Basic Medical Statistics Course

S7 Logistic Regression

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Logistic Regression

The concept of a relationship between the distribution of a dependent variable and a number of explanatory variables is also valid when the dependent variable is ***qualitative* (0 or 1)** instead of ***quantitative*** (with an unlimited range).

The relationship is in this case between explanatory variables and ***probability (1)***.

This cannot be a linear relationship, since probabilities have boundaries 0 and 1.

Examples: *dead / alive*
side effect / no side effect
disease / no disease

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Examples

Dataset N=24 (BMI, Blood Pressure, Diabetes)

BMI	BloodPr	BMI	BloodPr
17	120	33	118
22	130	32	170
34	144	37	160
23	122	22	100
43	119	18	101
34	115	23	103
29	132	26	128
19	121	26	110
20	124	33	134
29	140	19	121
25	134	18	123
27	118	25	122

BMI	Diabetes	BMI	Diabetes
17	0	33	0
22	0	32	1
34	1	37	1
23	1	22	0
43	1	18	0
34	0	23	0
29	0	26	0
19	0	26	1
20	0	33	0
29	0	19	0
25	0	18	0
27	0	25	0

Is BMI (x) predictive for Blood Pressure (y) ?

Linear Regression Model

Is BMI (x) predictive for Diabetes (y) ?

Linear Regression Model not appropriate

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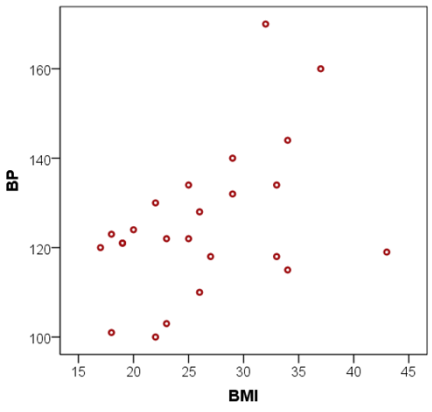
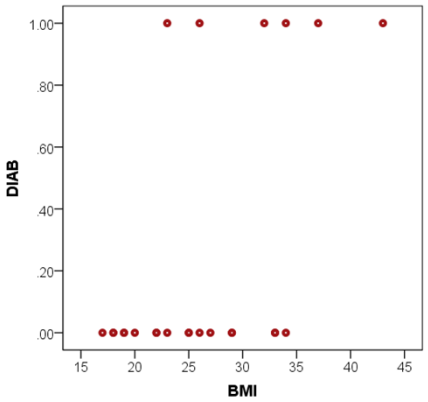
Scatter Plots





Clear pattern.
We can fit a regression line.

There is a pattern, but this is far from optimal for a linear regression model.

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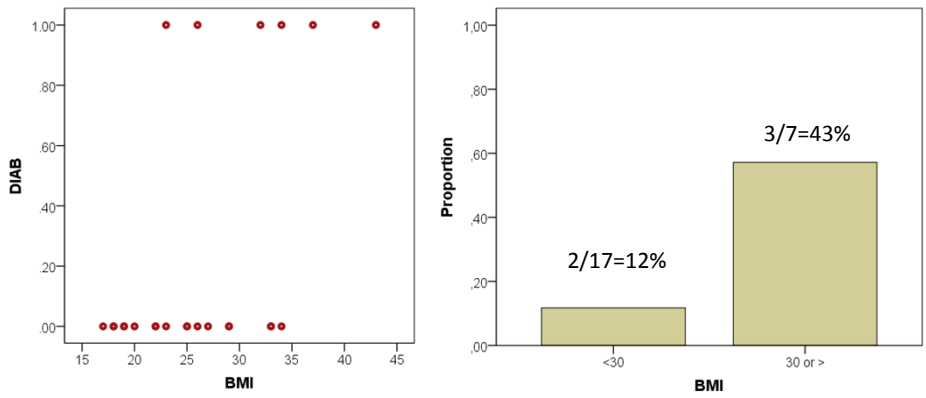
Relationship BMI - Diabetes



We can make the relationship visible in a simple way, by binning the BMI (e.g. <30, ≥30) and calculate the proportion of diabetes cases within each bin.

