 40 Years of Age (From the Rancho Bernardo Study)

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Abstract

To examine the sex-specific contributions of the metabolic syndrome and microalbuminuria to cardiovascular disease (CVD) and coronary heart disease (CHD) mortality in community-dwelling older adults, between 1992–1995, 869 women and 575 men aged 40–96 years (mean 71) completed questionnaires, physical examinations, and fasting laboratory tests. Participants were followed over an average of 8 years. CVD and CHD mortality were analyzed using Cox proportional hazards models. At baseline, 267 participants had the Adult Treatment Panel III metabolic syndrome, 151 had microalbuminuria, and 34 had both. During follow up, there were 180 CVD deaths, including 83 CHD deaths. In women, microalbuminuria was associated with a 2-fold increased risk of CVD and CHD mortality ($p \leq 0.01$). Women with both microalbuminuria and the metabolic syndrome (n = 18) had a 3-fold increased risk of CVD mortality and a 5-fold increased risk of CHD mortality compared with women without either (n = 657). A significant interaction existed between microalbuminuria and the metabolic syndrome in the prediction of both CVD and CHD ($p = 0.021$). In men, neither the combination of the metabolic syndrome and microalbuminuria (n = 16), nor either alone, significantly increased the risk of CVD or CHD mortality. In conclusion, in this cohort, microalbuminuria and the metabolic syndrome together were a more powerful predictor of CVD mortality than either alone in women but not in men. Screening for microalbuminuria in older women may identify women at high risk for CVD mortality, beyond that conferred by risk factors included in the metabolic syndrome.

Keywords

Cardiovascular disease; Elderly; Metabolic syndrome; Microalbuminuria

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Background

The 1998 World Health Organization definition of the metabolic syndrome differs from Adult Treatment Panel III definition in its emphasis on insulin resistance and its inclusion of microalbuminuria [1,2]. Microalbuminuria is an independent risk factor for CVD, and cardiovascular and all-cause mortality in diabetics [3, 4], hypertensives, [5, 6, 7, 8] and the general population [4, 9, 10], but it is unclear whether microalbuminuria adds to the prediction of CVD mortality in those with the metabolic syndrome. The Adult Treatment Panel III definition of metabolic syndrome is more widely used in the USA, therefore we used this definition. We examined the sex-specific separate and joint contributions of the metabolic syndrome and microalbuminuria to CVD and CHD mortality and explored whether including microalbuminuria might improve the utility of the Adult Treatment Panel III metabolic syndrome in identifying in older, community-dwelling men and women at risk for CVD death.

Methods

The Rancho Bernardo Study, a cohort of largely Caucasian, middle to upper middle class, community-dwelling adults in southern California, was established in 1972; the details of the initial study have been described previously [11, 12]. Between 1992 and 1995, 80% (n = 1778) of surviving local residents participated in a research clinic visit focused on diabetes. The research protocol was approved by the institutional review board of the University of California, San Diego; all participants gave written informed consent.

A total of 879 women and 585 men, ages 40 to 96, completed a 2-hour oral glucose tolerance test, and had levels of fasting lipids, and urine albumin and creatinine measured. Only 20 participants (1.4%) had macroalbuminuria (urine albumin/creatinine ratio >300mg/g); these 10 men and 10 women were excluded as our aim was to examine the risk conferred by microalbuminuria (a urine albumin/creatinine ratio 30–300mg/g) [13] an earlier marker of kidney dysfunction; the remaining 869 women and 575 men form the basis for this report (Figure 1).

At the 1992–1995 visit, participants also completed standardized questionnaires about medical history including cardiovascular disease and medication use; the latter was validated by examination of pills and prescriptions brought to the clinic for that purpose. Information about current cigarette smoking, alcohol consumption (number of drinks per day during the last 2 weeks), and exercise was also obtained using standard questionnaires. Participants were asked about a history of physician-diagnosed myocardial infarction, angina, stroke, and claudication, and completed the Rose cardiovascular questionnaire [14].

