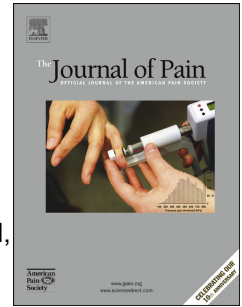


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Identifying Treatment Effect Modifiers in the STarT Back Trial: A Secondary Analysis

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Abstract: Identification of patient characteristics influencing treatment outcomes is a top low back pain (LBP) research priority. Results from the STarT Back Trial support the effectiveness of prognostic stratified care for LBP compared to current best care, however patient characteristics associated with treatment response have not yet been explored. The purpose of this secondary analysis was to identify treatment-effect modifiers within the STarT Back Trial at 4 months follow-up (n=688). Treatment response was dichotomized using back-specific physical disability measured by the Roland-Morris Disability Questionnaire (≥ 7). Candidate modifiers were identified using previous literature and evaluated using logistic regression with statistical interaction terms to provide preliminary evidence of treatment-effect modification. Socioeconomic status (SES) was identified as an effect modifier for disability outcomes (OR = 1.71, P=.028). High SES patients receiving prognostic stratified care were 2.5 times less likely to have a poor outcome compared to low SES patients receiving best current care (OR = 0.40, P=.006). Education level (OR = 1.33, P=.109) and number of pain medications (OR = 0.64, P=.140) met our criteria for effect modification with weaker evidence ($0.20 > P \geq 0.05$). These findings provide preliminary evidence for SES, education, and number of pain medications as treatment-effect modifiers of prognostic stratified care delivered in the STarT Back Trial.

Perspective: This analysis provides preliminary exploratory findings about the characteristics of patients who might least likely benefit from targeted treatment using prognostic stratified care for low back pain.

Keywords: low back pain, socioeconomic status, treatment effect modification, stratified care, subgrouping

Background

Identification of patients that are most likely to positively respond or gain the greatest benefit from different treatment approaches has been indicated as a top low back pain (LBP) research priority.^{15, 18, 60} The STarT Back trial³⁶ evaluated the clinical and cost effectiveness of stratified primary care that involved targeting treatment to subgroups based on their prognostic risk of persistent disabling pain.³⁶ The trial results were favorable for the overall comparison between stratified care compared to current best practice at both 4 and 12 month follow-ups and for the comparison between patients at low, medium and high risk of persistent pain in each arm of the trial.³⁶ In this paper, we focus on identifying the characteristics of patients who benefitted the most (and least) from this stratified care approach.

Identifying which patient level variables influence treatment outcomes has the potential to enhance clinical reasoning.³⁰ Methodological recommendations for study design, analysis and interpretation of such subgroup analyses are available including the need for clear terminology.^{7, 41, 59, 65, 69} In this study we attempt to distinguish between variables that demonstrated treatment effect modification for stratified care outcomes from those that were predictive of patient outcomes regardless of treatment. We use *treatment effect modifiers* are used for variables measured at baseline that demonstrated an interaction with the stratified care treatment outcomes (ie. in whom treatment was least effective).^{44, 59} For example, other study findings suggest older age as a potential treatment effect modifier for chronic LBP patients receiving Mechanical Diagnosis and Therapy (ie, McKenzie method) compared to Back School, indicating age may be an important factor to consider when identifying responders to this specific treatment.²⁴ We use *prognostic factors* for variables measured at baseline that were predictive of patient outcomes but did not interact with allocated treatment and were therefore not providing information specific to the stratified care intervention response.^{44, 59} For example, psychological factors have been found to be strong prognostic indicators for LBP outcomes, however not consistently predictive of response to physical therapist-led exercise and/or advice (ie, a specific treatment).⁶⁸

Most clinical trials are not adequately powered to investigate subgroup effects, however such analyses can still provide important hypothesis-generating information for future research.^{44, 59} Pincus et al.⁵⁹ recommend four key criteria for treatment effect modification analysis using clinical trial data: 1) potential modifiers should be measured prior to randomization; 2) selection of potential modifiers should be based on theory or evidence; 3) measurement of baseline factors should be reliable and valid; and 4) an explicit test of the interaction between potential modifiers and treatment is required. Gurung et al.²⁸ recently used these criteria in their systematic review of potential LBP treatment effect modifiers from four clinical trials, testing acupuncture,^{12, 78} exercise and manual therapy,⁷¹ and psychological treatment.⁴⁶ Variables associated with treatment outcome that had strong evidence included patients' age, employment status and type, back pain severity, narcotic medication use, treatment expectations and education level. Variables associated with treatment outcome that had weak evidence included gender, psychological distress, initial pain intensity, disability, and quality of life.

STarT Back trial³⁶ patient characteristics that interact with treatment outcome have not yet been evaluated and these have the potential to provide additional information about which patients might be less likely to benefit from matched treatment in this stratified care approach. Therefore, the purpose of this analysis was to explore potential patient level treatment effect modifiers at four months follow-up. Specifically, our strategy was twofold consisting of: 1) identification of potential treatment effect modification using descriptive statistics to explore the patient characteristics associated with treatment outcome in which there was no benefit from stratified care and 2) preliminary confirmation of treatment effect modification using formal moderation analysis with a test for statistical interaction.