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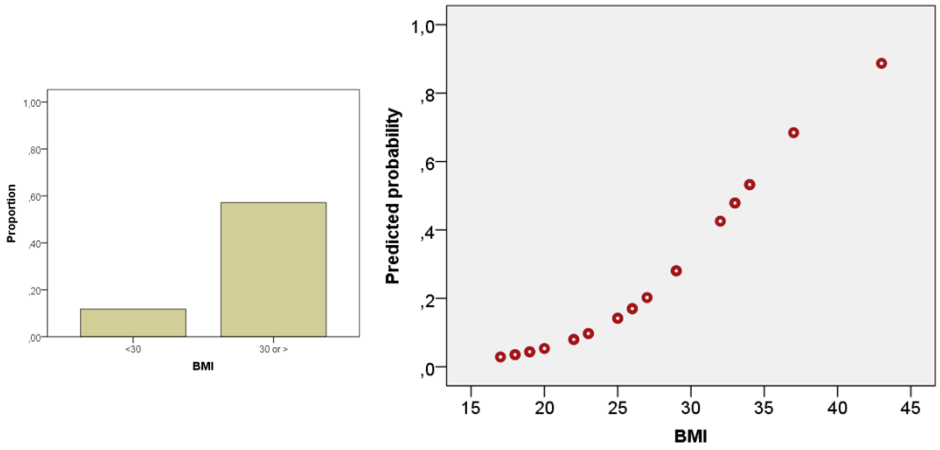
Relationship: Logistic Regression



The logistic regression model fits the data into a probability (DIAB=1) as function of BMI.

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Linear vs Logistic Regression

Linear regression:
Outcome is a continuous (dependent) variable Y which we try to predict / explain by an independent variable(s) X.

Binary logistic regression:
Outcome is a binary (0,1) (dependent) variable Y which we try to predict / explain by an independent variable(s) X.

In order to fit this relationship into the framework of linear regression, we need a transformation (the link function).

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Method of Logistic Regression

In logistic regression, we model the 'odds':

$$\ln\left(\frac{p}{1-p}\right) = \beta 0 + \beta 1X1 + \beta 2X2 \ldots$$

''ln odds', 'log odds', 'logit'

p = proportion/probability of 1
1 – p = proportion/probability of 0

$$\text{Probability } (1 \mid X1,X2,..) = \frac{e^{\beta 0 + \beta 1X1 + \beta 2X2\ldots}}{1 + e^{\beta 0 + \beta 1X1 + \beta 2X2\ldots}}$$

e = 2.7183..

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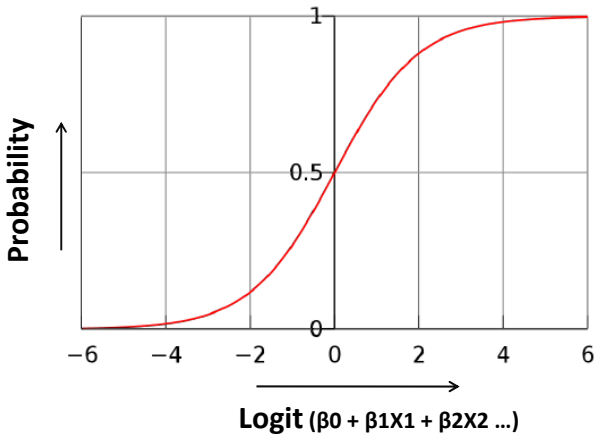
Relationship :Logit - Probability

The value of the logit is not restricted.

Probability is restricted (between 0 – 1).



