Can the inferences of the Paracetamol for Acute Low Back Pain (PACE) trial be reproduced?

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Submitted

ABSTRACT

Introduction

The aim of this study was to reanalyze and reinterpret data obtained in PACE, the first large randomized controlled trial evaluating the efficacy of paracetamol in acute low back pain, to assess the inferential reproducibility or the original conclusions.

Methods

Mixed effects models were used to reanalyze pain intensity (primary outcome; 11-point Numeric Rating Scale), and physical functioning, health-related quality of life, sleep quality and time until recovery (as secondary outcomes), according to the intention-to-treat principle. The original authors of the PACE study were not involved in the development of the methods for this reanalysis.

Results

The reproduction analyses indicated no effect of treatment on pain intensity and confidence intervals excluded clinically worthwhile effects (coefficient for regular paracetamol versus placebo 0.00 (-0.02- 0.01, p = 0.85); coefficient for paracetamol as-needed versus placebo 0.00 (-0.02 – 0.01, p = 0.92)). Similar results were obtained for all secondary outcomes.

Conclusions

This study indicates that the conclusions of the PACE trial are inferentially reproducible, even when using a different analytical approach. This reinforces the notion that management of acute low back pain should focus on providing patients advice and reassurance without the addition of paracetamol.

INTRODUCTION

Paracetamol (acetaminophen) used to be the first-choice analgesic for acute low back pain (LBP), but several recent clinical practice guidelines have abandoned this recommendation due to new evidence about its lack of efficacy (2-6). This evidence came from a 2016 Cochrane Review, which mainly based its results on the Paracetamol for Acute Low Back Pain (PACE) trial, the first and only large placebo-controlled randomized controlled trial (RCT) concerning the efficacy of paracetamol in acute LBP (7, 8). As this trial was highly influential on recent guidelines, the reproducibility of its results is of great importance (9).

Although the importance of reproducibility of scientific results is universally agreed upon, the terminology describing different types of reproducibility is not. In 2016, Goodman and colleagues introduced their 'new lexicon for research reproducibility', in which they described 3 types of reproducibility: methods reproducibility, results reproducibility and inferential reproducibility (10, 11). Methods reproducibility refers to the reproduction of an analysis using the same data, analysis plan and code, with the only difference being the analyst (12, 13). In results reproduction (also called 'replication'), new data is collected in the same population and consequently analyzed using the same analysis plan (12, 13). Finally, inferential reproducibility is the making of knowledge claims of similar strength from either a study replication or reanalysis of original data (10). In clinical research, reproduction studies are often the exception rather than the rule. However, early acceptance of scientific claims that are subsequently not reproducible may lead to harms; furthermore, reproduction is important in case only little evidence exists about a certain topic (14).

In the PACE trial, methods reproducibility was already addressed, as ***"Two statisticians who were masked to allocation independently did statistical analyses…"*** (8). Another RCT evaluating the result of the PACE trial (called the PACE Plus trial) was discontinued in 2017 due to insufficient recruitment of participants (15, 16). The primary outcome in the PACE trial was time until recovery from LBP, but this outcome is not among the outcome domains most relevant to patients with LBP (17). A core outcome set for LBP, published after the PACE trial had already been completed, included pain intensity, physical functioning, health-related quality of life (HRQoL) and number of deaths as core outcome domains (18). The first three core domains were included in the PACE original analysis as secondary outcomes, while no patients died during trial participation (8). In the analysis plan of the discontinued PACE Plus trial, pain intensity recorded in the daily pain diary was the primary outcome (15). The original analysis of the PACE trial reported results for pain intensity at one, two, four and 12 weeks of follow-up and presented only part of the data from the pain diary (up to 14 days of follow-up) in the appendix; not all collected diary data were used (8). The aim of this study is to reanalyze the original data obtained in the PACE trial in order to assess the inferential reproducibility of results obtained in PACE.

METHODS

Participants and data collection in the PACE trial

A brief description of participants and data collection in the original PACE trial is provided here; for a detailed description, see the original manuscripts (8, 19). The PACE trial was a randomized, placebo-controlled clinical trial that was conducted from November 2009 until March 2013 in Sydney, Australia. This RCT was conducted in a multicenter setting with a double-dummy design. The study protocol, analysis plan and main results of the PACE trial have been published (8, 19, 20). 1652 patients with a new episode of at least moderate-intensity LBP were randomly allocated to take paracetamol regularly (1330 mg of modified-release paracetamol 3 times a day, n = 550, which all were analyzed) or as-needed (up to a maximum of 1000 mg of regular paracetamol four times a day, n = 549, of which 546 were analyzed), or to receive placebo (n = 553, of which 547 were analyzed). Placebo tablets were identical in appearance to paracetamol tablets but did not contain the active component. Participants were instructed to use study medication until they had experienced seven consecutive days with pain scores of 0 or 1 out of 10 (measured on a numerical pain rating scale (NRS)), or for a maximum of four weeks, whichever occurred first. During the trial, participants, clinicians and researchers remained blinded to allocation of treatment.