Methods

STarT Back Trial

We conducted a secondary analysis of data from the STarT Back trial.³⁶ Briefly, the STarT Back trial was a parallel, two-armed, randomized controlled trial that evaluated the clinical and cost effectiveness of prognostic risk stratified primary care (intervention) with non-stratified current best care (control) for LBP patients with follow-up at 4 and 12 months. Participants were recruited from 10 general practices in the North West Midlands region of England, UK.

STarT Back Trial Procedures

All participants received an initial 30-minute physical therapy evaluation that was supplemented with a brief intervention consisting of LBP education and advice. Subsequent interventions were based on participant randomized allocation. Additional treatment for control group participants was at the discretion of the treating physical therapist, as per current best care. Additional treatment for intervention group participants was based on baseline risk stratification (low, medium, or high risk for persistent LBP disability) determined using the STarT Back tool.³⁴ Details of the matched treatments have previously been described elsewhere.³¹

Description of Candidate Treatment Effect Modifiers

Baseline factors were collected from each participant prior to randomization and treatment allocation. Selection of potential treatment effect modifiers for this secondary analysis was based on their influential relationship with LBP clinical outcome as indicated by previous literature (defined below). For this analysis we focused only on *treatment modifiers* that would not be expected to change during treatment and therefore could be used to characterize patients. Other factors such as pain intensity or psychological variables that were specifically targeted through stratified care interventions and therefore expected to change were not included based on a priori determination. The selected treatment effect modifiers are described below with the hypothesized direction of influence defined for each factor.

1. Age was categorized into one of three groups (≤ 44 ; 45-64; ≥ 65 years) similar to previous studies.⁶² We hypothesized that prognostic stratified care would be less effective compared to best current care for older (≥ 65 years) compared to younger patients.^{28, 32, 46, 63, 66, 76}
2. Gender was categorized into one of two groups (female or male). We hypothesized that prognostic stratified care would be less effective compared to best current care for females compared to males after controlling for baseline disability based on findings from previous review studies.^{3, 21}
3. Education level was categorized into one of four groups (further or higher education, other work or non-work related, compulsory education, or no qualifications).⁵⁷ Further education includes all non-advanced courses taken after the period of compulsory education including secondary school, whereas higher education is beyond secondary school commonly offered at the university level. Other work or non-work related education includes other types of non-school, non-university education and training. Compulsory education is required for all children between 5 and 16 years of age. We hypothesized that prognostic stratified care would be less effective compared to current best care for patients with lower levels of education.^{8, 16, 28, 46}
4. Socioeconomic status (SES) was assessed using the National Statistics Socio-economic Classification (NS-SEC) reduced method which is primarily based on job occupation.⁵⁶ Categorization was solely based on job occupation. The NS-SEC was collapsed into one of three classes of SES (Upper [higher managerial, administrative and professional occupations]; Middle [intermediate occupations]; and Lower [lower supervisory and technical occupations, semi-routine and routine occupations]). We hypothesized that prognostic stratified care would be less effective compared to current best care for patients with lower SES.^{8-10, 52}
5. Current employment status was dichotomized (yes or no). We hypothesized that prognostic stratified care would be less effective compared to current best care for patients that were not currently employed.^{27, 28, 46, 52, 76}
6. Work satisfaction was dichotomized (satisfied or not satisfied) based on responses to a five-point Likert scale. 'Very satisfied' and 'satisfied' responses were collapsed to create a 'satisfied' variable

and ‘no opinion’, ‘not very satisfied’, and ‘not at all satisfied’ responses were collapsed to create a ‘not satisfied’ variable. We hypothesized that prognostic stratified care would be less effective compared to current best care for patients that were not satisfied with their work.^{14, 47, 50}

7. Duration of current symptoms was categorized into one of three groups (<1 month; 1 to 3 months; or >3 months). We hypothesized that prognostic stratified care would be less effective compared to current best care for patients that reported a longer duration of symptoms.^{33, 63, 66, 76}
8. Number of current pain medications was categorized into one of three groups (0; 1 to 2; ≥ 3). We hypothesized that prognostic stratified care would be less effective compared to current best care for patients that reported using three or more pain medications.^{23, 25, 26, 38, 51, 61}
9. Expectations for recovery at four months was categorized into one of three groups (high, moderate, low) based on tertile cutoff scores from an 11-point scale with ‘0’ indicating ‘completely better’ to ‘10’ indicating ‘extreme pain’. We hypothesized that prognostic stratified care would be less effective compared to best current care for patients reporting lower expectations for recovery.^{4, 8, 22, 28, 33, 54}

Definition of Outcome

We defined outcome as LBP related physical disability at four months following randomization assessed using the Roland and Morris Disability Questionnaire (RMDQ).⁶⁴ The 24-item RMDQ assesses physical function over the past 24 hours and has a potential scoring range of 0 ‘no disability due to LBP’ to 24 ‘maximum disability due to LBP’, with higher scores indicating higher LBP related disability. The RMDQ has been found to have high levels of test-retest reliability, internal consistency, validity, and responsiveness.¹¹ To be consistent with previous research involving the STarT Back screening tool^{34, 77} disability outcome scores at four months were recoded into *Satisfactory Outcome* (RMDQ <7) and *Poor Outcome* (RMDQ ≥ 7). Our rationale for analyzing LBP related disability outcomes at 4 months was based on detection of larger between group effect sizes in the STarT Back trial at this time-point,³⁶ therefore identification of treatment effect modifiers was more likely at 4 months compared to 12 months.

