EPIDEMIOLOGY/BIOSTATS VHM 812/802 COURSE
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Index of Lecture 3a

INTRODUCTION TO LOGISTIC REGRESSION

Logistic regression:

- binary (0/1, dichotomous) outcomes, possibly grouped to binomial outcomes (e.g., 3 positive out of 10 animals),
- first of several regression-type models not relying on normal distribution assumptions,
  - ∗ sometimes called *generalised linear models* (glm's),
  - ∗ model building from the predictors similar to linear regression,
  - ∗ some common features in their analysis that distinguish them from linear regression analysis.

Today's session:

- review of simple logistic regression (one predictor) and its relation to known analyses, in particular 2×2-table analysis,
- predictions, in particular using `margins` command (Stata),
- computer-assisted using Stata (good facilities available, superior to many simpler programs).

VER/MER textbooks:

- today: $16.1–5, 8$ with some omissions (in next lecture).
- maybe also check Chapter 28 of VHM 801 textbook.

Homework for Tuesday: Last linear reg. exercise (VER 14.3).

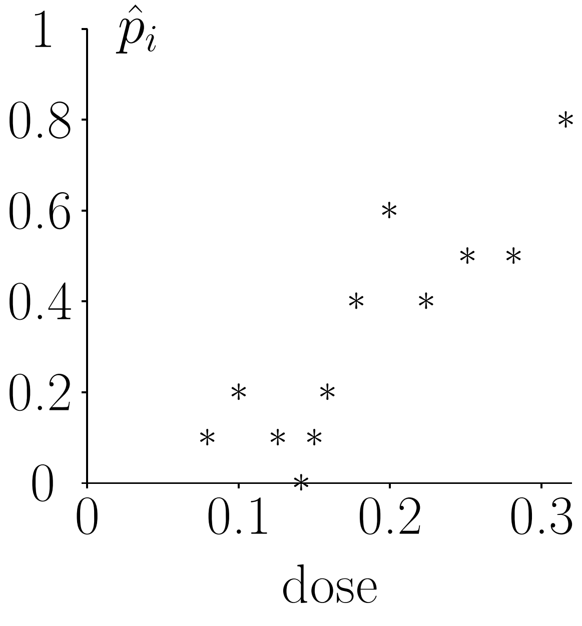
EXAMPLE DATASET MICE

Toxicity study of dose-response curve (Woodward 1941):

- lethality of different doses of chloracetic acid, measured as the mortality among 10 mice subjected to each dose,

group i	dose x_i	# mice died r_i	# mice total N_i	prop. died $\hat{p}_i = r_i/N_i$	$\text{logit}(\hat{p}_i)$
1	0.0794	1	10	0.1	-2.197
2	0.1000	2	10	0.2	-1.386
3	0.1259	1	10	0.1	-2.197
4	0.1413	0	10	0.0	undef.
5	0.1500	1	10	0.1	-2.197
6	0.1588	2	10	0.2	-1.386
7	0.1778	4	10	0.4	-0.405
8	0.1995	6	10	0.6	0.405
9	0.2239	4	10	0.4	-0.405
10	0.2512	5	10	0.5	0
11	0.2818	5	10	0.5	0
12	0.3162	8	10	0.8	1.386

- grouped binary data,
- statistical model: $r_i \sim \text{Bin}(N_i, p_i)$, and $r_1, \ldots, r_{12}$ independent,
- parameters: $p_1, \ldots, p_{12}$ (prob. of death in groups),
- question: how to use the doses?



WHY NOT LINEAR REGRESSION?

Regression for binary outcomes ($Y_i = 0$ or $Y_i = 1$)

$$Y_i = \beta_0 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki} + \varepsilon_i,$$

conflicts with the model assumptions:

(1) errors ε_i are far from normally distributed (can only take two possible values[1]),

(2) with $p_i = P(Y_i = 1)$, we have $\mathrm{Var}(Y_i) = p_i(1 - p_i)$, which is not constant when p_i is modelled by predictors,

(3) both Y_i and p_i are bounded (do not go beyond 0 and 1) but linear predictions by the x-variables can easily give predictions outside the interval.

