NTNU
Regionalt kunnskapssenter
for barn og unge
– Psykisk helse og barnevern

Analyse av endring i longitudinelle studier: Justering for utgangsverdi?

Presentasjon på RBUP, Oslo, 3 november 2014
og RKBU, Trondheim, 14 november 2014

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http://folk.ntnu.no/slyderse/Adjust_for_baseline/Pres3Nov2014

Forhåndsomtale:

I studier med to eller flere målingstidspunkt vil en ofte studere hva som predikerer endring: I en randomisert kontrollert studie, hvilken behandlingsgruppe får mest gunstig endring i utfallsmålet fra før til etter behandling? I en observasjonell studie, hvilke(n) eksponering(er) påvirker endring og i hvor stor grad?

Regresjonsanalyse med etter-verdi som avhengig variabel og før-verdi samt gruppe som kovariater (ANCOVA) er en egnet metode for en RCT. I en observasjonell studie derimot, vil ANCOVA vanligvis gi helt feil resultater, noe mange forskere ikke er klar over.

Mixed models er egnet både i RCT og observasjonelle studier. Dette er i prinsippet det samme som vekstmodeller i SEM (Structural equation modelling).

Eksempler:

- Randomisert kontrollert studie (RCT): (Vickers and Altman 2001)
- Observasjonell studie: (Breidablik et al. 2009)

3

Hva mener vi med endring?

Alternative definisjoner av og analysemodeller (Fitzmaurice et al. 2011;Twisk 2013)

Alternativ 1- 5:
Relevant ved analyse av bare en etter-verdi (av gangen).

Alternativ 6 og 7:
Mest relevant ved mer enn to tidspunkt.

1.
Absolutt endring: Relevant ved observasjonelle studier

$$\Delta Y_i = Y_{i2} - Y_{i1}$$

2.
Relativ endring:

$$\Delta Y_i = \frac{Y_{i2} - Y_{i1}}{Y_{i1}} \times 100\%$$

3.
Endring relativ til gulv/tak effekt:

$$\text{Når } Y_{i2} > Y_{i1}: \quad \Delta Y_i = \frac{(Y_{i2} - Y_{i1})}{(Y_{\max} - Y_{i1})} \times 100\%$$

$$\text{Når } Y_{i2} < Y_{i1}: \quad \Delta Y_i = \frac{(Y_{i2} - Y_{i1})}{(Y_{i1} - Y_{\min})} \times 100\%$$

$$\text{Når } Y_{i2} = Y_{i1}: \quad \Delta Y_i = 0$$

Merk at

$$\Delta Y_i = \frac{(Y_{i2} - Y_{i1})}{(Y_{\max} - Y_{\min})} \times 100\%$$

bare er en reskalering av absolutt endring.

4.
ANCOVA: Relevant (nesten bare) ved RCT

$$Y_{i2} = \beta_0 + \beta_1 Y_{i1} + \beta_2 Intervention + ... + \varepsilon_i$$

Enkelte forfattere foreslår regresjonsanalyse med absolutt endring som avhengig variabel og før-verdi som kovariat:

$$Y_{i2} - Y_{i1} = \beta_0 + \beta_1^* Y_{i1} + \beta_2 Intervention + ... + \varepsilon_i$$

Men dette er ekvivalent med ANCOVA:

$$Y_{i2} = \beta_0 + (\beta_1^* + 1) Y_{i1} + \beta_2 Intervention + ... + \varepsilon_i$$

Eksempel: Data fra Vickers & Altman (2001)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	23,997	9,108		2,634	,011	5,692	42,303
	pretreatment score	,710	,160	,493	4,432	,000	,388	1,032
	acupuncture	12,705	4,286	,330	2,958	,005	4,093	21,318

a. Dependent Variable: posttreatment score

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	23,997	9,109		2,634	,011	5,692	42,303
	pretreatment score	-,290	,160	-,243	-1,800	,077	-,612	,032
	acupuncture	12,705	4,286	,330	2,965	,005	4,093	21,318

a. Dependent Variable: change score

5.
Bare bruke etter-verdi:
Y_{i2}

Eksempel på analyse av RCT i Vickers & Altman (2001):

Follow-up (alternativ 5)
Change score (alternativ 1)
ANCOVA (alternativ 4)

6.
(Alternative 1 in (Fitzmaurice, Laird, & Ware 2011), page 128, Section 5.7)
Retain baseline as part of the outcome vector and make no assumptions about group differences at baseline

$Y_{i1} = \beta_0 + \beta_1 x_i + \varepsilon_{i1}$

$Y_{i2} = \beta_0 + (\beta_1 + \beta_3) x_i + \beta_2 + \varepsilon_{i2}$

Der man evt legger restriksjoner på kovarians-strukturen på $(\varepsilon_{i1}, \varepsilon_{i2})'$.
Hvis $x_i = 0(1)$ når individ nr i er i gruppe 0(1): Nullhypotese:
Ingen gruppe-effekt, dvs endring er lik i de to gruppene: $\beta_3 = 0$
Dette gir ca samme svar som å bruke absolutt endring som avhengig variabel (Alterantiv 1). (Samtale med Fitzmaurice, 23 aug. 2009)
Tilsvarer mixed model.