Data Analysis

All statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp, Armonk, New York). Descriptive statistics were used to evaluate for *treatment effect modification* within and between baseline factors and treatment allocation (ie, stratified care versus best current care) for disability outcome. Chi-square testing was used to compare the proportion of patients with poor outcome ($RMDQ \geq 7$) across treatment groups at each level of individual baseline factors to provide an indication of potential treatment effect modification from stratified care. Specifically, we were interested in potential modifiers associated with a greater proportion of patients with poor outcome for the stratified care group compared to best current care ($P < .05$), which would potentially provide an indication of treatment effect modification.

Once potential treatment effect modifiers were identified from the above descriptive analysis, they were confirmed with a formal moderation analysis using a test for statistical interaction.^{59, 69} We fully acknowledge that our sample size may not be adequately powered for these statistical interaction tests following guidance on minimal group size,⁵⁹ therefore the results should only be interpreted as preliminary. Separate binary logistic regression models were used to evaluate contributions of each individual baseline potential treatment effect modifier and treatment group allocation. We tested for *treatment modification* by incorporating a group x factor interaction term. Specifically, each model was built using three separate blocks: 1) baseline RMDQ score and treatment group; 2) baseline factor; 3) treatment group x baseline factor interaction term. All interactions with a p-value ≤ 0.20 were reported to ensure all possible treatment effect modifiers were identified and categorized into exploratory ($P < 0.05$) or additional exploratory evidence ($0.20 > P \geq 0.05$) similar to criteria used for a recent systematic review.²⁸

Results

Baseline characteristics of participants are described in **Table 1**.

Potential Treatment Effect Modifiers

The results from the descriptive analysis demonstrated, as expected, that there were similar and consistent within treatment arm relationships between several baseline potential treatment effect modifiers and the proportion of patients with poor outcome. General prognostic factors with an increased proportion of patients with a poor outcome in both stratified care and best current care groups included; older age, lower level of education, greater number of pain medications, and lower expectations for recovery (**Table 2**). Inspection of the between treatment arm comparisons generally and consistently revealed a higher proportion of best current care patients associated with poor outcome (in favor of stratified care), however there were several baseline factors where the proportion of stratified care patients associated with poor outcome was similar between treatment arms ($P > .05$) indicating stratified care did not benefit and signifying potential treatment effect modification (ie, lower education, low SES, lack of current employment, ≥ 3 pain medications, and low expectations for recovery) (**Table 2**). Each factor associated with non-significant ($P > .05$) between treatment arm relationships was selected for subsequent formal moderation analysis to test for statistical interactions using logistic regression.

Exploratory Evidence for Treatment Effect Modification

The results of the logistic regression are provided in **Table 3**. Socioeconomic status (SES) was identified as the only treatment effect modifier for poor treatment outcome ($RMDQ \geq 7$) at four months ($OR = 1.71$, 95% CI: 1.06, 2.77, $P = .028$) (**Figure 1**). Decomposition of the treatment x SES interaction term indicated that compared to those receiving best current care with low SES, those receiving stratified care with high SES were 2.5 times less likely to have a poor treatment outcome ($OR = 0.40$, 95% CI: 0.20, 0.77, $P = .006$) (**Figure 2**). Further exploratory descriptive analysis indicated a greater proportion of low SES patients with poor treatment outcome that received stratified care compared to best current care for low (13.0% and 9.5%) and medium (33.7% and 25.0%) risk subgroups, however this was not observed for the high risk subgroup (55.0% and 69.7%) and needs to be interpreted with caution as cell counts were very low. Similar trends were also observed for patients with low education (ie, no qualifications) for low (18.8% and 11.1%), medium (37.0% and 36.8%) and high (73.3% and 71.3%) risk subgroups. There

were no other STarT Back risk groups for whom stratified care produced worse treatment outcomes than those receiving current best care.

Additional Exploratory Evidence for Treatment Effect Modification

Other treatment effect modifiers meeting our criteria for treatment effect modification with additional exploratory evidence ($0.20 > P \geq 0.05$) included education level (OR = 1.33, 95% CI: 0.94, 1.90, $P = .109$) (**Figure 3**) and number of current pain medications (OR = 0.64, 95% CI: 0.35, 1.16, $P = .140$) (**Figure 4**). Decomposition of the treatment x education interaction term indicated that compared to those receiving best current care with ‘no qualifications’, those receiving stratified care who had ‘further or higher education’ were approximately 3 times less likely to have a poor treatment outcome (OR = 0.30, 95% CI: 0.14, 0.63, $P = .002$). Decomposition of the treatment x pain medication interaction term indicated that compared to those receiving best current care who were using ‘ ≥ 3 pain medications’, those receiving stratified care and using ‘no pain medications’ were approximately 5 times less likely to have a poor treatment outcome (OR = 0.19, 95% CI: 0.08, 0.45, $P < .001$).

Comparative Moderation Analysis Findings

Additional support for treatment effect modification was reduced when performing similar moderation analyses using linear regression with either RMDQ percent change or continuous scale scores at four months serving as the dependent variable in separate models (complete data not provided). Specifically, observed treatment x SES statistical interaction p-values changed from 0.028 (RMDQ ≥ 7 model) to 0.066 (RMDQ percent change score model) and 0.072 (RMDQ continuous scale score model).

