# A new sex-specific formula to estimate urine protein from protein to creatinine ratio.

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## Abstract

Background: The quantification of proteinuria with the protein to creatinine ratio is influenced by the excretion of creatinine, which, in turn, varies according to muscle mass and hence, to sex.

Aims: To assess the difference between urine protein to creatinine ratio and 24-hour urine proteinuria in men and women and to provide with a formula to overcome bias caused by sex.

Methods: 444 CKD patients were randomly divided in two parts, 70% were used to develop the models while the remaining 30% were reserved to validate the formula. Data were analyzed with Chi-square and Student's T. Association between 24-hour proteinuria and protein to creatinine ratio was studied with Spearman coefficient in men and women separately. Multivariate analysis was used to find variables predictive of disagreement between the 24-hour urine protein and the protein to creatinine ratio . Equations to predict 24-hour proteinuria from protein to creatinine ratio for men and women were plotted and validated.

Results: Disagreement between 24 hour proteinuria and protein to creatinine ratio was more pronounced in men (2.16 gr and 1.64 gr in mean, respectively) than in women (2.00 gr and 2.06 in mean respectively). Age and sex were independent predictors of disagreement. Sex-specific equations for predicting 24-hour proteinuria were: Males: 24-hour proteinuria=$1.3350*\exp^{0.9108*Ln(PCR)}$. Females: 24-hour-roteinuria=$1.0068*\exp^{0.9030*Ln(PCR)}$
Conclusions: Estimation of proteinuria with the protein to creatinine ratio improves accuracy if sex-specific equations are used. Use of the protein to creatinine ratio without correction for sex leads to underestimation of proteinuria in men and overestimation in women.

## Introduction

The detection of proteinuria is essential for the screening and diagnosis of many kidney diseases. After screening, accurate quantification of proteinuria is important for assessing prognosis and response to treatment during follow-up. Since protein excretion may follow a circadian rhythm and is modified by several factors (posture, physical activity etc.,) [1] protein measurement with 24-hour urine collection has traditionally been considered as the gold standard method, provided the urine collection is correctly done [2]. However, the frequent collection errors of this method have resulted in an increased use of the protein-to-creatinine ratio (PCR) in the clinical setting. Over the past 15 years, many studies have shown a strong association between 24-hour urine proteinuria (24UP) and either early morning [3,4] or random [5,6,7] PCR, both in diabetic [6,8] and non-diabetic proteinuric nephropathies [9,10]. Despite this finding, some of the earlier studies pointed to the limitations of this method in certain patient groups, particularly in those with higher degrees of proteinuria in whom the association between both methods is weaker [6,11,12,13,14,15,16,17,18], and shows significant variability in subsequent follow-up determinations [6,19,20]. Although accuracy of the PCR relies on the fact that glomerular haemodynamics affects both protein and creatinine excretion, there are additional factors that influence these parameters to a different extent [1,21,22]. Orthostasis is a case in point, since it affects protein but not creatinine excretion, whereas glomerular filtration rate, certain medications and muscular mass [23,24] affect almost exclusively urine creatinine [4]. As a general rule, it is therefore expected that patients with large body sizes will exhibit lower PCR than 24UP values [25]. Furthermore, the difference in muscular mass between males and females also suggests that assessment of proteinuria by means of the PCR could be subjected to a sex bias, as earlier described in other ethnic groups [26] and for microalbuminuria [27,28,29].
Thus, the aim of our study was to analyze the differences between 24UP and PCR in patients of both sexes.

