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# Designing and conducting observational studies in rehabilitation: challenges and opportunities

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Observational studies are conducted in "real world" scenarios differently from randomized clinical trials (RCTs) that manipulate the intervention. There are three main types of observational studies (Mann 2003): (i) case-control, (ii) cross-sectional, and (iii) cohort studies. The last one represents the best option when the objective is to analyze risk factors and identify predictors of response (Reps et al., 2021), and the design is flexible enough that allows us the exploration of multiple outcomes in the same cohort. Potentially, the main issue in such studies is the high cost of recruitment and follow-up, the necessity of robust statistical analysis to cover problems derived from the non-exchangeability (due to non-randomization), and the high risk of confounding and selection bias (Djannatian & Valim, 2018). Also, if observational studies are well designed and powered, their knowledge is faster transferred to the clinical practice (e.g., predictive or prognostic scales) than RCTs, which usually are not readily transferable due to the long process to prove whether a new drug or treatment is better or non-inferior to the currently available options (Gershon et al., 2018). Those kinds of research are the best option when RCTs are not ethically feasible for addressing diagnostic, therapeutic, and prognostic research questions. All these concerns should be carefully considered during the planning, execution, and analysis phases of the study.

In the context of physical rehabilitation studies, observational studies might be more feasible and advantageous than RCTs for specific questions (Behrman AL, Bowden MG, Rose DK, 2013). The special interested in observational studies in rehabilitation could be explained by the current necessity to propose predictors and predict treatment response, as happened previously in cardiology and oncology (Pepe et al., 2018) and which made those specialities progress in terms of capacity to suit treatment plans and responses to these to different patients. Also, we could mark out the treatment outcomes and increase research in this field. Thus, observational studies are completely acceptable to find biomarkers that may improve the measurement of an event for prognostic or prediction purposes. Still, for rehabilitation, it is not so settled, and it is the biggest expectation for one study we are running in Brazil.

As observational studies could give us more assertive prediction, we are currently running a cohort study (Simis et al., 2021) in four clinical groups (stroke, spinal cord injury, limb amputation, and osteoarthritis), whose main goal is to study possible inhibitory deficits as a marker of neuroplasticity, evaluated through linear and logistic regression models by controlling as much as possible all the confounders for each group, to find biomarkers for prognosis, prediction of clinical outcomes and transdiagnostic biomarkers. According to the National Institute of Mental Health (NIMH), the

complementary diagnosis, or "Transdiagnosis" aims to study, from a series of possible metrics, the constructs behind the phenomenon studied. For example, psychological constructs, still according to the NIMH, they can be defined as "a concept that summarizes data about a specific functional dimension of behavior". In relation to this project, the objective of transdiagnostic assessment is to assess the multiple factors involved (aspects neurophysiological) in the clinical conditions in question, to understand how the dysfunctions neurophysiological functions work and can be stopped. This valuation method is based on the Research Domain Criteria (RdoC), developed by the NIMH, which have been showing effective application in several studies and programs since its creation (Insel et al., 2010), mainly in the field of psychology (Schaeuffele et al., 2021) psychiatry (Fusar-Poli et al., 2019), and mental health in general (Dalgleish et al., 2020). In any case, as far as we are concerned, so far there are no studies demonstrating the application of a transdiagnostic approach in rehabilitation.

For that, we are assessing neurophysiological measures (transcranial magnetic stimulation, electroencephalography, and functional near-infrared spectroscopy), magnetic resonance imaging, and functional assessments with outcomes for pain, motor activities, sensitivity, quality of life, independence, depression, anxiety, cognition, balance, and genetic factors. The sample size will be large enough to support the statistical model planned (400 patients for each group and 100 for the control group). In fact, the pilot analysis has identified important risk factors for chronic pain in osteoarthritis (data collection and subsequent analysis of the other groups is still in progress).

Looking for literature data available at Scopus searching for "physical rehabilitation AND observational study" in the last five years, we found 1.846 observational studies published. Interestingly, when searching the subtypes independently, the following is observed, 3.548 cohort studies, 1.079 case-control, and 3.711 cross-sectional studies. As represented in **Figure 1**, cohort and cross-sectional studies have shown a similar increase since the 2000s, differing from the volume of case-control publications. Another interesting point to highlight is that only 22 cohort studies (0.56%) since 2013 sought biomarkers in rehabilitation, which reveals that although biomarkers are increasingly being integrated into observational studies, their investigation is still little significant given the volume of studies.