Discussion

Statement of Principal Findings

The aim of this secondary analysis was to explore for baseline patient level treatment effect modifiers for stratified care within the STarT Back trial, with a focus on those that were associated with a poor

treatment outcome. We found that stratified care was associated with fewer patients of high SES with poor outcome (19.3%) compared to best current care (38.9%). However, in patients categorized as low SES the proportion with poor outcome was similar (35.4% and 37.2%). Treatment effect modification was statistically significant ($P = .028$) for SES and decomposition of the interaction indicated that compared to those receiving best current care who were classed as low SES, those receiving stratified care classed as high SES were 2.5 times less likely to have a poor treatment outcome. This finding is consistent with previous studies that have reported treatment effect modification by SES for other health conditions.⁴⁸ Weaker evidence for treatment effect modification was found for education and number of pain medications, which although consistent with previous findings, require further exploration in adequately powered studies.

Socioeconomic Status

The observation in this exploratory analysis that the proportion of low SES patients with poor outcome was very similar in both treatment arms of the trial (35.4% and 37.2%) is of potential clinical importance. Although we were not able to definitively determine if stratified care was more beneficial for high SES participants or less beneficial for low SES participants, two plausible theories may provide explanation of the potential influence of SES. First, lower SES patients did not benefit from stratified care (ie, the matched treatments were not sufficiently tailored for lower SES patients, particularly it would seem from descriptive data only, in the STarT Back Tool's low and medium risk subgroups). Previous suggestions have indicated that increased patient commitment, motivation and potentially more intensive treatment may be required for patients at high risk with other health conditions.⁴⁵ It is also plausible that barriers to good health outcomes commonly encountered by low SES patients (eg. low health literacy, poorer access to care) involve complex interactions at both the environmental and individual level and these may have influenced our results.⁹ Therefore, modifying treatment approaches to meet the needs of different SES groups has been previously suggested⁷⁴ which may have implications for all patients regardless of risk status for clinical outcomes. Second, there is the potential that low SES patients

enrolled in the STarT Back trial³⁶ shared similar characteristics to patients that do not respond to LBP treatments in general. For example, secondary analysis of data (n = 949) from the UKBEAM trial where participants were randomized to receive either 1) best general practice care only or in addition: 2) spinal manipulation, 3) exercise or 4) combined spinal manipulation and exercise; found similar findings to our study with the intervention showing a less favorable treatment effect for certain individuals based on three SES indicators.⁵² Specifically, study participants from areas of high deprivation, with less education, and who were not working consistently (ie. those with low SES) reported greater LBP related disability across all treatment groups.⁵²

Socioeconomic disparities are associated with health inequalities for a variety of conditions including musculoskeletal disorders.^{53, 55} However, SES influence on LBP outcomes has not been extensively evaluated,^{10, 73} particularly in comparison to other health conditions. For example, those with higher SES have consistently achieved greater rates of long term abstinence compared to those with lower SES following participation in tobacco dependence treatment programs.^{67, 75} Therefore, it is not surprising that alternative or enhanced treatments have been suggested for health conditions^{19, 39, 74} including LBP^{9, 17} that specifically consider the circumstances of patients with low SES. Previous suggestions have also indicated that self-management approaches, particularly those incorporating cognitive behavioral principles, may be more appropriate for higher SES individuals.^{9, 10, 17} Consequently, identifying and addressing barriers that low SES patients commonly encounter such as low health knowledge or literacy^{6, 13, 70, 72} is appealing as it has potential to enhance LBP treatment outcomes for this often underserved patient population.

Additional Exploratory Evidence for Treatment Effect Modification

Treatment effect modification trends were also observed for education and use of pain medication, findings similar to a recent systematic review that identified potential moderators for response to LBP treatment.²⁸ Gurung, et al.²⁸ identified younger age, being employed or in sedentary occupations, less

narcotic medication use, higher levels of education, and greater positive treatment expectations as potential treatment effect modifiers for positive LBP treatment response using data generated from four randomized trials. In addition, prognostic capabilities associated with lower education level^{8, 16, 76} and using an increased number of pain medications^{23, 51} have been reported for musculoskeletal pain clinical outcomes in previous studies that have not specifically tested for treatment effect modification. Collectively, our findings support the need for further exploration of treatment effect modification through adequately powered studies and these should include patient level factors such as education level and use of pain medications.

Although we were not able to identify other treatment effect modifiers based on statistical interactions, several factors demonstrated prognostic capabilities for both intervention and control group outcomes. These findings can inform future LBP intervention studies by providing hypothesis generating information and highlight the fundamental nature of prognostic research from identifying priority areas for risk stratification to evaluating potential candidate factors that may predict treatment response.³⁷ For example, older age was associated with an increased proportion of patients with poor outcome compared to younger age, which is consistent with previous LBP prognostic study findings.^{32, 33, 63, 76} Moreover, patients with lower expectations for recovery were more likely to have a poor outcome compared to those with higher expectations, and this is also consistent with previous LBP prognostic study findings.^{8, 29, 42}

Strengths and Weaknesses

We conducted secondary analyses of data from a large randomized controlled trial.³⁶ We selected patient level factors as potential treatment effect modifiers based on influential relationships with LBP clinical outcomes previously reported in the literature. We acknowledge that certain selected factors did have potential to change during the course of treatment (ie, number of pain medications and recovery expectations); however including such factors in these analyses would potentially enhance the ability to characterize patients at baseline.