Pain scores and number of tablets used were recorded by participants into a daily pain and drug diary until recovery or for a maximum of 12 weeks. At one, two, four and 12 weeks after randomization, follow-up questionnaires were collected.

Outcomes used in this reanalysis

For this reanalysis, the predefined and published analysis plan from the PACE Plus trial was used (15). The PACE Plus trial was a randomized, placebo-controlled clinical trial that aimed to reproduce the results obtained in the PACE trial; however, this trial was discontinued due to insufficient patient recruitment (15, 16). As the groups and outcomes were similar but not identical between PACE and PACE Plus, we present primary and secondary outcomes of the current reproduction analysis here. The primary outcome of the PACE Plus trial was LBP-intensity measured with an 11-point Numeric Rating Scale (NRS, score range 0–10; higher score means more pain) (21); this outcome was therefore used as the primary outcome for this study. Data from the daily pain and drug diary collected up to 28 days of follow-up were used for the current analyses rather than data from the follow-up questionnaires that were collected after one, two, four and 12 weeks. Secondary outcome measures from the PACE Plus analysis plan that were also collected in the PACE trial were:

- Time to recovery assessed with the daily low back pain severity scores. Recovery is defined as the first day of 0 or 1 pain intensity on a 0-10 pain scale, maintained for seven consecutive days (primary outcome of the PACE trial).
- Physical functioning measured with the Roland Morris Disability Questionnaire (RMDQ; score range 0–24; higher score indicates poorer functioning) (22).
- HRQoL measured with the physical and mental component summary scores of the Short Form 12 (SF-12, range 0-100; higher score indicates better HRQoL) (23).
- Sleep quality measured with a 4-point Likert scale derived from the Pittsburgh Sleep Quality Index (PSQI). Scores will be dichotomized into good sleep quality (score 1 'very good' and 2 'fairly good') and poor sleep quality (score 3 'fairly bad' and 4 'very bad') (24).

Statistical analysis

The researchers who performed the original analysis of the PACE trial were not involved in the reanalysis of the data; two co-authors of the original trial (CM, CL) involved in this study were only allowed to view the results and to give their comments in a separate box at the end of the article, after the reanalysis and interpretation had already been completed. The statistical analysis was performed according to the intention-to-treat (ITT) principle. Software used for the statistical analysis was R version 3.5.3 (25). An overview of differences between the original analysis and the current inferential reproduction analysis can be found in Table 1.

Primary statistical analysis

For clinical effectiveness the between-group differences for the primary outcome, LBP-intensity, were evaluated using a repeated measurements analysis with Poisson mixed effects models with adequate specification of the fixed and random effects structures to account for possible nonlinear effects. The covariance structure was unstructured. Poisson mixed effects models rather than linear mixed effects models were used as pain data was found to be zero-inflated and non-normally distributed (Supplementary Figure 1A); Poisson models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data such as data obtained from the NRS (26, 27). The GLMMadaptive R package was used to create the Poisson mixed effects models (28). Results are presented as corrected coefficients for treatment with corresponding 95% confidence intervals and p-values.

Secondary statistical analysis

We used Poisson mixed effect models for physical functioning as data obtained using the RMDQ was found to be zero-inflated and non-normally distributed (see distribution of data in Supplementary Figure 1B), linear mixed effect models for HRQoL, a logistic

Table 1: Differences between the original analysis by Williams et al and the current inferential reproduction analysis for outcomes of PACE.