7.
(Alternative 2 in (Fitzmaurice, Laird, & Ware 2011) , page 128, Section 5.7)
Retain baseline as part of the outcome vector and assume the group means are equal at baseline, as might be appropriate in a randomized controlled trial.
Som ovenfor, uten β_1 i modellen.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	62,298	3,378		18,440	,000	55,511	69,085
	acupuncture	17,304	4,072	,449	3,551	,001	7,517	27,090

a. Dependent Variable: posttreatment score

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	8,370	2,940		2,809	,007	2,449	14,292
	acupuncture	10,830	4,262	,306	2,547	,014	2,290	19,356

a. Dependent Variable: change score

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	23,997	9,108		2,634	,011	5,692	42,303
	acupuncture	12,706	4,286	,330	2,965	,005	4,093	21,318
	pretreatment score	,710	,160	,493	4,432	,000	,388	1,032

a. Dependent Variable: posttreatment score

Mixed model: Need datafile in long format (one case per time point per subject)

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	53,825920	2,890594	79,090	18,031	,000	47,973203	59,678649
Time	8,370370	2,947901	50,000	2,839	,007	2,449177	14,291564
Acupuncture	6,474074	4,313241	79,090	1,501	,137	-2,111065	15,059213
Time * Acupuncture	10,828830	4,251838	50,000	2,547	,014	2,289363	19,368298

a. Dependent Variable: Score

As expected, the result is similar to using absolute change as dependent variable.

When is baseline adjustment useful in analyses of change?

Should we use absolute change (without adjusting for baseline) or ANCOVA?

"The answer depends critically on whether the data arouse from an observational study or a randomized trial. If the study is an observational one, …it is usually not advisable to employ the analysis of covariance …" (Fitzmaurice, Laird, & Ware 2011) page 124 - 128.

In a randomized trial, it is a good recommendation to adjust for baseline values by using after treatment score as dependent variable, and before treatment score and group indicator as covariates (Vickers & Altman 2001). (ANCOVA)

"In general, the analysis of longitudinal data from a randomized trial is the only setting in where we recommend adjustment for baseline through analysis of covariance. In that setting, in contrast to observational studies, adjustment leads to meaningful tests of hypotheses of scientific interest. Moreover the tests based on the analysis of covariance approach will be more powerful… "

"When the covariance among repeated measures is assumed to have a compound symmetry pattern, with common variance σ^2 and common correlation ρ, the relative efficiency (ratio of the variance of the two estimators) is given by

$$\frac{1}{n}\{1+(n-1)\rho\}."$$

(Fitzmaurice, Laird, & Ware 2011) page 126.

For example, with $n=2$ (one follow-up measure) and $\rho=0.4$ (realistic for within-person measurements), the relative efficiency is $\frac{1}{2}\{1+(2-1)0.4\}=0.7$.

"Adjustment for baseline in the analysis of longitudinal change is a topic that has generated heated debate among analysts. When longitudinal data arise from an observational study, the two methods of adjusting for baseline described in this section can yield discernibly different and, apparently different results. This conundrum is also known as *Lord's paradox* (named after Frederic Lord, who eloquently brought this issue into light) and **has led many researchers astray over the years.** The paradox lies in the interpretation of the two types of analyses and is resolved by noting that that these two alternative methods for adjusting for baseline answer qualitatively different scientific questions when the data arise from an observational study. This can be illustrated in the simplest setting where there are two groups or sub-populations (e.g. males and females) measured at two occasions. … " (Fitzmaurice, Laird, & Ware 2011) page 126.
See Figure 1 (Lord 1967)

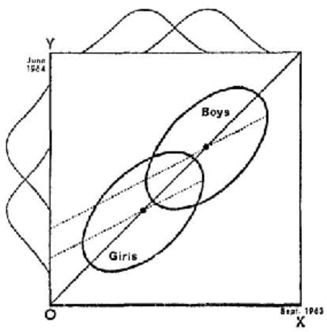
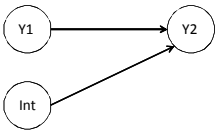


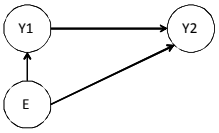
FIG. 1. Hypothetical scatterplots showing initial and final weight for boys and for girls.
Lord (1967)

Den store forskjellen:

RCT:
Utgangsverdi (Y1) er uanvhengig av behandling (Intervensjon)



Observasjonell studie:
Eksponering (E) som påvirker utgangsverdien (Y1)



Breidablik, H.J., Meland, E., & Lydersen, S. 2009. Self-rated health during adolescence: stability and predictors of change (Young-HUNT study, Norway). Eur.J.Public Health, 19, (1) 73-78

Feilaktig bruk av justering for utgangsverdi (ved T1) gjorde at deler av Tabell 4 ble feil. Dette ble senere kommentert i sammenskrivningen til avhandlingen til Breidablikk.

"In conclusion, it is the study design and the scientific question of interest … that should primarily determine the choice of analytic methods for adjusting for the baseline response. " (Fitzmaurice, Laird, & Ware 2011) page 127.

An in-depth coverage of analysis of observational data is given in (Glymour et al. 2005).

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22

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23