The aims of this study were exploratory following methodological criteria for moderator analysis suggested by Pincus et al.⁵⁹ Specifically, this current study is a secondary ‘post-hoc’ analysis with findings provided for hypothesis generating purposes as there was no pre-specified ‘a-priori’ moderator effect size reported in the original trial protocol. Our exploratory results provide important hypothesis generating information for future clinical trials which are needed⁴³ and may have specific implications for studies evaluating the clinical effectiveness of stratified care for LBP. Our findings reflect exploratory evidence that should be interpreted with caution and not considered as confirmatory as the factors selected for this secondary analysis were based on theory and previous research.⁵⁹ For example, lower education level^{8, 16, 76} and increased number of pain medications^{23, 51} have demonstrated prognostic capabilities for musculoskeletal pain related clinical outcomes in previous studies, however were only identified as having weak evidence to modify treatment response in our analysis. Future studies are required to confirm these findings prior to changes in clinical practice.

We were not adequately powered to analyze the influence of three-way interactions on poor outcome, which is disappointing as those findings may have provided further perspective to our findings. For example, incorporating three-way [treatment x SES x initial STarT Back tool risk subgroup] interaction terms into our logistic regression models may have provided preliminary support for stratified care being least effective for those patients at low SES also identified as at high risk of persistent pain. Therefore, we were not able to fully establish if stratified care was more beneficial for high SES participants or less beneficial for low SES participants and if so how these relationships were potentially influenced by other factors (eg, risk subgroup, work satisfaction, recovery expectations). Previous suggestions are that there should be a minimum of at least 20 individuals in the smallest group when conducting subgroup analyses⁵⁹ and many cell counts in this current study did not achieve this criterion when comparing the proportion of patients with poor outcome by SES across initial risk subgroup (or other factors included in these analyses).

We also acknowledge the relative strengths and weaknesses associated with our analyses that used an absolute cut point (≥ 7) as opposed to RMDQ change scores and the potential effect this may have on our conclusions. Our decision for using the ≥ 7 RMDQ cut point allows for direct comparisons to previous studies,^{34,77} while also considering the optimal method for analyzing responsiveness to LBP interventions is debatable. Recent recommendations include reporting the cumulative distribution of responses for treatment and control groups to provide the proportion of patients at each scale score who experience change at that level or better,¹⁸ however such an approach may be difficult to interpret group interactions. Others have suggested 30% improvement from baseline to be a useful threshold for identifying clinically meaningful improvement,⁵⁸ however these methods are also associated with limitations.²⁰ Our decision to use an absolute cut point is consistent with previous studies involving the STarT Back Tool^{34,77} and is a common method to assess LBP recovery,⁴⁰ however may be associated with several limitations including loss of statistical power and increased potential for type I and II errors.³⁷ Moreover, we were not able to determine if patient perspectives of poor outcome at 4 months was consistent with the RMDQ cut point used in this study.

For this secondary analysis, SES was assessed using the National Statistics Socio-economic Classification (NS-SEC) reduced method which is primarily based on job occupation, however we acknowledge that SES has been defined as a multidimensional construct that is commonly measured in health services research as a combination of education, income, and occupation.² Our rationale for using the NS-SEC reduced method, which collapses SES into three potential classes, was primarily based on the observation of extremely low cell counts when using alternative NS-SEC methods that collapse SES into eight potential classes. Although job occupation has been indicated as a valid proxy indicator for SES,¹ we acknowledge that the method used in this analysis did not specifically account for other important indicators such as education and income when classifying SES. We did however observe a trend for level of education as a treatment effect modifier providing further support to the SES finding.

Comparison to Other Studies

Comparison of our findings to others should be done with caution as previous studies have not focused on evaluating the influence of non-modifiable patient level factors for LBP treatment effect modification and have used alternative statistical methods.^{24, 49, 68} Previous studies have commonly used linear regression and incorporated specific thresholds (eg, one standard deviation change from baseline) to aid interpretation of the magnitude of treatment effect modification and determine clinically important interaction effects. Collectively, many of those studies have found that although most factors predicted outcomes regardless of treatment (indicating prognostic capabilities), very few were able to predict response to a particular treatment (indicating treatment effect modification). We used logistic regression because the treatment response outcome was dichotomous ($RMDQ \geq 7$) and reported all interactions with a p-value ≤ 0.20 to ensure that all potential modifiers were identified similar to the approach used by Gurung et al.,²⁸ however support for treatment effect modification was reduced when using linear regression modelling strategies.

Future studies should be designed and powered so they have the ability to distinguish between factors that demonstrate prognostic or treatment effect modification capabilities (or both) to further inform clinical reasoning.^{35, 37} We also recognize that for future randomized controlled trials to be adequately powered for robust detection of treatment effect modification, the sample size required should be increased at least fourfold the required sample size to detect main treatment effects,^{5, 59} presenting a key challenge to research planning, funding and delivery.

