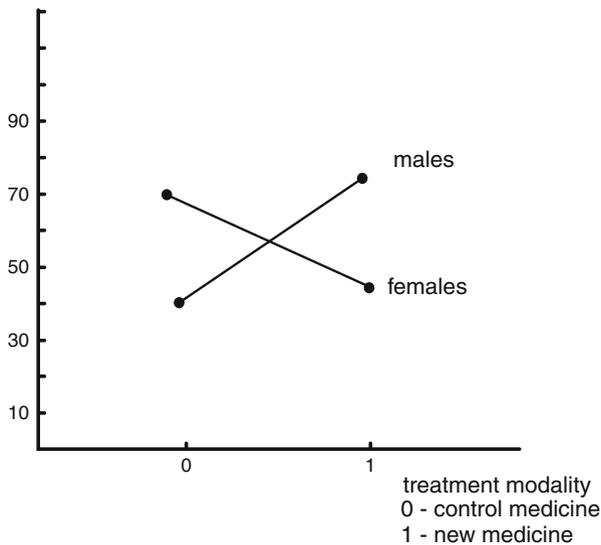# Chapter 23
Interaction, Random Effect Analysis of Variance (40 Patients)

1 General Purpose

In pharmaceutical research and development, multiple factors like age, gender, comorbidity, concomitant medication, genetic and environmental factors co-determine the efficacy of the new treatment. In statistical terms we say, they interact with the treatment efficacy.

Interaction is different from confounding. In a trial with interaction effects the parallel groups have similar characteristics. However, there are subsets of patients that have an unusually high or low response.

The above figure shows the essence of interaction: the males perform better than the females with the new medicine, with the control treatment the opposite (or no difference between males and females) is true.

2   Schematic Overview of Type of Data File

Outcome	predictor	predictor
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.

3   Primary Scientific Question

Are there not only independent effects of two predictors on the outcome, but also interaction effects between two predictors on the outcome.

4   Data Example

In a 40 patient parallel-group study of the effect of verapamil and metoprolol on paroxysmal atrial fibrillation (PAF) the possibility of interaction between gender and treatment on the outcome was assessed. The numbers of episodes of paroxysmal atrial tachycardias per patient, are the outcome variable. The entire data file is in extras.springer.com, and is entitled "chapter23interaction". The first ten patients of the data file is given below.

PAF	Treat	Gender
52,00	,00	,00
48,00	,00	,00
43,00	,00	,00
50,00	,00	,00
43,00	,00	,00

44,00	,00	,00
46,00	,00	,00
46,00	,00	,00
43,00	,00	,00
49,00	,00	,00

PAF = outcome = numbers of episodes of PAF
treat = 0 verapamil, 1 metoprolol
gender = 0 female, 1 male

5   Data Summaries

Verapamil	Metoprolol	
Males		
52	28	
48	35	
43	34	
50	32	
43	34	
44	27	
46	31	
46	27	
43	29	
49 +	25 +	
464	302	766
Females		
38	43	
42	34	
42	33	
35	42	
33	41	
38	37	
39	37	
34	40	
33	36	
34 +	35 +	
368	378	746
832	680	

Overall, metoprolol seems to perform better. However, this is only true for one subgroup (males). The presence of interaction between gender and treatment modality can be assessed several ways: (1) t-tests (see Chapter 18, Statistics on a pocket calculator part one, Springer New York, 2011, from the same authors),

(2) analysis of variance, and (3) regression analysis. The data file is given underneath.

6   Analysis of Variance

We will first perform an analysis of variance. Open the data file in SPSS.

For analysis the General Linear Model is required. It consists of four statistical models:
Univariate,

Multivariate,
Repeated Measures,
Variance Components.

We will use here Univariate.

Command:
Analyze….General Linear Model….Univariate Analysis of Variance …. Dependent: PAF….Fixed factors:treatment, gender….click OK.

