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Analysing change from baseline in trials: what is the best approach?

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Analysis of change

- Researchers commonly obtain measurements on participants at the beginning of the study (**baseline**) and then at some time point after an intervention has been applied (**post-intervention**).

Table 1. Study schedule

Evaluation	Screening	Entry	Post-Entry Evaluations (Weeks)							
			4	12	24	36	48	60	72	Discontinuation Evaluations
			± 7 days		± 14 days					
Medical/Medication History	X									
Clinical Assessments	X	X	X	X	X	X	X	X	X	X
Quality of Life **Questionnaires**		X					X			X
Demographics Questionnaire		**X**								
Adherence **Questionnaires**		**X**	X	X	X	X	X	X	X	X
Health Literacy Questionnaires		**X**								
Pill Count			X	X	X	X	X	X	X	X

Analysis of change

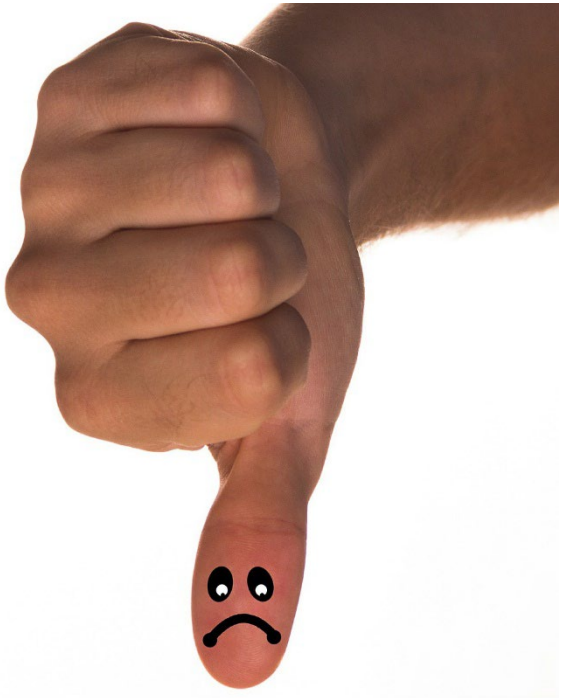
- After collecting this baseline information, we want to use these measurements in assessing the intervention effect.
- There are many possible analysis options so how do we choose the best one?

Analysis of change – problematic common approaches

- Differences: Outcome post-intervention **minus** outcome at baseline
- Percentage change:

  (Outcome post-intervention **minus** baseline)

  divided by baseline
- These approaches reduce the follow-up and baseline measurements to a **single value**.
- This makes them appealing for simple analysis (e.g., t-test).



Analysis of change – the best approach

- The best way of using baseline measurements is to **condition on baseline values** such as in a linear regression model by including them as a covariate in the model.
  - This type of approach is known as an analysis of covariance (ANCOVA).

- **Conditioning on baseline values**
  - Often referred to as ‘adjusting for baseline’ or ‘controlling for baseline’
  - Helps us assess the effect of treatment at follow-up among individuals who have the same baseline value.

Analysis of change – the best approach

- Although ‘adjusting for baseline’ is a recommended approach, many other methods are still used.
- The aim of this presentation is to highlight why ‘adjusting for baseline’ is the recommended approach and why others are less suitable.

