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Analyse av data fra randomiserte kontrollerte studier med repeterte målinger

Presented by Stian Lydersen, 9 February 2021
Revised 10 February 2021

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Analysis of randomised controlled trials (RCT) with baseline and post treatment measurements.

In an RCT with baseline and post treatment measurements, adjusting for the baseline will substantially improve the precision in the treatment estimate. Still, this is not done in many such RCTs. And there is some confusion on how to adjust. I will explain how this can be done, based on (Twisk et al., 2018). And I will show how we implemented this in some recent studies, including the Generation 100 study (Stensvold et al.,BMJ, 2020).

Presented by Stian Lydersen, 9 February 2021

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Different ways to estimate treatment effects in randomised controlled trials

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An eye-opener for me in July 2019!

ARTICLE INFO

Keywords:
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Analysis of changes
Regression to the mean

ABSTRACT

Background: Regarding the analysis of RCT data there is a debate going on whether an adjustment for the baseline value of the outcome variable should be made. When an adjustment is made, there is a lot of misunderstanding regarding the way this should be done. Therefore, the aims of this educational paper are: 1) to explain different methods used to estimate treatment effects in RCTs, 2) to illustrate the different methods with a real life example and 3) to give an advise on how to analyse RCT data.

Methods: Longitudinal analysis of covariance, repeated measures analysis in which also the baseline value is used as outcome and the analysis of changes were theoretically explained and applied to an example dataset investigating a systolic blood pressure lowering treatment.

Results: It was shown that differences at baseline should be taken into account and that regular repeated measures analysis and regular analysis of changes did not adjust for the baseline differences between the groups

Conclusion: Regarding the analysis of RCT data, it is advised to use longitudinal analysis of covariance or a repeated measures analysis without the treatment variable, but with the interaction between treatment and time in the model.

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Although it seems that the debate is ended in favour of an adjustment for baseline value of the outcome variable, in the literature there are still many RCT's that do not adjust for the baseline values of the outcome variable [11]. Moreover, in the CONSORT statement, which provides guidelines for reporting results of RCTs, there is no statement about the preferred way of analysing RCT data and whether or not an adjustment for the baseline value should be made.

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Two main alternatives

- Analysis of covariance (ANCOVA)
  - Most relevant when only two time points
  - Unbiased only if data are complete or missing completely at random (MCAR)
- Mixed models for longitudinal data (named repeated measures analysis in Twisk 2018)
  - Unbiased under the less restrictive missing at random assumption (MAR). For example, if participants with lower scores at baseline have more missing at follow-up, data are not MCAR but possibly MAR.

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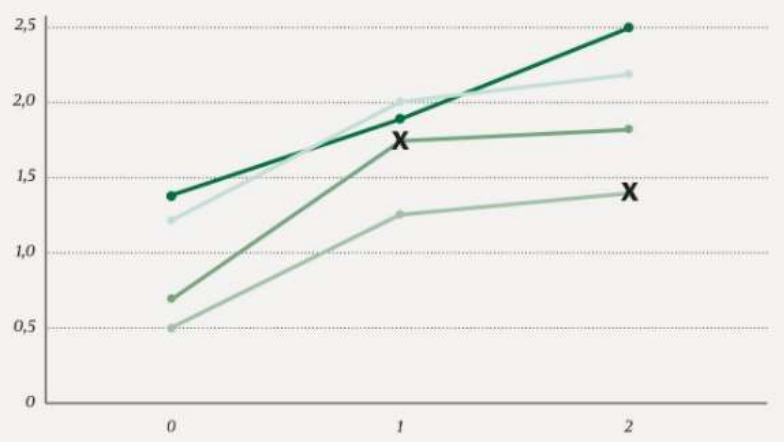
Mot MCAR but possibly MAR:



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:R 2020

Tidsskriftet
DEN NORSKE LEGEFORENING

FAGOMRÅDER UTGAVER FORFATTERVEILEDNING LE

Should we adjust for background variables in a randomised controlled trial?

MEDICINE AND NUMBERS

Stian Lydersen *About the author*

In a randomised controlled trial there should be no systematic differences in background variables between the groups before treatment. But sometimes it can be sensible to adjust for some pre-defined variables in the statistical analyses.

"Another example is analysis of covariance in a randomised controlled trial where the outcome variable is measured before treatment and at follow-up. The baseline value of the outcome variable is usually a very strong predictor and can increase the precision of the effect estimate."