Meaning of the Study: Implications for Clinicians

We have provided preliminary findings for SES, level of education, and number of pain medications as potential treatment effect modifiers for LBP prognostic stratified care; however future studies are required to confirm these findings prior to changing clinical practice. If our findings are validated in future studies,

the outcomes from stratified care may be improved through greater tailoring of stratified care for specific patient characteristics. For example, development of an enhanced treatment that better supports and meets the needs of low SES patients who are at high risk of persistent disability may provide a beneficial treatment option for this population.

Future Research

Future studies should evaluate complex interactions that may exist between factors identified in this analysis and other potentially influential patient characteristics (eg, health literacy, health knowledge, and motivation) that may be modified with treatment. For example, the feasibility of developing enhanced treatments that better meet the needs of low SES patients has strong potential to inform planning of future studies capable of informing best practice. Collectively, findings from this study provide additional support for future LBP trials to include SES, education, and pain medications as a means to define subgroups and evaluate treatment effect modification.

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Legends:

Figure 1. Poor treatment response by socioeconomic status

Figure 2. Decomposed treatment response by socioeconomic status interactions.

Figure 3. Poor treatment response by level of education.

Figure 4. Poor treatment response by number of pain medications.

Table 1. Baseline characteristics of STarT Back trial participants (n = 851).

Table 2. Baseline characteristics of participants with poor treatment outcome (RMDQ ≥ 7) at 4 months.

Table 3. Results of separate logistic regression models for 4 month RMDQ (≥ 7) poor outcome.

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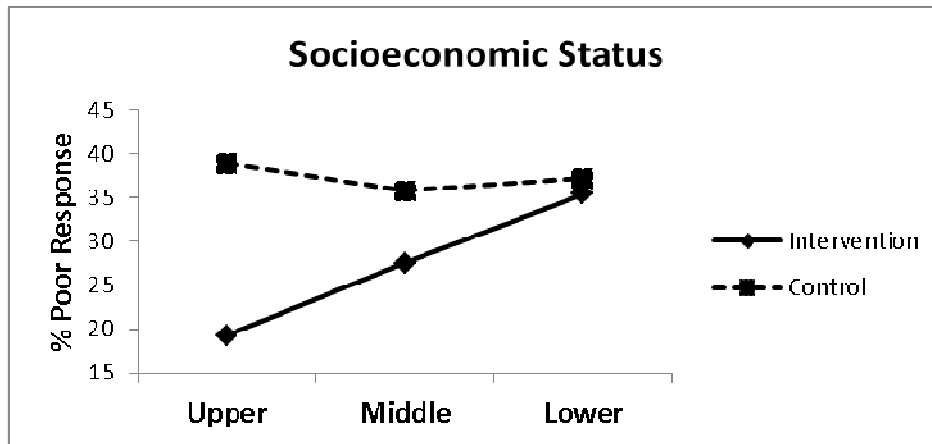


Figure 1.

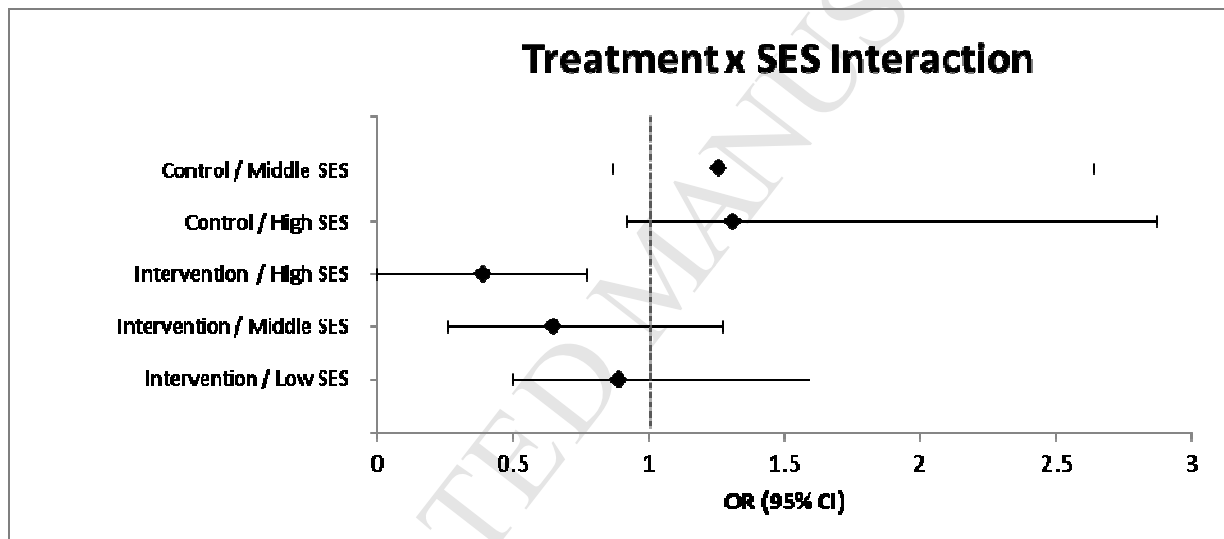


Figure 2.

Decomposed Treatment x SES interaction.

Reference: Control / Low SES

SES = socioeconomic status; OR = odds ratio; CI = confidence interval.