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Odds

Previous data:

Disease/Exposure	BMI ≥30		BMI <30	
Diabetes +	A	n=3	B	n=2
Diabetes -	C	n=4	D	n=15

exposed = BMI **≥30,** *not exposed = BMI <30.*

Odds p/(1-p) = A/C for exposed (3/4=0.75)
= B/D for not exposed (2/15= 0.13)

Odds ratio = the ratio of odds exposed / odd not exposed
(in this case: 0.75 / 0.13 = 5.77)

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Ratios

$$\text{Odds Ratio (OR)} = \frac{\text{Odds}_{\text{exposed}}}{\text{Odds}_{\text{unexposed}}}$$

OR **equal to 1** indicates a similar risk for the two groups

OR **> 1** indicates that the risk is higher in the exposed group.

OR **< 1** indicates that the risk is lower in the exposed group.

The OR can be interpreted as an estimate of the relative risk in case the disease under study is 'rare'.

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Maximum Likelihood Method

The maximum likelihood method is a method of estimation to fit the parameters (i.e. estimation of the regression coefficients and its standard errors), which are the ***most likely values given the data***.

The maximum likelihood estimates of the regression coefficients are those values that 'maximize the likelihood': the values for which the data are most likely to occur.

Likelihood: product of all probabilities over all individuals.

The procedure for fitting a model involves ***iteration***:
repeating calculations until a stable solution is reached.

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Example output regression coefficients

Linear Regression

BMI as predictor for Blood Pressure.

Function: **Y= constant + B*BMI**.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	97,092	12,570		7,724	,000
	BMI	1,071	,461	,444	2,322	,030

a. Dependent Variable: BP

Logistic Regression

BMI as predictor for Diabetes. /

Function: Prob(Y=1)= $e^{\text{constant + B*BMI}} / (1 + e^{\text{constant + B*BMI}})$

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BMI	,214	,100	4,624	1	,032	1,239
	Constant	-7,163	3,000	5,702	1	,017	,001

a. Variable(s) entered on step 1: BMI.

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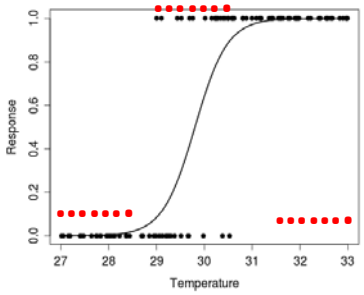
Goodness of Fit evaluation

A Goodness of Fit test measures the discrepancy between ***observed*** values and the values ***expected*** under the model.

- **(Pseudo) R square**: explained variance, predictive power. Looks at distances between predicted values and outcome (0/1) values.
- **Hosmer & Lemeshow**: is the model appropriate. Evaluates whether the data show deviations from the chosen model.

In case of the red values: Hosmer & Lemeshow test will detect that the model is not appropriate.
R Square test will just evaluate the distances between O – E.



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Hosmer & Lemeshow

This test evaluates the goodness-of-fit by creating 10 ordered groups, comparing the observed to the predicted no. of cases.

Test statistic is chi-square statistic.

Non-significance indicates that the model prediction does not significantly differ from the observed, i.e.: the model is appropriate.

Significance indicates that the model prediction does sign. differ from the observed data, i.e.: the model is ***not*** appropriate for the data.

Hosmer & Lemeshow test is not recommended for small sample sizes.

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Goodness of Fit Output

Example output with BMI – Diabetes data.

Contingency Table for Hosmer and Lemeshow Test

		Diabetes = 0		Diabetes = yes		
		Observed	Expected	Observed	Expected	Total
Step 1	1	3	2,900	0	,100	3
	2	2	1,913	0	,087	2
	3	3	2,787	0	,213	3
	4	1	1,806	1	,194	2
	5	2	1,716	0	,284	2
	6	1	1,660	1	,340	2
	7	3	2,237	0	,763	3
	8	2	1,617	1	1,383	3
	9	1	,935	1	1,065	2
	10	0	,429	2	1,571	2

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	7,777	8	,456

SPSS: Tick the box at "options"

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(Psuedo) R Square

There are several “pseudo R Square methods” to estimate the explained variance in the model.

