Chapter 10
Paired Continuous Data, Analysis with Help of Correlation Coefficients

1 General Purpose

The t-value obtained from an unpaired analysis of paired data produces biased results. This is, because the level of correlation between unpaired data is assumed to be zero, and this may not be true for paired observations. Particularly, repeated measurements in one subject produces usually results more similar than those from single measurements in separate subjects. Repeated measurements, thus, tends to produce a positive correlation. However, this is not always true. Negative correlations will be observed, if completely different treatment effects are examined in one subject. This is, because the responders to one treatment are more at risk of being non-responder to the other treatment and vice versa. Indeed, correlations is a very basic phenomenon in statistical analyses, and it almost entirely determines the results of regression analyses.

This chapter is to examine the performance of correlation coefficients (r-values or R-values) for testing paired data, alternative to the traditional paired t-test and Wilcoxon test. The advantage is, that correlation coefficients unmask, how the level of correlation between repeated measures affect the overall uncertainty in crossover study, and other repeated measures studies.

2 Schematic Overview of Type of Data File

Outcome 1	Outcome 2
.	.
.	.
.	.
.	.

(continued)

T.J. Cleophas, A.H. Zwinderman, *Clinical Data Analysis on a Pocket Calculator*,
DOI 10.1007/978-3-319-27104-0_10

Outcome 1	Outcome 2
.	.
.	.
.	.
.	.
.	.

3 Primary Scientific Question

Can analysis with help of correlation coefficients be used to test in a crossover study whether the first outcome significantly different from second one?

4 Data Example

In a crossover study 10 patients are treated with a sleeping pill and a placebo. The first 11 patients of the 20 patient data file is given underneath.

Outcome 1	Outcome 2
6.0	5.1
7.1	8.0
8.1	3.8
7.5	4.7
6.4	5.2
7.9	5.4
6.8	4.3
6.6	6.0
7.3	3.7
5.6	6.2

Outcome = hours of sleep after treatment

5 Unpaired T-Test of Paired Data, the Wrong Analysis

outcome 1:
6.0, 7.1, 8.1, 7.5, 6.4, 7.9, 6.8, 6.6, 7.3, 5.6

outcome 2:
5.1, 8.0, 3.8, 4.4, 5.2, 5.4, 4.3, 6.0, 3.7, 6.2

Mean group 1 = 6.93 SD = 0.806 SE = SD/√10 = 0.255
Mean Group 2 = 5.21 SD = 1.299 SE = SD/√10 = 0.411

Is there a significant difference between the two groups, which level of significance is correct (SD = standard deviation, SE = standard error of the mean)?

Mean	standard deviation (SD)
6.93	0.806
5.21 -	1.299
1.72	

$$\text{pooled SE} = \sqrt{\left(\frac{0.806^2}{10} + \frac{1.299^2}{10}\right)} = 0.483.$$

The t-value = (6.93 – 5.21) / 0.483 = 3.56.

6 Paired T-Test of Paired Data

Observations 1:
6.0, 7.1, 8.1, 7.5, 6.4, 7.9, 6.8, 6.6, 7.3, 5.6

Observations 2:
5.1, 8.0, 3.8, 4.4, 5.2, 5.4, 4.3, 6.0, 3.7, 6.2

Individual differences:
0.9, -0.9, 4.3, 3.1, 1.2, 2.5, 2.5, 0.6, 3.8, -0.6

A. not significant
B. $0.05 < p < 0.10$
C. $P < 0.05$
D. $P < 0.01$

Is there a significant difference between the observations 1 and 2, and which level of significance is correct?