Height and weight were measured using a calibrated stadiometer and balance-beam scale with participants wearing light clothing and no shoes. Systolic and diastolic blood pressures were measured twice in seated subjects after a five minute rest, using the Hypertension Detection and Follow-up Program protocol [15]. Body mass index was calculated as kg/m^2. Diabetes was defined according to the 1999 World Health Organization criteria [13]--fasting plasma glucose ≥ 7 mmol/L (126mg/dL) or 2-hour glucose after 75 g oral glucose tolerance test ≥ 11.1 mmol/L (200 mg/dL)--or if he or she was using diabetes medication (oral or insulin). People with missing information on the 2-hour glucose test and diabetes drug use were classified as having diabetes if they reported a history of physician-diagnosed diabetes even in the absence of an abnormal glucose. Fasting and 2-hour glucose was measured by the glucose oxidase method in a clinical laboratory. Fasting plasma cholesterol, triglyceride, and high density lipoprotein and low density lipoprotein cholesterol levels were measured in a Center for Disease Control Certified Lipid Research Clinic laboratory. Total cholesterol and triglyceride levels were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott

Laboratories, Irving, Texas). High density lipoprotein was measured after precipitation of the other lipoproteins with heparin and manganese chloride according to the standardized procedures of the Lipid Research Clinics manual [16], low density lipoprotein was estimated using the Friedewald formula [17].

The metabolic syndrome was defined using the 2001 Adult Treatment Panel III criteria [2] as three or more of the following: 1) abdominal obesity--waist circumference > 102 cm in men and > 88 cm in women; 2) hypertriglyceridemia--serum triglycerides ≥ 1.69 mmol/L (150 mg/dL); 3) low high density lipoprotein cholesterol--high density lipoprotein < 1.04 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women; 4) hypertension--systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg; 5) hyperglycemia--fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL). Participants reporting use of anti-hypertensive medications, and those with diabetes by World Health Organization 1999 criteria [13] were also categorized as meeting the hypertension and hyperglycemia criteria, respectively.

A single, clean-catch, untimed morning urine sample (usually second void of the day) was obtained, frozen, and shipped to the National Institute of Health laboratory (Phoenix, Arizona) of Dr. Peter Bennett. Urine albumin was measured using the Behring Nephelometer BNA. The inter-assay coefficient of variance was 4.5%. Urine creatinine was measured by the kinetic alkaline picrate method using the Ciba-Corning Express.

Vital status, determined annually by mailed questionnaire until 2003, was known for 94% of participants. Death certificates, available for 89% of decedents, were coded for the underlying cause of death by a certified nosologist using the International Classification of Disease—9th Revision. CHD deaths were those assigned codes between 410 and 414 (ischemic heart disease), including acute myocardial infarction (410), other acute and subacute forms of ischemic heart disease (411), old myocardial infarction (412), angina pectoris (413), and other forms of chronic ischemic heart disease (414). CVD deaths included all deaths assigned codes between 410 and 414 (above), and included conduction disorders (426), cardiac dysrhythmias (427), heart failure (428), cerebrovascular disease (430–438), and diseases of arteries, arterioles, and capillaries (440–448).

Most measures were normally distributed; serum triglycerides and the urine albumin/creatinine ratio were skewed; transformation was not necessary as categorical cutpoints were used. Sex-specific means were compared using ANalysis Of VAriance or Wilcoxon rank sum (if skewed) for continuous variables, and sex-specific prevalence was compared using the chi-squared statistic for categorical variables. Cox proportional hazards models were used to generate sex-specific hazard ratios (HR) with adjustment for: 1) age alone; 2) age plus prevalent CVD; 3) age plus microalbuminuria or metabolic syndrome; and 4) age plus prevalent CVD plus microalbuminuria or metabolic syndrome. Receiver operating curves using unadjusted logistic regression were performed to test whether adding microalbuminuria to metabolic syndrome improved prediction of CVD and CHD death. Statistical tests were 2-tailed, with statistical significance defined as $p<0.05$. SPSS (SPSS Inc. SPSS Base 11.0 for Windows) was used for all analyses.