Lydersen (2020)

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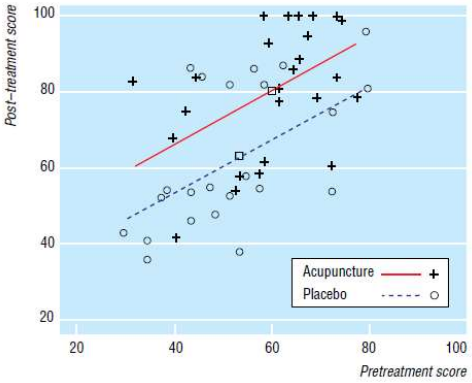
ANCOVA:
follow up score =
constant + a×baseline score + b×group

Idea:
Compare individuals with equal baseline scores



Results of trial of acupuncture for shoulder pain[4]

	Pain scores (mean and SD)			
	Placebo group (n=27)	Acupuncture group (n=25)	Difference between means (95% CI)	P value
Baseline	53.9 (14)	60.4 (12.3)	6.5	
Analysis				
Follow up	62.3 (17.9)	79.6 (17.1)	17.3 (7.5 to 27.1)	0.0008
Change score*	8.4 (14.6)	19.2 (16.1)	10.8 (2.3 to 19.4)	0.014
ANCOVA			12.7 (4.1 to 21.3)	0.005

Vickers and Altman, BMJ (2001)

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Twisk et al (2018)

Without adjusting for baseline:
Include main effects of treatment x (1 if treatment, 0 if control), time (0 at baseline, 1 after), and their interaction.

$$Y_t = \beta_0 + \beta_1 X + \beta_2 time + \beta_3 time \times X \quad (2a)$$

$$Y_t = \beta_0 + \beta_1 X + \beta_2 dummytime_1 + \beta_3 dummytime_2 + \beta_4 dummytime_1 \times X + \beta_5 dummytime_2 \times X \quad (2b)$$

Recommended: Adjusting for baseline.
Note that the term x is excluded, that is, assume no systematic treatment effect at baseline.

$$Y_t = \beta_0 + \beta_1 time + \beta_2 time \times X \quad (2c)$$

$$Y_t = \beta_0 + \beta_1 dummytime_1 + \beta_2 dummytime_2 + \beta_3 dummytime_1 \times X + \beta_4 dummytime_2 \times X \quad (2d)$$

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Effect of exercise training for five years on all cause mortality in older adults—the Generation 100 study: randomised controlled trial

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ABSTRACT

OBJECTIVE
To evaluate the effect of five years of supervised exercise training compared with recommendations for physical activity on mortality in older adults (70-77 years).

DESIGN
Randomised controlled trial.

SETTING
General population of older adults in Trondheim, Norway.

PARTICIPANTS
1567 of 6966 individuals born between 1936 and 1942.

INTERVENTION
Participants were randomised to two sessions weekly of high intensity interval training at about 90% of peak heart rate (HIIT, n=400), moderate intensity continuous training at about 70% of peak heart rate (MICT, n=387), or to follow the national guidelines for physical activity (n=780; control group); all for five years.

MAIN OUTCOME MEASURE
All cause mortality. An exploratory hypothesis was that HIIT lowers mortality more than MICT.

RESULTS
Mean age of the 1567 participants (790 women) was 72.8 (SD 2.1) years. Overall, 87.5% of participants reported to have overall good health, with 80% reporting medium or high physical activity levels at baseline. All cause mortality did not differ between the control group and combined MICT and HIIT group. When MICT and HIIT were analysed separately, with the control group as reference (observed mortality of 4.7%), an absolute risk reduction of 1.7 percentage points was observed after HIIT (hazard ratio 0.63, 95% confidence interval 0.33 to 1.20) and an absolute increased risk of 1.2 percentage points after MICT (1.24, 0.73 to 2.10). When HIIT was compared with MICT as reference group an absolute risk reduction of 2.9 percentage points was observed (0.51, 0.25 to 1.02) for all cause mortality. Control participants chose to perform more of their physical activity as HIIT than the physical activity undertaken by participants in the MICT group. This meant that the controls achieved an exercise dose at an intensity between the MICT and HIIT groups.

CONCLUSION
This study suggests that combined MICT and HIIT has no effect on all cause mortality compared with recommended physical activity levels. However, we observed a lower all cause mortality trend after HIIT compared with controls and MICT.

TRIAL REGISTRATION
ClinicalTrials.gov NCT01666340.