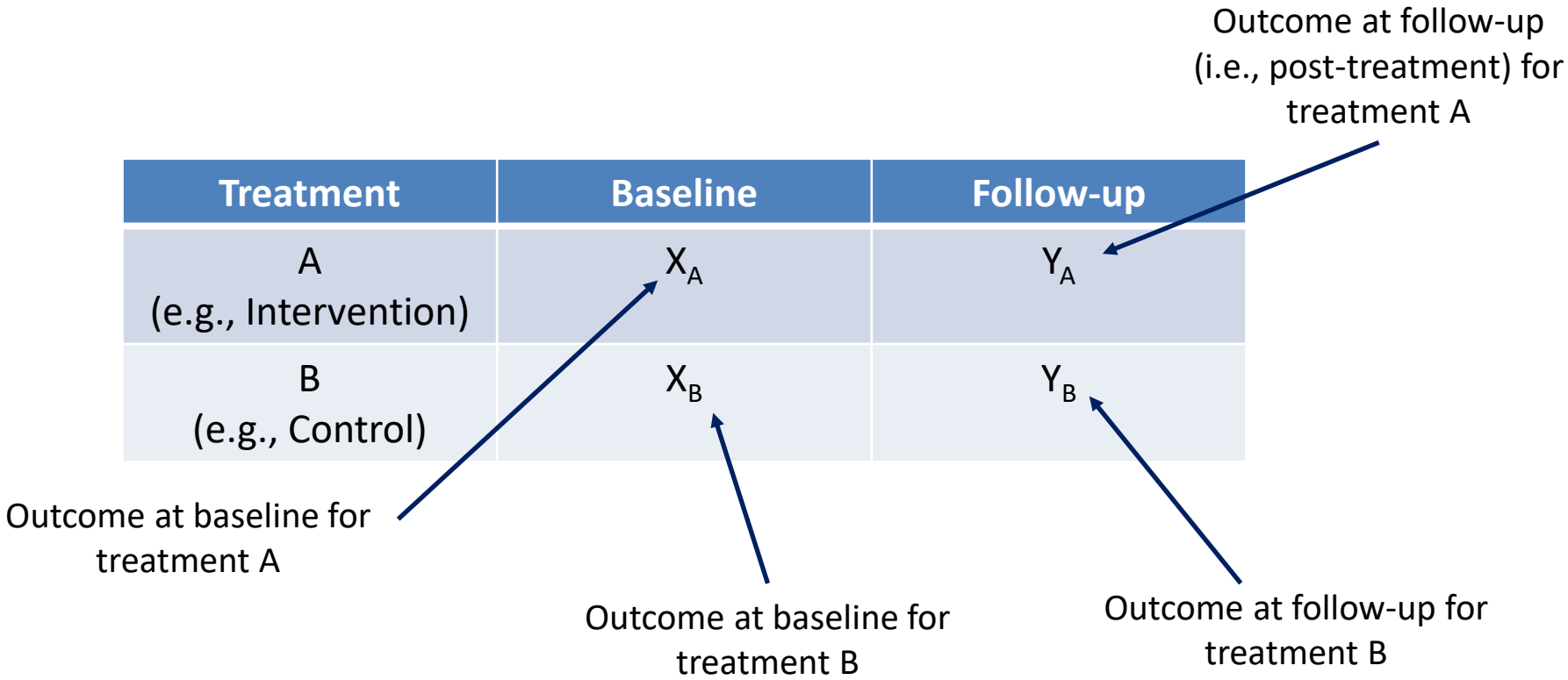
Handling baseline measurements in two-group comparisons

- Consider a clinical trial of an exercise program to reduce pain in people with knee osteoarthritis.
- Control group receives education only for 6 weeks.
- Intervention arm receives education and an exercise program for 6 weeks.
- Pain is measured before and after treatment on a numerical rating scale (NRS).

Treatment	Time 1 (Baseline)	Time 2 (Follow-up)
Exercise (Intervention)	Pain (NRS)	Pain (NRS)
Education (Control)	Pain (NRS)	Pain (NRS)

Mathematical notation to follow!

Handling baseline measurements in two-group comparisons



Handling baseline measurements in two-group comparisons

Treatment	Baseline	Follow-up
A (e.g., Intervention)	X_A	Y_A
B (e.g., Control)	X_B	Y_B

- $\overline{X_A}$ is the baseline mean for treatment A (e.g., the mean pain score before treatment for those who received exercise).

- $\overline{X_B}$ is the baseline mean for treatment B (e.g., the mean pain score before treatment for those who received education only).

Handling baseline measurements in two-group comparisons

Treatment	Baseline	Follow-up
A (e.g., Intervention)	X_A	Y_A
B (e.g., Control)	X_B	Y_B

- $\overline{Y_A}$ is the post-treatment mean for treatment A (e.g., the mean pain score after treatment for those who received exercise).