## MATERIALS AND METHODS

### Patients, clinical and laboratory data:

This is a retrospective analysis 11,151 CKD and hypertensive patients followed in the Nephrology out patient clinic of the Arnau de Vilanova University Hospital in Lleida (Spain). Since 2001 patient's data are included in a large data base used for clinical and research purposes and consent for the use of their anonymous data is implied since enrolling. Therefore, no specific written consent was requested for the present study.
The patients were Caucasian because the representation of other ethnical groups in our area at the time was too low to be analysed separately. Therefore, Afro-American patients were specifically excluded from the analysis in order to avoid race bias.
We selected all those who had 24 hour urine collection with proteinuria >300 mg/24h at least on one occasion and recorded their epidemiological and biochemical data at the time of their visit. For those patients who met criteria on

more than one visit, the clinical and analytical data selected were those from the first one.
Data included were serum creatinine from samples taken at the end of the 24-hour urine collecting period, urine creatinine, urine protein (in mg/dl and in 24UP), PCR, sex, age, body weight and height. The result of the arithmetic subtraction [24UP-PCR] was also included as a variable. Values were positive when 24UP was higher than PCR and negative when PCR was higher than 24UP. Body mass index (BMI) was calculated dividing the weigh in kg by the square of the height in cm. Body muscle mass was estimated using the lean body mass (LBM) formulas described by Hume for men (LBM=0.32810*weight + 0.33929*height - 29 5336) and women (LBM = 0.29569*Weight + 0.41813*Height – 43.2933) [30].

Statistical analysis:

Statistical analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA) and R (R Core Team 2016. R: A language and environment for statistical computing) and the threshold for signification was $p<0.05$.
The patients who met criteria were selected and randomly split into two subgroups for developing the model (70%) and for validation (30%). Comparison of variables between the two subgroups was done with Student's T and Chi-Square test. The thirty percent of the sample used for validation was excluded from further statistical analysis except for validation purposes.
Variability between 24UP and PCR was initially evaluated with Bland-Altman [31]. It was first plotted with 24UP in the X-axis and the difference between 24UP and PCR in the Y-axis and then with the same variables and after logarithmic transformation.
Epidemiological variables in men and women were analyzed using the Student's t and Chi-square tests. The variable [24UP-PCR] was also represented with an error bars graph. The association between the variables sex and 24-hour creatinine excretion was assessed with Spearman coefficient. The association between 24UP and PCR was also analyzed with the Spearman coefficient of correlation in the whole sample and thereafter in men and women separately. Association between these variables was represented with scatter plots with their respective lines of best fit for the whole sample and for each sex separately. The equations for the correlation between the variables 24UP and PCR were determined by linear regression in men and in women. Goodness of fit (coefficient of determination and residual analysis) and validation of the equations were performed in the subgroup of the initial sample randomly selected and reserved for such purposes.
Two multivariate models were also constructed in order to estimate the variables that predicted disagreement between 24UP and PCR. Thus, in both models the dependent variable was [24UP – PCR] and adjusts were made for age, sex and glomerular filtration rate (MDRD 4) in model 1 and for for age, sex, glomerular filtration rate (MDRD 4) and LBM in model 2.