Results

Baseline sex-specific characteristics and the sex-specific prevalence of metabolic syndrome and its components and microalbuminuria are summarized in Table 1. The mean age was 71 years. Hypertension was present in nearly 70% of men and women--more than twice as prevalent as any other component. Men were more likely than women to have the metabolic syndrome (22% vs. 16%, $p = 0.01$). Microalbuminuria was present in 151 participants (10%) and did not differ significantly by sex--89 women (10%) and 62 men (11%) ($p = 0.79$).

Although microalbuminuria was more common in those with metabolic syndrome (13% vs. 10%, respectively) and metabolic syndrome was more common in those with microalbuminuria (23% vs. 18%, respectively), these differences were not statistically significant (p = 0.18 for both).

Over a follow-up of 0.03 to 12 (mean 8) years, there were 180 CVD deaths (99 women, 81 men), including 83 (37 women and 46 men) CHD deaths; 11% of women versus 14% of men died due to CVD (p = 0.14 for sex difference), and 4% of women versus 8% of men died due to CHD (p = 0.004 for sex difference).

Metabolic syndrome was not significantly associated with CVD mortality in either sex (Table 2), nor was any individual metabolic syndrome component (data not shown). The metabolic syndrome was significantly associated with age-adjusted CHD mortality in women HR (95% CI) 1.99 (1.06–3.97), but not in men (sex interaction p = 0.03) (Table 2); the association in women was no longer significant in analyses adjusting for prevalent CVD (Table 2). No individual metabolic syndrome component was associated with age-adjusted CHD mortality in either sex (data not shown).

In contrast, microalbuminuria was associated with age-adjusted CVD mortality HR (95% CI) 2.31 (1.45–3.67), before and after adjustment for prevalent CVD, metabolic syndrome, or both (Table 2), but only in women (sex interaction p = 0.04) (Table 2). Microalbuminuria was also associated with age-adjusted CHD mortality in women HR (95% CI) 2.40 (1.15–5.02), but not in men (sex interaction p = 0.04), before and after adjustment for prevalent CVD, metabolic syndrome, or both (Table 2).

Women with both microalbuminuria and the metabolic syndrome had a 3-fold risk of CVD mortality HR (95% CI) 3.16 (1.34–7.43) (Figure 2A) and a 5-fold risk of CHD mortality HR (95% CI) 5.48 (1.80–16.64) (Figure 2B) compared to those with neither condition. A significant interaction existed between microalbuminuria and metabolic syndrome in the prediction of both CVD and CHD (p = 0.02). Associations did not differ by prevalent CVD (interaction p > 0.05 in each case), but tests did reveal a significant interaction between diabetes and microalbuminuria in the risk for CVD and CHD death (p = 0.02). Excluding women currently using estrogen did not materially change results. These associations were not seen in men.

Receiver operating curves using logistic regression were performed to test whether adding microalbuminuria to metabolic syndrome improved prediction of CVD and CHD death. In women only, the area under the curve (AUC) for the ability of both metabolic syndrome and microalbuminuria together to predict CVD death AUC (95% CI) 0.629 (0.575–0.683) was greater than either the metabolic syndrome alone AUC (95% CI) 0.551 (0.506–0.596) (p for difference < 0.001) or microalbuminuria alone AUC (95% CI) 0.590 (0.546–0.635) (p for difference = 0.03). In men, the AUC for the ability of the metabolic syndrome alone, microalbuminuria alone, or both together to predict CVD death did not differ significantly. For CHD death, results were similar in women, with the AUC for the ability of both metabolic syndrome and microalbuminuria together to predict CHD death showing a trend towards being greater than either metabolic syndrome or microalbuminuria alone, but the differences were not statistically significance (p for difference = 0.07 and 0.08, respectively), probably based on the smaller sample size. In men, the AUC for the ability of metabolic syndrome and microalbuminuria together to predict CHD death also suggested a trend towards being greater than metabolic syndrome alone (p for difference = 0.09).