Regression for grouped binary outcomes (proportions r_i/N_i)

- same problems (1)–(3), although (1) is less severe,
- transformation is a possibility, usually with *variance-stabilising* transformation:

  $Y_i = \arcsin(\sqrt{r_i/N_i})$, arcsin = inverse sine function,

  — however, not recommended unless

  - the denominators N_i are all "large" and approximately the same,
  - the prop.'s r_i/N_i are not too extreme (close to 0 or 1),

  and usually offers no advantages over logistic regression.

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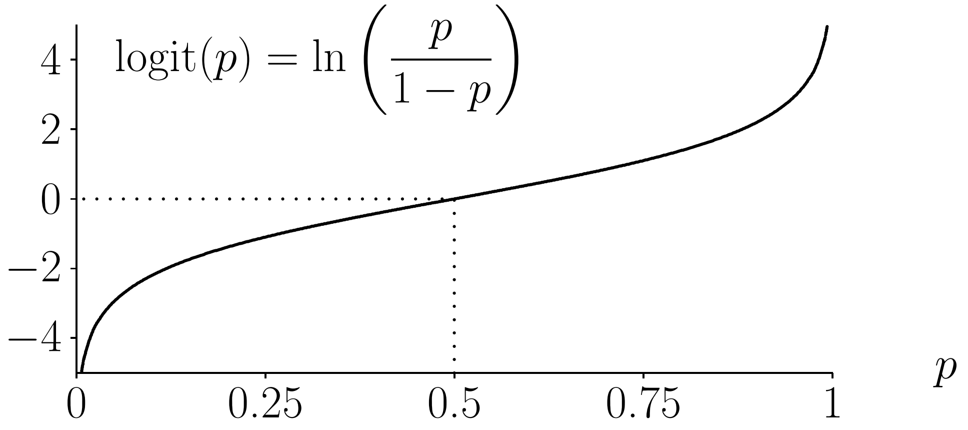
[1] Possible values for the error of obs. i are $\varepsilon_i = 1 - (\beta_0 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki})$, and $\varepsilon_i = -(\beta_0 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki})$.

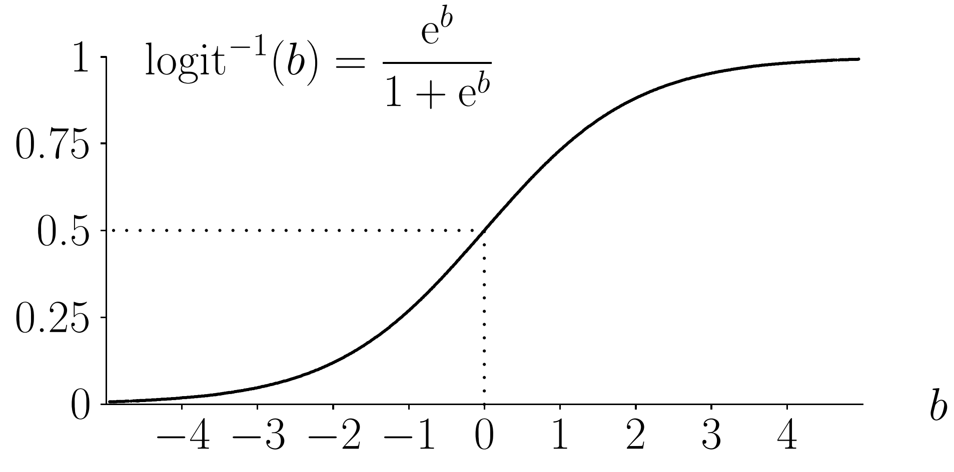
LOGIT TRANSFORMATION

Define for $0 < p < 1$ and any b,

$$\operatorname{logit}(p) = \ln\left(\frac{p}{1-p}\right) \quad \text{and} \quad \operatorname{logit}^{-1}(b) = \frac{\mathrm{e}^b}{1+\mathrm{e}^b} = \frac{1}{1+\mathrm{e}^{-b}},$$

- the logit function stretches the interval (0,1), excl. endpoints!, onto the entire real axis (from $-\infty$ to ∞),
- $\operatorname{logit}(\frac{1}{2})=0$, and $\operatorname{logit}(p)$ is increasing in p,
- with $\operatorname{odds}(p) = \frac{p}{1-p}$, we have $\operatorname{logit}(p) = \ln(\operatorname{odds}(p))$,
- logit and inverse logit functions:





