

# Do Smoking, Obesity, and Stress Cause Psoriasis?

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In this issue, Naldi *et al* (2005) report results from a case-control study conducted at 21 Italian dermatology centers from 1988 to 1997, comparing 560 patients with a new first diagnosis of psoriasis and 690 patients with a new first diagnosis of another dermatological illness. Their study identifies three modifiable risk factors associated with psoriasis: smoking, increased body mass, and stressful life events. Patients with psoriasis reported these risk factors almost twice as often as patients with other skin diseases.

Here, we comment on (1) the study's methodology and (2) whether smoking, increased body mass index (BMI), and stress are causal risk factors for triggering or aggravating psoriasis.

## Methodology

Because study limitations provide an excellent starting point for examining study validity, academic journals are increasingly requiring authors to delineate study limitations in their papers (Dellavalle, 2004). We lean heavily upon the thoughtful discourse of limitations that Naldi and colleagues provide in their discussion.

The authors state, "It is possible that the risk factors correlated with disease severity rather than . . . occurrence," and state that they were "unable to assess this relationship."

Examination of the questionnaire, however (provided online as supplemental material to the paper) uncovers questions that provide surrogate measures of disease severity: (1) Was the patient admitted to the hospital? and (2) What was the anatomical extent of initial and current anatomical localization of psoriasis lesions? Thus, the authors may still, to some degree, examine the relationship between disease severity and the behavioral risk factors.

The authors say, "The choice of dermatological controls . . ." may have resulted in "overmatching (i.e., choosing controls too similar to cases for the exposure variables)."

The case-control study design attempts to minimize bias, "systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease" (Schlesselman and Stolley, 1982). Although cases are frequently matched with controls on demographic variables such as age, sex, and race in case-control studies, matching may lead to the introduction of bias (Rothman and Greenland, Chapter 10, 1998a). Adjusting for co-variables using multiple logistic regression, as this study does, is therefore preferable to matching.

To minimize the effect of extraneous variables, cases should be like controls in every way except with regard to the disease in question. For this reason, a more methodologically rigorous, although logistically more difficult, study design would have compared psoriasis patients with controls randomly selected across the population. By instead choosing persons with other newly diagnosed skin diseases, the study risked introducing matching bias that might alter the strength of the risk associations. The actual effect on the strength of the associations cannot be fully determined, however, without the results of a valid study using the alternative set of population controls.

Using "the date of the first diagnosis by a specialist as the index date" makes accurate definition of the temporal relation of the proposed risk factor with onset of disease more difficult.

The authors argue that obesity, because of its long-term onset, and smoking, presumably because of its addictive nature, were exposures likely preceding the onset of psoriasis by years. Still, the onset of psoriasis may have preceded smoking, obesity, or particular stressful life events in some cases. Documentation tracking the timing of smoking initiation(s) (and cessation(s)), weight changes, and stressful life events against the clinical course would better elucidate the temporal relationship between the risks factors and psoriasis.

The retrospective study design allows for "the potential for recall and information bias."

Recall bias occurs when cases recall exposures more readily than controls because of the desire of patients to provide a reason for the onset of a disease (Barzilai *et al*, 2005). Questions assessing case and control attitudes regarding causes of psoriasis might have provided an insight into the nature and relative strength of potential recall bias.

Information bias occurs when inaccurate information is collected regarding exposures (risk factors) or outcomes (disease) (Barzilai *et al*, 2005). Along this line, patients with psoriasis might be more cognizant of behavioral lifestyle factors and report them more accurately than controls with other skin diseases. Prospectively tracking risk factors might lead to more uniform responses.

The statistical power of most subgroup and interaction analysis is inadequate . . . more weight should be given to our overall results rather than to any specific result in subgroups.

Underpowered subgroup analysis makes us question whether the analysis was carried out *a priori*, as originally

proposed prior to enrolling participants, or added at a later date, a practice sometimes unflatteringly described as “data dredging.” Despite difficulties posed by online information archiving (Dellavalle *et al*, 2003), online reference supplements now enable authors to provide readers with access to information too voluminous to include in print. Although readers can delight in poetic hidden details (e.g., dietary polenta intake) of the actual questionnaire used (see online supplemental text), unfortunately an English translation of the protocol approved by Bergamo General Hospital describing the original design of the analysis is not available. Whatever the circumstances, the stronger association of smoking and psoriasis in women, and the stronger association of increased BMI and psoriasis in women, provide fertile ground for subgroup hypothesis generation and further research.

### Causal Relations

Standards for causal relationship include one necessary criterion, *temporality* (causal exposures precede the disease) and additional strengthening criteria, *consistency* (results from different studies agree) and *biological gradient* (more exposure leads to more disease) (Rothman and Greenland, 1998b).

**Temporality** The onset of psoriasis might precipitate stressful life events, particularly sexual, social, work, and recreational difficulties. Do smoking, stress, and obesity increase the risk of developing psoriasis, worsen existing disease, or do they represent responses to developing psoriasis? As discussed above, better documentation that the behavioral risks precede the psoriasis diagnosis will better ground arguments that these risk factors cause or aggravate psoriasis.

**Consistency** The results of this trial are consistent with results of previous studies (Poikolainen *et al*, 1994; Naldi *et al*, 1999; Higgins, 2000). Interestingly, alcohol consumption was not statistically associated with psoriasis (Table I, Naldi *et al*, 2005) in this study in men or women, either before or after stratifying cases and controls for smoking status (Table III, Naldi *et al*, 2005). A significant, although weak, association between alcohol consumption and psoriasis was seen in men in prior interval analysis of this cohort (Naldi *et al*, 1999), and has also been noted by others (Poikolainen *et al*, 1990).

**Biological gradient** A dose–response relationship has been reported for psoriasis and smoking, increasing BMI, and stressful life events (Naldi *et al*, 1999, 2005; Higgins,

2000). Interestingly, male ex-smokers in this study displayed a stronger association with psoriasis than men who currently smoke. As suggested in the paper’s discussion, it has been hypothesized that the “withdrawal of the immunosuppressive effect of smoking triggers the disease onset.” Alternatively, the cessation of smoking could accompany other lifestyle changes in men not accounted for in this study, such as diet or exercise, whose potential associations with psoriasis remain uncovered.

### Conclusion

Our comments are but fly bites to the nape of a great work horse. The study by Naldi *et al* is a leap in the right direction pointing the way to possible causal associations and the design of more definitive trials to elucidate the relationship between modifiable behavioral risk factors and psoriasis. The door is now open for proposing more powerful study designs, including randomized-controlled trials of smoking cessation, weight reduction, and stress reduction, either alone or in combination in patients with these behavioral risk factors to determine whether in fact smoking, obesity, and stress do cause or aggravate psoriasis.

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