Outcome	Original Analysis (Williams et al, Lancet 2014)				Inferential Reproduction Analysis			
	P/S	Method	Presented outcome	SA	P/S	Method	Presented outcome	SA
Time until recovery	P	Cox Proportional Hazards Model; Recovery time and status considered after 12 weeks of follow-up	Hazard Ratios for recovery for overall comparisons between groups after 12 weeks of follow-up	No	S	Cox Proportional Hazards Model; Recovery time and status considered after 28 days of follow-up	Hazard Ratios for recovery for overall comparisons between groups after 28 days of follow-up	Yes
Pain intensity	S	Linear Mixed Model on pain data at 1, 2, 4 and 12 weeks follow-up;	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up; results for analysis of diary data presented up to 14 days	No	P	Poisson Mixed Model on pain diary data up to 28 days of follow-up	Coefficients for change in log average pain intensity for overall comparisons between groups	Yes
Physical functioning	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Poisson Mixed Model	Coefficients for change in log average physical functioning for overall comparisons between groups	Yes
Sleep Quality	S	Log-Binomial Regression	Fractions and percentages of poor sleep quality in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Logistic Regression	Odds ratios for poor sleep quality for overall comparisons between groups	No
HRQoL	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Linear Mixed Model	Coefficients for change in average HRQoL for overall comparisons between groups	No
Global rating of symptom change	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	NA	-	-	-

HRQoL: Health-Related Quality of Life; NA: Not analyzed (not in PACE Plus trial protocol); P: Primary outcome; PACE: Paracetamol in Acute Low Back Pain; S: Secondary outcome; SA: Subgroup Analyses for participants with severe pain intensity (defined as NRS ≥ 7) or severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline; SD: Standard Deviation.

regression model for sleep quality and a Cox proportional hazards model for time until first recovery from LBP to assess between-group differences (26, 27); respective R packages used for the analyses were GLMMadaptive, lme4, Stats and Survival (25, 28-30). Sensitivity to missing data in the recovery analysis was investigated by calculating a best-case scenario and a worst-case scenario for recovery from LBP. In the best-case scenario, we assumed all missing participants recovered after the first day of follow-up. In the worst-case scenario, we assumed none of the missing participants recovered within 28 days of follow-up.

As specified in the PACE Plus study protocol, exploratory subgroup analyses were conducted for participants with severe LBP intensity (defined as NRS ≥ 7) or severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline (15); for these subgroups, estimates were obtained for LBP intensity, physical function and time until recovery using Poisson mixed effects models and Cox proportional hazard analyses respectively. Results are presented as corrected coefficients for treatment with corresponding 95% confidence intervals and p-values.

RESULTS

Reproduced baseline characteristics of participants of the PACE trial can be found in Table 2. Treatment groups were comparable at the start of the trial.

Results for the intention-to-treat analysis of the primary and secondary outcomes are presented in Table 3. Comparisons between regular paracetamol and placebo, paracetamol as-needed and placebo, and regular paracetamol and paracetamol as-needed are presented. As an example, the coefficient for regular paracetamol versus placebo (0.00, 95% CI -0.02 – 0.01) is interpreted as no change in the log average pain intensity for regular paracetamol when compared to placebo, when all other predictors remain constant.

Pain intensity diary data was available for 1601 participants (538 from the regular paracetamol group, 530 from the paracetamol as-needed group and 533 from the placebo group). All treatment coefficients indicated no effect of treatment on pain intensity during 28 days of follow up (Table 3A); no estimates exhibited between-group differences (even without correction for multiple testing). Furthermore, confidence intervals for the coefficients were between-0.1 and +0.1 and did not include a clinically worthwhile effect of treatment with paracetamol (taken regularly or as-needed) on pain intensity when compared to placebo.

The estimates for treatment coefficients for physical functioning and HRQoL, odds ratios for poor sleep quality, and hazard ratios for recovery from LBP indicated no effect of treatment without correction for multiple testing (Table 3B). Furthermore, clinically worthwhile differences were not included in the confidence intervals for these estimates.