Mean difference = 1.59
SD of mean difference = 1.789 (SD = standard deviation)
SE = SD/√10 = 0.566 (SE = standard error)
t = 1,59 / 0,566 = 2.81

This t-value of 2.81 is a lot smaller than the one from the above unpaired t-test (3.56). Obviously, the correlation between the first and second observations is negative. We will first calculate the level of correlation, r, and then use the underneath 2nd equation for adjustment of the overestimated t-value instead of the first equation.

$$\text{Standard error unpaired differences} = \frac{\sqrt{\left(SD_1{}^2+SD_2{}^2\right)}}{n}$$

$$\text{Standard error paired differences} = \frac{\sqrt{\left(SD_1{}^2+SD_2{}^2-2\,r\,SD_1.SD_2\right)}}{n}$$

7 Linear Regression for Adjustment of Erroneous T-Value from Sect. 5

The equation of a linear regression model is given by

$$y = a + bx,$$

with y named the dependent variable and x the independent variable.

The line drawn from this linear function provides the best fit for the data given, where y = so-called dependent, and x = independent variable, b = regression coefficient, a = intercept:

a and b from the equation y = a + bx can be calculated.

$$b = \text{regression coefficient} = \frac{\sum (x-\bar{x})(y-\bar{y})}{\sum (x-\bar{x})^2}$$

$a = \text{intercept} = \bar{y} - b\bar{x}$

r = correlation coefficient = another important determinant and looks a lot like b.

$$r = \frac{\sum (x-\bar{x})(y-\bar{y})}{\sqrt{\sum (x-\bar{x})^2 \sum (y-\bar{y})^2}}$$

r = measure for the strength of association between y and x-data. The stronger the association, the better y predicts x, with +1 and −1 as maximal and minimal r-values.

We will use the Electronic Calculator (see Chap. 1).

Command:

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click ON....click MODE....press 3....press 1....press SHIFT, MODE,
and again 1....press=....start entering the data.... [1, 6,0]....[1,
7,1]....[1, 8,1] etc....
In order to obtain the b value, press: shift, S-VAR, ►, ►, 2, = .
In order to obtain the r value, press: shift, S-VAR, ►, ►, 3, = .
```

The b value equals 1.70, the r value equals −0.643.

Standard error paired differences (* is symbol of multiplication)

$$= \frac{\sqrt{\left(SD_1{}^2 + SD_2{}^2 - 2\ r\ SD_1.SD_2\right)}}{\sqrt{n}}$$

$$= \frac{\sqrt{\left(0.806^2 + 1.299^2 + 1,286 * 0.806 * 1.299\right)}}{\sqrt{10}}$$

$$= 0.607$$

Adjusted t-value = 1.72 / 0.607
=2.83

This adjusted t-value is approximately equal to the t-value obtained from the paired t-test in above Sect. 6. The small difference is due to shortening of the final digits during calculations.

8 T-Table

According to 9th row of the underneath t-table (10 subjects in one group means 9 degrees of freedom), with $t = 2.83$, the t-value is between 2.821 and 3.250. The corresponding p-values can be observed in the second top row. It is between 0.02 and 0.01, and, thus, < 0.02.

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.

df	One-Tail = .4 Two-Tail = .8	.25 .5	.1 .2	.05 .1	.025 .05	.01 .02	.005 .01	.0025 .005	.001 .002	.0005 .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

9 Conclusion

The t-value obtained from an unpaired analysis of paired data produces biased results. This is, because the level of correlation between unpaired data is assumed to be zero, and repeated measurements tend to produce a positive correlation. However, negative correlations may sometimes also be observed, if the responders to one treatment are more at risk of being non-responder to a subsequent treatment and vice versa. This chapter examines the use of correlation coefficients for testing paired data, as an alternative to the traditional paired t-test and Wilcoxon test (Chap. 5). The advantage of is that this method unmasks, how the level of correlation between repeated measures affects the overall uncertainty in a study.

Correlations is a phenomenon of major importance in statistical analyses, and must always taken into account.

10 Note

More examples of t-tests and linear regression analyses are given in Statistics applied to clinical studies 5th edition, Chaps. 1, 2, 14 and 15, Springer Heidelberg Germany, 2012, from the same authors.