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SPLINE-BASED STRATIFICATION FOR CONTINUOUS CONFOUNDERS IN OBSERVATIONAL STUDIES

By

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Abstract

In observational studies aimed at estimating the causal effect of an explanatory variable X on an outcome Y in the presence of confounding variables Z , we propose a novel spline-based stratification method for confounding adjustment when both X and Z are continuous. The proposed method utilizes inflection points of smoothing splines to define cut-off values for stratifying the data into relatively homogeneous subgroups. We demonstrate the utility of the approach using a stroke rehabilitation dataset, revealing essential findings that are overlooked by conventional regression-based adjustment methods.

Key Words and Phrases: causal inference, continuous confounding, spline regression, stratification, heterogeneous treatment effects

1. Introduction

In observational studies, estimating the causal effect of an explanatory variable X on an outcome Y is fundamentally complicated by confounding variables Z . If confounding is not adequately addressed, the observed association between X and Y may substantially deviate from the true causal effect. Over the past two decades, substantial progress has been made in causal inference methodology, particularly when X is a categorical treatment variable. In such settings, propensity score-based methods—including matching, weighting, and stratification—have become standard tools for adjusting for confounding (Rosenbaum and Rubin, 1983). In contrast, when X is a continuous variable, the methodological framework is considerably less developed. Although several extensions of the propensity score have been proposed for continuous treatment settings (Hirano and Imbens, 2004; Imai and van Dyk, 2004), their practical implementation remains challenging in many real-world applications.

Confounding is often addressed by including Z as a covariate in a regression model for Y . However, this approach is valid only under the assumption that the effect of X on Y is homogeneous across the entire population, conditional on Z . Such an assumption is often unrealistic, particularly in biomedical and rehabilitation research, where treatment effects may vary substantially by baseline functional status or disease severity. In this

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study, we propose a novel method for adjusting for continuous exposure X in the presence of a continuous confounder Z . Our approach models the relationship between Z and the outcome Y using spline regression (Eilers and Marx, 1996) and identifies inflection points in the fitted regression curve. These inflection points are then used as cut-off values to define strata, aiming to form relatively homogeneous subgroups for causal effect estimation.

To illustrate the utility of the proposed method, we apply it to an observational dataset of 104 patients with stroke undergoing inpatient physiotherapy, initially reported by Yoshida and Yanagawa (2023). The first author accessed the data table summarizing the information collected in the original study for research purposes on December 1, 2023. All data were fully anonymized, and individual participants could not be identified; therefore, informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kyushu Nutrition Welfare University (approval number: 2326).

The remainder of this paper is organized as follows. Section 2 describes the proposed spline-based stratification method for continuous confounders. Section 3 illustrates the method through an application to an observational dataset of patients with stroke undergoing inpatient physiotherapy. Section 4 discusses the methodological and practical implications of the findings. Finally, Section 5 concludes the paper.

2. Spline-based stratification using continuous confounders

2.1. Spline-Based Stratification

Let X_i , Y_i , and $\mathbf{Z}_i$ denote the exposure, outcome, and confounding variables for the i -th patient, respectively, where $i = 1, 2, \dots, n$. Here, X_i and Y_i are univariate variables, and $\mathbf{Z}_i = (Z_{i1}, Z_{i2}, \dots, Z_{ip})^\top$ is a p -dimensional vector representing multiple confounders. We assume that X_i , Y_i , and all Z_{ij} are continuous.

We propose a spline-based stratification procedure consisting of three steps.

Step 1. For each confounder Z_{ij} , model the marginal relationship between Y_i and Z_{ij} using a univariate regression function:

$$Y_i = m_j(Z_{ij}) + \varepsilon_{ij}, \quad j = 1, 2, \dots, p, \quad (1)$$

where $m_j(z) = E(Y_i \mid Z_{ij} = z)$ is modeled using a cubic smoothing spline, and ε_{ij} denotes the residual term. The function m_j is estimated by minimizing the following penalized least squares criterion:

$$\frac{1}{n} \sum_{i=1}^n \{Y_i - m_j(Z_{ij})\}^2 + \lambda_j \int \{m_j''(z)\}^2 dz, \quad (2)$$

where $m_j''(z)$ denotes the second derivative of $m_j(z)$, and $\lambda_j > 0$ is a smoothing parameter controlling the trade-off between goodness of fit and smoothness.

Step 2. Plot the fitted spline curve $m_j(z)$ and identify its inflection point. If multiple inflection points are present, we recommend selecting the one corresponding to the most pronounced change in curvature. These points are typically visually identifiable in the spline plot as locations where the curvature changes markedly. Denote the selected inflection point by c_j .