- $\overline{Y_B}$ is the post-treatment mean for treatment B (e.g., the mean pain score after treatment for those who received education only).

Handling baseline measurements in two-group comparisons

Treatment	Baseline	Follow-up
A (e.g., Intervention)	X_A	Y_A
B (e.g., Control)	X_B	Y_B

- Interested in comparing the groups
  - E.g., comparing the mean outcome after treatment between the groups (i.e., $\overline{Y_A} - \overline{Y_B}$).

- You notice that the distribution of the baseline measurements differs between the two groups (i.e., there is some imbalance in the outcome at baseline).
- That is, the mean baseline pain score for those who received exercise (i.e., $\overline{X_A}$) does not equal the mean baseline pain score for those who received education (i.e., $\overline{X_B}$).
- Want to ensure baseline values (i.e., X_A , X_B) are accounted for.

Handling baseline measurements in two-group comparisons

Here are three possible methods:

1) Estimate the between-group **difference in means for post-intervention outcomes** only (i.e., ignore baseline values altogether).

2) Estimate the between-group **difference in means for post-intervention minus baseline values** (e.g., derive the change in outcome for each participant).

3) Estimate the between-group **difference in means for either i) post-intervention outcomes adjusted for baseline or ii) change in outcomes (e.g. post – baseline) adjusted for baseline** (i.e. condition on baseline values).
   - E.g., using analysis of covariance (ANCOVA) or multivariable linear regression.

Vickers & Altman (2001) BMJ 323: 1123

Method 1: Difference in post-intervention means

- This approach ignores the baseline measurements altogether. The treatment effect (or between-group difference) is estimated as $\overline{Y_A} - \overline{Y_B}$.
- This approach assumes the **baseline measurements** are **balanced**.
- In other words, it is assumed that the baseline mean for treatment A is the same as the baseline mean for treatment B (i.e., $\overline{X_A} - \overline{X_B} = 0$).
- Ignoring values of the outcome at baseline can lead to an over- or under-estimation of the treatment effect.

Difference in post-intervention means

- Comparing post-intervention means when there is baseline imbalance results in **biased** findings.
- **'Biased'** means the mean treatment effect is **over- or under-estimated**.
- Considering only the post-intervention outcomes is also **inefficient**.
- This means it generally has **lower power** so you need a larger sample size to detect differences in post-intervention outcomes if baseline and follow-up scores are correlated.

Method 2: Difference in means for change (post-intervention minus baseline)

- This approach completely takes into account the baseline measurement in that it becomes part of the outcome. The treatment effect is estimated as $(\overline{Y_A} - \overline{X_A})$ - $(\overline{Y_B} - \overline{X_B})$ = $(\overline{Y_A} - \overline{Y_B})$ - $(\overline{X_A} - \overline{X_B})$

- However, it does not take into account the actual **correlation** between the baseline and post-intervention scores.

- Ignoring the correlation will **attenuate** the estimate of the true treatment effect.

Method 1 and Method 2

- Both method 1 and method 2, neither of which adjust for baseline, result in **biased estimates** of the treatment effect when baseline imbalance exists.
- Need to find an estimator that is **unbiased** and appropriately takes into account the correlation between baseline and post-intervention measurements.

Method 3: Adjust for baseline values

- When the outcome is post-intervention scores, the treatment effect, adjusted for baseline, is estimated as $(\overline{Y_A} - \overline{Y_B}) - \boldsymbol{\rho}(\overline{X_A} - \overline{X_B})$.
- We can adjust for baseline values of the outcome using ANCOVA or multivariable linear regression.
- This is an **unbiased** method to account for baseline values.
- It is also generally the **most efficient**.
  - More efficient = narrower confidence intervals

