Associations of Microalbuminuria With Inflammation Markers in Hypertensive Men

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In this issue of the Journal, Tsioufis et al. describe associations between urinary albumin/creatinine excretion rate (ACR) and several inflammation markers (IM). Their article provides an opportunity to illustrate common methodologic problems related to the validity and interpretation of this and similar studies.

Although frequently used, cross-sectional data are of limited value in mechanistic studies, because the sequence of changes in one variable and changes in another variable cannot be established. For example, whether elevated ACR preceded or followed an elevation in IM cannot be verified in their study.1

Lack of evidence of a difference is commonly interpreted as evidence of no difference. The authors report that levels of interleukin (IL)–18 were not different in patients with and without microalbuminuria, because the difference was not statistically significant.1 However, a 95% confidence interval for the difference (–29.4, 34.7 pg/mL) suggests that the study power was too low to obtain a precise measurement of it. Although there was little evidence supporting the absence of a difference in IL–18, this lack of evidence was mistaken as evidence of no difference.

Restriction of the study sample to subjects without some risk factors is sometimes used to prevent confounding; but it limits generalizability, complicates recruitment, and is rarely needed. Tsioufis et al.1 restricted their study to nonobese subjects. If ACR–IM associations differ in obese and nonobese individuals, then study findings would not apply to those who are obese. Also, ascertaining obesity status probably increased the cost and complexity of recruitment. Moreover, restriction is rarely justifiable, as confounding can be controlled efficiently using multiple regression analysis.

Testing strategies for clinical care are not necessarily appropriate for research. Following clinical guidelines, Tsioufis et al.1 measured C-reactive protein (CRP) twice and improved the precision of their results by analyzing the average of the two measurements. However, it is uncertain whether the precision and cost of a study with two CRP measurements per subjects would be better than those of a study with one measurement and a larger sample size.2

Stepwise regression is prone to biased selection of variables retained in the final model and to biased estimates of the effect of those variables. Bias occurs because statistical tests are used for variable selection with little consideration of subject matter and validity issues. For example, one could argue that even if diastolic blood pressure were not statistically significantly associated with ACR, it should be retained in the final model for biological reasons or if it confounds the IM–ACR relationship.3

Finally, correlation coefficients (r) should be used with caution. Crude r are likely confounded by other variables. For instance, the strong correlation between ACR and CRP (r = 0.62) could be partly explained by body mass index (BMI), which was correlated with both factors.1 Even though r is valid under the assumption of a straight-line relationship, evidence supporting this assumption is rarely mentioned. Statistical tests are of little value in the interpretation of r, because the null hypothesis of no correlation between the two variables (r = 0) is highly unlikely. Confidence intervals may be more useful. For example, a 95% confidence interval for the correlation between CRP and BMI (r = 0.235; P = .036) would be 0.048 to 0.406, reflecting a large degree of uncertainty in the magnitude of r, despite a significant P value.

References