Step 3. Classify individuals into two subgroups according to whether $Z_{ij} < c_j$ or $Z_{ij} \geq c_j$, for each individual $i = 1, 2, \dots, n$.

Repeating this classification for $j = 1, 2, \dots, p$ yields up to 2^p subgroups. In practice, some strata may contain few or no observations. In such cases, we recommend iteratively merging strata by reducing the number of confounding variables considered, thereby ensuring that each subgroup retains a sufficient sample size for statistically reliable inference. We refer to the finalized subgroups as *strata* and to the corresponding threshold values c_j as *cut-off points*.

2.2. Stratified Analysis

Within each stratum, the exposure–outcome association is estimated using the following linear model:

$$Y = \alpha + \beta X + \varepsilon, \quad (3)$$

where β represents the stratum-specific effect of the exposure.

The application presented below demonstrates that this spline-based stratification approach can detect effect heterogeneity that may not be captured by a single global regression model.

3. Application

We apply the developed method to an observational dataset of patients with stroke undergoing inpatient physiotherapy, initially reported by Yoshida and Yanagawa (2023). In this application, the explanatory variable X is the total time allocated to basic movement exercises (basic movement exercise hours), the outcome variable Y is the gain in supine–to–sitting transition time (STS-gain), and two confounders, Z_1 and Z_2 , are considered. Specifically, Z_1 denotes the pre-intervention supine–to–sitting transition (pre-STS) time, and Z_2 denotes the Motor Functional Independence Measure (Motor-FIM) score.

3.1. Results from a conventional regression adjustment

First, for reference, we present in Table 1 the results obtained by applying a conventional regression-based adjustment to the data, in which the confounders Z_1 and Z_2 are incorporated into the regression model as follows:

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 Z_{1i} + \beta_3 Z_{2i} + \varepsilon_i, \quad (4)$$

where Y_i denotes the STS-gain and X_i represents the basic movement exercise hours.

The table shows that the number of hours of basic movement exercises has a statistically significant effect on STS-gain ($p = 0.01$). Interestingly, when the confounding variables were not accounted for, the effect was not statistically significant ($p = 0.11$). Although this result may appear encouraging, more clinically informative findings for physical therapists are presented below, derived from the spline-based stratification method developed in this study.

Table 1: Results of the conventional multiple linear regression model for STS-gain

	β	Standard error	p -value
Intercept	-1.75	0.71	0.01
Basic movement exercise hours (X)	0.03	0.01	0.01
Pre-STS time (Z_1)	0.36	0.04	< 0.01
Motor-FIM score (Z_2)	0.01	0.00	0.15

3.2. Results from the spline-based stratification method

3.2.1. Stratification

Figure 1 (left panel) shows the fitted spline curve of STS-gain against the pre-STS time. The curve exhibits a monotonically increasing trend, with a clear inflection point around 3.6 seconds, indicating that patients with longer baseline STS time tend to show greater improvement. In contrast, Figure 1 (right panel) presents the fitted spline curve of STS-gain against the Motor-FIM score. The curve displays a plateau beyond approximately 76 points, suggesting a ceiling effect among patients with high baseline functional independence.

Based on these spline structures, 3.6 seconds for the pre-STS time and 76 points for the Motor-FIM score were selected as potential cut-off values for stratification. The combination of these cut-off points yields a four-fold stratification table (Table 2), in which the subgroup defined by pre-STS time < 3.6 seconds and Motor-FIM score ≥ 76 contains only seven observations.

Table 2: Four-fold stratification based on pre-STS time and Motor-FIM score.

	Motor-FIM < 76	Motor-FIM ≥ 76
Pre-STS < 3.6	17	7
Pre-STS ≥ 3.6	65	15

Thus, we merged the subgroups and finally established the following three strata:

- **Stratum 1** ($n = 24$): pre-STS < 3.6 s, regardless of Motor-FIM score (poor task-specific capacity);
- **Stratum 2** ($n = 65$): pre-STS ≥ 3.6 s and Motor-FIM score < 76 (intermediate baseline function);
- **Stratum 3** ($n = 15$): pre-STS ≥ 3.6 s and Motor-FIM score ≥ 76 (excellent overall function).