Conclusions

Microalbuminuria is used by clinicians as both a screening and diagnostic test, primarily for diabetic nephropathy. The spot test for microalbuminuria is useful because of the simplicity

of its collection, a reduced collection error compared with timed urine specimens, and a strong correlation with twenty-four hour urinary albumin excretion rates [18, 19]. Age is an important predictor of albumin/creatinine ratio; the age-related decline in urine creatinine excretion results in a higher albumin/creatinine ratio in older people [20].

The findings of our study are consistent with many prior prospective studies in which microalbuminuria has been shown to be a powerful, graded, predictor of CVD [3, 4, 5, 6, 7, 8, 9, 10, 21, 22, 23]. Few studies have explored whether microalbuminuria adds to the risk of CVD mortality differentially in those with or without metabolic syndrome. In the only study of which we are aware, Ko and colleagues followed 5202 Chinese men and women with diabetes, and found that the World Health Organization definition was better than the Adult Treatment Panel III for predicting cardiovascular death, a difference they attributed to the inclusion of microalbuminuria in the World Health Organization definition [24].

The significant interaction ($p = 0.02$) between microalbuminuria and metabolic syndrome for the prediction of CVD or CHD in women explains the disproportionately increased risk in those who have both conditions. This observation may lend support to adding microalbuminuria to traditional cardiovascular risk factors, such as those in the metabolic syndrome, for improved risk stratification, at least in women. Further, because diabetics were included in our metabolic syndrome definition, the microalbuminuria and metabolic syndrome interaction in women may be driven by diabetes (which showed the same interaction); microalbuminuria may identify those with the most severe metabolic dysfunction and thus the highest mortality rate. The improved ability of microalbuminuria to predict CVD mortality may stem from its role as a marker for the diffuse endothelial injury that is associated with impaired arterial reactivity, endothelial activation and impaired fibrinolytic capacity--critical precursors in the pathogenesis of vascular disease [25, 26]. This endothelial dysfunction may confer a greater risk for CVD because it is a marker of a more advanced stage in the atherosclerotic pathway than the traditional risk factors captured by the metabolic syndrome alone.

The reasons for the sex difference in the ability of microalbuminuria to predict CHD and CVD mortality are unexplained; it was not explained by estrogen use. Tests revealed significant interactions between sex and both metabolic syndrome and microalbuminuria in the risk of both CVD and CHD death. One possible explanation for the absent association in men may be survival bias; it is likely that men at increased risk of CVD had died prior to this study visit, leaving men at lower risk in the studied cohort. Because women develop CVD at an older age than men, they would have been more likely to have survived to be in this cohort. Although the sex difference could be due to chance, Ko and colleagues also found a significant association between microalbuminuria and CVD mortality only in women (RR; 95% CI 6.10; 2.62–15.19 in women vs. 1.77; 0.91–3.44 in men) [24]. It may be that some components of the metabolic syndrome (such as waist girth, hyperglycemia, and hypertriglyceridemia) convey a greater risk for CVD mortality in older women than they do in men [27, 28, 29].

We note a few limitations of the present study. Our population was homogeneous (largely Caucasian and middle class), therefore the results may not be generalizable to other populations. The average age of participants was 71 at baseline, so they were potentially at higher risk of fatal CVD than younger cohorts, although the observed mortality rates were quite low for this age group. The prevalence of the metabolic syndrome was much lower in our Caucasian cohort (20%) than that predicted for US adults of this age by the ethnically diverse third National Health and Nutrition Examination Survey (40%), which oversampled members of underrepresented minority groups [30]. Women in our cohort were also leaner at baseline than those of similar age from the Health and Nutrition Examination Survey [12]. Urine albumin and creatinine were measured only once using a spot urine test, increasing the possibility of

misclassification [19]. However, the urine albumin/creatinine ratio has been shown to be a good surrogate for a 24 hour urine albumin excretion [19], and misclassification usually results in bias towards the null, reducing the observed association.