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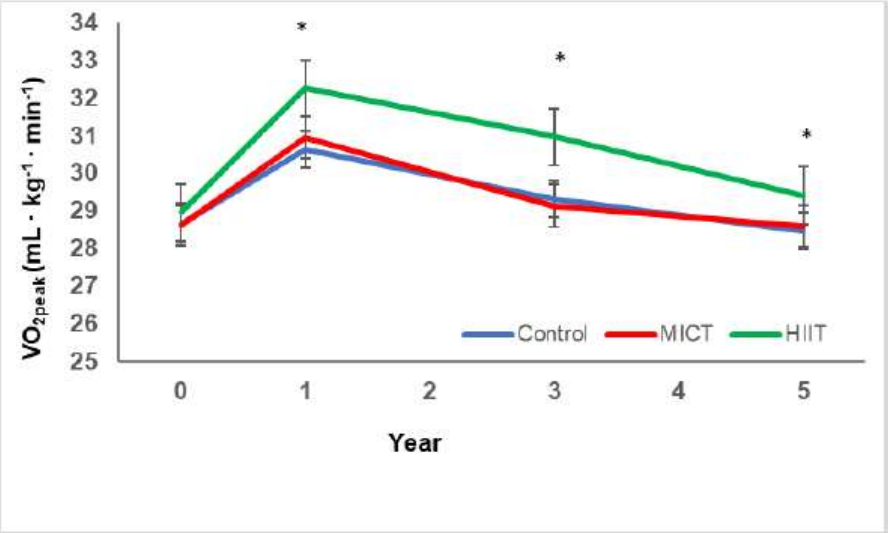

Figure S1 in Stensvold et al (2020). Descriptive mean, SE.

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~~Without~~ adjusting for baseline of the outcome variable:

$$Y_t = \beta_0 + \sout{\beta_1 MIIT} + \sout{\beta_2 HIIT} + \beta_3 year1 + \beta_4 year3 + \beta_5 year5$$
$$+ \beta_6 year1 \times MIIT + \beta_7 year3 \times MIIT + \beta_8 year5 \times MIIT$$
$$+ \beta_9 year1 \times HIIT + \beta_{10} year3 \times HIIT + \beta_{11} year5 \times HIIT$$
$$+ \beta_{12} female + \beta_{13} age + \beta_{14} cohabiting + A_j + \varepsilon_{ij}$$

~~Effect of HIIT (compared to control) at time 1 year is $\beta_2 + \beta_9$.~~

~~Estimate, CI, p-value: 1.22 (0.43 to 2.01), p=0.002~~

Effect of HIIT (compared to control) at time 1 year is β_9.

Estimate, CI, p-value: 1.00 (0.51 to 1.50), p<0.001

~~Effect of HIIT (compared to control) at time 5 years is $\beta_2 + \beta_{11}$.~~

~~Estimate, CI, p-value: 0.89 (0.05 to 1.72), p=0.038~~

Effect of HIIT (compared to control) at time 5 years is β_{11}.

Estimate, CI, p-value: 0.67 (0.10 to 1.23), p=0.021

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Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2020;101:939-47

ORIGINAL RESEARCH

Effects of High-Intensity Interval Training After Stroke (the HIIT-Stroke Study): A Multicenter Randomized Controlled Trial

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Abstract

Objective: To examine if 8 weeks of high-intensity interval training (HIIT) in addition to standard care would increase and maintain peak oxygen uptake (Vo_{2peak}) more than standard care alone in patients with stroke.

Design: This was a single-blind, multicenter, parallel group, randomized controlled trial.

Setting: Specialized rehabilitation units at 3 Norwegian hospitals.

Participants: Participants (N=70), 3 months to 5 years after first-ever stroke, were randomly assigned to the intervention group (n=36) or the control group (n=34); 42% were women, mean age was 57.6±9.3 years, mean time post stroke was 26.4±14.5 months.

Intervention: The intervention was 8 weeks: 3 times a week with HIIT treadmill training with work periods of 4 × 4 minutes at 85%-95% of peak heart rate interspersed with 3 minutes of active recovery at 50%-70% of peak heart rate. The control group received standard care according to national guidelines.

Outcomes: The primary outcome, analyzed by intention-to-treat, was Vo_{2peak} measured as liters per minute 12 months after inclusion. Secondary outcome measures were blood pressure and blood profile.

Results: Mean baseline Vo_{2peak} was 2.63±1.08 L·min^{-1} vs 2.87±0.71 L·min^{-1}, while at 12 months Vo_{2peak} was 2.70±1.00 L·min^{-1} vs 2.67±0.76 L·min^{-1} (P=.068) in the intervention and control groups, respectively. There was a significant and greater improvement in the intervention group compared with the control group at 12 months in 3 of 6 secondary outcomes from the peak test but no significant differences for blood pressure or blood profile.