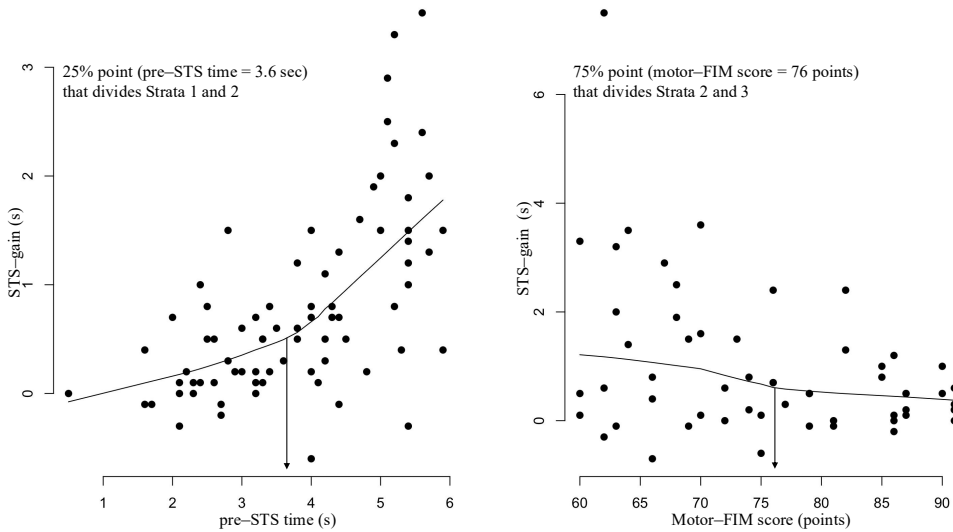


Figure 1: Spline-based identification of cut-off points for stratification. Left: STS-gain versus pre-intervention supine-to-sitting (pre-STTS) time. Right: STS-gain versus Motor Functional Independence Measure (Motor-FIM) score. Dashed lines indicate the selected cut-off values.

These strata represent patients with poor, intermediate, and excellent functional status, respectively, integrating both task-specific and global functional measures.

3.2.2. Regression analysis in each stratum

Linear regression of Y (STS-gain) on exposure X (basic movement exercise hours) was performed separately within each stratum. In Stratum 1, the estimated slope was $\beta = 0.006$ ($p = 0.59$), indicating no detectable association between exercise time and functional improvement. In Stratum 3, the estimated slope was $\beta = -0.01$ ($p = 0.44$), similarly indicating no statistically significant relationship. In contrast, Stratum 2 exhibited a statistically significant positive association ($\beta = 0.04$, $p = 0.01$), suggesting that greater time spent on basic movement exercises was associated with larger improvements in STS performance.

Figure 2 illustrates these exposure–outcome relationships within each stratum. These results demonstrate pronounced effect heterogeneity that is not captured by the conventional regression adjustment described in the preceding section.

3.2.3. A ceiling effect in the responsive stratum

Additional clinically relevant findings were obtained from the responsive stratum. Figure 3 presents the fitted spline curve of Y (STS-gain) plotted against X (basic movement exercise hours) in Stratum 2, showing an apparent plateau beyond approximately 15 hours of training.

To formally assess this pattern, a segmented regression model was fitted using the `segmented` package in R (Muggeo, 2003, 2008), yielding an estimated breakpoint of $\hat{c} =$

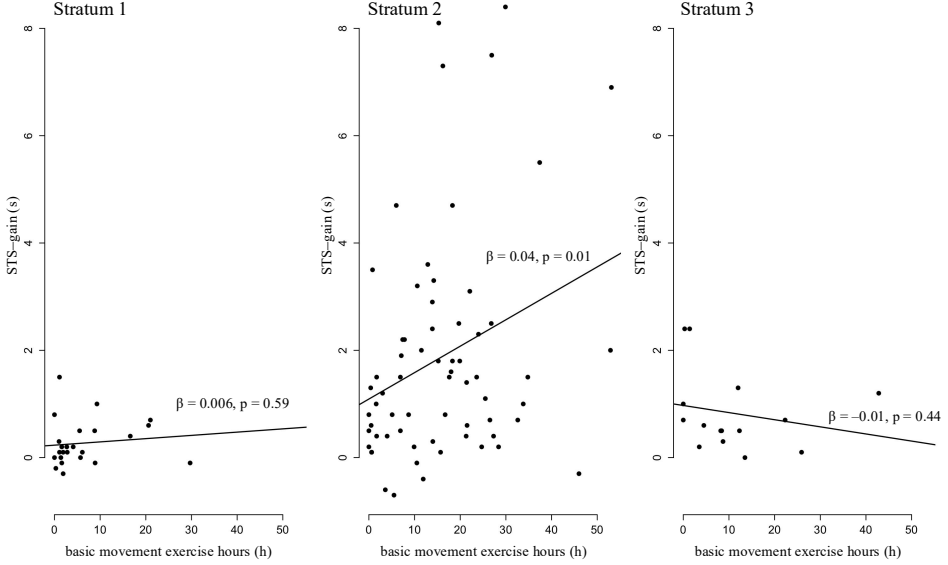


Figure 2: Relationship between STS-gain and basic movement exercise hours within each stratum. Panels correspond to Strata 1, 2, and 3, with fitted linear regression lines.