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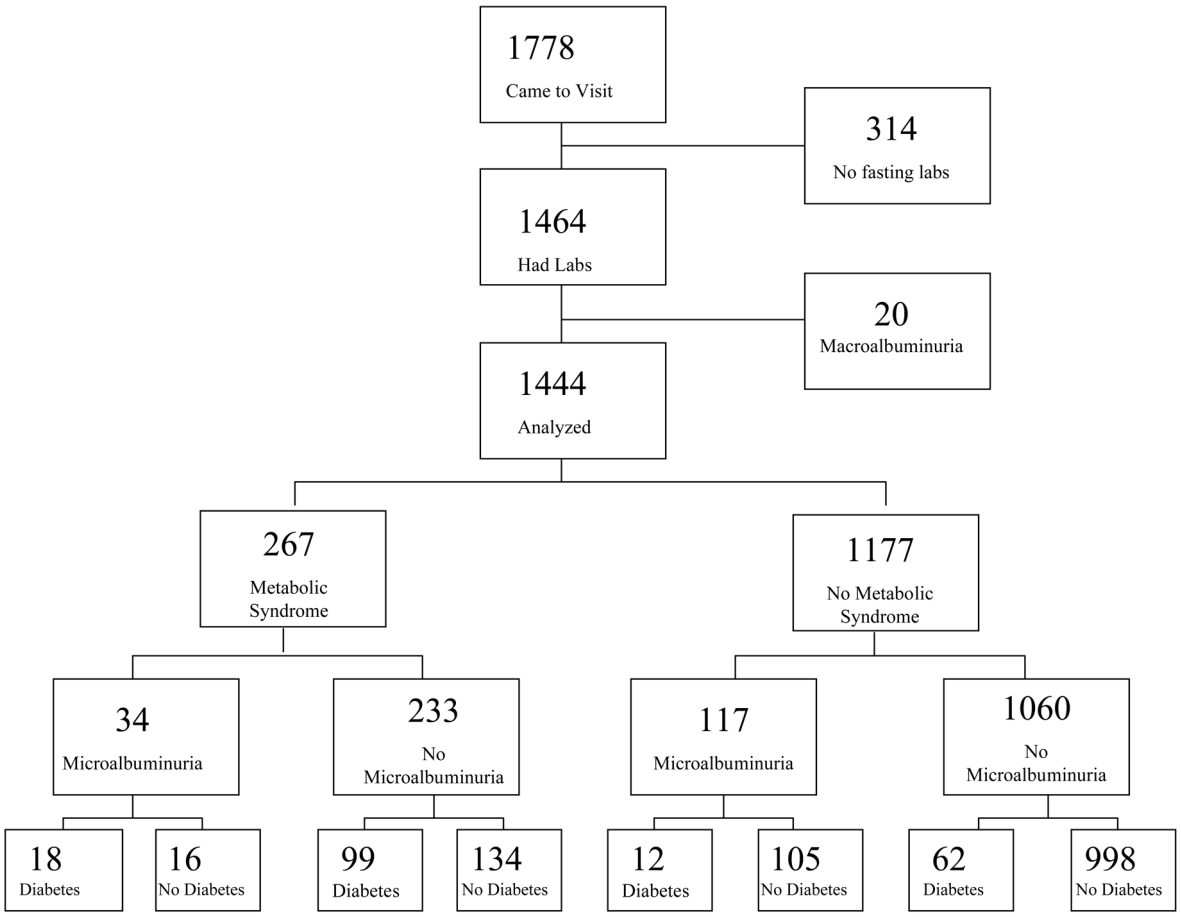