LOGISTIC REGRESSION MODEL

= a *different transformation approach*:

- keep observations (binary/grouped binary) untransformed,
- transform probability parameter p by logit function to logit scale where linear modelling takes place, e.g.

$$\ln\left(\frac{p_i}{1-p_i}\right) = \text{logit}(p_i) = \beta_0 + \beta_1 x_{1i}, \qquad (1)$$

where

$$\begin{aligned} p_i &= \text{P}(Y_i = 1), \\ Y_i &= \begin{cases} 1 & \text{“success”} \\ 0 & \text{“failure”} \end{cases} \quad \text{for } i = 1, \ldots, n, \\ x_i &= \text{predictor variable for observation } i. \end{aligned}$$

Model assumptions:

- independence of all the observations (Y_i's),
- linearity of relation (1) on logit scale.[2]

Grouped binary data (with N_i repl. in ith group)

- equation (1) for p_i = prob. of “success” in group i,
- same model as if set up as binary data (with $n = \sum_i N_i$).

Multiple logistic regression model for predictors $x_1, \ldots, x_k$:

$$\text{logit}(p_i) = \beta_0 + \beta_1 x_{1i} + \ldots + \beta_k x_{ki}.$$

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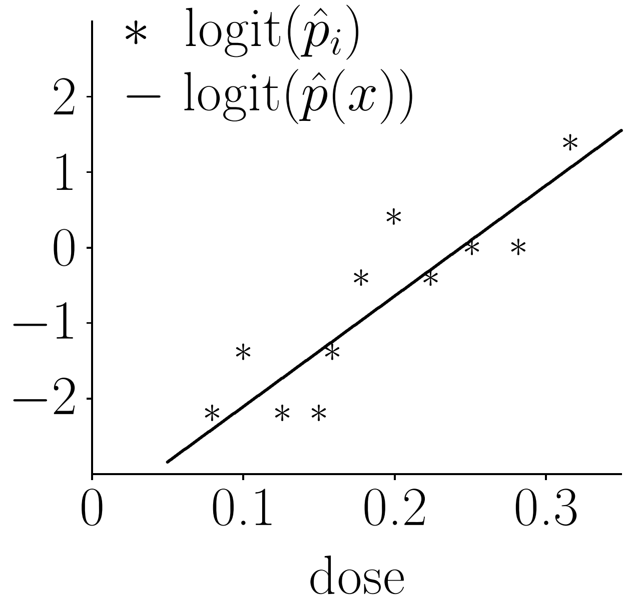
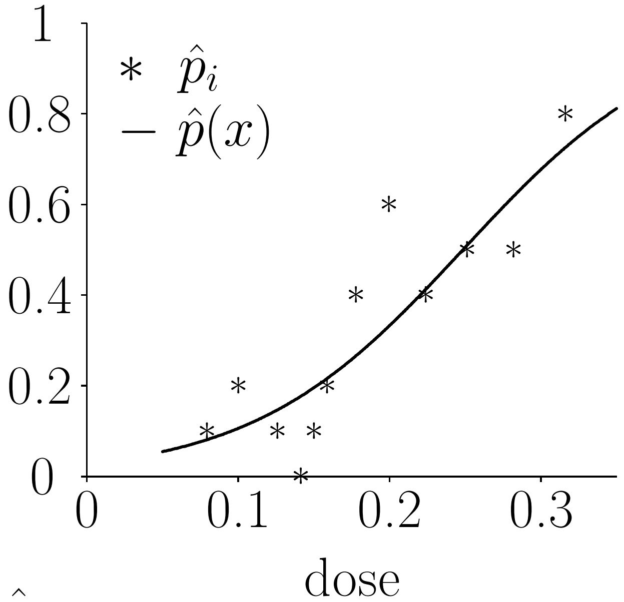
[2] For a single predictor model, the linearity assumption applies only to the case where x_1 is continuous.

LOGISTIC REGRESSION FOR MICE DATA



Estimates (with SE):
$\hat{\beta}_0 = -3.57\,(0.71)$,
$\hat{\beta}_1 = 14.64\,(3.33)$.