Table 2: Patients and episode characteristics

Patient characteristics	Regular group (N = 550)	As-needed group (N = 546)	Placebo group (N = 547)
Age (years)	44.1 (14.8), N = 550	45.5 (16.5), N = 546	45.4 (15.9), N = 546
Women	263/547 (48%)	256/546 (47%)	245/544 (45%)
Private health insurance	275/550 (50%)	240/545 (44%)	248/544 (46%)
Currently employed	424/550 (77%)	403/546 (74%)	389/542 (72%)
Household income per week (per year)			
Negative or no income	19/540 (4%)	11/531 (2%)	22/531 (4%)
AUD 1-649 (1-33799)	133/540 (25%)	167/531 (31%)	168/531 (32%)
AUD 650-1699 (33800-88399)	243/540 (45%)	243/531 (46%)	226/531 (43%)
AUD 1700-3999 (88400-207999)	119/540 (22%)	92/531 (17%)	97/531 (18%)
≥AUD 4000 (≥208000)	26/540 (5%)	18/531 (3%)	18/531 (3%)
Use of drugs for another disorder	201/550 (37%)	227/543 (42%)	202/544 (37%)
Episode characteristics	**Regular group (N = 550)**	**As-needed group (N = 546)**	**Placebo group (N = 547)**
Days since onset of pain	10.1 (10.1), N = 550	9.8 (10.0), N = 546	9.7 (9.8), N = 546
Number of previous episodes	6.3 (13.7), N = 547	7.2 (14.9), N = 544	7.2 (16.8), N = 544
Presence of pain extending beyond the knee	108/547 (20%)	113/546 (21%)	99/544 (18%)
Number of days reduced usual activity	3.8 (6.5), N = 548	3.6 (5.9), N = 546	3.4 (5.3), N = 545
Physical functioning (RMDQ)	12.8 (5.6), N = 543	13.2 (5.4), N = 532	13.3 (5.5), N = 531
Feelings of depression in last week	3.2 (2.9), N = 547	3.1 (2.9), N = 546	3.1 (2.9), N = 546
Perceived risk of persistent pain	4.6 (2.8), N = 548	4.6 (2.8), N = 546	4.4 (2.8), N = 545
Back pain episode compensable	31/546 (6%)	44/543 (8%)	43/546 (8%)
Pain intensity (NRS)	6.3 (1.9), N = 550	6.3 (2.0), N = 545	6.2 (1.8), N = 546
Global rating of change	0.0 (2.1), N = 548	-0.1 (2.2), N = 545	-0.1 (2.1), N = 546
Poor sleep quality	273/549 (50%)	272/545 (50%)	272/546 (50%)
Function (Nominated Activity)	3.5 (1.7), N = 547	3.6 (1.9), N = 544	3.7 (1.9), N = 545
Quality of life – physical (SF-12)	42.7 (9.1), N = 537	41.8 (9.7), N = 543	42.1 (9.2), N = 538
Quality of life – mental (SF-12)	44.1 (7.7), N = 537	44.6 (7.7), N = 543	44.4 (7.9), N = 538
Credibility score (CEQ)	19.0 (4.9), N = 544	18.5 (5.2), N = 542	19.4 (4.9), N = 540
Expectation score (CEQ)	19.7 (5.3), N = 544	19.6 (5.1), N = 542	20.2 (5.1), N = 542

Data are mean (SD) or n/N (%). AUD: Australian Dollars; CEQ: Credibility/Expectancy Questionnaire; LBP: Low Back Pain; NRS: Numerical Rating Scale; PSQI: Pittsburgh Sleep Quality Index; RMDQ: Roland Morris Disability Questionnaire; SF-12; 12-item Short Form Survey.

Table 3: Coefficients for effect of treatment on log average pain intensity (primary outcome) during 28 days of follow-up and for secondary outcomes during 12 weeks of follow-up.

A. Primary outcome	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	0.0 (-0.02, 0.01) p = 0.85	0.0 (-0.02, 0.01) p = 0.92	0.00 (-0.02, 0.01) p = 0.92
B. Secondary outcomes	**Regular Paracetamol vs Placebo [β (95% CI)]**	**Paracetamol as needed vs Placebo [β (95% CI)]**	**Regular Paracetamol vs Paracetamol as needed [β (95% CI)]**
Physical functioning (RMDQ, scale range 0-24)	-0.06 (-0.13, 0.01) p = 0.11	-0.03 (-0.10, 0.04) p = 0.39	-0.03 (-0.09, 0.04) p = 0.46
hrQoL-mental (SF-12)	-0.13 (-0.72, 0.47) p = 0.67	0.17 (-0.42, 0.76) p = 0.58	-0.30 (-0.89, 0.30) p = 0.33
hrQoL-physical (SF-12)	0.0 (-0.77, 0.77) p = 1.00	-0.14 (-0.91, 0.62) p = 0.71	0.14 (-0.62, 0.91) p = 0.71
Sleep Quality (PSQI)	OR 1.03 (0.90, 1.19) p = 0.62	OR 1.04 (0.91, 1.19) p = 0.59	OR 1.00 (0.87, 1.14) p = 0.97
Time until first recovery	HR 1.02 (0.88, 1.18) p = 0.82	HR 1.02 (0.88, 1.19) p = 0.76	HR 0.99 (0.86, 1.15) p = 0.93

All numbers rounded to 2 decimal places. All models were corrected for sex, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; NRS: Numerical Rating Scale; OR: Odds Ratio; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-12: Short Form 12.