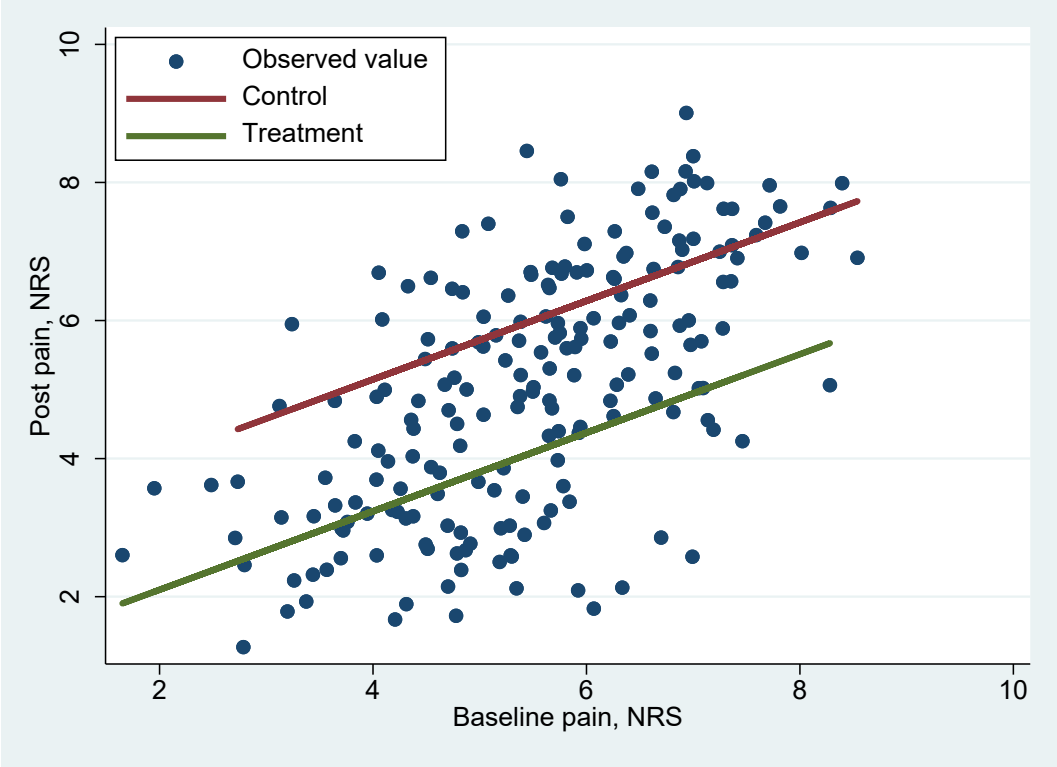
Correlation between baseline and post-intervention measures

Simulated example of pain

	Exercise (Intervention/ Treatment A) N = 100 Mean (SD)	Education (Control/ Treatment B) N = 100 Mean (SD)	Mean difference (Intervention – Control)
Baseline pain (NRS)	5.0 (1.3)	6.0 (1.2)	-1.0
Post pain (NRS)	3.8 (1.4)	6.3 (1.3)	-2.5
Post *minus* baseline pain (NRS)	-1.2 (1.3)	0.3 (1.1)	-1.5

- Difference in mean pain at baseline ($\overline{X_A} - \overline{X_B}$) is **-1.0**.
- Difference in mean pain at follow-up ($\overline{Y_A} - \overline{Y_B}$) is **-2.5**.
- Difference in mean change in pain ($\overline{Y_A} - \overline{X_A}$) - ($\overline{Y_B} - \overline{X_B}$) is **-1.5**.

Simulated example of pain



Positive correlation between baseline and post pain scores

Simulated example of pain: method 1

- Estimate difference in means for **post-intervention measurements** only:

```
regress post treatment

------------------------------------------------------------------------------
        post |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |  -2.474202   .1871793   -13.22   0.000    -2.843323   -2.105081
       _cons |    6.26208   .1323558    47.31   0.000     6.001072    6.523088
------------------------------------------------------------------------------
```

Note: -2.5 = ($\overline{Y_A} - \overline{Y_B}$)

Simulated example of pain: method 2

- Estimate difference in means for **change (post – baseline)**:

```
regress post_baseline treatment
------------------------------------------------------------------------------
post_basel~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |  -1.482263   .1754506    -8.45   0.000    -1.828255   -1.136271
       _cons |   .3016277   .1240623     2.43   0.016     .0569746    .5462808
------------------------------------------------------------------------------
```