Model performance is estimated by measuring the distances between predicted and actual outcome. Higher values of R Square indicate better fit.

Example of SPSS output with Diabetes – BMI Data :

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	20,084[a]	,250	,370

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

SPSS: by default in output

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Variable Types

In logistic regression, a variable (covariate) is analyzed as a continuous variable or a categorical variable.

Continuous variable: for each increase of 1 unit, the same regression coefficient is estimated. So the Odds Ratio is the Ratio of the Odds for value X with the Odds of value X-1 as the reference.

Categorical variable: for each category, a separate regression coefficient is estimated, with the ‘reference category’ as a reference. The ‘reference category’ has to be chosen (*in SPSS it can be the lowest or highest value).*

Binary variables and ordinal variables: they should be handled as categorical variables *(rule of thumb: ordinal variables with >7 levels, could be handled as continuous as well*) .

In case of (too) many categories, or categories with few observations, you can merge categories.

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Example Dummies

In case of categorical data, we need dummies. These are automatically coded by SPSS and you can find the codings in the output.

Example of dummies for tumor stages in lung cancer are shown below.

Categorical Variables Codings

		Frequency	Parameter coding (1)	(2)	(3)	(4)	(5)
tumorstage	1A	16	.000	.000	.000	.000	.000
	1B	18	1.000	.000	.000	.000	.000
	2A	4	.000	1.000	.000	.000	.000
	2B	8	.000	.000	1.000	.000	.000
	3A	27	.000	.000	.000	1.000	.000
	3B	15	.000	.000	.000	.000	1.000

Merging of categories would be better.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	tumorstage			3.584	5	.611	
	tumorstage(1)	.990	.921	1.156	1	.282	2.692
	tumorstage(2)	.847	1.380	.377	1	.539	2.333
	tumorstage(3)	1.435	1.051	1.864	1	.172	4.200
	tumorstage(4)	1.415	.855	2.743	1	.098	4.118
	tumorstage(5)	1.540	.922	2.794	1	.095	4.667
	Constant	-1.946	.756	6.626	1	.010	.143

a. Variable(s) entered on step 1: tumorstage.

(*dependent is 'recurrence')*

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Models with >1 Covariate

- The purpose of models with >1 covariates, can be:
  - 1) unbiased estimate of B for the covariate of interest, or
  - 2) obtain a multivariate model with all the significant predictors.
- No. of events is limiting the maximum number of covariates you can include in the model. Rule of thumb: at least **10 *events*** per covariate

  (*which is a rough indication when you might run into trouble*).

  This is a guideline first provided by Hosmer and Lemeshow.
- Case to Variable ratios: general rule of thumb is 20 to 1.
- Stepwise method (forward conditional in SPSS): variables are selected in the order in which they maximize the statistically significant contribution to the model.

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Nested Models

Does a model significantly improve (i.e. better goodness of fit), adding other covariate(s) ?

The likelihood-ratio test (based on Chisquare statistics) uses the ratio of the maximized value of the likelihood function for the full model (L_1) over the maximized value of the likelihood function for the simpler/reduced model (L_0).

χ^2 = 2 [LL (model L_1) – LL(model L_0)],

with df = # parameters model 2 - # parameters model 1

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Overview Linear vs Logistic Regression

	Lin Reg	Log Reg
Normality is assumed / prerequisite	yes	no
Outliers can be a problem	yes	yes
Multicollinearity can be a problem	yes	yes
Create dummy variables is needed	yes	no (SPSS coded)
Extrapolation can be tricky	yes	yes