Test of H_0: $\beta_1 = 0$:
$z = \hat{\beta}_1 / \mathrm{SE}(\hat{\beta}_1) = 4.39$
very sign. in N(0,1)
⇒ strong effect of dose.



Estimated line:
$\hat{\beta}_0 + \hat{\beta}_1 \cdot \text{dose}$
– on logit-scale.

Estimated curve $\hat{p}(x)$:
$\text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_1 \cdot \text{dose})$
– on probability-scale.

Interpretation of $\hat{\beta}_1$:
change in dose of
a units ⇒

- change in logit(p) of $a\hat{\beta}_1$ units,
- change in odds(p) by factor $\exp(a\hat{\beta}_1)$ (= *odds-ratio*), where $\text{odds}(p) = p/(1-p)$.

Test of model: (goodness-of-fit test)
$X^2 = 8.74$, $P = 0.56$ ⇒ no lack of fit (model ok).

2×2–TABLE ANALYSIS

Mice data: outcome = mortality, explanatory = dichotomous version of dose (for illustration only):

	`dose`> 0.16		
`dead`	1	0	Total
1	32	7	39
0	28	53	81
Total	60	60	120

Statistical model (with binary dose predictor):
two binomial distributions $\text{Bin}(60, p_1)$ and $\text{Bin}(60, p_0)$,
– analyzed in VHM 801 by computing:

$$\begin{aligned}
\hat{p}_1 &= 32/60 = 0.533, \quad \text{SE}(\hat{p}_1) = \sqrt{\hat{p}_1(1-\hat{p}_1)/60} = 0.0644, \\
\hat{p}_0 &= 7/60 = 0.117, \quad \text{SE}(\hat{p}_0) = \sqrt{\hat{p}_0(1-\hat{p}_0)/60} = 0.0414, \\
\hat{p}_1 - \hat{p}_0 &= 0.533 - 0.117 = 0.417, \quad \text{SE} = \sqrt{0.0644^2 + 0.0414^2} = 0.077.
\end{aligned}$$

Alternative ways of comparing the probabilities $\hat{p}_1$ and $\hat{p}_0$:

$$\begin{aligned}
\text{relative risk}: \ \text{RR} &= \hat{p}_1/\hat{p}_0 = 0.533/0.117 = 4.57, \\
\text{odds-ratio}: \ \text{OR} &= \text{odds}(\hat{p}_1)/\text{odds}(\hat{p}_0) = [\hat{p}_1/(1-\hat{p}_1)]\,/\,[\hat{p}_0/(1-\hat{p}_0)] \\
&= [0.533/(1-0.533)]\,/\,[0.117/(1-0.117)] \\
&= 1.143/0.132 = 8.653 = (32 \cdot 53)/(28 \cdot 7).
\end{aligned}$$

Advantages of these statistics (over the simple $\hat{p}_1 - \hat{p}_0$):

- multiplicative effects are more meaningful than additive effects for proportions bounded by 0 and 1,
- when both probabilities "close" to zero: $\underline{\text{OR} \approx \text{RR}}$ (clearly not the case in the example),
- both statistics more useful than $(\hat{p}_1 - \hat{p}_0)$ when multiple factors studied simultaneously.

2×2–TABLE AND LOGISTIC REGRESSION

Mice data: (same as on previous slide):
outcome = mortality, predictor = `dose2` (dichotomous version of dose):

	`dose2` = (`dose`> 0.16)		
`dead`	1	0	Total
1	32	7	39
0	28	53	81
Total	60	60	120

Logistic regression model with `dose2` as predictor:

$$\text{logit}(p_i) = \beta_0 + \beta_1 \texttt{dose2}_i,$$

gives the estimates

$$\begin{aligned}\hat{\beta}_1 &= 2.158 = \ln(8.653) = \ln(\text{OR}),\\ \hat{\beta}_0 &= -2.024 = \text{logit}(0.117) = \text{logit}(\hat{p}_0).\end{aligned}$$

Interpretations (valid also in multiple logistic regression):

- odds-ratio for effect of `dose2` $= \mathrm{e}^{\hat{\beta}_1} = \mathrm{e}^{2.158} = 8.653$,
- baseline prob. $= \text{logit}^{-1}(\hat{\beta}_0) = \text{logit}^{-1}(-2.024) = 0.117$.