Tests of Between-Subjects Effects
Dependent Variable: outcome

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	1327,200[a]	3	442,400	37,633	,000
Intercept	57153,600	1	57153,600	4861,837	,000
Treatment	577,600	1	577,600	49,134	,000
Gender	10,000	1	10,000	,851	,363
Treatment * gender	739,600	1	739,600	62,915	,000
Error	423,200	36	11,756		
Total	58904,000	40			
Corrected total	1750,400	39			

[a]R Squared = ,758 (Adjusted R Squared = ,738)

The above table shows that there is a significant interaction between gender and treatment at $p = 0,0001$ (* is sign of multiplication). In spite of this, the treatment modality is a significant predictor of the outcome. In situations like this it is often better to use a socalled *random* effect model. The "sum of squares treatment" is, then, compared to the "sum of squares interaction" instead of the "sum of squares error". This is a good idea, since the interaction was unexpected, and is a major contributor to the error, otherwise called spread, in the data. This would mean, that

we have much more spread in the data than expected, and we will lose a lot of power to prove whether or not the treatment is a significant predictor of the outcome, episodes of PAF. Random effect analysis of variance requires the following commands:

Command:
Analyze. . . .General Linear Model. . ..Univariate Analysis of Variance . . .. Dependent: PAF. . ..Fixed Factors: treatment. . ... Random Factors: gender. . ..click OK

The underneath table shows the results. As expected the interaction effect remained statistically significant, but the treatment effect has now lost its significance. This is realistic, since in a trial with major interactions, an overall treatment effect analysis is not relevant anymore. A better approach will be a separate analysis of the treatment effect in the subgroups that caused the interaction.

Tests of between-subjects effects
Dependent Variable:outcome

Source		Type III sum of squares	df	Mean square	F	Sig.
Intercept	Hypothesis	57153,600	1	57153,600	5715,360	,008
	Error	10,000	1	10,000[a]		
Treatment	Hypothesis	577,600	1	577,600	,781	,539
	Error	739,600	1	739,600[b]		
Gender	Hypothesis	10,000	1	10,000	,014	,926
	Error	739,600	1	739,600[b]		
Treatment * gender	Hypothesis	739,600	1	739,600	62,915	,000
	Error	423,200	36	11,756[c]		

[a]MS (gender)
[b]MS (treatment * gender)
[c]MS (Error)

As a contrast test we may use regression analysis for these data. For that purpose we first have to add an interaction variable:

interaction variable = treatment modality * gender
(* = sign of multiplication).

Underneath the first 10 patients of the above data example is given, now including the interaction variable.

PAF	Treat	Gender	Interaction
52,00	,00	,00	,00
48,00	,00	,00	,00
43,00	,00	,00	,00
50,00	,00	,00	,00
43,00	,00	,00	,00
44,00	,00	,00	,00
46,00	,00	,00	,00
46,00	,00	,00	,00
43,00	,00	,00	,00
49,00	,00	,00	,00

PAF = outcome = numbers of episodes of PAF

treat = o verapamil, 1 metoprolol
gender = 0 female, 1 male
interaction = interaction between treat and gender = treat * gender

7   Multiple Linear Regression

The interaction variable will be used together with treatment modality and gender as independent variables in a multiple linear regression model. For analysis the statistical model Linear in the module Regression is required.

Command:
Analyze….Regression….Linear….Dependent: PAF …Independent (s): treat, gender, interaction….click OK.

Coefficients[a]

Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	46,400	1,084		42,795	,000
	Treatment	−16,200	1,533	−1,224	−10,565	,000
	Gender	−9,600	1,533	−,726	−6,261	,000
	Interaction	17,200	2,168	1,126	7,932	,000

[a]Dependent Variable: outcome

The above table shows the results of the multiple linear regression. Like with fixed effect analysis of variance, both treatment modality and interaction are statistically significant. The t-value-interaction of the regression = 7,932. The F-value-interaction of the fixed effect analysis of variance = 62,916 and this equals $7,932^2$. Obviously, the two approaches make use of a very similar arithmetic.

Unfortunately, for random effect regression SPSS has limited possibilities.

8   Conclusion

Interaction is different from confounding (Chap. 22). In a trial with interaction effects the parallel group characteristics are equally distributed between the groups. However, there are subsets of patients that have an unusually high or low response to one of the treatments. Assessments are reviewed.

9   Note

More background, theoretical, and mathematical information of interaction assessments is given in Statistics applied to clinical studies 5th edition, Chap. 30, Springer Heidelberg Germany, 2012, from the same authors.