A graphical representation of the effects of treatment during follow-up is shown in Figure 1; graphs were obtained from uncorrected regression models containing only treatment and time as covariates. The lines for different treatment groups are very close in all graphs (and sometimes nearly indistinguishable), emphasizing no difference in effect between paracetamol and placebo. Pain intensity (Figure 1A) steadily declines over time in all treatment groups. For physical functioning (Figure 1B), a sharp decline can be observed during the first four weeks of follow-up followed by a stable phase until 12 weeks of follow-up. While the mental component of HRQoL remained constant during the trial (Figure 1C), the physical component of HRQoL steadily increased during 12 weeks of follow-up, indicating an improvement of HRQoL over time (Figure 1D). The probability of poor sleep quality steadily declined during 12 weeks of follow-up.

Figure 1F illustrates the recovery curves as well as median recovery times for the 3 treatment groups; recovery information could be obtained from pain diary information for 1601 participants; for 13 additional patients with all pain diary data missing, a recov-

ery date was available, yielding a total of 1614 patients for the analysis (542 in the regular paracetamol group, 535 in the paracetamol as-needed group and 537 in the placebo group). 1186 out of 1614 participants (73%) had recovered from LBP after 28 days of follow-up. Median recovery times were 13 days (95% CI 11-14 days), 14 days (95% CI 13-15 days) and 12 days (95% CI 10-14 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no difference between the 3 recovery curves (log-rank p = 0.7).

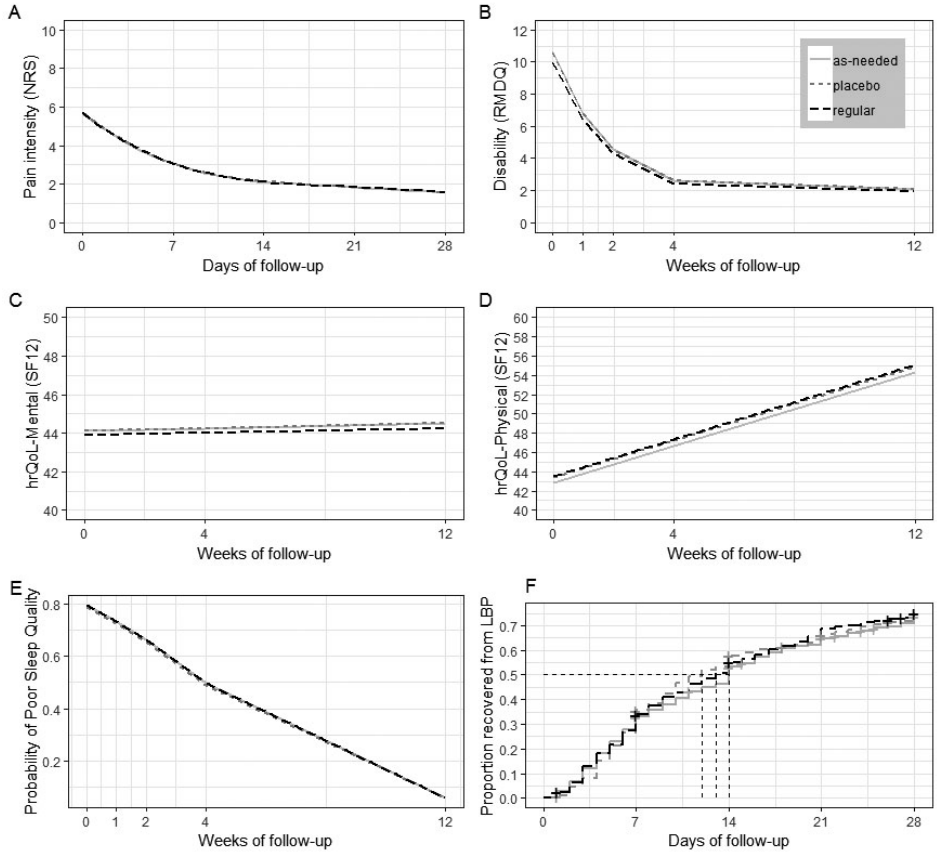

Figure 1: Effects of treatment on core outcomes of LBP (Pain intensity (A), Physical functioning (B) and hrQoL (C and D), Sleep Quality (E) and Time until first recovery from LBP (F). Graphs obtained from uncorrected regression models containing only treatment and time as covariates. Y-axis was truncated for plots B, C, D, E and F in order to improve visibility of results. Red line indicates placebo group, green line indicates paracetamol as-needed group, blue line indicates regular paracetamol group. hrQoL: health-related Quality of Life; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF12: Short Form 12

In Supplementary Figure 2, results of the analysis for the sensitivity to missing data were presented. Results did not substantially change in the sensitivity analyses when compared to the available data analysis.