Even in the well-designed studies, methodological problems are presented; thus, it is important to know about the limitations and opportunities of each method. As for observational studies, the main consensuses about challenges are (Boyko, 2013; Gueyffier, Cucherat, 2019; Hess, Abd-Elsayed, 2019; Wang, Bolland, Grey, 2015): 1) The need for large samples to validate research inquiries in physical rehabilitation studies may represent an issue,

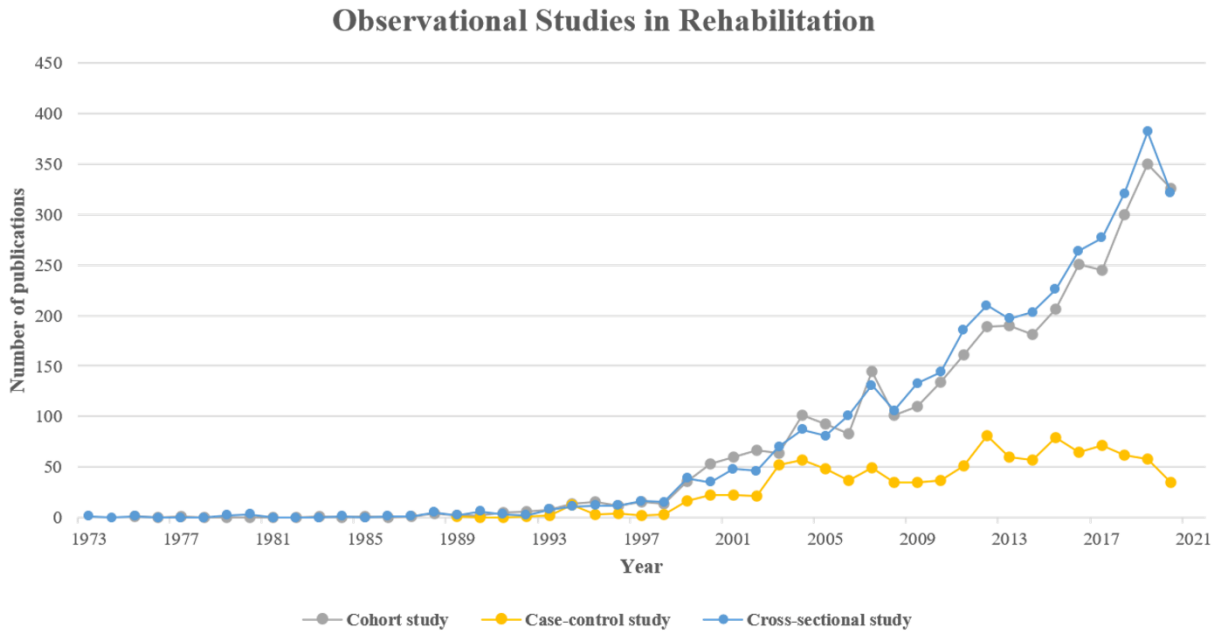


**Figure 1.** Scopus-indexed production of observational studies in rehabilitation.

as patients usually stay for a long period of treatment and have lower turnover, reducing the possibility of recruiting new patients. 2) Time and financial resources to implement large and long studies, also funding agencies are usually more likely to provide resources for RCT. iii) The need to control the confounders should be clearly declared, also recognized that some of that will be impossible to control (unobserved confounders). iv) The risk of being considered "less innovative" proposals compared to therapeutic RCTs; thus, it is fundamental to highlight the clinical applicability of the observational studies results. 4) Regardless of confounding variables, observational studies are strongly susceptible to bias, such as participant selection, missing data, and selection of the reported result.

Nevertheless, investigators can manage the mentioned by limitations: 1) including cohort studies in clinical practice and institutional protocols of hospitals, thus, reducing the overall cost and administrative burden. 2) Recruiting a sample size large enough to support statistical robustness and considering potential attrition rates. 3) Including a control group that reduces the impact of non-randomization and developing a direct acyclic graph framework to identify confounders and selection bias (for a review see Rohrer 2018 and https://cran.r-project.org/web/packages/ggdag/vignettes/intro-to-dags.html). 4) Performing multivariate regression models and stratified analysis in the analysis phase to reduce the impact of confounding. Therefore, under adequate circumstances, the results from observational studies could drive causality findings and applicable conclusions to improve clinical practice (Ligthelm et al., 2007). On the other hand, observational studies may reveal some interesting opportunities, such as: 1) Possibility to perform multi-center observational studies to increase power and external validity. 2) Possibility to answer more practical questions and possible to impact clinical practice faster than with RTCs. 3) Possibility to assess biomarkers of improvement or non-improvement of the rehabilitation process under real-world circumstances. 4) Heterogeneity of rehabilitation patients, which can compromise the integrity of a RCT (Behrman & Bowden & Rose, 2013), is not a big issue in observational studies since real-world patients do not have such homogeneous and strict criteria to be part of the study. 5) Even though cohort studies are expensive, RCTs are more costly and, depending on the research questions, for that reason, a well-designed observational study is always a valid choice (for example, following the STROBE checklist; Knottnerus & Tugwell, 2008).