Conclusions: The HIIT intervention, which was well-tolerated in this sample of well-functioning survivors of stroke, was not superior to standard care in improving and maintaining Vo_{2peak} at the 12-month follow-up. However, secondary results from the peak test showed a significant improvement from before to immediately after the intervention.

Archives of Physical Medicine and Rehabilitation 2020;101:939-47

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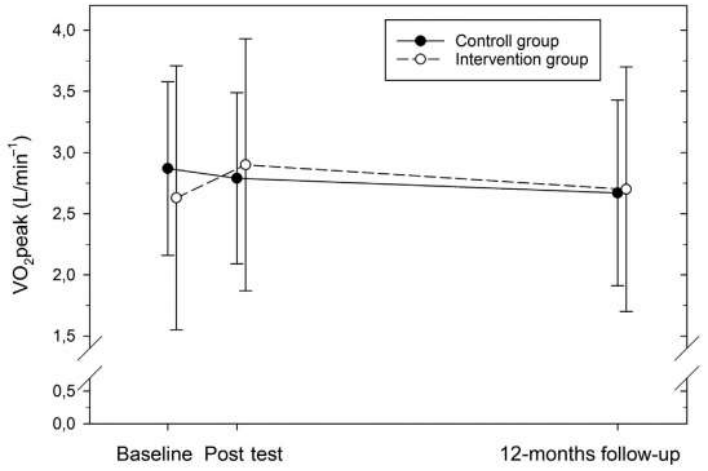

Fig 2 Mean VO_{peak} in L·min^{-1} at baseline, post test, and follow-up. Error bars represent SD.

Change from baseline to post test was significantly higher in the intervention group (Linear mixed model adjusting for baseline, p=0.009)

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Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial

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Summary

Background Most patients with hip fractures are characterised by older age (>70 years), frailty, and functional deterioration, and their long-term outcomes are poor with increased costs. We compared the effectiveness and cost-effectiveness of giving these patients comprehensive geriatric care in a dedicated geriatric ward versus the usual orthopaedic care.

Methods We did a prospective, single-centre, randomised, parallel-group, controlled trial. Between April 18, 2008, and Dec 30, 2010, we randomly assigned home-dwelling patients with hip-fractures aged 70 years or older who were able to walk 10 m before their fracture, to either comprehensive geriatric care or orthopaedic care in the emergency department, to achieve the required sample of 400 patients. Randomisation was achieved via a web-based, computer-generated, block method with unknown block sizes. The primary outcome, analysed by intention to treat, was mobility measured with the Short Physical Performance Battery (SPPB) 4 months after surgery for the fracture. The type of treatment was not concealed from the patients or staff delivering the care, and assessors were only partly masked to the treatment during follow-up. This trial is registered with ClinicalTrials.gov, number NCT00667914.

Findings We assessed 1077 patients for eligibility, and excluded 680, mainly for not meeting the inclusion criteria such as living in a nursing home or being aged less than 70 years. Of the remaining patients, we randomly assigned 198 to comprehensive geriatric care and 199 to orthopaedic care. At 4 months, 174 patients remained in the comprehensive geriatric care group and 170 in the orthopaedic care group; the main reason for dropout was death. Mean SPPB scores at 4 months were 5·12 (SE 0·20) for comprehensive geriatric care and 4·38 (SE 0·20) for orthopaedic care (between-group difference 0·74, 95% CI 0·18–1·30, p=0·010).

Interpretation Immediate admission of patients aged 70 years or more with a hip fracture to comprehensive geriatric care in a dedicated ward improved mobility at 4 months, compared with the usual orthopaedic care. The results suggest that the treatment of older patients with hip fractures should be organised as orthogeriatric care.