In Table 4, results for the subgroups for severe baseline LBP intensity (defined as NRS ≥ 7) and severe baseline impairment of physical functioning (defined as RMDQ ≥ 16) are displayed. Results did not substantially change in the subgroups when compared to the main analysis. Figure 2 shows recovery curves for these subgroups. In the severe baseline LBP intensity subgroup, 547 out of 776 participants (70%) had recovered from LBP after 28 days of follow-up. Median recovery times were 14 days (95% CI 13-19 days), 16 days (95% CI 14-18 days) and 13 days (95% CI 11-17 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no difference be-

Table 4: Coefficients for subgroups for effect of treatment on average pain intensity (primary outcome) and time until first recovery during 28 days of follow-up and on average physical function during 12 weeks of follow-up.

Subgroup 1: Severe baseline LBP intensity (defined as NRS ≥ 7)	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	-0.02 (-0.09, 0.05) p = 0.49	0.0 (-0.07, 0.07) p = 0.96	-0.02 (-0.09, 0.05) p = 0.53
Physical functioning (RMDQ, scale range 0-24)	-0.01 (-0.11, 0.08) p = 0.80	-0.01 (-0.10, 0.09) p = 0.88	-0.01 (-0.10, 0.09) p = 0.91
Time until recovery	HR 1.04 (0.83, 1.30) p = 0.74	HR 1.09 (0.88, 1.36) p = 0.44	HR 0.95 (0.77, 1.19) p = 0.67
Subgroup 2: Severe baseline impairment of physical functioning (defined as RMDQ ≥ 16)	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	0.0 (-0.10, 0.10) p = 0.99	0.03 (-0.07, 0.12) p = 0.58	-0.03 (-0.12, 0.07) p = 0.59
Physical functioning (RMDQ, scale range 0-24)	0.02 (-0.06, 0.11) p = 0.56	-0.03 (-0.11, 0.05) p = 0.50	0.05 (-0.03, 0.13) p = 0.20
Time until recovery	HR 1.02 (0.79, 1.30) p = 0.89	HR 1.08 (0.84, 1.38) p = 0.53	HR 0.94 (0.73, 1.21) p = 0.64

Subgroups were: severe LBP intensity (defined as NRS ≥ 7) and severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline. All numbers rounded to 2 decimal places. All models were corrected for sex, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire.

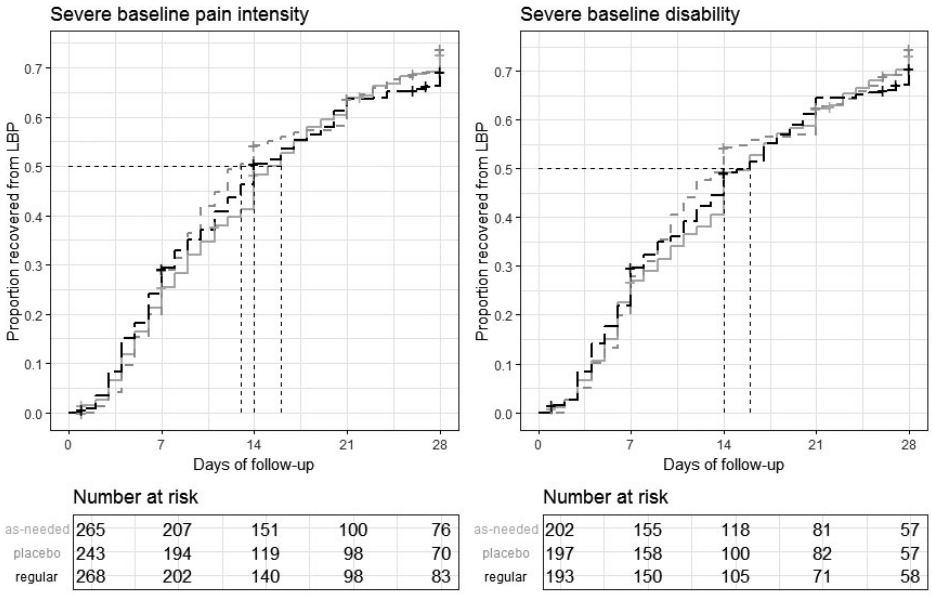

Figure 2: Survival curves for time until first recovery in subgroups. Subgroups were: A: severe baseline LBP intensity (defined as NRS ≥ 7) and B: severe baseline physical functioning (defined as RMDQ ≥ 16).

tween the 3 recovery curves (log-rank p = 0.8). In the severe baseline impairment of physical functioning subgroup, 420 out of 592 participants (71%) had recovered from LBP after 28 days of follow-up. Median recovery times were 16 days (95% CI 13-19 days), 16 days (95% CI 14-19 days) and 14 days (95% CI 11-21 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no significant difference between the 3 recovery curves (log-rank p = 0.9).

