

Reply to: The association between sex and disease impact cannot be confounded by clinical risk factors

Sirs,

We have read with great interest the letter by Heckert *et al.* (1) commenting on our work recently published in this journal regarding the confounding factors in the relationship between sex and disease impact in recent-onset psoriatic arthritis (2). Although some epidemiological definitions suggest that the confounding factor must be pre-exposure, in our manuscript we have followed the classic definition of a confounding factor: variable associated with the disease, associated with exposure, and not an intermediate step in the causal chain. Therefore, we consider a variable to be a confounder when it has the following three properties:

1. A true confounding factor is predictive of the outcome even in the absence of the exposure. Although a potential confounding factor (PCF) may be causative, it might not be. The primary requirements are that an independent relationship between the factor and the outcome exists, and that the

PCF not be the result of the exposure (or the outcome).

2. A confounding factor is also associated with the exposure being studied but is not a proxy or surrogate for the exposure.

3. A confounder cannot be an intermediate between the exposure and the outcome. For example, the relationship between diet and coronary heart disease may be explained by measuring serum cholesterol level. Cholesterol is not a confounder because it may be a causal link between diet and coronary heart disease.

The second property implies that the PCF must be unequally distributed between the exposed and non-exposed groups, but it does not imply that the PCF is a cause of the exposure.

This definition of confounding has been used by different authors (3-5).

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