## RESULTS

444 individuals met the inclusion criteria previously detailed. The randomized partition of the whole sample into two uneven parts generated two subgroups of 311 and 133 patients that were used for statistical analysis and validation respectively. There were no significant differences in terms of LBM, 24-hour urine creatinine, PCR, MDRD, age or BMI between the two subgroups (table I).
The mean proteinuria values obtained by 24UP and PCR did not match (mean 24-hour proteinuria 2.11 gr, mean PCR 1.77), resulting in an overall mean difference of 0.34 gr between the two methods. However, disagreement between 24UP and PCR was not uniform across the sample, as seen in Bland-Altman graph (figure 1). Panel A shows increasing variability of [24UP – PCR] values (Y axis) as 24UP increases (X axis). Panel B represents how after logarithmic transformation, some degree of variability persists irrespective of 24UP degree.
The main age of the 311 patients was 58.2 years. They were a 68.5% of males and had an average GFR of 58.2 ml/min. Column 1 of Table II summarizes the epidemiological data of the population. Columns 2 and 3 show epidemiological data for men and women separately. Differences in age, GFR, BMI, 24UP and protein to creatinine ratio were not statistically significant between both sexes. Statistically significant differences were found in LBM, urine creatinine and in the individual means of the variable [24UP-PCR] . Accordingly, [24UP-PCR] rendered positive values among men (0.52) and slightly negative values among women (-0.06), showing statistically significant differences between men and women ($p<0.001$), as seen in figure 2.
The Spearman coefficient showed an association between lean body mass and creatinine excretion (R2: 0.57, $p<0.001$). Comparison of 24-hour creatinine excretion between sexes by Student's T yielded higher values in men than women (males 1436 mg/24h, females 1036 mg/24h, $p<0.001$), which accounts for the lower PCRs they have.
Multiple regression analysis with [24UP- PCR] as the dependent variable, adjusting for age, sex and MDRD-4 glomerular filtration rate showed that age and sex were predictive factors (Table III, model 1) and that the sex-associated differences were partially associated with the LBM differences between men and women, as reflected by the change on the sex coefficient when adjusting by LBM (Table III, model 2). This adjustment however, given the strong association between sex and LBM, introduces and estimation problem, since low LBM are mostly observed for women meanwhile high LBM are mostly observed for men.
The Spearman coefficient showed a strong association between 24UP and PCR in the whole sample (r2= 0.88, $p<0.001$) and also for the subgroups of men and for women analyzed separately (men: r2=0.89, $p<0.001$, women: r2=0.90, $p<0.001$). This is represented in figure 3, that shows 24UP (X axis) and PCR (Y axis) and the respective best fit lines in the whole sample (A) and by sexes (B). As seen in the figure, the slope was steeper in the male group and flatter in the female group, obeying to a different pattern that was defined by the following sex-specific equations**:**

**Males: 24-hour proteinuria=1.335*exp$^{0.911*Ln(PCR)}$**

**Females: 24-hour-proteinuria=1.007*exp$^{0.903*Ln(PCR)}$**

The equations were then applied to the validation samples showing good performance (explaining 80.8% and 83.4% in men and women, respectively) and no systematic bias (with an estimated residual mean non-significantly different from zero). Adding to these formulas the significant contribution of LBM and age achieved 86.5% and 90.0% of explained variability in men and women of the training sample but increased only to 83.4% and 86.6% respectively in the validation sample. The simpler formula is provided since the systematic bias between 24HP and PCR in the men of the validation sample reached a significant median reduction of 0.36 units (95% CI [0.32,0.40], $p<0.001$), even higher than the one obtained by applying the complete model (0.32 units in median). Although there was not such a bias in women, correction with their corresponding equation systematically reduced the distance between methods to 0.05 units in median (95% CI [0.02, 0.10], $p<0.001$), while with the more complex formula it was reduced to 0.08 in median.

## DISCUSSION

The present study confirms a good association between the PCR and 24UP in a large Caucasian population, as Spearman coefficient demonstrates ($r2= 0.88$, $p=0.00$). It also shows that there is important disagreement between the two methods in patients with higher degrees of proteinuria. The Bland-Altman graph constructed with the 24UP in the X axis and the difference between 24UP and PCR in the Y axis, showed increasing variability of the difference between methods as 24UP increased. None of these statements is new, since they have long been known and reported in numerous populations before [32,33]. In our study, we applied logarithmic transformation in order to overcome the variability associated with proteinuria severity. In spite of it, the resulting graph showed persistent dispersion which did not depend on the degree of proteinuria, suggesting an additional variable being responsible for it.

Creatinine excretion varies depending on numerous factors. Those that depend on hydration or other hemodynamic changes, supposedly affect urine proteinuria as well, resulting in a reliable PCR in most situations. Yet, there are other factors directly influencing urine creatinine excretion that do not alter protein excretion to the same extent. Namely, GFR and muscle mass.

In order to assess the influence of GFR in our population, we included it as a variable in the linear regression analysis and it did not show a significant influence. Therefore, we interpreted that this was not the main factor causing disagreement between the two methods. However, taking into consideration that our population had nearly normal GFR (58.2 ml/min), this variable might have turned significant should the study had been carried out in patients with more advanced CKD.