15.3 hours. The estimated slope before the breakpoint was 0.10 ($p = 0.04$). In contrast, the slope after the breakpoint was 0.01 ($p = 0.58$), indicating that additional training beyond this threshold results in little or no further improvement (Table 3). A Wald test for the change in slope confirmed that the two segments differed significantly ($p = 0.03$), providing statistical evidence for a ceiling effect in the dose–response relationship.

Table 3: Results of piecewise linear regression analysis in Stratum 2 with an estimated breakpoint at 15.3 hours.

	β	Standard error	p -value
Intercept	0.66	0.54	0.22
≤ 15.3 hours	0.10	0.05	0.04
> 15.3 hours	0.01	0.03	0.58

4. Discussion

Overall results obtained through regression-based adjustment for continuous confounding variables are not always directly informative in real-world settings, even when mathematically sophisticated models are employed. In contrast, as demonstrated in this study, stratification-based adjustment of continuous confounders can yield results that are more interpretable and practically relevant in applied contexts. In this study, we proposed a spline-based stratification framework to adjust for continuous confounders in observational studies with continuous treatments. The proposed approach facilitates the identification of heterogeneous and nonlinear exposure–outcome relationships that

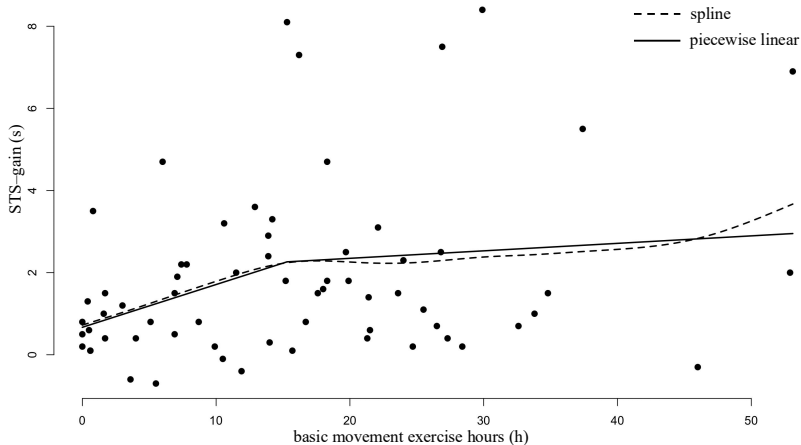


Figure 3: Dose-response relationship between STS-gain and basic movement exercise hours in Stratum 2, showing a plateau beyond approximately 15 hours.

may remain obscured under conventional regression-based methods. Application of the method to a dataset of patients with stroke undergoing inpatient physiotherapy illustrates its practical utility and yields clinically interpretable findings.

Specifically, the basic movement exercise program showed no statistically significant association with STS-gain in Stratum 1 and Stratum 3, whereas a significant positive association was observed in Stratum 2. Given that Stratum 1 comprises patients with poor baseline functional status and Stratum 3 includes patients with excellent functional status, these findings are empirically plausible. Patients with limited functional capacity may not benefit sufficiently from increased training duration, whereas patients with high functional independence may already be close to their performance ceiling.

The identification of a ceiling effect in the responsive stratum (Stratum 2) is particularly noteworthy. This result suggests that increasing the duration of basic movement exercises beyond a threshold yields diminishing returns. From a clinical perspective, these findings highlight the importance of tailoring exercise intensity and duration to patients' functional status, rather than uniformly increasing training volume.

Several limitations of this study should be acknowledged. First, spline-based identification of inflection points may be sensitive to sample size and the choice of smoothing parameters (Eilers and Marx, 1996). Alternative approaches, such as ℓ_1 trend filtering (Kim et al., 2009), could also be used to identify change points in confounder-outcome relationships. A systematic comparison of such methods is beyond the scope of this study and remains for future research. Second, although the present study focused on two continuous confounders for clarity and therefore considered two inflection points, the combination of multiple inflection points used to construct strata can become complex and may not yield a unique stratification. In such cases, empirical or clinical knowledge may be required to determine an appropriate stratification scheme. Finally, although the current framework was illustrated using continuous confounders, it can be extended to incorporate discrete confounding variables in future applications.

5. Conclusion

We introduced a spline-based stratification method to adjust for continuous confounders in observational studies with continuous treatments. Application of the proposed method to an observational dataset of patients with stroke undergoing inpatient physiotherapy demonstrated its practical utility. The approach provides a helpful framework for identifying heterogeneous and nonlinear exposure–outcome relationships that may be overlooked by conventional regression-based adjustment.

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