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Psoriasis and Cardiovascular Risk: Strength in Numbers Part 3

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Over the last decade a large body of epidemiological, translational, and animal model research has suggested that psoriasis may be a risk factor for cardiovascular and metabolic disease. Outcome based studies often suggest that patients with more severe psoriasis have an increased risk of major cardiovascular events independent of traditional risk factors that are captured in electronic health data. The study by Parisi and colleagues finds that incident severe psoriasis is associated with a non-statistically significant increased risk of major cardiovascular events, HR 1.28 (95% CI 0.96–1.69) in their primary model and a statistically significant increased risk, HR 1.46 (95% CI 1.11, 1.92), in a sensitivity analysis that excludes patients with inflammatory arthritis. These results are usefully consistent with prior studies published using the same or similar databases. Here we review three key biostatistical and epidemiological principles that are commonly misunderstood (over reliance on *P*-values, confounding versus effect modification, and inception versus prevalent cohort design) and often lead to controversy in analyzing and interpreting results.

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Parisi *et al*. (2015) conducted an elegant series of analyses of patients with incident psoriasis using a population-based data source (the Clinical Practice Research Datalink) that has previously been shown to be scientifically valid for epidemiological studies, and they conclude that neither psoriasis nor severe psoriasis is associated with a risk of major CV events after adjusting for known CV disease risk factors. Using the same inception cohort design and the same database, Dregan *et al*. (2014), writing in *Circulation*, reached the opposite conclusion, finding that psoriasis, in particular severe psoriasis, is associated with an increased risk of coronary heart disease independent of traditional risk factors. Indeed, nearly a decade earlier, using the same database and a prevalent psoriasis design, we found that psoriasis is associated with an increased risk of myocardial infarction, stroke, and CV mortality independent of traditional CV risk factors and that the risk is most significant in patients with more severe psoriasis (Gelfand *et al*, 2006,Gelfand *et al*, 2009,Mehta *et al*, 2010). So how do sophisticated analyses using the same data set yield such opposing conclusions? In this commentary, we review key biostatistical and epidemiological principles that are commonly misunderstood and often lead to controversy in analyzing and interpreting results. For a discussion of statistical power, selection bias, and information bias, the reader is referred to our earlier editorials (Gelfand *et al*., 2010; Gelfand *et al*., 2011).

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Over-reliance on *P*-values

A common misinterpretation of inferential statistics for two-group comparisons is that a *P*-value >0.05 means that there is no difference between the groups. In the original discussion of the *P*-value by Fisher (1926), the finding of a *P*-value >0.05, particularly in the setting of previous studies finding a significant difference, meant that the experiment needed to be repeated, not that no difference existed. As Dr Steven Goodman, who has written extensively on this topic, summarized nicely in his paper, "Twelve *P*-value misconceptions," "The effect best supported by data from a given experiment is always the observed effect, regardless of its significance." (Goodman, 2008). In other words, interpretation of the point estimate of association takes precedence, followed by an evaluation of the precision of this estimate (e.g., a 95% confidence interval (CI)). Indeed, Parisi *et al*. (2015) report that the point estimate of the risk of major adverse cardiac events (MACE) in patients with severe psoriasis is 1.28; this exceeds the risk they estimate in patients with diabetes (point estimate 1.18), which is widely accepted as a major CV risk factor. The estimate by Parisi *et al*. (2015) was not very precise (95% CI 0.961.69), however, and thus the *P*-value was 0.089. Using Fisher's development of the *P*-value concept, the appropriate interpretation is that the probability of Parisi *et al*. (2015) observing a hazard ratio (HR) of $\geqslant 1.28$ is 8.9%; this is then arbitrarily determined to be not statistically significant based on standards developed in the agricultural sciences (Fisher, 1926). Indeed, Dregan *et al*. (2014), using the same database and inception cohort design, found nearly identical results; their point estimate of the HR of coronary heart disease in severe psoriasis was 1.29 (95% CI 1.01–1.64). Their *P*-value was 0.042, (which we provide solely because readers love *P*-values; who said science

is not romantic!) making the result statistically significant using the arbitrary (although well-accepted) standard. The larger point is that these two results are usefully consistent and lead to the same general conclusion: any controversy arises only because the two *P*-values find themselves on opposite sides of the artificial fence erected at the 0.05 level.