Summary:
The 2×2-table analysis and the logistic regression analysis are equivalent (also, the P-values are similar[3]).

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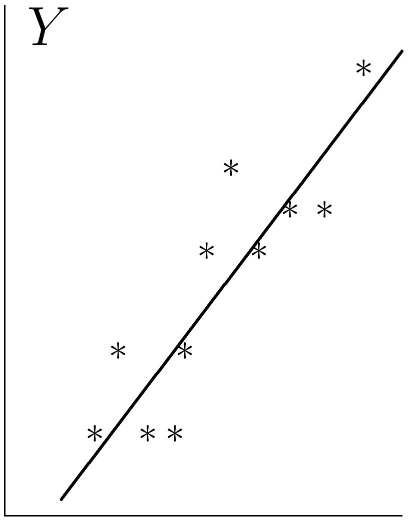
[3] The likelihood-ratio tests (next lecture) of the two models are identical.

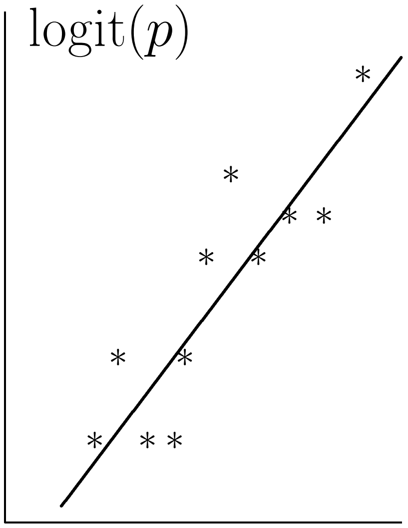
LINEAR VS. LOGISTIC MODELLING

Linear regression



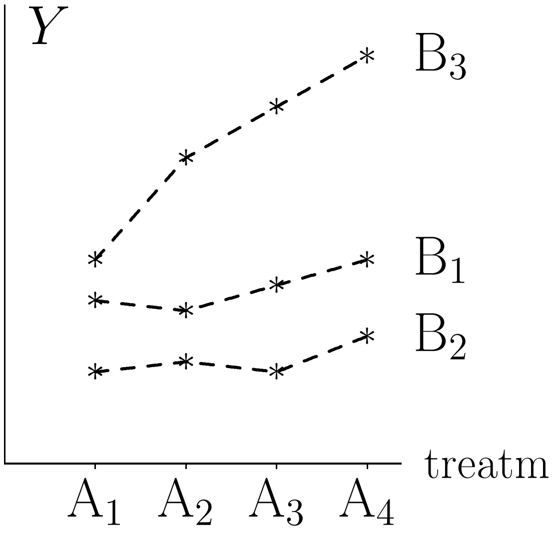
Model: $Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$
where ε_i's $\sim \mathrm{N}(0,\sigma^2)$

Logistic regression



Model: $\mathrm{logit}(p_i) = \beta_0 + \beta_1 x_i$
where $p_i = \mathrm{P}(Y_i\!=\!1)$

Factorial design

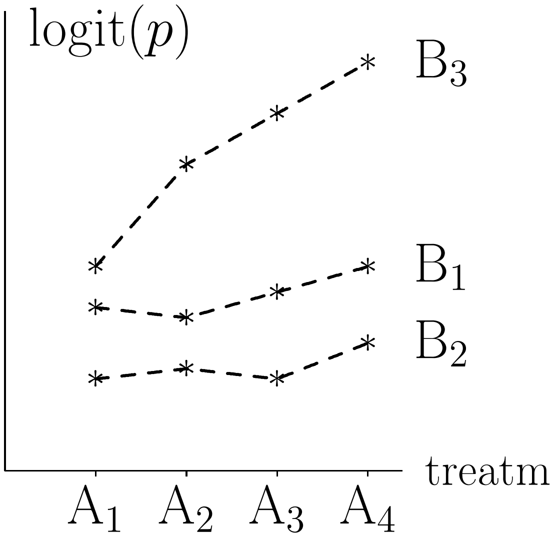


Model:

$$Y_{ij} = \mu + \alpha_i + \beta_j + \varepsilon_{ij}$$

where ε_{ij}'s $\sim \mathrm{N}(0,\sigma^2)$

Logistic factorial design



Model:

$$\mathrm{logit}(p_{ij}) = \mu + \alpha_i + \beta_j$$

where $p_{ij} = \mathrm{P}(Y_{ij}\!=\!1)$

COMPUTING PREDICTIONS IN LINEAR MODELS

We distinguish between two types of predictions (or purposes):

i) for individual observations: “real” prediction,

ii) for purposely selected combinations of predictor values: “illustrative” prediction.