Muscle mass depends on anthropometric parameters such as height, weight and the proportion of body fat, which in turn, vary according to sex. Out of the several

existing muscle mass estimating formulas, we selected the one described by Hume [30] because it is has been a reference for many investigators since it was first published . Applying this formula to our population revealed higher LBM in men (54.9 kg) than in women (44.8 kg), a fact that was consistent with the finding of higher creatinine excretion in the former.

After establishing the association between sex and creatinine excretion, we proceeded to evaluate the association between PCR and 24UP in men and women separately. Despite being strong in both subgroups, women showed higher PCR than 24UP values and the opposite occurred in men. This resulted into different steepness of the regression lines, reflecting a different equation to define the relationship between 24UP and PCR in each sex. Previous authors have reported disagreement between 24UP and PCR depending on sex in smaller populations [24,26]. Nayak [26] studied one hundred patients (81 men and 19 women) with CKD and provided a correction factor for creatinine excretion that minimized disagreement between 24UP and PCR in females [26]. However, our study is the first to provide and validate an equation to estimate 24UP directly from PCR in a large Caucasian population adjusting for sex.

A limitation of the present study is that if focuses on a particular type of patients. The new formulas provide a useful tool to evaluate proteinuria in middle-aged Caucasians with nearly normal renal function but they shouldn't be extrapolated to other populations. The elderly in particular, have marked physiological loss of muscle mass and higher prevalence of advanced CKD. This could also lead to bias in PCR values so it would be of interest to do further research such groups and find specific correction factors for creatinine excretion in them.

In conclusion, present data suggest that this newly-described formula improves precision of the PCR overcoming much of the bias caused by sex. Thus, correction of the PCR for sex would improve accuracy and allow better clinical decisions both at the time of diagnosis and at follow up, while remaining an easy-to-use straightforward method. As a result, our suggestion is to include this formula on calculators, similar to the GFR estimation formulas [33,34,35], which invariably include a correction factor for sex.

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**Table I.** Epidemiological data of the whole population and on the training and validation groups. Significance with Student's or Chi-Square. Values are expressed as means and standard deviation (in brackets).

| | **Whole population** | **Training** | **Validation** | **P** |
|---|---|---|---|---|
| **N** | 444 | 311 | 133 | - |
| **Sex = Male, n(%)** | 304(68.5) | 213(68.5) | 91(68.4) | 1 |
| **Age** | 58.7(16.7) | 58.3(16.6) | 59.7(16.8) | 0.408 |
| **GFR (MDRD 4)** | 57.4(29.9) | 58.2(30.5) | 55.3(28.3) | 0.353 |
| **BMI** | 28.8(5.31) | 28.8(5.39) | 28.7(5.13) | 0.762 |
| **LBM (kg)** | 51.5(7.99) | 51.7(8.20) | 51.0(7.48) | 0.417 |
| **Urine creatinine (mg/dl)** | 1309(452) | 1303(429) | 1324(510) | 0.711 |
| **24-hour proteinuria (gr/24h)** | 2.05(1.99) | 2.11(2.03) | 1.91(1.89) | 0.340 |
| **Protein/creatinine ratio.** | 1.73(1.82) | 1.77(1.82) | 1.64(1.80) | 0.474 |
| **[24h-p] – [PC ratio]** | 0.32(0.96) | 0.34(0.94) | 0.28(1.02) | 0.579 |

**Table II:** Epidemiological data of the population and on the training and validation groups. Significance with Student's or Chi-Square. Values are expressed as means and standard deviation (in brackets).