Confounding versus effect modification

The relationship between psoriasis and CV disease is complicated because they share a number of common confounding factors. A confounder is defined as a factor that is "associated with the exposure and, independent of that exposure, is a risk factor for the disease" (Hennekens and Buring, 1987). Critically, a confounding variable must be predictive of outcome independent of its association with the exposure variable. A classic example of a confounding variable is smoking status. Smoking is known to be associated with psoriasis and, independent of its association with psoriasis, is associated with CV disease. Methods of accounting for confounding in an epidemiologic study include stratification on that variable (to examine the exposure–outcome relationship at each level of the confounder rather than averaging over levels of the confounder), matching on the confounder to balance the groups included in the analysis, restricting the cohort to a particular level of the confounder, or adjusting for the confounder using a multivariable model. When we adjust for smoking in the model examining the relationship of the exposure (psoriasis) with the outcome (MACE), it means that the final estimate measures the relationship between exposure and outcome for any given level of the confounder (smoker, nonsmoker, or past smoker).

An effect modifier may also have a significant relationship with the exposure and the outcome but differs from a confounder in that it moderates the relationship between exposure and outcome. Effect modification is defined as "a measure of exposure effect across levels of another variable" (Greenland, Rothman and Lash, 2008). Effect modification is often referred to as heterogeneity of effect or statistical interaction. The key difference is that epidemiologists try to eliminate confounding (through the approaches described above) but want to detect and describe effect measure modification (Greenland, Rothman and Lash, 2008). There are several variables from the statistical model reported by Parisi *et al*. (2015) that are likely effect modifiers and therefore should not be adjusted for as confounding variables. Psoriatic arthritis (PsA) is one example. First, PsA seems unlikely to meet the definition of a confounder as its association with the outcome is unlikely to be independent of its association with cutaneous psoriasis: they are part of the same clinical disease presentation. Thus, instead of trying to eliminate the effect of PsA through multivariable adjustment, it would be more clinically and scientifically appropriate to detect and describe the effect of psoriasis and psoriatic arthritis on CV risk. An intuitive and simple approach is to use stratification. In Supplementary Table S1 online, when Parisi removed all patients with PsA (a form of stratification) we see that the fully adjusted HR of severe psoriasis is 1.46 (95% CI 1.11–1.92) (apologies to *P*-value enthusiasts but no *P*-value was reported). This result indicates that patients who have not been diagnosed with psoriatic arthritis but have psoriasis being treated with systemic or phototherapy (i.e., severe psoriasis) have a 46% increased risk major CV events even when adjusting for many common CV risk factors. It would be helpful to clinicians and patients if a similar estimate were provided for severe PsA and mild skin disease, but this is admittedly difficult to determine using the amount of information provided in automated medical record databases.

> "Parisi's results are consistent with previous studies suggesting that more severe psoriasis is a risk factor for major cardiovascular (CV) events independent of traditional risk factors routinely assessed in the clinical setting."

