

**The association between sex and disease impact cannot be confounded by clinical risk factors**

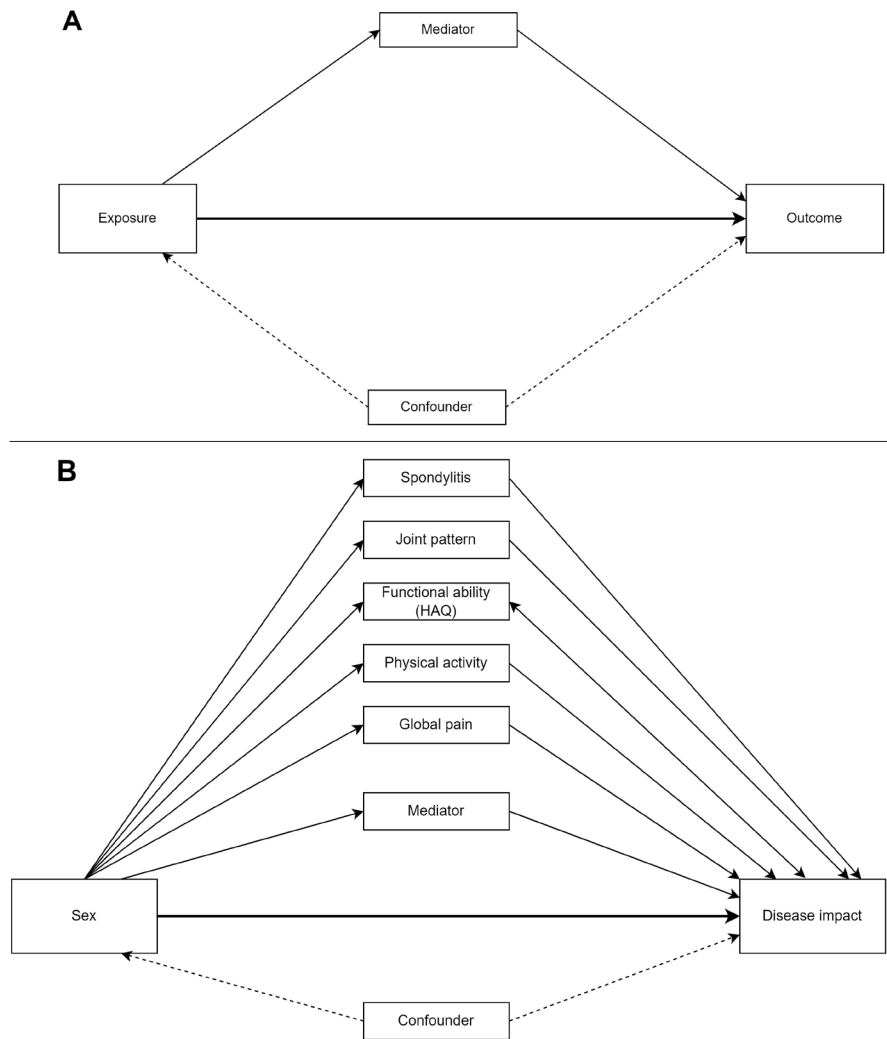
Sirs,

We read with interest the article by R. Queiro *et al.* entitled ‘Confounders contributing to explain the association between sex and disease impact in patients with recent-onset psoriatic arthritis’ (1). In this article the authors studied 158 patients with recent-onset psoriatic arthritis to evaluate the association that was previously found between sex and disease impact (measured by the Psoriatic Arthritis Impact of Disease questionnaire, PsAID): physical functioning was found to be lower in women with psoriatic arthritis (PsA) than in men. The authors describe that they evaluated ‘the effect of potential confounders on the association between sex and disease impact’. However, we would like to explain why this statement is incorrect.

The theory of confounders has been described extensively in causal inference literature. The term confounding describes the situation in which one studies the association between a factor and an outcome and the apparent association is disturbed by another factor that is a common cause of both the evaluated factor and the outcome. Figure 1A shows a causal diagram of such an association between an exposure and an outcome, that is confounded by a third factor (2). For example: the relationship between the choice of a drug and treatment outcomes can be confounded by disease activity at diagnosis. A higher disease activity at treatment start is likely to affect the choice of treatment, but is also likely to affect the prognosis.

To meet the definition of confounding, the suspected factor must thus be a common cause for both the exposure and the outcome. As sex can only be affected by pre-conceptive or sex-linked genetic factors, associations with sex and any clinical outcome can by definition not be confounded. This can probably explain why Queiro *et al.* did not find previous reports on confounding of the association between sex and disease impact. Also, the method that the authors used to assess ‘confounding’ was based on assessment of statistically significant correlations and associations of all available variables, without a hypothesis of which variables are relevant. However, the requirement of a common cause for both exposure and outcome means it is important to identify potential confounders based on previous knowledge and clinical reasoning. The fact that the authors tested all available variables separately, carries an even higher risk of chance findings (3).

As also shown in Figure 1A, mediating factors can play a role in the relation between sex and disease outcome. A mediator is influenced by the exposure and influences the outcome but does not affect the exposure.



**Fig. 1. A:** Causal diagram of mediation and confounding of the association between an exposure and an outcome. **B:** Causal diagram of the association between sex and disease impact with factors studied by Queiro *et al.* The relationships are based on associations described by Queiro *et al.* We did not verify these associations, but drafted this diagram based on clinical reasoning.

Finding mediators might also have been the underlying research question of Queiro *et al.* since they state in their conclusion that they ‘observed that the association could be explained by the influence of other variables’. In Figure 1b, we added the exposure (sex) and outcome (PsAID) and factors that according to Queiro *et al.* had an ‘influence’ on the association between female sex and greater disease impact, and showed that these factors are not confounders, but might be mediators in the association between sex and disease impact, requiring a different analysis method.

To conclude, confounding has to be assessed in the framework of causal interpretation. For the association between sex and disease outcomes, there are little variables that could confound this association. Assessment of mediation could help to gain more insight in the relationship between sex and disease impact.

S.L. HECKERT, MD  
C.F. ALLAART, MD, PhD  
S.A. BERGSTRA, PhD

Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.

Please address correspondence to:  
Sascha Heckert  
Rheumatology, Leiden University Medical Center,  
Albinusdreef 2,  
2333 ZB Leiden, The Netherlands.  
E-mail: s.l.heckert@lumc.nl

Competing interests: none declared.

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