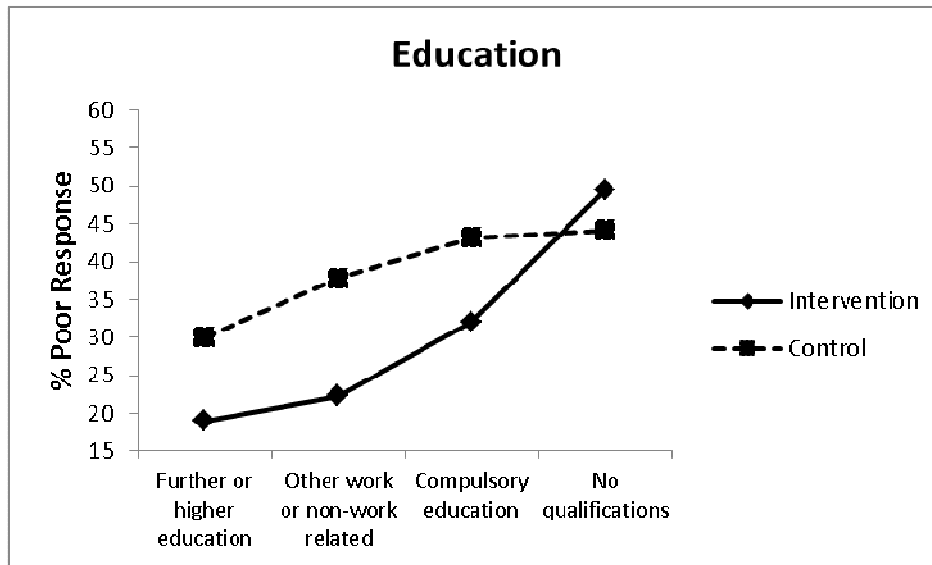


Figure 3.

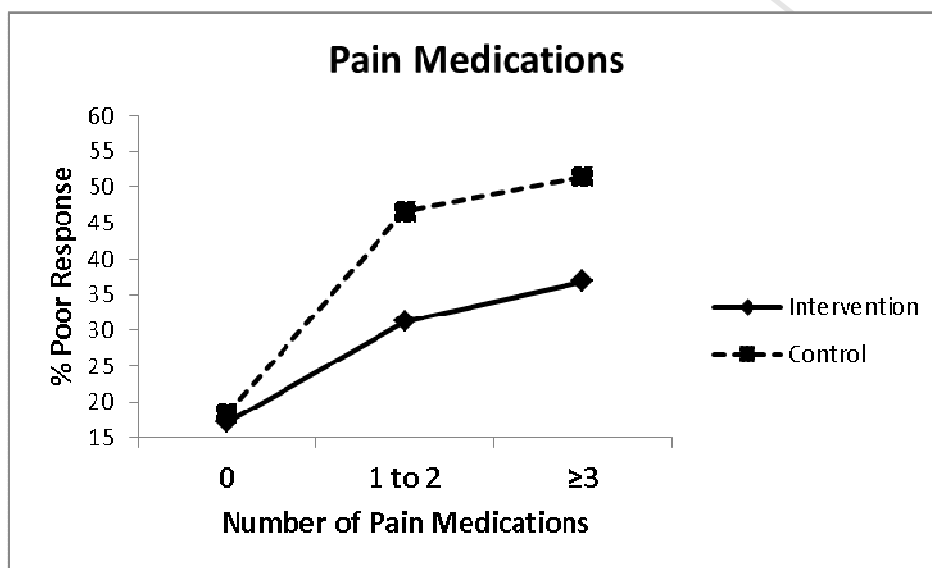


Figure 4.

Table 1. Baseline characteristics of STarT Back trial participants (n = 851).

Variable	Total Sample	Intervention	Control
Age			
≤44	329 (38.7%)	221 (38.9%)	108 (38.2%)
45-64	374 (43.9%)	240 (42.3%)	134 (47.3%)
≥65	148 (17.4%)	107 (18.8%)	41 (14.5%)
Gender			
Female	500 (58.8%)	330 (58.1%)	170 (60.1%)
Male	351 (41.2%)	238 (41.9%)	113 (39.9%)
Education			
Further or higher education	230 (27.1%)	156 (27.5%)	74 (26.2%)
Other work or non-work related	280 (32.9%)	185 (32.6%)	95 (33.7%)
Compulsory education	164 (19.3%)	104 (18.3%)	60 (21.3%)
No qualifications	176 (20.7%)	123 (21.7%)	53 (18.8%)
Socioeconomic status			
Upper	233 (28.6%)	162 (29.9%)	71 (26.0%)
Middle	209 (25.6%)	132 (24.4%)	77 (28.2%)
Lower	373 (45.8%)	248 (45.8%)	125 (45.8%)
Currently employed			
Yes	524 (61.6%)	350 (61.6%)	174 (61.5%)
No	327 (38.4%)	218 (38.4%)	109 (38.5%)
Work satisfaction*			
Satisfied	427 (81.5%)	288 (82.3%)	139 (79.9%)
Not satisfied	97 (18.5%)	62 (17.7%)	35 (20.1%)
Duration of symptoms (How long since whole month without pain?)			
< 1 month	151 (17.7%)	97 (17.1%)	54 (19.1%)
1-3 months	190 (22.3%)	124 (21.8%)	66 (23.3%)
> 3 months	510 (59.9%)	347 (61.1%)	163 (57.6%)
Pain medications			
0	223 (26.2%)	136 (23.9%)	87 (30.7%)
1 to 2	444 (52.2%)	289 (50.9%)	155 (54.8%)
≥3	184 (21.6%)	143 (25.2%)	41 (14.5%)
Expectation for recovery at 4-months			
High	342 (40.4%)	222 (39.2%)	120 (42.7%)
Moderate	384 (45.3%)	261 (46.1%)	133 (43.8%)
Low	121 (14.3%)	83 (14.7%)	38 (13.5%)

*Work satisfaction estimates based on participants that were currently employed (n=524).