Note: -1.5 = -2.5-(-1.0) = $(\overline{Y_A} - \overline{Y_B}) - (\overline{X_A} - \overline{X_B})$

Simulated example of pain: method 3

- Estimate difference in means for **post-intervention outcomes adjusting for baseline**:

Correlation between baseline and follow-up scores (ρ_1)

```
regress post baseline treatment
------------------------------------------------------------------------------
        post |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    baseline |   .5686661   .0640396     8.88   0.000     .4423749    .6949574
   treatment |  -1.91012    .170831    -11.18   0.000    -2.247012   -1.573228
       _cons |   2.872573   .3978353     7.22   0.000      2.08801    3.657136
------------------------------------------------------------------------------
```

Note: -1.9 = -2.5 - 0.6 x -1

$$= (\overline{Y_A} - \overline{Y_B}) - \rho_1(\overline{X_A} - \overline{X_B})$$

Simulated example of pain: method 3

- Estimate difference in means for **change in outcomes (post – baseline) adjusting for baseline**:

Correlation between baseline & change scores (ρ_2) = Correlation between baseline & follow up scores - 1

```
regress post_baseline baseline treatment
------------------------------------------------------------------------------
post_basel~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    baseline |  -.4313339   .0640396    -6.74   0.000    -.5576251   -.3050426
   treatment |   -1.91012    .170831   -11.18   0.000    -2.247012   -1.573228
       _cons |   2.872573   .3978353     7.22   0.000      2.08801    3.657136
------------------------------------------------------------------------------
```

Note: -1.9 = -2.5-(-1.0) – (-0.4 x -1.0) = -1.5 – 0.4

$$= (\overline{Y_A} - \overline{Y_B}) - (\overline{X_A} - \overline{X_B}) - \rho_2(\overline{X_A} - \overline{X_B})$$

$$= (\overline{Y_A} - \overline{Y_B}) - (1 + \rho_2)(\overline{X_A} - \overline{X_B})$$

Simulated example of pain: method 3 comparisons

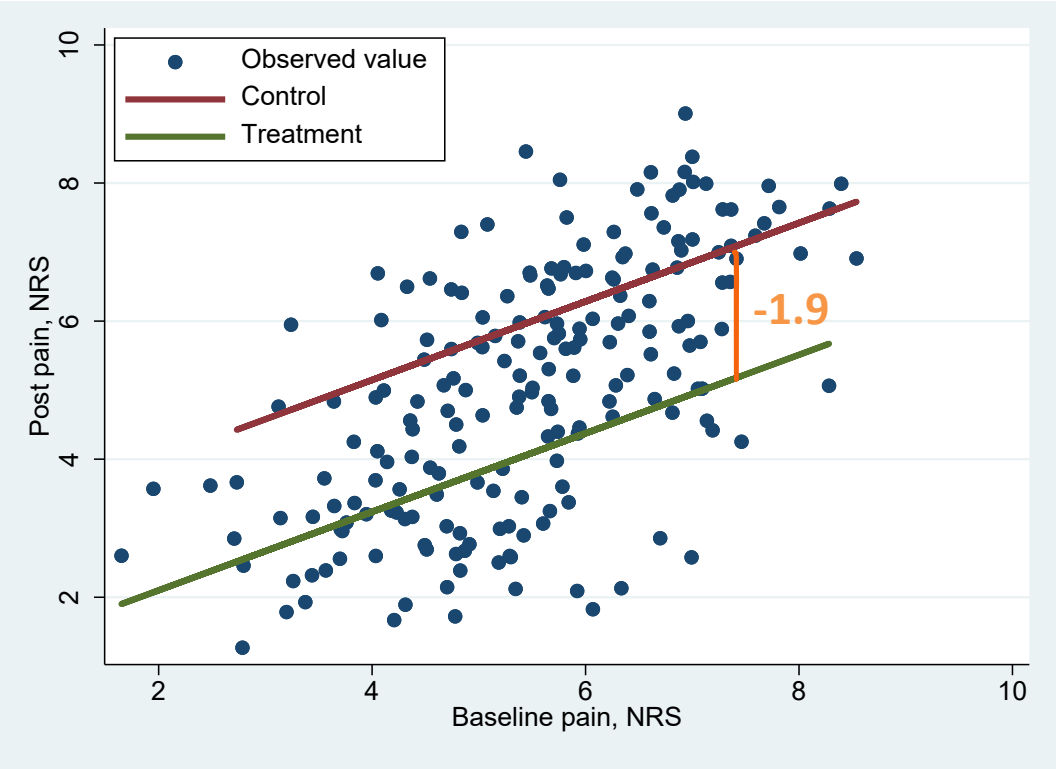
	Correlation between baseline and outcome	Mean difference (Intervention – Control) [95% confidence interval]
Post pain, adjusted for baseline (Method 3)	0.57	-1.91 [-2.25, -1.57]
Change in (post – baseline) pain, adjusted for baseline (Method 3)	-0.43	-1.91 [-2.25, -1.57]