Figure 1.
Cohort Flow Diagram

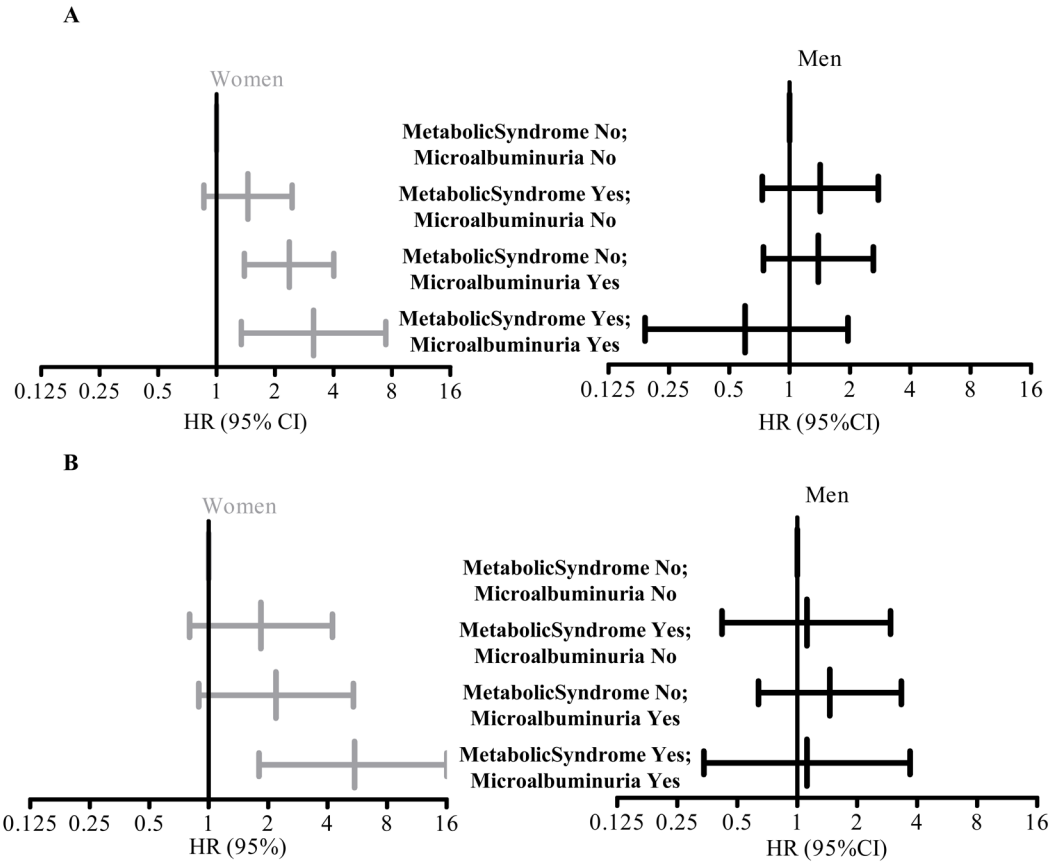

Figure 2.

Age Adjusted Hazard Ratios (95% CI) for Cardiovascular Disease (A) and Coronary Heart Disease (B) Mortality by Metabolic Syndrome and Microalbuminuria Group