| | Whole population | Males | Females | P |
|---|---|---|---|---|
| **N** | 311 | 213 | 98 | - |
| **Age** | 58.3(16.6) | 59.5(15.6) | 55.6(18.5) | 0.074 |
| **GFR (MDRD 4)** | 58.2(30.5) | 56.5(28.2) | 62.1(34.9) | 0.190 |
| **BMI** | 28.8(5.39) | 28.4(4.32) | 29.8(7.12) | 0.091 |
| **LBM (kg)** | 51.7(8.20) | 54.9(6.25) | 44.8(7.75) | <0.001 |
| **Urine creatinine (mg/dl)** | 1303(429) | 1436(395) | 1036(366) | <0.001 |
| **24-hour proteinuria (gr/24h)** | 2.11(2.03) | 2.16(1.96) | 2.00(2.18) | 0.534 |
| **Protein/creatinine ratio.** | 1.77(1.82) | 1.64(1.54) | 2.06(2.31) | 0.102 |
| **[24h-p] – [PC ratio]** | 0.34(0.94) | 0.52(0.86) | -0.06(0.97) | <0.001 |

**Table III.** Multivariate model. Dependent variable: [24UP-PCR]. Co-variables: age, sex, MDRD-4 (Model A, explaining 15.7% of variability) and an alternative model including also LBM (Model B, explaining 19.5% of variability).

| | **Model A** | **Model B** |
|---|---|---|
| **Age (per 10 years)** | -0.16(0.03), p<0.001 | -0.13(0.03), p<0.001 |
| **Sex (F vs M)** | -0.55(0.10), p<0.001 | -0.27(0.12), p=0.033 |
| **MDRD-4 (per 10 units)** | -0.01(0.02), p=0.63 | -0.02(0.02),p=0.29 |
| **LBM (per 10 kg)** | - | +0.26(0.07),p<0.001 |

