Chapter 18
Multivariate Analysis of Variance (35 and 30 Patients)

1 General Purpose

Multivariate analysis is a method that, simultaneously, assesses more than a single outcome variable. It is different from repeated measures analysis of variance and mixed models, that assess both the difference between the outcomes and the overall effects of the predictors on the outcomes. Multivariate analysis, simultaneously, assesses the separate effects of the predictors on one outcome adjusted for the other. E.g., it can answer clinically important questions like: does drug-compliance not only predict drug efficacy, but also, independently of the first effect, predict quality of life. Path statistics can be used as an alternative approach to multivariate analysis of variance (MANOVA) (Chap. 17). However, MANOVA is the real thing, because it produces an overall level of significance of a predictive model with multiple outcome and predictor variables.

2 Schematic Overview of Type of Data File

Outcome 1	outcome 2	predictor 1	predictor 2
.	.	.	.
.	.	.	.
.	.	.	.
.	.	.	.
.	.	.	.
.	.	.	.
.	.	.	.

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T.J. Cleophas, A.H. Zwinderman, *SPSS for Starters and 2nd Levelers*,
DOI 10.1007/978-3-319-20600-4_18

3 Primary Scientific Question

Does the inclusion of additional outcome variables enable to make better use of predicting variables.

4 First Data Example

The effects of non compliance and counseling on treatment efficacy of a new laxative were assessed in the Chap. 16. For multivariate analysis quality of life scores were added as additional outcome variable. The first 10 patients of the data file also used in Chap. 17 is given underneath.

Stools	Qol	Counsel	Compliance
24,00	69,00	8,00	25,00
30,00	110,00	13,00	30,00
25,00	78,00	15,00	25,00
35,00	103,00	10,00	31,00
39,00	103,00	9,00	36,00
30,00	102,00	10,00	33,00
27,00	76,00	8,00	22,00
14,00	75,00	5,00	18,00
39,00	99,00	13,00	14,00
42,00	107,00	15,00	30,00

stools = stools per month
qol = quality of life scores
counseling = counselings per month
compliance = non-compliance with drug treatment

The entire data file is entitled "chapter17multivariatewithpath", and is in extras.springer.com. Start by opening the data file in SPSS. The module General Linear Model consists of four statistical models:

Univariate,

Multivariate,
Repeated Measures,
Variance Components.

We will use here the statistical model Multivariate.

We will first assess whether counseling frequency is a significant predictor of (1) both frequency improvement of stools and (2) improved quality of life.

Command:
Analyze. . .General Linear Model. . .Multivariate. . ..In dialog box Multivariate: transfer "therapeutic efficacy" and "qol" to Dependent Variables and "counseling" to Fixed factors .. . .OK.

Multivariant tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	,992	1185,131[b]	2,000	19,000	,000
	Wilks' Lambda	,008	1185,131[b]	2,000	19,000	,000
	Hotelling's Trace	124,751	1185,131[b]	2,000	19,000	,000
	Roys Largest Root	124,751	1185,131[b]	2,000	19,000	,000
Counseling	Pillai's Trace	1,426	3,547	28,000	40,000	,000
	Wilks' Lambda	,067	3,894[b]	28,000	38,000	,000
	Hotelling's Trace	6,598	4,242	28,000	36,000	,000
	Roys Largest Root	5,172	7,389[c]	14,000	20,000	,000

[a]Design: Intercept + counseling
[b]Exact statistic
[c]The statistic is an upper bound on F that yields a lower bound on the significance level

The above table shows that MANOVA can be considered as another regression model with intercepts and regression coefficients. Just like analysis of variance (ANOVA) it is based on normal distributions and homogeneity of the variables. SPSS has checked the assumptions, and the results as given indicate that the model is adequate for the data. Generally, Pillai's method gives the best robustness and Roy's the best p-values. We can conclude that counseling is a strong predictor of both improvement of stools and improved quality of life. In order to find out which of the two outcomes is most important, two ANOVAs with each of the outcomes separately must be performed.