Table 1

Baseline Characteristics: The Rancho Bernardo Study 1992–1995

Characteristic	Women(n=869)	Men(n=575)	
	Mean (SD)	Mean (SD)	p value
Age (yrs)	70 (12)	71 (11)	0.50
Body Mass Index (kg/m^2)	25 (4)	26 (4)	<0.001
Waist Circumference (cm)	80 (11)	95 (11)	<0.001
Systolic Blood Pressure (mmHg)	136 (23)	134 (20)	0.06
Diastolic Blood Pressure (mmHg)	75 (9)	77 (9)	<0.001
Fasting Plasma Glucose (mg/dL)	96 (21)	102 (22)	<0.001
Triglycerides (mg/dL) †	102 (75–144)	104 (70–153)	0.96
High Density Lipoprotein (mg/dL)	65 (17)	49 (13)	<0.001
Low Density Lipoprotein (mg/dL)	129 (33)	125 (30)	0.03
Urine Albumin/Creatinine (g/mg) †	6 (4–13)	6 (3–13)	0.06
Blood Urea Nitrogen (mg/dL)	16 (6)	18 (6)	<0.001
Serum Creatinine (mg/dL)	0.9 (0.2)	1.1 (0.2)	<0.001
Alcohol (g/week) †	20 (0–70)	53 (0–126)	<0.001
Hemoglobin A1C (%)	4.2 (0.6)	4.3 (0.8)	0.64
Abdominal obesity	22%	20%	0.47
Hypertriglyceridemia	22%	27%	0.04
Low High Density Lipoprotein	20%	26%	<0.01
Hypertension	66%	66%	0.96
Hyperglycemia	15%	21%	<0.01
Metabolic Syndrome	16%	22%	0.01
Microalbuminuria	10%	11%	0.79
Exercise >3x/week	70%	76%	0.02
Current smoking	7%	7%	0.92
Diabetes	11%	16%	0.01
Current ERT Use	45%	n/a	n/a

Values for continuous variables are mean if normally distributed or

† median (25–75%ile) if skewed

Values for categorical variable are percentages within each level

p value for ANOVA (normally distributed) or Wilcoxon rank sum (if skewed) for continuous variables and chi-square for categorical variables

Table 2

Age and Prevalent Cardiovascular Disease Adjusted Hazard Ratios (95% CI) for Metabolic Syndrome and Microalbuminuria as Predictors for Cardiovascular Disease and Coronary Heart Disease Death

	Women HR (95% CI)	Men HR (95% CI)
Cardiovascular Disease Death		
Metabolic Syndrome		
Age adjusted	1.40 (0.89–2.21)	1.04 (0.58–1.86)
+Adjusted for Prevalent Cardiovascular Disease	1.38 (0.88–2.18)	1.15 (0.64–2.06)
+Adjusted for Microalbuminuria	1.42 (0.90–2.23)	1.02 (0.56–1.87)
+Adjusted for Prevalent Cardiovascular Disease & Microalbuminuria	1.34 (0.85–2.12)	1.14 (0.62–2.07)
Microalbuminuria		
Age adjusted	2.31 (1.45–3.67)	1.06 (0.60–1.88)
+Adjusted for Prevalent Cardiovascular Disease	2.19 (1.37–3.50)	1.07 (0.61–1.89)
+Adjusted for Metabolic Syndrome	2.32 (1.46–3.70)	1.06 (0.59–1.91)
+Adjusted for Prevalent Cardiovascular Disease & Metabolic Syndrome	2.17 (1.36–3.46)	1.04 (0.58–1.86)
Coronary Heart Disease Death		
Metabolic Syndrome		
Age adjusted	1.99 (1.06–3.97)	1.06 (0.49–2.28)
+Adjusted for Prevalent Cardiovascular Disease	1.96 (0.98–3.90)	1.19 (0.55–2.60)
+Adjusted for Microalbuminuria	2.02 (1.01–4.02)	0.98 (0.44–2.17)
+Adjusted for Prevalent Cardiovascular Disease & Microalbuminuria	1.89 (0.94–3.78)	1.13 (0.51–2.49)
Microalbuminuria		
Age adjusted	2.40 (1.15–5.02)	1.32 (0.65–2.69)
+Adjusted for Prevalent Cardiovascular Disease	2.26 (1.08–4.74)	1.34 (0.66–2.72)
+Adjusted for Metabolic Syndrome	2.43 (1.16–5.08)	1.33 (0.64–2.78)
+Adjusted for Prevalent Cardiovascular Disease & Metabolic Syndrome	2.20 (1.04–4.64)	1.32 (0.64–2.70)