All software packages for linear models offer predictions of type *i)*, directly for observed predictor patterns and for new predictor patterns:

- Stata/SAS: add extra observations to data with missing outcome,
- Minitab/R: specify new observations in separate columns/ dataset,
- Stata/SAS: special commands (`lincom`/`estimate`) give estimates for linear combinations of regression coefficients.

Fully specified predictions of type *ii)*: may be done using methods for type *i)* (perhaps tedious).

Some software offer both fully and partially specified predictions of type *ii)*:

- Stata: the `margins` command,
- Minitab/SAS: least squares means[4]; i.e., all predictors not included in prediction are set at their average value.

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[4] “Least squares means” originate from experimental designed studies/data where factors are often balanced by design.

STATA: THE `MARGINS` COMMAND

- very flexible command (from version 12) with a wide range of options and setups;
  so flexible that caution is needed to not use it wrongly. . . ,
- strongly recommended to always check your predictions with simpler methods (in a few examples),
- linkage to the `marginsplot` command allows easy plotting of predicted values; in particular, this is the easiest way to generate an interaction plot,
- mainly intended for "illustrative" predictions, and uses predictions from the `predict` command behind the scenes to come up with the requested predictions,
- the online help is pretty confusing ⇒ recommended to work from well-established examples, and to avoid use of numerous extra "fancy" options.

Coverage in course: worked examples (from simple to more complex) illustrating the basic features of command:

- 1-predictor settings (categorical and continuous),
- 2-predictor settings, and the questions arising from omitting a predictor from a prediction,
- VER 14.16 worked example,
- plots and transformations as needed.

SIMPLEST EXAMPLES: 1 PREDICTOR

(1a) categorical: simple means, with model-based SE,

```
regress wpc i.herd
margins herd
lincom _cons+2.herd
```

(1b) continuous: predictions at specified set of values, with subsequent plot by `marginsplot`:

```
regress wpc milk120
margins , at( milk120=(1200(1000)5600) )
marginsplot
lincom _cons+milk120*3200
```

note: flexible format of "atspec"; e.g., 1200(1000)5600 = 1200, 2200, . . . , 5200, but list can also include statistics (e.g., mean and percentiles) and the special names "asobserved" and "asbalanced",

(1c) continuous with quadratic effect: predictions as above, but need to use factor notation,

```
regress wpc c.milk120##c.milk120
margins , at( milk120=(1200(1000)5600) )
marginsplot
```

(1d) backtransformation from transformed scale: can be specified by formula, but note CI problems,[5]

```
regress lnwpc milk120
margins , at( milk120=(1200(1000)5600))
margins , at( milk120=(1200(1000)5600)) expression(exp(predict(xb)))
marginsplot
```

---

[5] The correct CIs are obtained by backtransformation, but the method used by `margins` command is based on an approximate SE on original scale.

EXAMPLES WITH 2 CATEGORICAL PREDICTORS

(2a) <u>additive model</u>: predictions require decision about how to weight contributions from other predictor, e.g.:

- equally/balanced (standard in least squares means),
- total data weights (default choice),
- choices corresponding to specific prediction settings,

```
regress wpc i.rp i.vag_disch
margins rp vag_disch
table rp vag_disch, row col
lincom _cons+1.rp+1.vag_disch*82/1574 /* rp=1 */
margins rp vag_disch, asbalanced
lincom _cons+1.rp+1.vag_disch*0.5 /* rp=1 */
margins rp, over(vag_disch) /* same as: at(vag_disch=(0 1)) */
lincom _cons+1.rp+1.vag_disch /* rp=1, vag_disch=1 */
```

(2b) <u>model with interaction</u>: combined effect $\sim$ simple means, separate effects require decision about how to weight contributions from other predictor (as above for additive model),

```
regress wpc rp##vag_disch
margins rp#vag_disch
marginsplot, noci /* this is the interaction plot! */
marginsplot, noci x(vag_disch) /* x() to control variable on x */
marginsplot, noci x(rp) /* same as default */
margins rp
lincom _cons+1.rp+(1.vag_disch+1.rp#1.vag_disch)*82/1574 /* rp=1 */
margins rp, asbalanced
lincom _cons+1.rp+(1.vag_disch+1.rp#1.vag_disch)*0.5  /* rp=1 */
```

EXAMPLES WITH 2 PREDICTORS (CONT.)