- Between-group mean difference and 95% confidence interval are exactly the same, irrespective of whether post or change is the outcome!

Simulated example of pain: comparisons

	Exercise (Intervention/ Treatment A) N = 100	Education (Control/ Treatment B) N = 100	Mean difference (Intervention – Control)	Confidence interval width (standard error x 2)
Baseline pain (NRS)	5.0 (1.3)	6.0 (1.2)	-1.0	-
Post pain (NRS) (Method 1)	3.8 (1.4)	6.3 (1.3)	-2.5 (overestimates)	0.37
Post *minus* baseline pain (NRS) (Method 2)	-1.2 (1.3)	0.3 (1.1)	-1.5 (underestimates)	0.35
Post *or* change in pain, adjusted for baseline (Method 3)	-	-	-1.9 (unbiased)	0.34

Handling baseline in two-group comparisons



- Adjustment for baseline values compares groups while **holding the baseline values constant**

- Interpretation:

*After adjusting for baseline differences in pain, mean pain **decreased by 1.9** NRS units in those receiving exercise compared with those receiving education.*

Assumptions of adjusting for baseline

- Assumes **linear relationship** between baseline and follow-up values.
- Assumes **no interaction** between baseline outcome measurement and treatment.
  - This means it assumes that the relationship between baseline and post-intervention outcomes are the same for each intervention (i.e., treatment and control).
    - Assumes baseline outcomes do not modify the association between treatment and post-intervention outcomes.

Additional benefit of adjusting for baseline

- Adjusting for baseline generally has **greater statistical power** than the other two approaches.

- Assuming a correlation of 0.4 between baseline and follow-up pain scores, a clinically important difference of 1.8 NRS units, a standard deviation of 3 NRS units, power of 80% and significance level of 5%, the following sample sizes are required:

  - **Follow-up scores (Method 1):** a sample size of **59** per group is required.
  - **Change scores (Method 2):** a sample size of **71** per group is required.
  - **Adjusting for baseline (Method 3):** a sample size of only **50** per group is required.

In Stata: `sampsi 0 1.8, sd(3) pre(1) post(1) r01(0.4)`

What about % change?

- % Change:

  (Outcome post-intervention **minus** baseline) **divided** by baseline

- The numerator is simply the calculated change between baseline and post-intervention outcome scores.

- This means it suffers from the same problem as discussed for change from baseline when we do not adjust for baseline.