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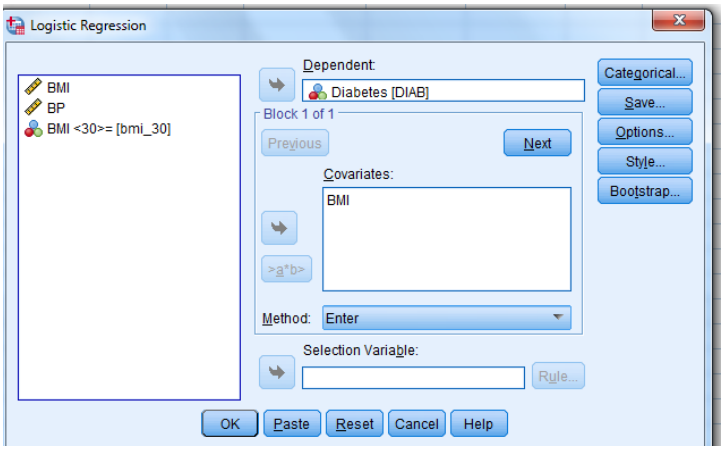
SPSS

Analyze - Regression – Binary logistic



Univariate analysis: 1 covariate in the model.

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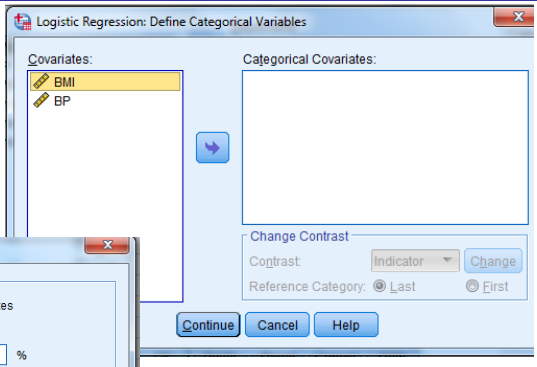
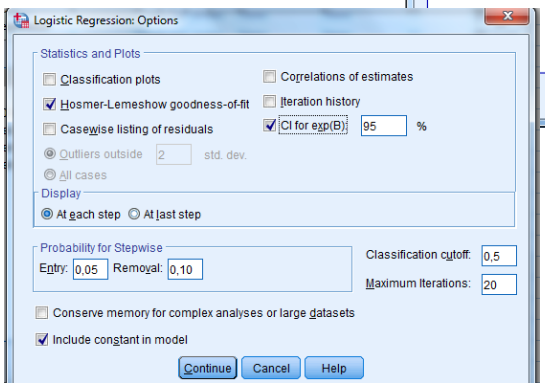
SPSS

Submenus





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SPSS Output

SPSS runs the logistic regression in two steps:

Block 0: Beginning Block.
No predictors are included, only the constant (also named "intercept").

It includes a table "Variables not in the Equation", where it is predicted whether an independent predictive variables that is not included yet, would be significant in the model.

Block 1: Method=Enter.
"Method=Enter" is the default.
This is the interesting part of the output where you can find the results for the covariate(s) you are investigating.

It includes (by default) a Table "Variables in the equation" where you can find the estimates for the constant and B.

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SPSS Output

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			Diabetes		Percentage Correct
			0	yes	
Step 0	Diabetes	0	18	0	100,0
		yes	6	0	,0
	Overall Percentage				75,0

a. Constant is included in the model.

b. The cut value is ,500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-1,099	,471	5,431	1	,020	,333

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	BMI	6,568	1	,010
	Overall Statistics		6,568	1	,010

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SPSS Output

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	6,908	1	,009
	Block	6,908	1	,009
	Model	6,908	1	,009

Comparison between model with covariate and model with only constant (**likelihood ratio test**), with H0: 'no difference between model with covariate" (which is rejected).

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	20,084[a]	,250	,370

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

If we ask SPSS for a stepwise model, these rows would also compare -2LLs of newest model with previous one.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BMI	,214	,100	4,624	1	,032	1,239
	Constant	-7,163	3,000	5,702	1	,017	,001

a. Variable(s) entered on step 1: BMI.

Wald Statistic: test the statistical significance of *each* coefficient (b) in the model, and is based on Z statistics.

