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THE AUTHOR REPLIES

I thank Dr. Wartenberg and his colleagues for their comments (1). I appreciate their interest, but the concerns they raise dispute recommendations that were neither made nor implied in my commentary (2). Specifically, I did not advocate the use of undefined “epidemiologic methods” in lieu of exploratory factor analysis (EFA) to identify a unique syndrome in Gulf War veterans, nor did I suggest comparisons among Gulf War veterans and other veterans for that purpose.

I did comment that, since wartime exposure data are, for the most part, unavailable for the Persian Gulf conflict, epidemiologic methods traditionally used in the absence of individual exposure data could be useful in generating etiologic hypotheses regarding the unexplained illnesses reported by Gulf War veterans. Differences in illness prevalence and profiles associated with Gulf veteran subgroups defined by, for example, place and time of deployment have the potential to identify associations between illness and experiences in theater. This suggested use of traditional epidemiologic methods was separate from, and unrelated to, observations made regarding the use of EFA.

My comments questioning the use of EFA related only to its suitability for determining whether there is or is not a unique “Gulf War syndrome.” Wartenberg et al. appear to have mistaken that point for a broader one regarding the use of EFA in general. The distinction between the use of EFA for statistically defining symptom domains and its use to address the question of the presence/absence of a unique “Gulf War syndrome” is not a minor one.

In a growing number of studies (3–9), first-order factors obtained from general lists of symptoms endorsed by heterogeneous groups of Gulf veterans have been found to be similar to symptom factors observed in comparison veteran populations. Does this general similarity in symptom factors mean that there is no “Gulf War syndrome”? The answer is, it doesn’t really address the issue. EFA identifies latent constructs that underlie groups of correlated variables. In factor analyses of symptoms, these constructs tend to represent symptom domains associated with difficulties in particular organs or systems. Neurologic difficulties, for example, are often represented by factors that include symptoms such as difficulty concentrating, memory problems, and mood changes—regardless of the etiology or pathophysiology of the problems being expressed. Respiratory conditions often manifest symptoms such as coughing, wheezing, and shortness of breath, which are highly correlated in a population, independently of the diversity of conditions giving rise to those symptoms. Thus, even if subgroups of Gulf veterans experienced, for example, unique combinations of neurotoxic and respiratory insults, the symptoms and first-order factors expressed would probably be similar to those of populations that included persons experiencing other types of neurologic and respiratory difficulties.

While it is interesting that one group of investigators has identified a unique symptom factor among a minority of symptomatic Gulf veterans (8), the absence of unique first-order factors in other studies indicates only that symptoms associated with dysfunction in specific organs or systems tend to be correlated in similar ways in different populations, regardless of the specific diseases in those populations.

A more straightforward observation relates to familiar medical conditions found in any population group, including veterans. When symptoms from these populations are subjected to EFA, “unique” symptom factors are not generally identified for common chronic conditions such as diabetes or hypothyroidism. It is unclear why investigators expect that putative “new” conditions associated with Gulf War service should emerge when comparing the results of EFA between Gulf veterans and other populations.

REFERENCES

We read with great interest the meta-analysis by Korte et al. (1), which addressed the controversial relation between alcohol consumption and lung cancer. Although we agree with their general conclusions, a few issues should be taken into account when interpreting the results of their meta-analysis and the overall evidence for an association.

First, although the effect of the different alcoholic beverages on lung cancer risk is not completely understood, studies have generally reported a stronger positive association for beer (2, 3) than for other alcoholic beverages, with some indication that wine—at moderate consumption levels—may decrease risk (3). Korte et al. (1), ignoring these findings, limited their analyses to total alcohol consumption. Perhaps their results would have been different if they had evaluated the effect of the different alcoholic beverages. Second, when studies presented results about recent and lifetime consumption, Korte et al. chose results “based on consumption frequency over as long a time span as possible” (1, p. 497). They offered no justification for this assumption. The latency period between exposure to alcohol and lung cancer development is unknown. However, there is some indication that alcohol and beer may act during the later stages of carcinogenesis (2, 4, 5) and, therefore, recent exposure may be the relevant exposure period.

Korte et al. (1) misclassified the Iowa Women’s Health Study (4), listing it in table 1 and including it in their analysis as a case-control study when it should have been listed as a cohort study. In addition, when they raised the issue of residual confounding by cigarette smoking, they cited an example the Iowa Women’s Health Study (4), specifically as showing “an excess of extremely heavy smokers among the cases” (1, p. 504). In fact, Korte et al. attributed their findings of increased lung cancer risk among heavy drinkers to residual confounding. It is true that the proportion of heavy smokers was higher among cases than controls in the Iowa Women’s Health Study (4). However, mean pack-years was similar for cases and controls in each category of pack-years, except for heavy smokers (>50 pack-years). In this group, mean pack-years of cigarette smoking among cases was only slightly higher when compared with controls (77 vs. 70, \( p = 0.16 \)). Furthermore, this subanalysis was undertaken specifically to explore whether residual confounding by tobacco explained the association found with beer consumption (4); it showed quite specifically that it did not.

The stronger association between total alcohol consumption and lung cancer reported by Korte et al. (1) for hospital-based case-control studies compared with population-based case-control studies could be due to geographic variation. For example, as their table shows, the strongest evidence comes from two hospital-based studies by De Stefani et al. (6) and Dosemeci et al. (7). These two studies were conducted in Uruguay and Turkey, respectively, and participants reported much higher levels of alcohol intake than in other studies. All other population-based case-control studies that adjusted for cigarette smoking listed in table 1 were conducted in the United States, where alcohol consumption tends to be lower and less socially accepted, therefore increasing the probability of underreporting. We again emphasize that results shown in this meta-analysis are for total alcohol only, and examining results for beer or liquor consumption may have provided a different picture.

For example, the population-based case-control study by Carpenter et al. (8) listed in table 1 as finding no association for total alcohol (odds ratio = 0.68, 95 percent confidence interval: 0.33, 1.41) in fact found an elevated risk for those drinking one or more drinks of liquor per day (odds ratio = 1.9, 95 percent confidence interval: 1.0, 3.4). Furthermore, we found a relation between beer consumption and lung cancer in the Western New York Diet Study (9) and the Iowa Women’s Health Study (4), two population-based studies.

In summary, the meta-analysis of the relation between alcohol consumption and lung cancer by Korte et al. (1) raised again the important issue of residual confounding by cigarette smoking. However, when the evidence is evaluated, heavier weight should be given to studies that carefully assessed smoking and alcohol and controlled for cigarette smoking and other factors. Furthermore, we need to look at the effect of alcoholic beverages separately. If beer increases risk and wine decreases risk, as some studies have suggested, evaluating only total alcohol will mask associations. Residual confounding by cigarette smoking remains a challenge to studies examining the role of alcohol in lung cancer. However, the association observed among nonsmokers in some studies (1, 3) is intriguing, particularly considering their typically lower level of alcohol consumption. Although Korte et al. made efforts to conduct a comprehensive assessment of the epidemiologic evidence of an association between alcohol and lung cancer, their approach needs both greater specificity in relation to exposure and somewhat more careful assessment of the studies being meta-analyzed.

REFERENCES