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Letter to the Editor

Confounding Factors: Mind it to Avoid

Dear Editor ,

The medical subject heading (MeSH) definition [1] of the confounding factors read as "Factors that can cause or prevent the outcome of interest, are not intermediate variables, and are not associated with the factor (s) under investigation. They give rise to situations in which the effects of two processes are not separated, or the contribution of causal factors cannot be separated, or the measure of the effect of exposure or risk is distorted because of its association with other factors influencing the outcome of the study".

These confounding factors/confounders are the variables where the researcher is not directly interested in, but can interfere with the results of research question under investigation; thereto the inferences to be drawn. Confounding is a possible source of bias due to confounding factors on the study outcome. It questions the validity of research findings. While studying disease and its effect relationship, for example, the effect of hypothyroidism on lipid peroxidation. If hypothyroid patients are known to be cigarette smokers, and the researcher relates lipid peroxidation to hypothyroidism but not smoking, the results show the effect of hypothyroidism on lipid peroxidation, which is not true. This is because the hypothyroid patients are smokers and smoking may also affect the status of lipid peroxidation. Here, in this example, smoking is that factor confounding the study results. However, the effect of confounding can be avoided by appropriate study design excluding confounding factors. In example, for lipid peroxidation to be studied in hypothyroid patients, smokers has to be excluded from the study to avoid confounding (due to smoking) of final outcome (effect of hypothyroidism on lipid peroxidation). Perhaps, it is not always easy to avoid all the confounders while designing a study. If this is the case, if a researcher identifies a confounding factor later in the process, the effect of confounding can be adjusted/ avoided in the data analysis. In example, if some of the hypothyroid patients are smokers and are included in the study, researcher may be able to study to what extent smoking influence lipid peroxidation in hypothyroidism by stratifying patients into smoking and non-smoking categories. Likewise, there are many confounding factors. To state few, age, sex, and body mass index (BMI) are also known to influence the lipid peroxidation status and are considered as potential confounding factors.

There are statistical methods to control the influence of the third factor between two factors in association. Generally, Pearson or Spearman correlation tests will be employed to study the relationships between two variables. However, to study the influence or to control the effect of third variable on the association between two variables, researcher would opt for Partial correlation analysis where the role/ influence of third factor, that may have, on the actual relationship between two could be nullified. To control the effects of several factors at a time and to study the independent associations among variables of direct research interest, independent factor analysis will be carried out using multivariate regression analysis so as to avoid factors that confound the study results. Research not describing/avoiding confounding factors may lead to biased results without discovering true cause and effect.

It is noteworthy to state our research experience in recent past. In an interesting article on lipid peroxidation and protein carbonylation in hypothyroidism [2], there were significant positive associations of thyrotropin (TSH) levels with both malondialdehyde (MDA) and protein carbonyl (PCO) concentrations. This suggests the effect of hypothyroid disease on increased MDA and PCO levels, as the potential confounding factors (viz., smokers, and alcoholics) were excluded during the study design. What is interesting is that, during literature review and by further delving into the concepts, it was found that increased lipid peroxidation resulting in

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high MDA levels are involved in the mechanism of increased protein carbonylation forming high PCO levels [3]. With this previous evidence in mind, a correlation analysis was done between MDA and PCO to find significant association between them. This finding is in line with the previous evidence of the role of MDA on PCO formation indicate that the increased PCO in hypothyroidism is not only due to TSH, but also due to MDA. Therefore, it is not scientifically valid to conclude that hypothyroidism per se or increased lipid peroxidation per se cause increase in PCO concentrations.

What to conclude? How to draw conclusions? As it was found that both TSH and MDA are influencing the PCO level, at first, the role of MDA on the relationship of TSH with PCO was nullified. Second, the role of TSH on the relationship of MDA with PCO was nullified by partial correlation analysis in hypothyroidism. In both cases, when nullified for the third factor (MDA in 1st case, TSH in 2nd case), the significance of relationship between the other two (between TSH and PCO in 1st case, between MDA and PCO in 2nd case) was lost. This clearly concludes that both TSH and MDA are mutually responsible for increased PCO in hypothyroidism.

When our research experience is put in the context of confounding, a question arises. Does MDA be called as a confounding factor in this case? Reviewing the MeSH definition of confounding factors can cause or prevent the outcome of interest influencing the study results; MDA influenced the outcome result of relationship of TSH with PCO. Likewise, TSH also influenced the outcome result of relationship of MDA with PCO. Therefore, if yes for MDA, so as for TSH also. However, in our opinion, all the three variables (TSH, MDA and PCO) stated in our experience were the variables of outcome interest under investigation where the researcher is directly interested in. Therefore, they are not confounders of outcome, but a rare observation of an outcome variable influencing an outcome variable.

It is believed that this letter would provide valuable information on confounding and the importance of avoiding confounding factors while researching for a true cause or effect.

Varikasuvu Seshadri Reddy[1*], Pullaiah Pasupuleti[2], Himanshu Madaan[1], Poonam Agrawal[1], Renu Garg[1]

1. *Department of Biochemistry, BPS Govt. Medical College, Khanpur Kalan, Sonepat, Haryana, India.*
2. *Department of Biochemistry, Sri Muthukumaran Medical College, Chennai, Tamil Nadu, India.*

*Correspondence: Dr. Varikasuvu Seshadri Reddy
Email ID: lifeschemistry@live.com

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