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SPSS Output

Classification Table[a]

Observed			Predicted		
			Diabetes		Percentage Correct
			0	yes	
Step 1	Diabetes	0	17	1	94,4
		yes	3	3	50,0
	Overall Percentage				83,3

a. The cut value is ,500

The overall Percentage correct in Block 0 (by chance) was already 75%.

This Table gives information whether or not the covariates are useful predictors to separate (distinguish) the cases into 0 and 1.

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Interpretation

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BMI	,214	,100	4,624	1	,032	1,239
	Constant	-7,163	3,000	5,702	1	,017	,001

a. Variable(s) entered on step 1: BMI.

'Sig'. indicates the probability of the Wald statistic: the null hypothesis of 'b=0' is rejected since $p < 0.05$.

Exp(B) is the **Odds Ratio** for a unit increase.

A value of 1.24 implies a relative increase of the odds of +24%, for each unit increase.

In this case, 1 unit = 1 kg / cm^2 (BMI).

- *increase of BMI from 22 to 23: odds ratio 1.24*
- *increase of BMI from 33 to 34: odds ratio also 1.24 (assumption model)*

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Numerical problems

Issues that can affect the accuracy of the estimation of B:

- Multicollinearity among the independent variables.
- 'Complete separation' whereby the two groups in the dependent event variable can be perfectly separated by scores on one of the independent variables.
- Zero cells for a dummy-coded independent variable because all of the subjects have the same value for the variable.

Output that indicate numerical problems should not be interpreted.

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Multicollinearity

2 covariates with high correlation (Pearson correlation = 0.99).
We put them separately and together in the Logistic Regression Model.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	.056	.012	22.530	1	.000	1.058
	Constant	-3.449	.620	30.921	1	.000	.032

a. Variable(s) entered on step 1: vol30gy.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy2	.056	.012	22.573	1	.000	1.058
	Constant	-3.508	.631	30.874	1	.000	.030

a. Variable(s) entered on step 1: vol30gy2.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	.182	1.056	.030	1	.863	1.200
	vol30gy2	-.126	1.057	.014	1	.905	.881
	Constant	-3.315	1.269	6.826	1	.009	.036

a. Variable(s) entered on step 1: vol30gy, vol30gy2.

We can detect the problem by examining the errors (S.E.): it has become much larger.

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Separation

1 covariate perfectly predicts outcome: no results in SPSS.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	.000[a]	.688	1.000

a. Estimation terminated at iteration number 18 because a perfect fit is detected. This solution is not unique.

1 covariate almost perfectly predicts outcome.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	.052	.045	1.344	1	.246	1.054
	factor_perfect	24.876	6206.669	.000	1	.997	6.363E+10
	Constant	-6.313	2.507	6.342	1	.012	.002

a. Variable(s) entered on step 1: vol30gy, factor_perfect.

We can detect the problem by examining the error (S.E.): it is large (as well as the Exp(B)).

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Category with 1 value

1 covariate has a category with only 1 outcome value.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	.055	.014	16.731	1	.000	1.057
	cat_1value			.459	4	.977	
	cat_1value(1)	-.593	1.011	.344	1	.558	.553
	cat_1value(2)	.029	.566	.003	1	.959	1.030
	cat_1value(3)	-.018	.750	.001	1	.981	.982
	cat_1value(4)	-18.111	17731.913	.000	1	.999	.000
	Constant	-3.371	.664	25.753	1	.000	.034

a. Variable(s) entered on step 1: vol30gy, cat_1value.

We can detect the problem by examining the error (S.E.): it is large.

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Example

We have a data set of lung cancer patients who received radiotherapy and chemotherapy. Some patients developed esophagitis (inflammation of esophagus.

Research Questions

- Is development of this toxicity associated with dose to the esophagus ?
  - If yes, which dose levels are predictive ? (*we will look at 2 dose vars*).
- Is this toxicity associated with chemotherapy ?
- Does the model significantly improve, when we add chemotherapy to a model with the dose variable 'Vol30Gy' ?
  Is the Goodness-of-Fit acceptable ?