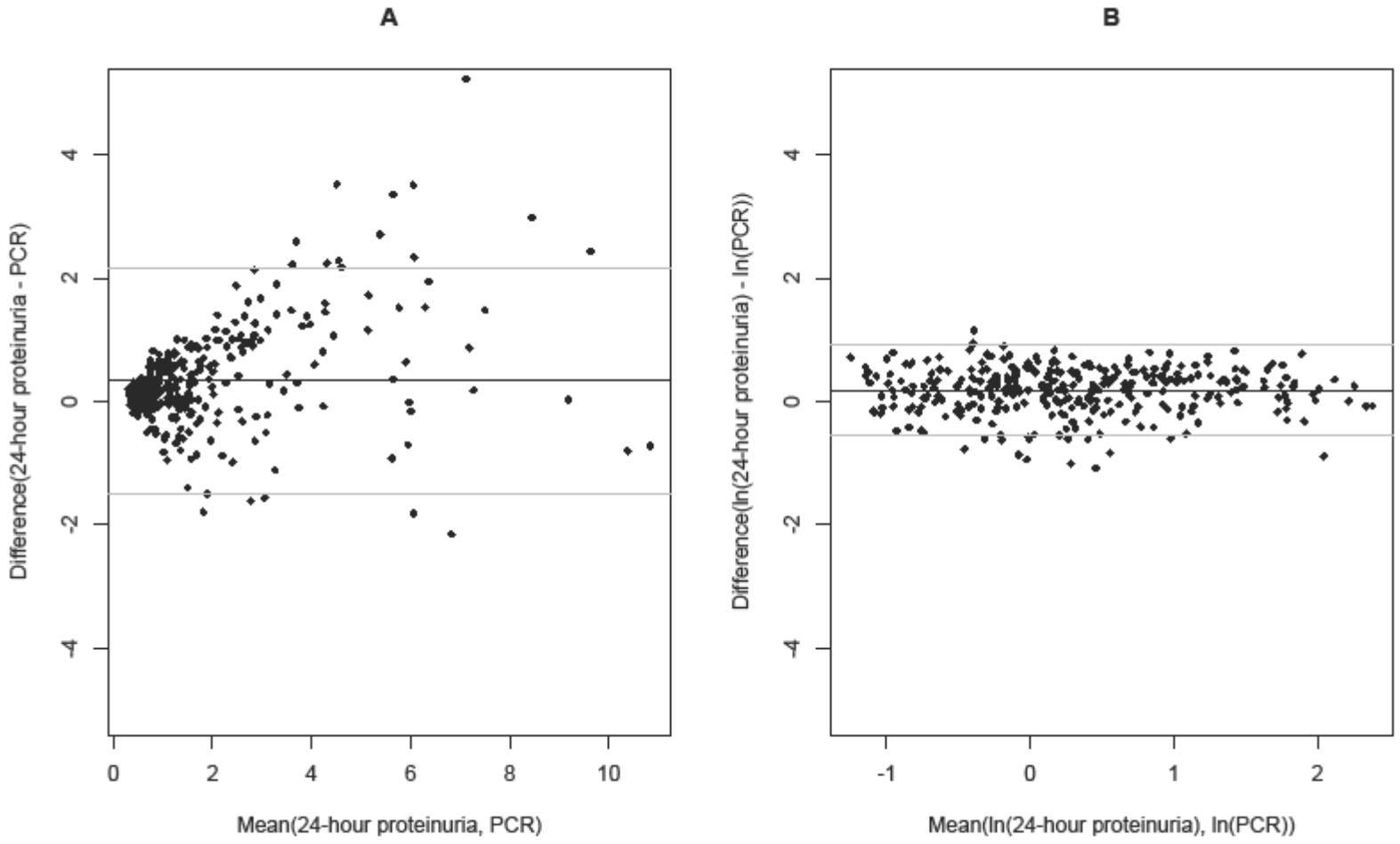


**Figure 1:** Variability between 24UP and PCR with Bland-Altman. Panel A: 24UP in the X-axis and the difference between 24UP and PCR in the Y-axis Panel B: the same variables and after logarithmic transformation.

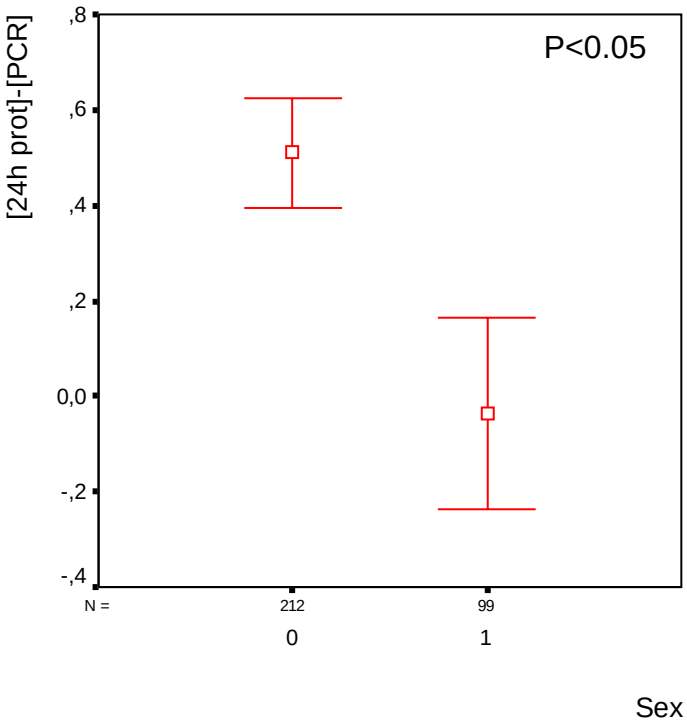


**Figure 2**: Comparison of the difference between 24-hour proteinuria minus protein to creatinine ratio [24UP-PCR] (Y axis) between men (left bar) and women (right bar) and statistical significance with Student's T.

