

Chapter 40

Heterogeneity in Clinical Research: Mechanisms Responsible (20 Studies)

General Purpose

In clinical research similar studies often have different results. This may be due to differences in patient-characteristics and trial-quality-characteristics such as the use of blinding, randomization, and placebo-controls. This chapter is to assess whether 3-dimensional scatter plots and regression analyses with the treatment results as outcome and the predictors of heterogeneity as exposure are able to identify mechanisms responsible.

Primary Scientific Question

Are scatter plots and regression models able to identify the mechanisms responsible for heterogeneity in clinical research.

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Example

Variables			
1	2	3	4
% ADEs	study size	age	investigator type
21,00	106	1	1
14,40	578	1	1
30,40	240	1	1
6,10	671	0	0
12,00	681	0	0
3,40	28411	1	0
6,60	347	0	0
3,30	8601	0	0
4,90	915	0	0
9,60	156	0	0
6,50	4093	0	0
6,50	18820	0	0
4,10	6383	0	0
4,30	2933	0	0
3,50	480	0	0
4,30	19070	1	0
12,60	2169	1	0
33,20	2261	0	1
5,60	12793	0	0
5,10	355	0	0

ADEs = adverse drug effects

age 0 = young, 1 = elderly

investigator type, 0 = pharmacists, 1 = clinicians

In the above 20 studies the % of admissions to hospital due to adverse drug effects were assessed. The studies were very heterogeneous, because the percentages admissions due to adverse drug effects varied from 3.3 to 33.2. In order to identify possible mechanisms responsible, a scatter plot was first drawn. The data file is in extras.springer.com and is entitled "heterogeneity".

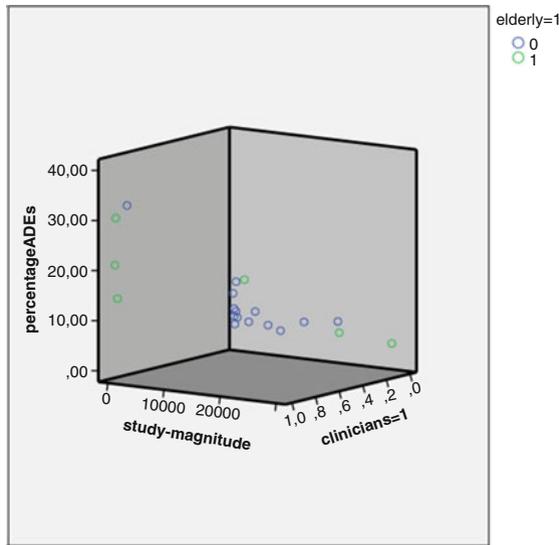
Start by opening the data file in SPSS statistical software.

Command:

click Graphs....click Legacy Dialogs....click Scatter/Dot....click 3-D Scatter....click Define....Y-Axis: enter percentage (ADEs)....X Axis: enter study-magnitude....Z Axis: enter clinicians =1....Set Markers by: enter elderly = 1....click OK.

The underneath figure is displayed, and it gives a 3-dimensional graph of the outcome (% adverse drug effects) versus study size versus investigator type (1 = clinician, 0 = pharmacist). A 4th dimension is obtained by coloring the circles

(green = elderly, blue = young). Small studies tended to have larger results. Also clinician studies (clinicians = 1) tended to have larger results, while studies in elderly had both large and small effects.



In order to test whether the observed trends were statistically significant, a linear regression is performed.

Command:

Analyze....Regression....Linear....Dependent: enter "percentage ADEs"....
Independent(s): enter "study-magnitude, elderly = 1, clinicians = 1"....click OK.

Coefficients ^a						
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	6,924	1,454		4,762	,000
	Study-magnitude	-7,674E-5	,000	-,071	-,500	,624
	Elderly = 1	-1,393	2,885	-,075	-,483	,636
	Clinicians = 1	18,932	3,359	,887	5,636	,000

^aDependent variable: percentage ADEs

The output sheets show the above table. The investigator type is the only statistically significant predictor of % of ADEs. Clinicians observed significantly more ADE admissions than did pharmacists at $p < 0.0001$. This is in agreement with the above graph

Conclusion

In clinical research similar studies often have different results. This may be due to differences in patient-characteristics and trial-quality-characteristics such as the use of blinding, randomization, and placebo-controls. This chapter shows that 3-dimensional scatter plot are able to identify the mechanisms responsible. Linear regression analyses with the treatment results as outcome and the predictors of heterogeneity as exposure are able to rule out heterogeneity due to chance. This is particularly important, when no clinical explanation is found or when heterogeneity seems to be clinically irrelevant.

Note

More background, theoretical and mathematical information of heterogeneous studies and meta-regression is in *Statistics applied to clinical studies* 5th edition, Chap. 33, Meta-analysis, review and update of methodologies, pp 379–390, and Chap. 34, Meta-regression, pp 391–397, Springer Heidelberg Germany, both from the same authors as the current work.