Categorical + continuous predictor:

(2c) similar to single continuous predictor, with multiple groups (intercepts and lines),

```
regress wpc i.dyst milk120
margins dyst, at( milk120=(1200 2200 3200 4300 5500))
marginsplot, noci
lincom _cons+1.dyst+milk120*3200 /* dyst=1, milk120=3200 */
margin dyst, atmeans
lincom _cons+1.dyst+milk120*3215.096
* interaction model
regress wpc dyst##c.milk120
margins dyst, at( milk120=(1200 2200 3200 4300 5500))
marginsplot, noci /* this is the interaction plot! */
lincom _cons+1.dyst+(c.milk120+1.dyst#c.milk120)*3200
/* dyst=1, milk120=3200 */
```

Two continuous predictors:

(2d) need values (possibly lists) for both predictors ⇒ predictions usually fully specified (no averaging/weighting),

```
regress wpc parity milk120
margins , at( parity=(1(1)6) milk120=(1200 2200 3200 4300 5500))
marginsplot, noci
margins , at( milk120=(1200 2200 3200 4300 5500) parity=(1(1)6) )
marginsplot, noci /* changing roles in plot */
margins , at( milk120=(1200 2200 3200 4300 5500) (median)parity)
marginsplot
lincom _cons+milk120*1200+parity*2 /* milk120=1200, parity=2 */
margins, atmeans
lincom _cons+milk120*3215.096+parity*2.73628 /* both at means */
```

PREDICTION IN MULTIVARIABLE MODELS

Main challenge/thing to remember: predictions need values or weights for all predictor terms in model
⇒ no software can do this automatically (so that it always makes sense)!

Some issues to consider when setting up predictions:

- the purpose (e.g., "real" versus "illustrative"),
- should the prediction correspond to an average or a real situation? (e.g., when using weights for categorical predictors, the predictions will not correspond to real situations),[6]
- is the predictor distribution in the observed data representative for the population or the targeted setting?[6]
- are the predictor distributions independent enough to set the values for different predictors independently?[6]
- for categorical predictors, are predictions intended to facilitate pairwise comparisons beyond comparisons with baseline? (perhaps the main motivation of least squares means),
- if modelling is carried out on transformed scale, should any weighting take place on transformed or original scale? (as they will lead to different results).

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[6] Using `margins` with its default settings implies that your answer to this question is "yes".

Predictions for VER Example 14.16

Model summary:

- outcome: `wpc`, on square-root transformed scale,
- categorical predictors: `aut_calv`, `twin`, `dyst`, `rp##vag_disch`,
- continuous predictors: `parity`, `herd_size` with quadratic term.

Some possible prediction aims:

1) illustrate combined effect of diseases (`rp`,`dyst`,`vag_disch`) on `wpc`,
2) illustrate interaction `rp#vag_disch` (effectively included under 1),
3) illustrate effect of `herd_size` on `wpc`.

1): Prediction/Estimates for combinations of disease, with backtransformed (squared) means ∼ *median* `wpc`-values:

Estimates*		$\sqrt{\texttt{wpc}}$ (mean)		`wpc` (median)	
`rp`	`vag_d`	`dyst`=0	`dyst`=1	`dyst`=0	`dyst`=1
0	0	7.517	8.059	56.50	64.95
0	1	7.503	8.046	56.30	64.73
1	0	7.906	8.448	62.51	71.38
1	1	9.384	9.926	88.06	98.53

* at: `parity`=1, `twin`=0, `herd_size`=251, `aut_calv`=0
(∼ the mean herd size, and the most frequent categories)

3): Prediction/Estimates for the 7 observed herd sizes:

Estimates*	herd sizes						
scale	125	185	201	235	263	294	333
$\sqrt{\texttt{wpc}}$	7.092	7.013	7.079	7.448	7.674	8.177	9.002
`wpc`	50.29	49.19	50.11	53.85	58.90	66.86	81.03

* at: `parity`=1, `twin`=0, `aut_calv`=0, all diseases=0

PREDICTIONS IN LOGISTIC REGRESSION

Predictions/presentation of effects on probability scale:

- easier to understand probabilities than OR's,
- not additive ⇒ more complicated (care is needed).