Table 2. Baseline characteristics of participants with poor treatment outcome (RMDQ ≥ 7) at 4 months.

Variable	Treatment Allocation		
	Intervention	Control	
Age			
≤ 44	32 (20.1%)	22 (33.3%)	P = .052
45-64	70 (33.2%)	46 (39.7%)	P = .292
≥ 65	35 (36.5%)	17 (42.5%)	P = .644
Gender			
Female	85 (31.0%)	53 (39.3%)	P = .119
Male	52 (27.1%)	32 (36.8%)	P = .134
Education			
Further or higher education	23 (19.0%)	18 (30.0%)	P = .140
Other work or non-work related	35 (22.3%)	28 (37.8%)	P = .021
Compulsory education	26 (32.1%)	19 (43.2%)	P = .298
No qualifications	53 (49.5%)	19 (44.2%)	P = .684
Socioeconomic status			
Upper	26 (19.3%)	21 (38.9%)	P = .009
Middle	30 (27.5%)	24 (35.8%)	P = .322
Lower	70 (35.4%)	35 (37.2%)	P = .866
Currently employed			
Yes	57 (20.6%)	44 (32.8%)	P = .010
No	80 (42.3%)	41 (46.6%)	P = .588
Work satisfaction			
Satisfied	48 (20.9%)	33 (30.8%)	P = .065
Not satisfied	9 (19.1%)	11 (40.7%)	P = .081
Duration of symptoms (How long since whole month without pain?)			
< 1 month	23 (28.4%)	16 (40.0%)	P = .281
1-3 months	13 (12.9%)	13 (23.2%)	P = .150
> 3 months	101 (35.6%)	56 (44.4%)	P = .114
Pain medications			
0	18 (17.1%)	13 (18.3%)	P = .997
1 to 2	77 (31.2%)	54 (46.6%)	P = .006
≥ 3	42 (36.8%)	18 (51.4%)	P = .179
Expectation for recovery at 4-months			
High	32 (16.9%)	26 (28.9%)	P = .031
Moderate	67 (31.9%)	36 (36.7%)	P = .483
Low	36 (55.4%)	23 (71.9%)	P = .179

RMDQ – Roland and Morris Disability Questionnaire.

% indicates – percent of those that had poor treatment outcome (RMDQ ≥ 7).

Table 3. Results of separate logistic regression models for 4 month RMDQ (≥ 7) poor outcome.

	Factor	Treatment Allocation	Factor x Group Term
Age	1.14 (0.72, 1.80), P=.567	0.46 (0.15, 1.41), P=.173	1.12 (0.65, 1.95), P=.682
Gender	0.94 (0.50, 1.77), P=.846	0.62 (0.19, 1.96), P=.414	0.95 (0.43, 2.07), P=.890
Education	1.09 (0.82, 1.45), P=.558	0.28 (0.11, 0.71), P=.008	1.33 (0.94, 1.90), P=.109
Socioeconomic status	0.87 (0.59, 1.28), P=.474	0.18 (0.06, 0.54), P=.003	1.71 (1.06, 2.77), P=.028
Employment	1.63 (0.87, 3.06), P=.128	0.44 (0.13, 1.42), P=.169	1.18 (0.54, 2.57), P=.676
Current status	1.31 (0.59, 2.91), P=.515	0.57 (0.12, 2.59), P=.465	0.96 (0.35, 2.66), P=.934
Work satisfaction	1.37 (0.53, 3.53), P=.513	0.83 (0.17, 4.09), P=.822	0.68 (0.19, 2.42), P=.554
Symptom duration	1.58 (1.05, 2.39), P=.029	0.60 (0.16, 2.22), P=.443	0.96 (0.58, 1.60), P=.889
Medication	1.60 (0.97, 2.62), P=.063	1.36 (0.39, 4.72), P=.634	0.64 (0.35, 1.16), P=.140
Expectation	1.70 (1.07, 2.69), P=.025	0.35 (0.12, 1.05), P=.062	1.28 (0.72, 2.25), P=.403

Values are odds ratio (95% confidence intervals) and associated P value for the effect of the factor, the main effect of treatment group, and the interaction between factor and treatment group on 4 month RMDQ (≥ 7) poor outcome status. Binary logistic final model estimates (baseline RMDQ included in all models). Treatment allocation (reference = control group)

Highlights

- We conducted a secondary analysis to identify treatment-effect modifiers within the STarT Back Trial at 4 months follow-up.
- Socioeconomic status was identified as an effect modifier for disability outcomes with education level and number of pain medications meeting criteria for effect modification with weaker evidence.
- We have provided preliminary exploratory findings about characteristics of patients who might least likely benefit from prognostic stratified care treatment for low back pain.