Chapter 41
Interaction

1 General Purpose

In the Chap. 25 interaction of continuous outcome data has been assessed. The efficacy of one treatment is better in one of the subgroups, and the efficacy of the other treatment is better in the other subgroup. With interaction an overall data analysis is pretty meaningless, and separate analyses of the subgroups must be presented. Of course, with multiple treatments and subgroups interaction is possible as well, but the analysis is much more complex. In the current chapter we will demonstrate how to assess interaction of binary outcome data instead of continuous outcome data.

2 Schematic Overview of Type of Data

Treatment modality	outcome (binary)
(0 and 1)	(1 and 2)
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T.J. Cleophas, A.H. Zwinderman, *Clinical Data Analysis on a Pocket Calculator*,
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3 Primary Scientific Question

Does one treatment perform better in one subgroup and does the other treatment so in the other subgroup.

4 Interaction, Example 1

We will use the example of the Chap. 40, Sect. 40.4, once more to assess the presence of interaction between males and females on the outcome.

	males	females
proportion treat 1	0.42	0.71
SE	0.05	0.08
proportion treat 2	0.22	0.60
SE	0.05	0.03
Differences	0.20	0.11
pooled SE	0.07	0.09

Differences between males and females $0.20-0.11=0.09$ with a pooled SE of $\surd[(0.07^2)+(0.09^2)]=0.11$. Z-value $=0.09/0.11=0.82$. This z-value not statistically significantly different from zero (see the underneath t-table). It means that, although confounding of genders has been demonstrated in these data (Chap. 40), no interaction between the genders is in the data.

df	One-Tail = .4	.25	.1	.05	.025	.01	.005	.0025	.001	.0005
	Two-Tail = .8	.5	.2	.1	.05	.02	.01	.005	.002	.001
1	0.325	1.000	3.078	6.314	12.706	31.821	63.657	127.32	318.31	636.62
2	0.289	0.816	1.886	2.920	4.303	6.965	9.925	14.089	22.327	31.598
3	0.277	0.765	1.638	2.353	3.182	4.541	5.841	7.453	10.214	12.924
4	0.271	0.741	1.533	2.132	2.776	3.747	4.604	5.598	7.173	8.610
5	0.267	0.727	1.476	2.015	2.571	3.365	4.032	4.773	5.893	6.869
6	0.265	0.718	1.440	1.943	2.447	3.143	3.707	4.317	5.208	5.959
7	0.263	0.711	1.415	1.895	2.365	2.998	3.499	4.029	4.785	5.408
8	0.262	0.706	1.397	1.860	2.306	2.896	3.355	3.833	4.501	5.041
9	0.261	0.703	1.383	1.833	2.262	2.821	3.250	3.690	4.297	4.781
10	0.260	0.700	1.372	1.812	2.228	2.764	3.169	3.581	4.144	4.587
11	0.260	0.697	1.363	1.796	2.201	2.718	3.106	3.497	4.025	4.437
12	0.259	0.695	1.356	1.782	2.179	2.681	3.055	3.428	3.930	4.318
13	0.259	0.694	1.350	1.771	2.160	2.650	3.012	3.372	3.852	4.221
14	0.258	0.692	1.345	1.761	2.145	2.624	2.977	3.326	3.787	4.140
15	0.258	0.691	1.341	1.753	2.131	2.602	2.947	3.286	3.733	4.073
16	0.258	0.690	1.337	1.746	2.120	2.583	2.921	3.252	3.686	4.015
17	0.257	0.689	1.333	1.740	2.110	2.567	2.898	3.222	3.646	3.965
18	0.257	0.688	1.330	1.734	2.101	2.552	2.878	3.197	3.610	3.922
19	0.257	0.688	1.328	1.729	2.093	2.539	2.861	3.174	3.579	3.883
20	0.257	0.687	1.325	1.725	2.086	2.528	2.845	3.153	3.552	3.850
21	0.257	0.686	1.323	1.721	2.080	2.518	2.831	3.135	3.527	3.819
22	0.256	0.686	1.321	1.717	2.074	2.508	2.819	3.119	3.505	3.792
23	0.256	0.685	1.319	1.714	2.069	2.500	2.807	3.104	3.485	3.767
24	0.256	0.685	1.318	1.711	2.064	2.492	2.797	3.091	3.467	3.745
25	0.256	0.684	1.316	1.708	2.060	2.485	2.787	3.078	3.450	3.725
26	0.256	0.684	1.315	1.706	2.056	2.479	2.779	3.067	3.435	3.707
27	0.256	0.684	1.314	1.703	2.052	2.473	2.771	3.057	3.421	3.690
28	0.256	0.683	1.313	1.701	2.048	2.467	2.763	3.047	3.408	3.674
29	0.256	0.683	1.311	1.699	2.045	2.462	2.756	3.038	3.396	3.659
30	0.256	0.683	1.310	1.697	2.042	2.457	2.750	3.030	3.385	3.646
40	0.255	0.681	1.303	1.684	2.021	2.423	2.704	2.971	3.307	3.551
60	0.254	0.679	1.296	1.671	2.000	2.390	2.660	2.915	3.232	3.460
120	0.254	0.677	1.289	1.658	1.980	2.358	2.617	2.860	3.160	3.373
∞	0.253	0.674	1.282	1.645	1.960	2.326	2.576	2.807	3.090	3.291