Command:
Analyze.. . .General Linear Model.. . .Univariate.. . .In dialog box Univariate transfer "therapeutic efficacy" to Dependent Variables and "counseling" to Fixed Factors.. . .OK.

Do the same for the predictor variable "compliance".

Tests of between-subjects effects

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	2733,005[a]	14	195,215	6,033	,000
Intercept	26985,054	1	26985,054	833,944	,000
Counseling	2733,005	14	195,215	6,033	,000
Error	647,167	20	32,358		
Total	36521,000	35			
Corrected total	3380,171	34			

Dependent Variable: therapeutic efficacy
[a]R Squared = ,809 (Adjusted R Squared = ,675)

Tests of between-subjects effects

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	6833,671[a]	14	488,119	4,875	,001
Intercept	223864,364	1	223864,364	2235,849	,000
Counseling	6833,671	14	488,119	4,875	,001
Error	2002,500	20	100,125		
Total	300129,000	35			
Corrected total	8836,171	34			

Dependent Variable:qol
[a]R Squared = ,773 (Adjusted R Squared = ,615)

The above tables show that also in the ANOVAs counseling frequency is a strong predictor of not only improvement of frequency of stools but also of improved quality of life (improv freq stool = improvement of frequency of stools, improve qol = improved quality of life scores)

In order to find out whether the compliance with drug treatment is a contributory predicting factor, MANOVA with two predictors and two outcomes is performed. Instead of "counseling" both "counseling" and "compliance" are transfered to Fixed factors. The underneath table shows the results.

Multivariate tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	,997	384,080[b]	1,000	1,000	,032
	Wilks' Lambda	,003	384,080[b]	1,000	1,000	,032
	Hotelling's Trace	384,080	384,080[b]	1,000	1,000	,032
	Roy's Largest Root	384,080	384,080[b]	1,000	1,000	,032
Counseling	Pillai's Trace	,933	1,392[b]	10,000	1,000	,583
	Wilks' Lambda	,067	1,392[b]	10,000	1,000	,583
	Hotelling's Trace	13,923	1,392[b]	10,000	1,000	,583
	Roy's Largest Root	13,923	1,392[b]	10,000	1,000	,583
Compliance	Pillai's Trace	,855	,423[b]	14,000	1,000	,854
	Wilks' Lambda	,145	,423[b]	14,000	1,000	,854
	Hotelling's Trace	5,917	,423[b]	14,000	1,000	,854
	Roy's Largest Root	5,917	,423[b]	14,000	1,000	,854
Counseling * compliance	Pillai's Trace	,668	,402[b]	5,000	1,000	,824
	Wilks' Lambda	,332	,402[b]	5,000	1,000	,824
	Hotelling's Trace	2,011	,402[b]	5,000	1,000	,824
	Roy's Largest Root	2,011	,402[b]	5,000	1,000	,824

[a]Design: Intercept + counseling + compliance + counseling * compliance
[b]Exact statistic

After including the second predictor variable the MANOVA is not significant anymore. Probably, the second predictor is a confounder of the first one. The analysis of this model stops here.

5 Second Data Example

As a second example we use the data from Field (Discovering SPSS, Sage London, 2005, p 571) assessing the effect of three treatment modalities on compulsive behavior disorder estimated by two scores, a thought-score and an action-score (Var = variable).

Action	Thought	Treatment
5,00	14,00	1,00
5,00	11,00	1,00
4,00	16,00	1,00
4,00	13,00	1,00
5,00	12,00	1,00
3,00	14,00	1,00
7,00	12,00	1,00
6,00	15,00	1,00
6,00	16,00	1,00
4,00	11,00	1,00

action = action outcome score
thought = thought outcome score
treatment = predictor with treatment modalities 0–2

The entire data file is in extras.springer.com, and is entitled "chapter18multivariateanova". Start by opening the data file. The module General Linear Model consists of four statistical models:

Univariate,
Multivariate,
Repeated Measures,
Variance Components.