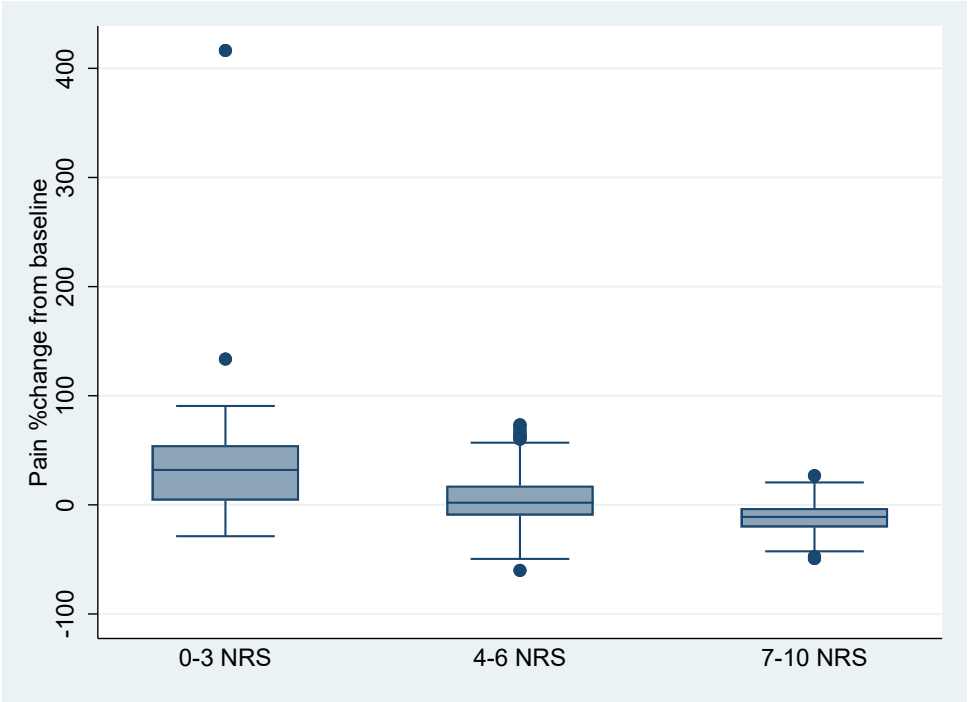
- It is an inefficient measure of treatment effect.

Vickers (2001) BMC Medical Research Methodology 1: 6

What about % change?

- In addition, % change often violates the assumptions of normality (of a normal distribution) required for the statistical tests to compare the means between groups.

- Also, the magnitude of % change depends on the baseline value.



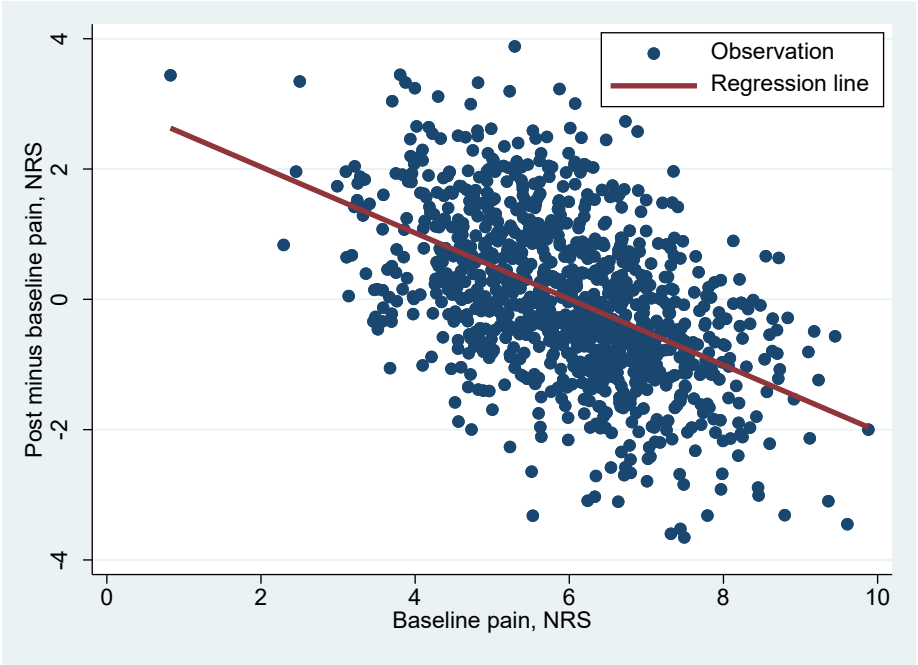
What about % change?

- What if interest lies in % change?
- If this statistic is of interest, still analyse post-intervention outcome scores with adjustment for baseline values to estimate the effect of treatment on outcome scores (95% confidence interval and p-value).
- Next, the results should be **converted** to percentage change using mean baseline and post-intervention scores for treatment and control groups.