The t-table has a left-end column giving degrees of freedom (≈ sample sizes), and two top rows with p-values (areas under the curve = p – values), one-tail meaning that only one end of the curve, two-tail meaning that both ends are assessed simultaneously. The t-table is, furthermore, full of t-values, that, with ∞ degrees of freedom, are equal to z-values (Chap. 36). The t-values are to be understood as mean results of studies, but not expressed in mmol/l, kilograms, but in so-called SEM-units (Standard error of the mean units), that are obtained by dividing your mean result by its own standard error. With many degrees of freedom (large samples) the curve will be a little bit narrower, and more in agreement with nature.

A z-value of 0.82 is a lot smaller than 1.960, and the corresponding two-tail p-value is, thus, > 0.05, and not significant.

5 Interaction, Example 2

The hypothesized data from the above example have been slightly changed.

	responders	non-responders	total	proportion	SE = √[p(1–p)/n)]
males:					
treat 1	36	50	86	36/86 = 0.42	√(0.42 × 0.58/86) =0.05
treat 2	14	50	64	14/64 = 0.22	=0.05
total	50	100	150		
females:					
treat 1	120	80	200	0.60	=0.03
treat 2	24	10	34	0.71	=0.08
total	144	90	234		

p = proportion, n = sample size, SE = standard error

	males	females
proportion treat 1	0.42	0.60
SE	0.05	0.03
proportion treat 2	0.22	0.71
SE	0.05	0.08
—		
Differences	0.20	−0.11
pooled SE	0.07	0.09

Difference in proportion between males and females 0.20 + 0.11 = 0.31 with a pooled SE of $\sqrt{[(0.07^2) + (0.09^2)]} = 0.11$. The z-value = 0.31/0.11 = 2.82. This z-value statistically larger than 1.960, the p-value is significantly different from zero (see above t-table). It means that a significant interaction between genders is in these data. In the males the treatment 1 performs better, in the females the treatment 2.

6 Conclusion

A two-sample t-test (or rather z-test) (see also Chap. 36) can be used to test whether the differences in treatment efficacies of two subgroups are significantly different from one another. The above example shows that a significant interaction between genders can be demonstrated in such data. In the males the treatment 1 performed better, in the females the treatment 2 did so.

7 Note

More background, theoretical and mathematical information of interaction assessments can be found in Statistics applied top clinical studies 5th edition, Chap. 30, Springer Heidelberg Germany, from the same authors.