Statistical Analysis Plan - additional exploratory analysis of preoperative predictors of class membership in longitudinal pain-disability trajectories

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1. Study Overview and Objectives

1.1 Objective

This exploratory analysis aims to identify distinct pre- and postoperative pain disability trajectories in patients with endometriosis and to examine preoperative psychological, clinical, and demographic factors associated with trajectory class membership.

1.2 Main Outcome and Assessment Schedule

Endometriosis-related pain disability will be assessed using the German version of the Pain Disability Index (PDI)[1] at seven measurement occasions: preoperatively (t0) and six postoperative follow-up assessments at four-week intervals (t1–t6). A two-step approach will be used to relate predictors to trajectory class membership.

1.3 Statistical analysis overview

A two-step approach will be used to identify predictors of trajectory class membership. Latent classes will first be identified using a piecewise Growth Mixture Model (GMM). Subsequently, associations between baseline variables and trajectory class membership will be examined using multinomial logistic regression. Following selection of the optimal class solution, participants will be assigned to the trajectory class corresponding to their highest posterior class membership probability (maximum posterior assignment) for subsequent multinomial regression analyses. Classification quality and assignment uncertainty will be evaluated by reporting the contingency table of class membership stability, maximum posterior probabilities, mean posterior class membership probabilities, the percentage of participants with posterior probabilities above 0.80, and entropy. The potential influence of classification uncertainty will be considered when interpreting the regression results.

2. Statistical methods

2.1 Identification of Pain Trajectories

2.1.1 Piecewise Growth Mixture Model specification

Pain trajectories will be identified using a piecewise Growth Mixture Model (GMM). The model will include:

- Intercept representing baseline endometriosis-related pain disability (t0),
- Surgery effect representing the change from baseline (t0) to the first postoperative assessment (t1),
- Postoperative linear slope representing change across follow-up assessments (t1–t6).
- Random effects will be specified for the intercept and postoperative linear slope.

Models with an increasing number of latent classes will be estimated. To reduce the risk of local maxima, each model will be estimated using multiple sets of random starting values. Convergence to the global maximum will be assessed by verifying that the best log-likelihood is consistently reproduced across independent sets of random starting values.

2.1.2 Model selection and evaluation of latent class solutions

The optimal latent class solution will be selected based on a combination of statistical fit, classification quality, model stability, and substantive interpretability.

Model fit and classification criteria will include:

- Akaike Information Criterion (AIC)[2],
- Bayesian Information Criterion (BIC)[3],
- entropy,

- convergence diagnostics,
- class sizes,
- mean posterior class membership probabilities,
- substantive interpretability of the identified classes.

Preference will be given to solutions with lower AIC and BIC values, adequate entropy, sufficiently large class sizes, stable convergence, and clinically meaningful distinctions between classes. No single fit criterion will solely determine the final model selection. Mean posterior class membership probabilities for each latent class, maximum posterior probabilities, and the percentage of participants with posterior probabilities above 0.80 will additionally be reported as indicators of classification quality.
The stability of class assignment across alternative trajectory model specifications (e.g., linear versus quadratic postoperative slopes) will be evaluated using contingency tables of class membership and classification certainty based on maximum posterior class membership probabilities. Agreement between model specifications will be considered when assessing the robustness of the identified latent class structure.

2.1.3 Missing data handling

Missing outcome data will be handled using maximum likelihood estimation under the missing-at-random (MAR) assumption as implemented in the model estimation procedure.

2.1.4 Sensitivity analyses

Where model convergence and sample size permit, alternative variance structures (e.g., class-invariant versus class-specific random-effect variances and different residual variance specifications) will be explored in sensitivity analyses. The final model will be selected based on statistical fit, model stability, and substantive interpretability.

2.2 Predictors of Trajectory Class Membership

2.2.1 Multinomial logistic regression model

To identify predictors of trajectory class membership, multinomial logistic regression models will be performed, with trajectory class assignment based on maximum posterior assignment (i.e., assignment to the class with the highest posterior class membership probability) as the dependent variable and prespecified baseline characteristics as independent variables. The largest clinically meaningful trajectory class will serve as the reference category in the multinomial logistic regression. All selected predictors will be entered simultaneously into the multinomial logistic regression model. Results will be reported as regression coefficients (β), odds ratios (ORs), 95% confidence intervals (CIs), and p-values. A two-sided significance level of $\alpha = 0.05$ will be used.

2.2.2 Prespecified predictors of trajectory class membership

A predefined set of clinically and theoretically relevant baseline variables will be included as prespecified predictors of trajectory class membership, including:

- Treatment expectations
    - Disability expectations (PDI_expect [sum score])
    - Improvement; worsening and side effects expectations (GEEE_expect [three domain single item scores])[4]
- Depression and anxiety (PHQ-4 [sum score])[5]
- Duration of symptoms (in years)
- Endometriosis subtype (deep infiltrating endometriosis [yes/no])
- Hormone therapy (yes/no)
- Prior experience of laparoscopic surgery for endometriosis (GEEEpre [yes/no])[5]
- Desire to have children (yes/no)

2.2.3 Assessment of multicollinearity and model stability

Prior to model estimation, multicollinearity among candidate predictors will be assessed using correlation matrices and appropriate collinearity diagnostics. If substantial multicollinearity is identified, highly correlated variables may be excluded from the same model to ensure stable and interpretable parameter estimates. Variable selection in such cases will be guided by clinical relevance and theoretical considerations. To minimize the risk of model overfitting, all prespecified predictors will be included whenever supported by the available sample size and trajectory class distribution. If model stability is compromised due to small class sizes, the predictor set may be restricted based on theoretical relevance, clinical importance, and data availability. Interaction effects will not be examined, as no specific a priori hypotheses regarding effect modification were formulated and inclusion of interaction terms would increase model complexity and the risk of overfitting.

2.2.4 Missing data handling

Missing data in baseline predictor variables will be examined descriptively. If the proportion of missing data is negligible, complete-case analyses will be performed. If substantial missingness is observed, multiple imputations may be considered under the missing-at-random assumption.

2.2.5 Exploratory analyses

Following completion and reporting of the prespecified primary analyses, exploratory analyses may be undertaken to evaluate additional baseline characteristics as potential predictors of trajectory class membership. These analyses will be considered exploratory and hypothesis-generating, and their results will be interpreted accordingly.

2.2.6 Presentation of Results

The identified trajectory classes will be presented graphically using estimated class-specific trajectories over time. Associations between baseline predictors and class membership will be summarized in tables and visualized using forest plots displaying odds ratios and corresponding 95% confidence intervals.

3. Preliminary feasibility analyses

Preliminary exploratory growth mixture models (GMM) were estimated prior to completion of the Statistical Analysis Plan to assess the feasibility of trajectory modeling and to determine whether the longitudinal data supported the identification of distinct pain disability trajectories. These preliminary analyses were limited to model estimation and evaluation of model convergence and did not include model selection, analyses of baseline predictors or hypothesis testing.

4. References

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