DISCUSSION

We performed an inferential reproduction analysis of data collected in the PACE trial, using the predefined and published analysis plan from the PACE Plus trial; key differences between the original analysis and the current reanalysis include a different primary outcome and different analysis methods, follow-up time points, presented outcomes and subgroup analyses (8, 15). In our reanalysis of the PACE-trial data the treatment of patients with acute LBP with paracetamol (taken regularly or as-needed) had no effect on pain intensity, physical functioning, HRQoL and time until recovery from LBP when compared to placebo; our study thus confirmed the original results of the PACE trial (8).

A strength of this study is the fact that the predefined and published analysis plan from a discontinued replication trial of PACE was used (15). Furthermore, Poisson mixed

models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data such as data obtained from the NRS and the RMDQ than linear mixed models (26, 27). A weakness of this study is the fact that the published analysis plan could not be completely used as intended, due to differences between the PACE trial and the PACE Plus trial (15). Whereas the PACE trial had 3 treatment groups (regular paracetamol, paracetamol as-needed and placebo), the PACE Plus trial had four treatment groups (regular paracetamol, regular diclofenac, placebo and advice-only). Furthermore, as mentioned in the 'Methods' section, not all outcome domains were the same between both trials, meaning we could only use part of the analysis plan as well as part of the available data collected in the PACE trial; however, despite some differences, the core outcome domains and instruments for LBP were included in the reproduction analysis (18, 21). Finally, the authors deviated from the original protocol by using Poisson mixed effect models rather than the predefined linear mixed effects models, but the nature of the data obligated this change.

As the PACE Plus protocol only specified the collection of pain diary data up to 28 days of follow-up (upon which the recovery analysis was based), the authors decided not to use any data gathered in the PACE trial after 28 days of follow-up, as this would not have been available in the PACE Plus study; furthermore, the analysis for this reproduction analysis was conducted on available data with sensitivity analyses for missing data, whereas in the original report, data was imputed in order to obtain complete groups for the recovery analysis. A consequence of these decisions is that patients who recovered after 28 days of follow-up will be considered censored in the current version of the recovery analysis; this may be an explanation for the difference in median recovery times (13, 12 and 14 days in the regular paracetamol, paracetamol as-needed and placebo groups, respectively versus 17, 16 and 17 days as reported in the original report).

This reanalysis of the PACE data yielded no substantially different results and therefore, the interpretation of the PACE trial remains the same: paracetamol (taken regularly or as needed) did not improve outcomes of LBP when compared to placebo. Thus, this study supports the notion that paracetamol has a limited role in the management of acute LBP in general practice. Furthermore, this reanalysis confirms that prognosis of acute LBP is favorable and that natural course or regression to the mean (Figure 1), rather than pharmacological treatment, are important factors influencing core outcomes' trajectory in patients with acute LBP.

While method reproducibility and inferential reproducibility have now been addressed for the PACE trial, results reproducibility (also called replication) has not (8, 10, 11). In other words, the highest level of evidence for the (lack of) efficacy of paracetamol for acute LBP is still based on a single trial that was conducted in a single country (7, 8). In order to definitively rule out efficacy of paracetamol for acute LBP, the authors highly recommend a replication of PACE, ideally in a multi-country collaboration.

CONCLUSION

This inferential reproduction analysis indicates that treatment of patients with acute LBP with paracetamol (taken regularly or as-needed) has no effect on core outcomes of LBP when compared to placebo, and thus confirms the original results of the PACE trial (8). This means the original conclusions of the PACE trial are inferentially reproducible, even when using a different approach to the statistical analysis.

