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Journal

Rheumatology International, 38(2)

ISSN

0172-8172

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Publication Date

2018-02-01

DOI

10.1007/s00296-017-3902-3

Peer reviewed

HHS Public Access

Author manuscript

Rheumatol Int. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Rheumatol Int. 2018 February ; 38(2): 313–314. doi:10.1007/s00296-017-3902-3.

The impact of smoking on disease measures in rheumatoid arthritis: the need for appropriate adjustment of time-varying confounding

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Abstract

In a recent publication, Quintana-Dunque et al. studied patients with early onset rheumatoid arthritis (RA) and showed that baseline smoking status was inversely associated with disease activity and disability at 36 months. The authors conclude that smoking may not be as deleterious as previously considered in RA disease course. However, the authors fail to highlight several limitations of study design and analysis, including time-varying confounding, which may have a direct impact on results and corresponding conclusions.

In the publication, "*The impact of smoking on disease activity disability, and radiographic damage in rheumatoid arthritis: is cigarette protective?*" [1], Quintana-Dunque et al. studied 129 patients with early onset rheumatoid arthritis (RA) and showed that baseline smoking status (ever vs. never; current vs. never) was inversely associated with disease activity and disability at 36 months. There was no association between smoking status and erosive disease, radiographic progression, or Sharp scores. The authors conclude that smoking may not be as deleterious as previously considered in RA disease course.

However, the authors fail to highlight several limitations of study design and analysis, which have a direct impact on results and corresponding conclusions. We outline a few of those limitations below.

First, by capturing smoking status only at baseline and not accounting for changes over time, the authors make an assumption that smoking status did not change during the course of three years. This may result in exposure misclassification, which potentially may bias findings toward or away from the null.

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Second, there may be other factors that also vary with time. For example, therapy (medication) is likely to change over time, and we are only presented with baseline information. Additionally, factors such as therapy, depression, and obesity are likely strong predictors of disease activity and disability, but are not adjusted for in the analyses.

Improper adjustment for time-varying confounding variables (i.e. changes in exposure status or covariates over time) can lead to biased results, specifically when a covariate serves as both a confounder and an intermediate variable for an exposure of interest [2]. Variables such as medication use, depression, and obesity, serve as both confounders and intermediate variables in the relationship between smoking and disease activity or disability (Figure 1): adjusting for these variables may attenuate the estimated association between exposure and outcome because they lie in the causal pathway as intermediate variables; but not adjusting for them can lead to biased results as they still represent confounders. Standard regression methods fail to appropriately account for this type of bias, but other methods, including marginal structural models (MSMs), through g-computation or inverse probability weighting, or even further, models that do not make assumptions on model form, such as targeted maximum likelihood estimation, are available [3–6].

Differences in results between standard analytic methods and MSMs, which account for time-varying confounding, have been conducted in previous studies in a variety of fields [7, 8]. A review found substantial differences between MSMs and standard analyses in studies where time-varying confounding was suspected [8]. MSM estimates differed from estimates derived through standard analyses by at least 20% in approximately 40% of exposure-outcome associations in which the direction of the effect was the same, and approximately 11% of papers showed opposite interpretations between the two types of analyses [8].

Given that large differences in conclusions may be found depending on the type of statistical analysis conducted, especially in the context of longitudinal studies and time-varying confounding, it is important for researchers to be mindful of the limitations of certain methods and the biases they may produce.

Acknowledgments

FUNDING

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health [grant number F32 AR070585 to M.G. and K23 AR063770 to G.S.]; and the Agency for Healthcare Research and Quality [grant number R01 HS024412 to J.Y.]. Drs. Yazdany and Schmajuk are also supported by the Russell/Engleman Medical Research Center for Arthritis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality or National Institutes of Health.

References

1. Quintana-Duque MA, Rondon-Herrera F, Calvo-Paramo E, Yunis JJ, Varela-Narino A, Iglesias-Gamarra A. The impact of smoking on disease activity disability, and radiographic damage in rheumatoid arthritis: is cigarette protective? Rheumatol Int. 2017; 37:2065–2070. [PubMed: 29022134]
2. McCulloch CE. Observational studies, time-dependent confounding, and marginal structural models. Arthritis Rheumatol. 2015; 67:609–611. [PubMed: 25371384]

3. Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period- Application to control of the healthy worker survivor effect. Mathematical models in medicine: Diseases and epidemics. Part 2. Math Modelling. 1986; 7:1393–1512.

4. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; 11:550–560. [PubMed: 10955408]

5. Taubman SL, Robins JM, Mittleman MA, Hernan MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. Int J Epidemiol. 2009; 38:1599–1611. [PubMed: 19389875]

6. Schuler MS, Rose S. Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies. Am J Epidemiol. 2017; 185:65–73. [PubMed: 27941068]

7. Li L, Evans E, Hser YI. A Marginal Structural Modeling Approach to Assess the Cumulative Effect of Drug Treatment on the Later Drug Use Abstinence. J Drug Issues. 2010; 40:221–240. [PubMed: 21566677]

8. Suarez D, Borras R, Basagana X. Differences between marginal structural models and conventional models in their exposure effect estimates: a systematic review. Epidemiology. 2011; 22:586–588. [PubMed: 21540744]

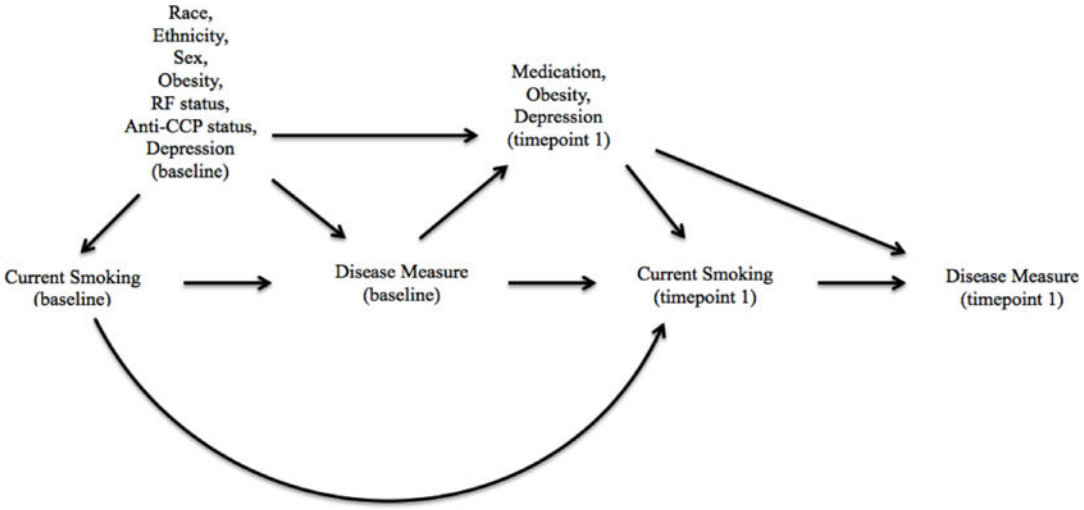

Figure 1.

Directional acyclic graph demonstrating the longitudinal relationship between current smoking and disease activity over time