Figure 3

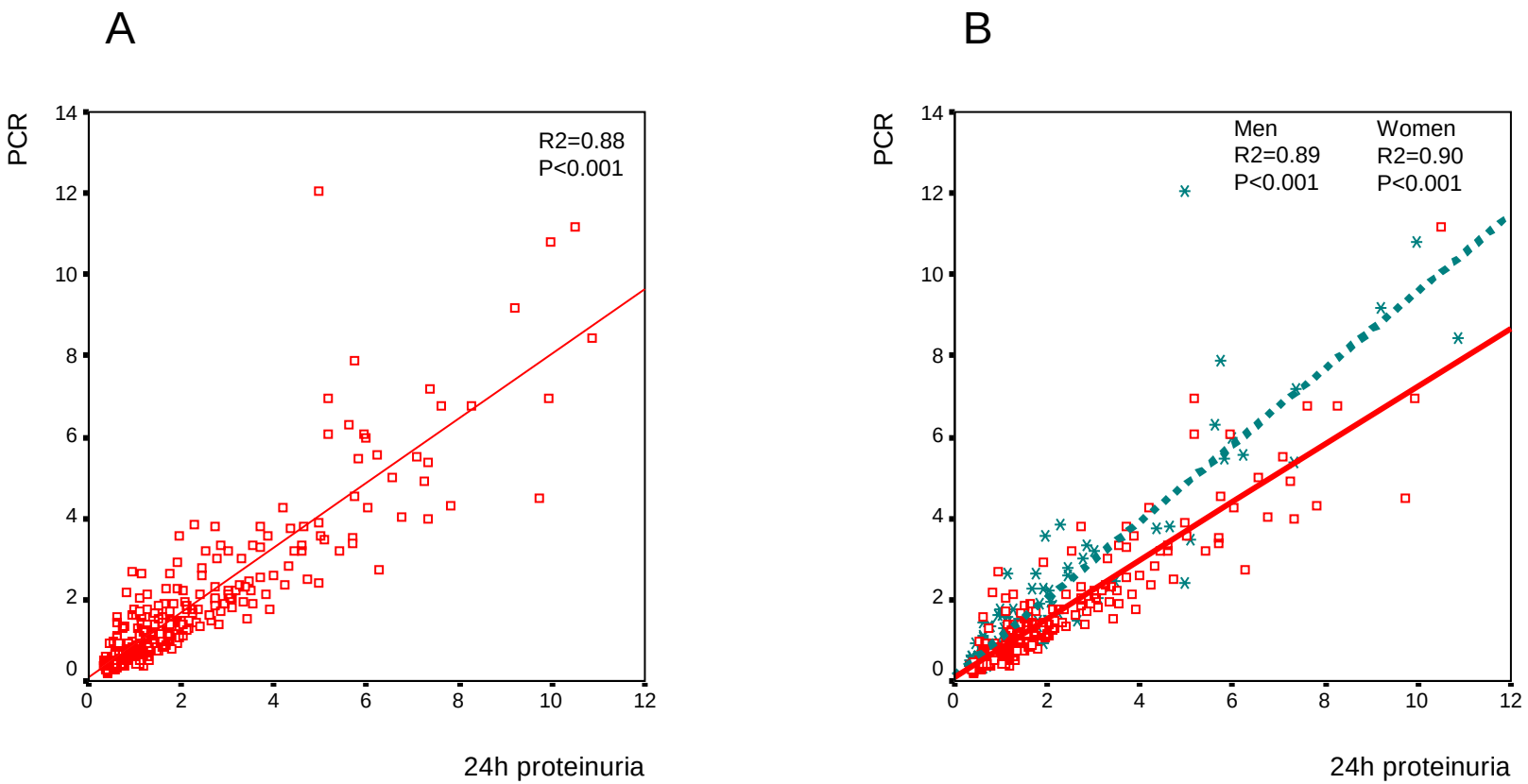


**Figure 3:** Panel A: Association between 24-hour proteinuria (X axis) and PCR (X axis) in the whole population (N=311). Panel B: Association between 24-hour proteinuria (X axis) and PCR (X axis) in men (solid line, N=213) and in women (dotted line, N=98). R2 and significance with Spearman coefficient. and also for the subgroups of men and for women analyzed separately.