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See Comment page 1594

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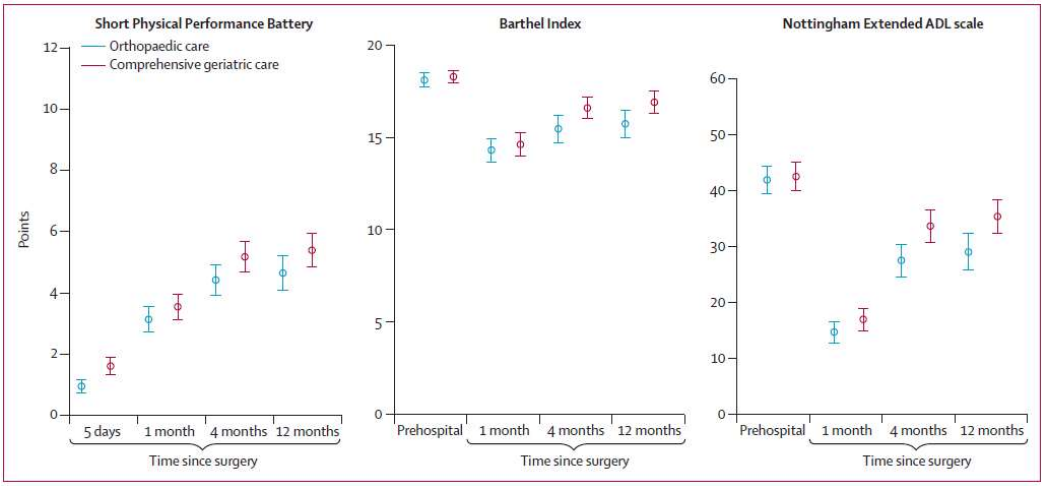

No baseline available:
Effect at 4 m is main effect in a model with interaction

Could (should?) have adjusted for baseline and measure effect as interaction

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Journal of Child and Family Studies (2019) 28:805–813
https://doi.org/10.1007/s10826-018-01324-1

ORIGINAL PAPER

Does the Transdiagnostic EMOTION Intervention Improve Emotion Regulation Skills in Children?

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Published online: 7 January 2019

Abstract

Objectives Emotion regulation is thought to be an important transdiagnostic process across internalizing disorders in youth, and the regulation of emotions is believed to play a central role in both adaptive and maladaptive development. Several preventive interventions focus on improving children's emotion regulation skills, but research regarding the outcomes of emotion regulation skills are scarce.

Methods We therefore investigated whether a new transdiagnostic indicated prevention intervention for anxiety and depressive symptoms, the EMOTION program, improves emotion regulation skills as reported by parents of children aged 8–12 years. Data from a large national cluster randomized control trial (RCT) study, Coping Kids, performed in Norway were used, including data from 601 children and their parents.

Results Using mixed models, we found a decrease in dysregulation of emotions ($\Delta = .06$, CI = (0.00 to .11), $p = .040$) and an increase in emotion regulation ($\Delta = .11$, CI = (0.05 to .17) $p < .001$) in the intervention group compared to the control group.

Conclusions The EMOTION intervention has a potential positive effect on children's emotional regulation skills. One opportunity in transdiagnostic interventions lies in targeting common underlying processes in internalizing disorders and thereby reaching a larger proportion of the youth population than is possible with single-disorder approaches.

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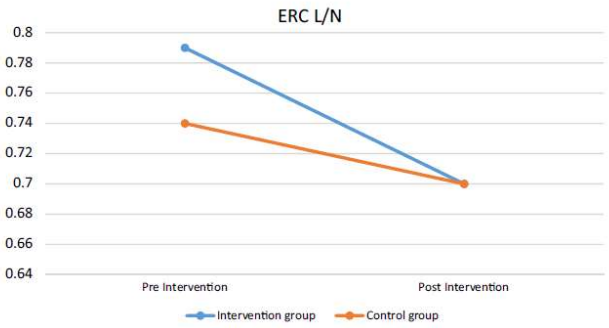

Fig. 2 ERC L/N Mean item scores, pre-intervention and post-intervention, separated by group. ERC L/N = Emotion Regulation Checklist, liability/negativity subscale. Higher score indicates greater dysregulation

Systematic difference at baseline due to lack of blinding.
Effect is the interaction term in a model not adjusting for baseline.

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Circadian preference moderate's intervention outcome in digital cognitive behavior therapy for insomnia (dCBT-I)

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Submitted January 2021

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Methods: Planned analysis of data from a randomized control trial (N=1721) of dCBI-I compared to patient education (PE). Assessments were performed at baseline and 9-weeks follow-up. Baseline scores on the reduced version of the Horne-Östberg Morningness Eveningness Questionnaire (rMEQ) were categorized into five groups reflecting circadian preference: Definitely evening-type (DET, n=142), moderately evening-type (MET, n=382), neither-type (NT, n=846), moderately morning-type (MMT, n=323) and definitely morning-type (DMT, n=27).

