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Causal Forest Estimation of Treatment Heterogeneity: Identifying Subgroups of Women Benefiting Most from Mindfulness-Based Stress Reduction for Chronic Pain

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1. Round 1

1.1. Reviewer 1

Reviewer:

The use of a randomized controlled trial combined with causal forest modeling is a clear methodological strength; however, the manuscript does not provide sufficient detail on sample size, power considerations (both for detecting ATE and heterogeneity), or the stability/uncertainty of CATE estimates (e.g., confidence intervals, sensitivity analyses), which is crucial when making claims about individualized treatment effects and phenotypes.

While the outcome selection is appropriate and the average treatment effects on pain interference, severity, and psychological distress are clearly presented, the manuscript underreports effect sizes, trajectories over follow-up, and clinical significance thresholds (e.g., minimal clinically important differences), which weakens the reader's ability to judge the practical importance of both the ATE and the high-benefit subgroup effects.

The decision to dichotomize CATEs at the median to define "high-benefit" versus "low-benefit" subgroups is methodologically convenient but conceptually crude; the paper should discuss the limitations of this median split (e.g., loss of information, potential misclassification) and consider presenting continuous relationships or more data-driven clustering approaches to better characterize treatment-response heterogeneity.

The discussion appropriately links findings to mechanisms such as catastrophizing, emotion regulation, and neuroplasticity, but it remains largely speculative; integrating mediation-oriented perspectives, even at a conceptual level, and distinguishing more clearly between empirically supported inferences and hypothesis-generating narratives would strengthen the theoretical contribution.

Important practical aspects of the intervention—such as detailed description of the MBSR protocol, instructor training and fidelity, group size, adherence and dropout patterns, and concurrent treatments—are either absent or insufficiently elaborated in the extracted text; without this information, it is difficult to assess whether implementation factors might interact with the identified moderators or bias heterogeneity estimates.

Authors revised the manuscript and uploaded the document.

1.2. Reviewer 2

Reviewer:

The description of the causal forest pipeline is generally sound (honest splitting, orthogonalization, variable importance), but the paper would benefit from a more transparent reporting of tuning parameters, cross-validation procedures, handling of overfitting, and robustness checks (e.g., alternative specifications, placebo tests, or comparison with simpler models) to reassure readers that the observed heterogeneity is not an artifact of model complexity.

The identification of anxiety, non-judging, and pain duration as key moderators is clinically plausible and theoretically coherent; nevertheless, the interpretation occasionally overreaches by presenting the “optimal responder phenotype” as if it were a validated clinical rule, rather than a preliminary, model-derived profile that still requires replication, external validation, and formal decision-analytic evaluation.

The restriction of the sample to women with chronic non-malignant pain in a Spanish setting enhances internal consistency but substantially limits external validity; the discussion should more clearly acknowledge how gender, cultural context, healthcare system characteristics, and pain etiology might constrain generalizability and the applicability of the proposed phenotype in other populations.

Authors revised the manuscript and uploaded the document.

2. Revised

Editor’s decision: Accepted.
Editor in Chief’s decision: Accepted.

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