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Abstract

New Standards for Nutrition Science, Concepts and Methods—Novel Approach to Substantiate Cause- and -Effect Relationships in Nutritional Science by Ranking Studies and Subsequent Statistical Modelling †

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In any scientific field, demonstrating cause-and-effect relationships is of the utmost importance, however difficult to achieve. The present study aims to establish an objective approach to substantiate cause-and-effect relationships. Our approach consisted of ranking published studies and subsequently using the best performing studies to construct and validate a statistical model. For the first part, studies on the association between vitamin D status and COVID-19 severity (morbidity/mortality) in hospitalized patients were identified and ranked using a combination of physiological and statistical relevance, including dose-dependency, power evaluation, confounding, physiological mechanisms, and target population. The various ranking criteria were developed in an iterative process, taking into account the Bradford Hill criteria. For the second part, a two-step statistical modelling strategy was implemented. Firstly, a multivariate model was constructed and secondly, this model was validated using data from at least one other independent study with a similar design. The sensitivity (percentage of correctly detected cases by the model) and specificity (percentage of correctly detected non-cases by the model) was assessed in both studies, and the results of both studies (model-making and model-testing) were compared using the Chi-square test with expectation. Five ranking criteria were defined with a maximum score of 67 points. Six studies were selected with scores ranging between 27 and 47 points [1–6]. The highest score was obtained by Hernandez et al., 2021 [1]. Unfortunately, it was not possible to obtain complete independent datasets of these studies. Therefore, to evaluate our approach in cause- and -effect relationships, two datasets were selected of studies on the effects of postbiotic intake on the incidence of pulmonary and gastrointestinal infections in children aged 1 to 4 years [7,8]. A logistic confounding model in combination with a discriminant analysis was applied on the first (model-making) study resulting in an internal sensitivity and specificity of 78% and 100%, respectively ($p < 0.001$), showing a treatment effect on the reduction of infections ($p < 0.001$). An external validation of the acquired model in a second independent (model-testing) study showed sensitivity and specificity of 76% and 80% ($p < 0.001$), again showing a treatment effect ($p < 0.001$). The sensitivity and specificity were not statistically different indicating similarity of the impact by the explanatory variables in both datasets. Overall, the combination of ranking studies and statistical modelling supports the validation of cause-and-effect relationships using

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objective criteria. Demonstrating consistency in associations by replication and robustness testing contributes to proof of concept in causative relations.

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