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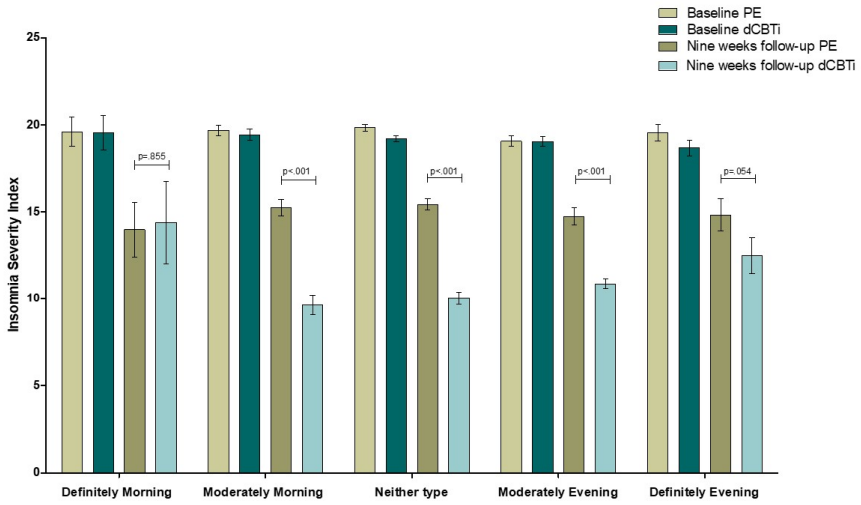

Figure 1. Observed means and standard deviations (SD) for dCBT-I and PE at baseline and 9-week follow-up for five circadian preferences. The p-values summarizes the results from baseline adjusted linear mixed models, with Insomnia Severity Index as depended variable.

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Linear mixed models were used with ISI, HADS and CFQ, one at a time, as dependent variables. The individual was included as a random effect. Time, group (dCBT-I versus PE), and rMEQ category were included as covariates as follows: Main effect of time and rMEQ, the two way interactions group x time and time x rMEQ, and the three way interaction group x time x rMEQ. In this way, by omitting a (systematic) main effect of group (at baseline) and the interaction group x rMEQ (at baseline), we adjust for baseline as recommended by Twisk et al (2018). All analyses were adjusted for age and sex. The three-way interaction terms are used to test if the estimated mean difference between dCBT-I and PE is different between the five different rMEQ subgroups. The effect of dCBT-I versus PE at 9-week follow-up for the outcome variables (ISI, CFQ, HADS) within each of the five rMEQ subgroups, is estimated as the difference in change from baseline for the two groups in terms of the coefficient of the corresponding interaction term group x time.

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$$ISI_{ij} = \beta_0 + \beta_1 trt + \beta_2 time + \beta_3 DET + \beta_4 MET + \beta_5 NT + \beta_6 MMT + \beta_7 DMT$$
$$+ \beta_8 time \times trt$$
$$+ \beta_9 time \times DET + \beta_{10} time \times MET + \beta_{11} time \times MT + \beta_{12} time \times MMT + \beta_{13} time \times DMT$$
$$+ \beta_{14} trt \times DET + \beta_{15} trt \times MET + \beta_{16} trt \times MT + \beta_{17} trt \times MMT + \beta_{18} trt \times DMT$$
$$+ \beta_{19} time \times trt \times DET + \beta_{20} time \times trt \times MET + \beta_{21} time \times trt \times MT + \beta_{22} time \times trt \times MMT + \beta_{23} time \times trt \times DMT$$
$$+ A_j + \varepsilon_{ij}$$

Delete one rMEQ subtype, for example DET (reference category)

Omit a (systematic) main effect of group (at baseline) and the interaction trt x rMEQ (at baseline)

Hypothesis test: Does the effect differ between rMEQ groups?

Effect of trt for DET (the reference rMEQ category)

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Gjellesvik, T. I., Becker, F., Tjonna, A. E., Indredavik, B., Nilsen, H., Brurok, B., Torhaug, T., Busuladzic, M., Lydersen, S., & Askim, T. (2020). Effects of High-Intensity Interval Training after Stroke (The HIIT-Stroke study) - A Multicenter Randomized Controlled Trial. Archives of Physical Medicine and Rehabilitation.

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Twisk, J., Bosman, L., Hoekstra, T., Rijnhart, J., Welten, M., & Heymans, M. (2018). Different ways to estimate treatment effects in randomised controlled trials. Contemporary Clinical Trials Communications, 10, 80-85.

Vickers, A. J., & Altman, D. G. (2001). Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ, 323(7321), 1123-1124.

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