Vickers (2001) BMC Medical Research Methodology 1: 6

Additional challenge with change scores

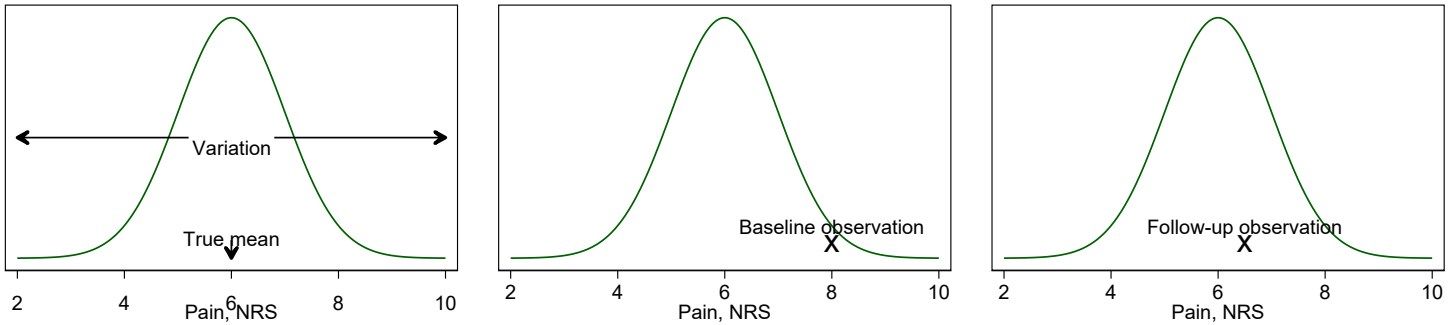
- Change scores, where there is no adjustment for baseline, do not appropriately account for regression to the mean.
- Baseline values are negatively correlated with change: patients with high pain at baseline generally improve more than those with less baseline pain.
- Points with largest change values have highest or lowest baseline.



Vickers & Altman (2001) BMJ 323: 1123

Regression to the mean

- Regression to the mean occurs when repeated measurements are made on the same subject.
- It occurs because measurements are taken with random error ("a non-systematic variation in the observed values around a true mean").
  - Repeated measures attenuate towards the average.
- Data are rarely observed without random error.



Graphical example of true mean and variation, and of regression to the mean using a Normal distribution. The distribution represents pain intensity in a single subject with a true mean of 6 NRS units and standard deviation of 2 NRS units.

Regression to the mean and single arm studies

- Consider a **single-arm study** of a new exercise treatment.
- In this study, patients are selected because their pain is higher than a certain threshold.
- As individual pain levels vary randomly over time, this could lead to the selection of patients when their pain level is above their individual long-term average.
- Subsequent reductions may be due to regression to the mean, rather than a true treatment effect.
- Without a control arm, the treatment effect cannot be separated from regression to the mean!
  - Cannot make inferences based on within-group changes.

Howard (2016) Circ Cadiovasc Qual Outcomes 9: 14-22

Extensions to multiple follow-up time points

- Some trials follow patients at multiple time-points after intervention.
- How should these be analysed?
- Baseline measurements can be considered in (constrained) longitudinal analyses.
- This is where every measurement of the outcome of interest (e.g., pain score) at all time points (e.g., baseline, follow-up 1, follow-up 2) are all considered as the outcome variable in a linear mixed model.
- In constrained longitudinal analyses, the baseline measurements are treated as equal.

Coffman (2016) BMJ Open 6: e013096

Conclusions

- ‘Adjusting for baseline’, using either the outcome at follow-up or change scores, is the best method to account for baseline values in trials with 1 baseline and 1 follow-up outcome measurement.
- Even if randomisation is designed to ensure baseline balance, adjusting for baseline protects against chance imbalance in the outcomes at baseline.
- Although change scores, without adjusting for baseline, are still commonly used, these results do not protect against regression to the mean.
- Single arm studies should be avoided as the treatment effect cannot be separated from regression to the mean.

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Faculty of Medicine, Dentistry and Health Sciences

Thank you

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