! SPSS will automatically predict the highest value of the binary outcome var.
So we have to code for example 0=no tox, 1=tox.

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Example: results I

Results (univariate) for 2 dose parameters

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	,056	,012	22,530	1	,000	1,058
	Constant	-3,449	,620	30,921	1	,000	,032

a. Variable(s) entered on step 1: vol30gy.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol60gy	,048	,012	16,298	1	,000	1,049
	Constant	-1,954	,327	35,725	1	,000	,142

a. Variable(s) entered on step 1: vol60gy.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	146,714[a]	,201	,292

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

V30

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	163,735[a]	,109	,158

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than ,001.

V60

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Example: results II

Results (univariate) for concurrent chemotherapy (0=no, 1=yes).
First table: reference category = first category.
Second table: with last category as reference.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	conc(1)	1.646	.406	16.465	1	.000	5.187
	Constant	-1.484	.236	39.475	1	.000	.227

a. Variable(s) entered on step 1: conc.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	conc(1)	-1,646	,406	16,465	1	,000	,193
	Constant	,163	,330	,243	1	,622	1,176

a. Variable(s) entered on step 1: conc.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	164,981[a]	,102	,148

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than ,001.

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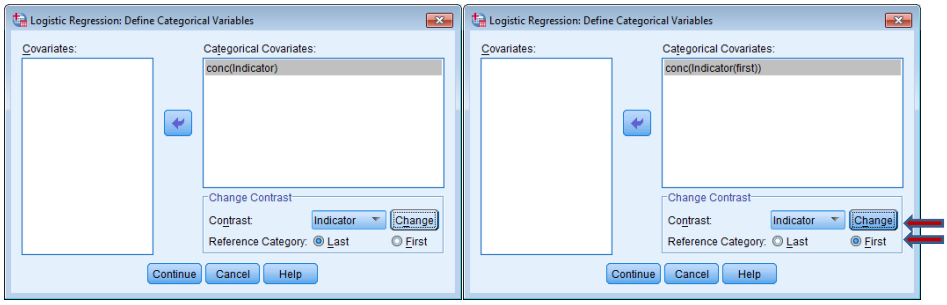
Example: results II

SPSS default: reference = last category.

Reference = first: tick box & push 'change'.



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Example Nested Model

Results (nested model) for Vol30Gy and concurrent chemotherapy.
Stepwise model (method = Forward Conditional).

The minimum ratio of valid cases to independent variables for stepwise logistic regression is 10 to 1.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	35.024	1	.000
	Block	35.024	1	.000
	Model	35.024	1	.000
Step 2	Step	4.678	1	.031
	Block	39.702	2	.000
	Model	39.702	2	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	146,714[a]	,201	,292
2	142,036[b]	,225	,327

Likelihood ratio test: model significantly improves.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	vol30gy	,056	,012	22,530	1	,000	1,058
	Constant	-3,449	,620	30,921	1	,000	,032
Step 2[b]	conc	,942	,436	4,671	1	,031	2,565
	vol30gy	,051	,012	16,771	1	,000	1,052
	Constant	-3,509	,642	29,858	1	,000	,030

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Example Nested Model

Goodness of Fit (comparing observed and expected no. of cases)

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	4.419	7	.730

Non-significance indicates that the model is appropriate.

Contingency Table for Hosmer and Lemeshow Test

		G0-1 vs G2+ = G0-1		G0-1 vs G2+ = G2+		Total
		Observed	Expected	Observed	Expected	
Step 1	1	24	23.303	0	.697	24
	2	16	15.428	0	.572	16
	3	15	14.651	1	1.349	16
	4	11	13.348	5	2.652	16
	5	12	12.137	4	3.863	16
	6	10	10.542	6	5.458	16
	7	10	9.397	6	6.603	16
	8	8	8.363	8	7.637	16
	9	8	6.832	12	13.168	20

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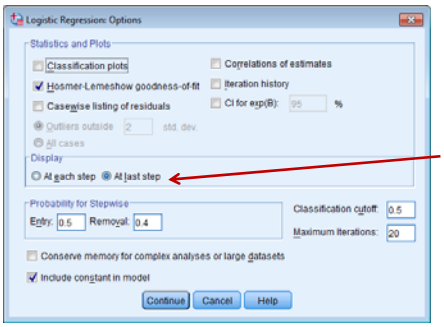
Example Nested Model



You can obtain a summary of all steps by choosing ''at last step'.