We will use here again the statistical model Multivariate.

Command:
Analyze. . ..General Linear Model.. . .Multivariate.. . .In dialog box Multivariate transfer "action" and "thought" to Dependent Variables and "treatment" to Fixed Factors .. . .OK.

Multivariate tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	,983	745,230[b]	2,000	26,000	,000
	Wilks'Lambda	,017	745,230[b]	2,000	26,000	,000
	Hotelling's Trace	57,325	745,230[b]	2,000	26,000	,000
	Roy's Largest Root	57,325	745,230[b]	2,000	26,000	,000
treatment	Pillai's Trace	,318	2,557	4,000	54,000	,049
	Wilks'Lambda	,699	2,555[b]	4,000	52,000	,050
	Hotelling's Trace	,407	2,546	4,000	50,000	,051
	Roy's Largest Root	,335	4,520[c]	2,000	27,000	,020

[a]Design: Intercept + treatment
[b]Exact statistic
[c]The statistic is an upper bound on F that yields a lower bound on the significance level

The Pillai test shows that the predictor (treatment modality) has a significant effect on both thoughts and actions at p = 0,049. Roy's test being less robust gives an even better p-value of 0,020.

We will use again ANOVAs to find out which of the two outcomes is more important.

Command:
Analyze.. . .General Linear Model. . ..Univariate.. . .In dialog box Univariate transfer "actions" to Dependent variables and "treatment" to Fixed factors.. . .OK.

Do the same for variable "thought".

Tests of between-subjects effects

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	10,467[a]	2	5,233	2,771	,080
Intercept	616,533	1	616,533	326,400	,000
Treatment	10,467	2	5,233	2,771	,080
Error	51,000	27	1,889		
Total	678,000	30			
Corrected total	61,467	29			

Dependent Variable:action score
[a]R Squared = ,170 (Adjusted R Squared = ,109)

Tests of between-subjects effects

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	19,467[a]	2	9,733	2,154	,136
Intercept	6336,533	1	6336,533	1402,348	,000
Treatment	19,467	2	9,733	2,154	,136
Error	122,000	27	4,519		
Total	6478,000	30			
Corrected total	141,467	29			

Dependent Variable:thought score
[a]R Squared = ,138 (Adjusted R Squared = ,074)

The above two tables show that in the ANOVAs nor thoughts nor actions are significant outcomes of treatment modality anymore at $p < 0{,}05$. This would mean that the treatment modality is a rather weak predictor of either of the outcomes, and that it is not able to significantly predict a single outcome, but that it significantly predicts two outcomes pointing into a similar direction.

What advantages does MANOVA offer compared to multiple ANOVAs.

1. It prevents the type I error from being inflated.
2. It looks at interactions between dependent variables.
3. It can detect subgroup properties and includes them in the analysis.
4. It can demonstrate otherwise underpowered effects.

Multivariate analysis should not be used for explorative purposes and data dredging, but should be based on sound clinical arguments.

A problem with multivariate analysis with binary outcome variables is that after iteration the data often do not converse. Instead multivariate probit analysis available in STATA statistical software can be performed (see Chap. 25 in. Statistics Applied to clinical studies 5th edition, Springer Heidelberg Germany, 2012, from the same authors)

6 Conclusion

Multivariate analysis, simultaneously, assesses the separate effects of the predictors on one outcome variable adjusted for another outcome variable. For example, it can answer clinically important questions like: does drug-compliance not only predict drug efficacy, but also, independently of the first effect, predict quality of life. Path statistics can be used as an alternative approach to multivariate analysis of variance (MANOVA) (Chap. 17). However, MANOVA is the real thing, because it produces an overall level of significance of a predictive model with multiple outcome and predictor variables. Post hoc ANOVAS are required to find out which of the outcomes is more important.

7 Note

More background, theoretical, and mathematical information of multivariate analysis with path statistics is given in Statistics applied to clinical trials 5th edition, Chap. 25, Springer Heidelberg Germany, 2012, from the same authors.