Box 1: Comments on this inferential reproduction analysis of PACE by the original authors:
The inferential reproduction analysis of the PACE study, conducted by an independent group based on a pre-defined statistical analysis plan of a similar study (PACE Plus), agrees with the conclusion from the original PACE analysis – that paracetamol has no effects on pain or other core outcomes compared to placebo in patients with acute low back pain.
This study joins other secondary analyses of the PACE study showing the lack of benefits of paracetamol: we have also found that paracetamol did not improve pain intensity even in patients who complied with the regular treatment regimen (article to be published in 2019), and taking paracetamol did not confer any economic benefits in patients with acute low back pain (1). However we await the most important and currently missing step in definitively confirming the results of PACE – a replication of the PACE study. We would encourage other triallists to make their data sets available to allow reanalysis of the data by independent groups.

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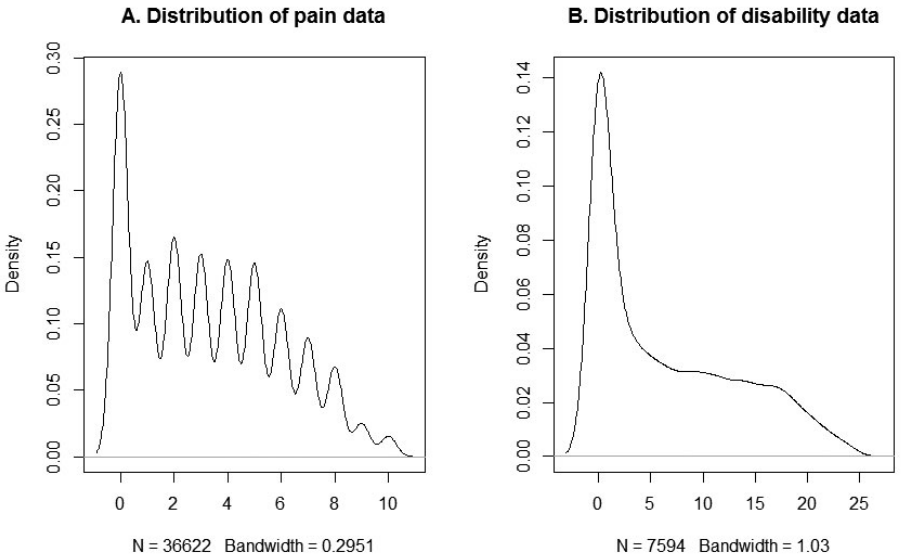
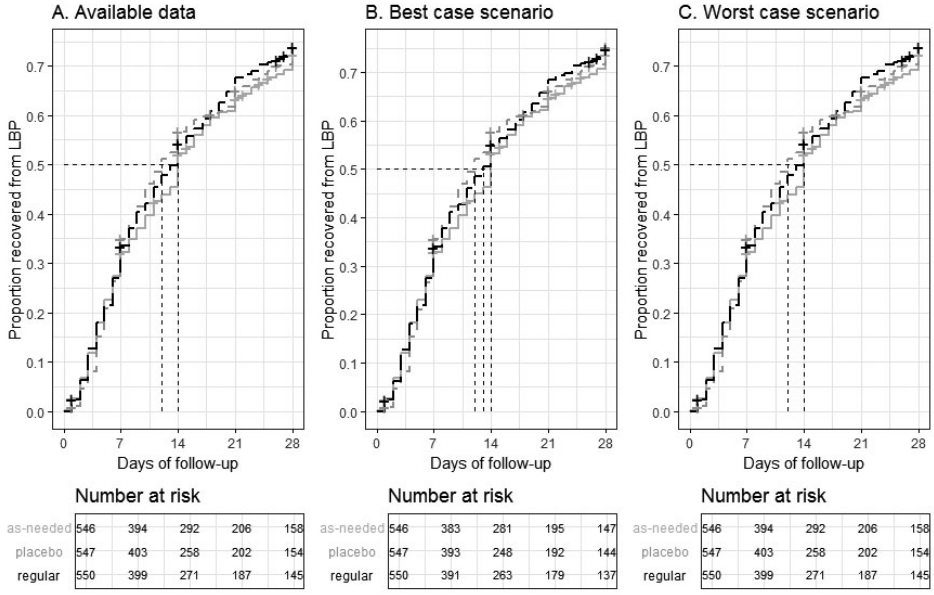


Supplementary Figure 1: Distribution of pain data (A) and physical functioning data (B) in the PACE trial.



Supplementary Figure 2: Sensitivity analysis for missing data in the recovery analysis for time until first recovery. A: Recovery curve using available data for recovery (n = 1614). B: Recovery curve with best case scenario assumed for missing cases (i.e. all missing participants recovered after 1 day of follow-up; n = 1643). C: Recovery curve with worst case scenario assumed for missing cases (i.e. none of the missing participants recovered within 28 days of follow-up; n = 1643).