Illustration for Nocardia data and effect of `dcpct`:

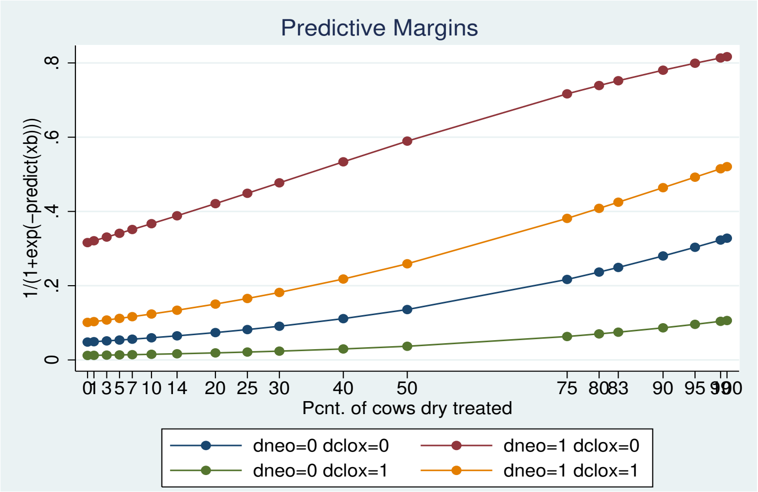
$$\text{logit}(\hat{p}) = -2.984 + 0.023\,\texttt{dcpct} + 2.212\,\texttt{dneo} - 1.412\,\texttt{dclox},$$

- OR for 1% "change" in `dcpct` $= e^{0.023} = 1.023$,
- OR for 10% "change" in `dcpct` $= e^{0.023 \cdot 10} = e^{0.23} = 1.25$.

or on probability scale[7]

$$\hat{p} = \text{logit}^{-1}(\text{logit}(\hat{p})) = 1/(1 + e^{-\text{logit}(\hat{p})})$$

can be plotted against `dcpct` values in a suitable range, for *fixed* values of all other predictors (here `dneo` and `dclox`):



note: non-linear relation!
non-parallel curves!

How to compute predictions – same options as for linear models:

- predicted values for actual/new observations,
- Stata: `margins` and `marginsplot` commands.[8]

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[7] For demonstration purposes only; in a case-control design predicted probabilities *do not make sense* because the proportion of cases and controls is controlled.

[8] See next page for discussion of averaging or weighting.

SCALE-DEPENDENCE OF PREDICTIONS
WITH AVERAGING/WEIGHTING

Main message: in models involving transformations (e.g. logistic regression), any averaging of predictions involves a choice of scale:

- different results (even after transformation to same scale),
- different interpretations.

Consider again the logistic "predictive" equation

$\text{logit}(\hat{p}) = -2.984 + 0.023\,\texttt{dcpct} + 2.212\,\texttt{dneo} - 1.412\,\texttt{dclox}$,

— Table of predictions for `dcpct` $= 0$:

`dneo`	`dclox`	$\text{logit}(\hat{p})$	$\hat{p} = \text{logit}^{-1}(\hat{p})$
0	0	-2.984	0.0481
0	1	-4.397	0.0123
1	0	-0.772	0.316
1	1	-2.184	0.101
weighted*		-1.821	0.198
(transformed)		0.139	-1.399

* based on data counts for the 4 categories of (`dneo`,`dclox`): 22, 12, 59, 15

Interpretations:

- $\hat{p}$ (averaged): ∼ averaged probabilities, might correspond to a population (if data representative),
- $\text{logit}(\hat{p})$ (averaged and then transformed): simpler, because backtransformation of a "natural" value.