In conclusion, observational studies can be useful to generate hypotheses, describe disease prevalence and incidence, discover and validate biomarkers (for prognosis and prediction), and suggest causal inference. There is an especial need for biomarkers research in the rehabilitation field, where the observational studies could play a fundamental role. Therefore, the PPCR journal editorial team is opening a special issue on observational studies and biomarkers in rehabilitation to support clinical researchers and all other specialists interested in this growing field and provide new insights for future observational studies in rehabilitation.

## Details for authors

Review articles and original papers focusing on rehabilitation, observational study design and regression models for biomarkers are welcome.

Hot topics include, but are not limited to:

1. Linear and logistic regression models for rehabilitation outcomes.
2. Retrospective and prospective rehabilitation cohort, cross-sectional and case-control studies.
3. Neurorehabilitation biomarkers.

## Conflict of Interest

Dr. Fregni is the editor-in-chief of the Principles and Practice of Clinical Research journal. Therefore, he excused himself from the peer-review process and followed the journal guidelines for peer-reviewing when an editor co-authors a manuscript. He did not influence the editorial process and final publication decision.

## REFERENCES

Behrman AL, Bowden MG, Rose DK. Clinical trials in neurorehabilitation. Handb Clin Neurol. 2013;110:61-6. doi: 10.1016/B978-0-444-52901-5.00005-8. PMID: 23312630.

Boyko, E. J. (2013). Observational research—opportunities and limitations. Journal of Diabetes and its Complications, 27(6), 642-648.

Dalgleish, T., Black, M., Johnston, D., & Bevan, A. (2020). Transdiagnostic approaches to mental health problems: Current status and future directions. Journal of consulting and clinical psychology, 88(3), 179.

Djannatian, M. & Valim, Clarissa. (2018). Observational studies. In F. Fregni & B.M.W. Illigens (Ed.), Critical thinking in clinical research: applied theory and practice using case studies (pp. 324-361). New York, NY: Oxford University Press.

Fusar-Poli, P., Solmi, M., Brondino, N., Davies, C., Chae, C., Politi, P., ... & McGuire, P. (2019). Transdiagnostic psychiatry: a systematic review. World Psychiatry, 18(2), 192-207.

Gershon AS, Jafarzadeh SR, Wilson KC, Walkey AJ. Clinical Knowledge from Observational Studies. Everything You Wanted to Know but Were Afraid to Ask. Am J Respir Crit Care Med. 2018 Oct 1;198(7):859-867. doi: 10.1164/rccm.201801-0118PP. PMID: 29733678.

Gueyffier, F., & Cucherat, M. (2019). The limitations of observation studies for decision making regarding drug's efficacy and safety. Therapies, 74(2), 181-185.

Hess, A. S., & Abd-Elsayed, A. (2019). Observational studies: uses and limitations. In Pain (pp. 123-125). Springer, Cham.

Knottnerus, A., & Tugwell, P. (2008). STROBE--a checklist to Strengthen the Reporting of Observational Studies in Epidemiology. Journal of clinical epidemiology, 61(4), 323.

Ligthelm, R. J., Borzì, V., Gumprecht, J., Kawamori, R., Wenying, Y., & Valensi, P. (2007). Importance of observational studies in clinical practice. Clinical therapeutics, 29(6), 1284-1292.

Mann, C. J. (2003). Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal, 20(1), 54-60.

Pepe, M. S., Feng, Z., Janes, H., Bossuyt, P. M., & Potter, J. D. (2008). Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. Journal of the National Cancer Institute, 100(20), 1432–1438. https://doi.org/10.1093/jnci/djn326

Reps, J.M., Ryan, P.B., Rijnbeek, P.R. et al. Design matters in patient-level prediction: evaluation of a cohort vs. case-control design when developing predictive models in observational healthcare datasets. J Big Data 8, 108 (2021). https://doi.org/10.1186/s40537-021-00501-2.

Rohrer, J. M. (2018). Thinking clearly about correlations and causation: Graphical causal models for observational data. Advances in Methods and Practices in Psychological Science, 1(1), 27-42.

Schaeuffele, C., Schulz, A., Knaevelsrud, C., Renneberg, B., & Boettcher, J. (2021). CBT at the crossroads: The rise of transdiagnostic treatments. International Journal of Cognitive Therapy, 14(1), 86-113.

Simis M, Imamura M, Sampaio de Melo P, Marduy A, Battistella L, Fregni F. Deficit of Inhibition as a Marker of Neuroplasticity (DEFINE Study) in Rehabilitation: A Longitudinal Cohort Study Protocol. Front Neurol. 2021 Aug 9;12:695406. doi: 10.3389/fneur.2021.695406. PMID: 34434160; PMCID: PMC8380986.

Wang, M. T., Bolland, M. J., & Grey, A. (2015). Reporting of limitations of observational research. JAMA internal medicine, 175(9), 1571-1572.