Step Summary[a,b]

Step	Improvement			Model			Correct Class %	Variable
	Chi-square	df	Sig.	Chi-square	df	Sig.		
1	13.230	1	.000	13.230	1	.000	84.7%	IN: IM_mean
2	1.688	1	.194	14.918	2	.001	82.7%	IN: CM_mean

a. No more variables can be deleted from or added to the current model.

b. End block: 1

In the Step Summary table we see which variable was added or removed at each step.

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Research questions

Research Questions

- *Is development of esophagitis associated with dose to the esophagus ?*
  yes, we found a statistically sign. relationship with dose.
  → the model significantly improved adding a dose variable,
  → the estimated B was significant,
  → there were no signs of numerical problems.
- *If yes, which dose levels are predictive* ?
  both investigated dose levels were predictive.
- *Is this toxicity associated with chemotherapy* ? **yes**

- *Does the model significantly improve, when we add chemotherapy to a model with Vol30Gy* ? **Yes,** the likelihood ratio test of the extended model compared to the model with 1 covariate, indicated that the model significantly improved. The Goodness of Fit was acceptable.

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Example

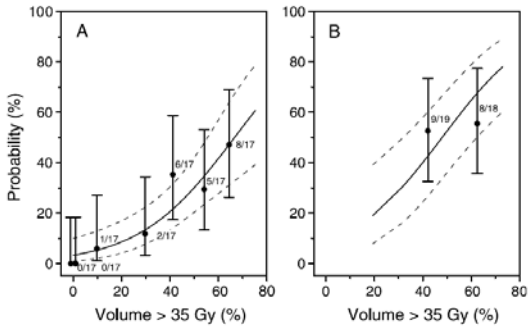

Fig. 1. In both figures the probability of acute esophagus toxicity≥grade 2 is plotted as a function of the esophagus volume receiving 35 Gy or more (solid lines with corresponding 95% confidence intervals in dotted lines). On the left (A) the group of patients treated with sequential CRT or RT only. On the right (B) the group of patients treated with concurrent CRT. In both graphs the corresponding actual incidence of ≥grade 2 is plotted in solid circles with corresponding error bars (95% confidence interval), for dose bins of about 17 patients each.

Belderbos *et al* 2005

Final Remarks

Logistic Regression is a tool to analyze the effect of covariates on a binary outcome.

In Logistic Regression, we assume that **follow-up time** is constant or not an issue, for the studied outcome. If this is not the case: Cox Regression (*lecture on Friday*).

We have looked at ***Unconditional Binary*** Logistic Regression.

Other types of Logistic Regression:

- Mutinomial & Ordinal Logistic Regression.
- Conditional (binary) Logistic Regression.

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Practical

Head & Neck cancer patients treated with chemoradiation are at risk for developing ***trismus*** (reduced maximum mouth opening < 35 mm) as a result of damaged muscles used for opening and closing the mouth.

When the tumor is close to these muscles, it will receive radiation dose as well.

In the practical, we are going to investigate whether the dose delivered to the Masseter Muscle is predictive for developing Trismus. The Masseter is a bilateral muscle (left and right), involved in mouth opening.

We have data on the mean dose to the ipsilateral muscle (at the tumor site, i.e. the muscle receiving the highest dose), and the mean dose to the contralateral muscle (i.e. the masseter muscle receiving the lowest dose).

The database also contains a **quantitative** / ***continuous outcome*** (reduction of mouth opening), next to the **qualitative / binary** outcome of Trismus (0, 1).

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