Inception design versus prevalent cohort design

In an incident disease cohort, disease duration is assumed to be zero at entrance into the cohort (although the determination of when disease actually begins is complex and the validity of identifying truly incident psoriasis in a medical records database has not been shown). An incident disease cohort (also known as an inception cohort) is the preferred design for fully capturing risk when disease-related outcomes occur early. This type of design is especially important for drug safety studies. However, in the setting of psoriasis and CV risk, disease duration (and thus long-term exposure to inflammation) is related to the outcome, with increased risk of the outcome as the duration increases. For example, rheumatoid arthritis patients with longer disease duration have a higher risk of CV events than patients with shorter disease duration (Masuda *et al*, 2014). This issue has been similarly demonstrated in patients with psoriasis (Armstrong *et al*, 2012, Li *et al*, 2012). Thus use of an inception cohort with only short-term follow-up will result in underestimation of the true effect; for this reason, we have chosen to use prevalent disease designs in our studies to better represent psoriasis patients in the general population. For example, the average patient with psoriasis in the general population has had it for two decades, suggesting that an inception design will not be generalizable to a large percentage of patients. Prevalent designs, however, may lead to underestimation of the effect through a phenomenon known as deletion of susceptibles if the outcome is related to mortality (as in the case of MACE); a prevalent cohort design has limitations as well. Nevertheless, limiting the size of the cohort through the use of the incident disease design reduces the generalizability of the findings and results in lower power to detect a difference in the risk of outcomes between the exposure groups and, subsequently, leads to wider confidence intervals.

In summary, Parisi *et al*. (2015) addressed the risk of CV disease among patients with psoriasis but arrived at a different conclusion compared with other studies performed using the same or

similar databases. Important differences in the study design, including the use of disease severity and inflammatory arthritis as confounders rather than effect modifiers and the use of an incident disease cohort, likely explain the small differences in the final point estimates. When excluding patients with inflammatory arthritis, the results were nearly identical to those reported in our study using The Health Improvement Network (a database similar to the Clinical Practice Research Datalink; Ogdie *et al*, 2015). An advantage of both our study and that of Dregan *et al*. (2014) is that they simultaneously assessed the risk for CV disease in inflammatory arthritis (rheumatoid arthritis and PsA); Dregan *et al*. (2014) also examined Crohn's disease and vasculitis. In both of these studies, severe psoriasis carried the same or higher risk than all of these conditions. These simultaneous comparisons aid in interpreting the results, and they place the results into a clinical context. Similar to patients with rheumatoid arthritis and other systemic inflammatory disorders, patients with severe psoriasis have an elevated risk of CV disease, one that appears to be independent of common CV risk factors recorded in the primary care setting. Patients with psoriasis, in particular severe psoriasis, should be screened for traditional CV risk factors and these risk factors should be managed appropriately (Takeshita *et al.*, 2015). Because psoriasis, even when severe, often remains untreated, a critical question is whether control of inflammation leads to a decreased risk of major adverse CV events. Observational data, largely in rheumatoid arthritis and to a lesser degree in psoriasis, indicate that tumor necrosis factor inhibitors and methotrexate are associated with a reduction in CV risk (Roubille *et al.*, 2015). To extend these results experimentally, we are conducting the Vascular Inflammation in Psoriasis Trials (NCT01553058, NCT02187172, NCT01866592); these are randomized, placebo-controlled clinical trials to determine the impact of psoriasis treatments such as adalimumab, ustekinumab, and phototherapy on key pathways of CV disease, including aortic inflammation measured by [18F]-fluorodeoxyglucose positron emission tomography–computed tomography (Mehta *et al.*, 2011; Mehta *et al.*, 2012). Furthermore, Ridker and colleagues are conducting a randomized clinical trial investigating whether taking low-dose methotrexate reduces heart attacks, strokes, or death in people with type 2 diabetes or metabolic syndrome who have had a heart attack or multiple coronary blockages (NCT01594333) (Ridker, 2010). Ultimately, these trials will provide greater insight into the clinical significance and potentially causal nature of psoriasis-associated CV risk.

CONFLICT OF INTEREST

JMG served as a consultant for Abbvie, Amgen, Celgene, Coherus, Eli Lilly, Janssen Biologics (formerly Centocor), Leo, Merck, Novartis, Endo, and Pfizer, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Eli Lilly, Janssen, Novartis Corp, Regeneron, and Pfizer; and received payment for continuing medical education work related to psoriasis. NNM is a full-time US government employee.

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