



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 [†]

Wim Calame ^{1,*} , Isabel Slurink ²  and Andrea Budelli ³

¹ StatistiCal BV, Strandwal 148, 2241 MN Wassenaar, The Netherlands

² Center of Research on Psychological Disorders and Somatic Diseases (CoRPS), Department of Medical and Clinical Psychology, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands; i.a.l.slurink@tilburguniversity.edu

³ Dipartimento di Ingegneria Chimica, dei Materiali e della Produzione Industriale, University of Naples “Federico II”, 80125 Naples, Italy; andrea.budelli@kraftheinz.com

* Correspondence: w.calame@kpnplanet.nl

[†] Presented at the 14th European Nutrition Conference FENS 2023, Belgrade, Serbia, 14–17 November 2023.

Keywords: cause-and-effect; Bradford Hill criteria; hierarchy of evidence; statistical validation



Citation: Calame, W.; Slurink, I.; Budelli, A. 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. *Proceedings* **2023**, *91*, 96. <https://doi.org/10.3390/proceedings2023091096>

Academic Editor: Sladjana Sobajic and Philip Calder

Published: 30 November 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

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

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

Author Contributions: Conceptualization, W.C. and I.S.; methodology, W.C. and I.S.; formal analysis, W.C. and I.S., resources, A.B. and W.C.; writing—original draft preparation, W.C. and I.S.; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: 3rd Party Data Restrictions apply to the availability of these data. The data presented in this abstract are available on any reasonable request from the corresponding author and on approval by the responsible scientist of the datasets on which the present study was based.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hernández, J.L.; Nan, D.; Fernandez-Ayala, M.; García-Unzueta, M.; Hernández-Hernández, M.A.; López-Hoyos, M.; Muñoz-Cacho, P.; Olmos, J.M.; Gutiérrez-Cuadra, M.; Ruiz-Cubillán, J.J.; et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. *J. Clin. Endocrinol. Metab.* **2021**, *106*, e1343–e1353. [[CrossRef](#)] [[PubMed](#)]
2. Bianconi, V.; Mannarino, M.R.; Figorilli, F.; Cosentini, E.; Batori, G.; Marini, E.; Lombardini, R.; Gargaro, M.; Fallarino, F.; Scarponi, A.M.; et al. Prevalence of vitamin D deficiency and its prognostic impact on patients hospitalized with COVID-19. *Nutrition* **2021**, *91–92*, 111408. [[CrossRef](#)]
3. Annweiler, C.; Beaudenon, M.; Simon, R.; Guenet, M.; Otekpo, M.; Célarier, T.; Gautier, J. Vitamin D supplementation prior to or during COVID-19 associated with better 3-month survival in geriatric patients: Extension phase of the GERIA-COVID study. *J. Steroid Biochem. Mol. Biol.* **2021**, *213*, 105958. [[CrossRef](#)]
4. Campi, I.; Gennari, L.; Merlotti, D.; Mingiano, C.; Frosali, A.; Giovanelli, L.; Torlasco, C.; Pengo, M.F.; Heilbron, F.; Soranna, D.; et al. Vitamin D and COVID-19 severity and related mortality: A prospective study in Italy. *BMC Infect. Dis.* **2021**, *21*, 566. [[CrossRef](#)]
5. Desai, A.P.; Dirajlal-Fargo, S.; Durieux, J.C.; Tribout, H.; Labbato, D.; A McComsey, G. Vitamin K & D Deficiencies Are Independently Associated With COVID-19 Disease Severity. *Open Forum Infect. Dis.* **2021**, *8*, ofab408. [[CrossRef](#)]
6. Angelidi, A.M.; Belanger, M.J.; Lorinsky, M.K.; Karamanis, D.; Chamorro-Pareja, N.; Ognibene, J.; Palaiodimos, L.; Mantzoros, C.S. Vitamin D Status Is Associated With In-Hospital Mortality and Mechanical Ventilation: A Cohort of COVID-19 Hospitalized Patients. *Mayo Clin. Proc.* **2021**, *96*, 875–886. [[CrossRef](#)] [[PubMed](#)]
7. Corsello, G.; Carta, M.; Marinello, R.; Picca, M.; De Marco, G.; Micillo, M.; Ferrara, D.; Vigneri, P.; Cecere, G.; Ferri, P.; et al. Preventive Effect of Cow's Milk Fermented with *Lactobacillus paracasei* CBA L74 on Common Infectious Diseases in Children: A Multicenter Randomized Controlled Trial. *Nutrients* **2017**, *9*, 669. [[CrossRef](#)] [[PubMed](#)]
8. Nocerino, R.; Paparo, L.; Terrin, G.; Pezzella, V.; Amoroso, A.; Cosenza, L.; Cecere, G.; Marco, G.D.; Micillo, M.; Albano, F.; et al. Cow's milk and rice fermented with *Lactobacillus paracasei* CBA L74 prevent infectious diseases in children: A randomized controlled trial. *Clin. Nutr.* **2017**, *36*, 118–125. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.