Faculty of Health Sciences

Day 6: logistic regression

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Outline

Overview
- ILO: to outline what the (univariate) logistic model is about

One binary covariate
- ILO: to interpret the model fit when using only one binary covariate

One categorical (non binary) covariate
- ILO: to interpret the model fit when using only categorical binary covariate
- ILO: to use the model to perform a powerful multiple testing adjustment

One continuous covariate
- ILO: to interpret and check the model, when using only one continuous covariate

Multiple regression: two binary covariates
- ILO: to interpret the fit of a multiple regression (i.e. an adjsuted model)

Multiple regression: one continuous and one binary covariate
- ILO: to interpret the fit of a multiple regression (i.e. an adjsuted model)

Multiple regression: interaction
- ILO: to interpret interactions and explain their meaning to others

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Regression

Different types of outcome can be analyzed by different models:

Quantitative (continuous) outcome

- Linear regresssion.
  - To model means.
  - Association parameters: differences between mean values

0-1 (binary) outcome

- Logistic regression.
  - To model probabilities.
  - Association parameters: odds ratio (OR) or equivalently differences between log(odds).

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Case: Framingham study[1]

Data, n=1,363:

	AGE	FRW	SBP	DBP	CHOL	CIG	sex	disease
1	45	93	100	62	220	0	Female	0
2	48	93	108	70	340	0	Male	0
3	45	91	160	100	171	0	Female	0
4	50	110	110	70	224	0	Male	0
5	48	85	110	70	229	25	Male	0
6	55	101	134	84	224	0	Male	0

Outcome: coronary heart disease (CHD) during follow-up (1=yes/no=0).

[1] Mahmood et al. "The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective." The Lancet 383.9921 (2014): 999-1008.
Andersson, Charlotte, et al. "70-year legacy of the Framingham Heart Study." Nature Reviews Cardiology 16.11 (2019): 687-698.

- **sex:** Male/Female
- **AGE:** age (years) at baseline (45-62)
- FRW: "Framingham relative weight" (pct.) at baseline (52-222; 11 persons have missing values)
- SBP: systolic blood pressure at baseline (*mmHg*) (90-300)
- **DBP:** diastolic blood pressure at baseline (*mmHg*) 50-160)
- CHOL: cholesterol at baseline (*mg/100ml*) (96-430)
- **CIG:** cigarettes per day at baseline (0-60; 1 person has missing value)
- **disease:** 1 if coronary heart disease (CHD) during follow-up, 0 otherwise

Categorical explanatory variable (K groups, $k = 1, \ldots, K$)

Linear regression, continuous outcome Y

$$\text{mean}(Y|\text{group } k) - \text{mean}(Y|\text{reference group})$$

E.g., the average blood pressure was higher in males compared to females.

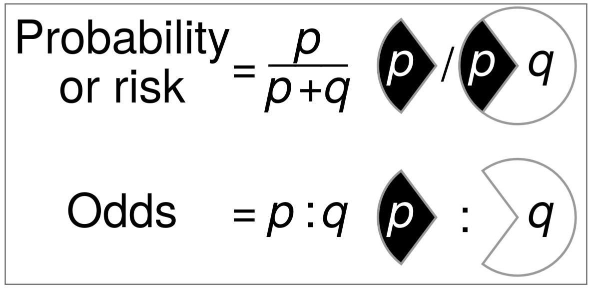
Logistic regression, binary outcome

$$\text{OR} = \frac{\text{odds(group } k)}{\text{odds(reference group)}}$$

E.g., the risk (or the odds [2]) of coronary heart disease was higher in males compared to females.

[2] remember: odds(p)= $p/(1-p)$ and "higher odds" is equivalent to "higher risk".

Reminder: odds vs risk



The odds (in favor) of an event (here 1/2=0.5) is the ratio of the probability that the event will happen (p, here 1/3=0.33) to the probability that the event will not happen ($q = 1 - p$, here 2/3=0.67).

Figure from `https://en.wikipedia.org/wiki/Odds`.

Software parametrization

By default, software report log(Odds ratio)= difference in log(odds).

$$\begin{aligned} \log(\text{OR}) &= \log\left\{\frac{\text{odds(group k)}}{\text{odds(reference group)}}\right\} \\ &= \log\left\{\text{odds(group k)}\right\} - \log\left\{\text{odds(reference group)}\right\} \end{aligned}$$

But it does not matter for the **interpretation**.

- $OR > 1 \Leftrightarrow \log(\text{OR}) > 0 \Leftrightarrow RR > 1$ (higher risk)
- $OR = 1 \Leftrightarrow \log(\text{OR}) = 0 \Leftrightarrow RR = 1$ (same risk)
- $OR < 1 \Leftrightarrow \log(\text{OR}) < 0 \Leftrightarrow RR < 1$ (lower risk)

Quantitative (continuous) predictor variables

Linear regression, continuous outcome Y

Differences in mean values per unit of X:

$$\text{mean}(Y|x+1) - \text{mean}(Y|x)$$

E.g., the average systolic blood pressure increased with age.

Quantitative (continuous) predictor variables

Linear regression, continuous outcome Y

Differences in mean values per unit of X:

$$\text{mean}(Y|x+1) - \text{mean}(Y|x)$$

E.g., the average systolic blood pressure increased with age.

Logistic regression, binary outcome

Ratio of odds per unit of X

$$\text{Odds ratio} = \frac{\text{odds}(x+1)}{\text{odds}(x)}$$

Differences in log(odds) per unit of X

$$\log(OR) = \log\{\text{odds}(x+1)\} - \log\{\text{odds}(x)\}$$

E.g., the risk (odds) of coronary heart disease increased with age.

Linearity in regression models

For a continuous variable X (e.g. age), linearity means that the effect of a unit change of X on the outcome does not depend on the value of X.

- Linear regression, continuous outcome Y

$$\begin{aligned}\text{mean}(Y|45+1) - \text{mean}(Y|45) &= \text{mean}(Y|46+1) - \text{mean}(Y|46)\\ &= \cdots = \text{mean}(Y|61++1) - \text{mean}(Y|61)\end{aligned}$$

- Logistic regression, binary outcome

$$\frac{\text{odds}(45+1)}{\text{odds}(45)} = \frac{\text{odds}(46+1)}{\text{odds}(46)} = \cdots = \frac{\text{odds}(61+1)}{\text{odds}(61)}$$

Linearity is a model assumption which should be checked![3]

[3] Categorizing a continuous covariate can be useful when linearity does not hold.

Binary outcome regression: why not linear?

If the outcome variable is binary:

$$Y_i = \begin{cases} 1 & \text{if } i \text{ is diseased} \\ 0 & \text{if } i \text{ is not diseased} \end{cases}$$

then linear regression

$$Y_i = \alpha + \beta X_i + \varepsilon_i$$

is **not good** for many reasons.

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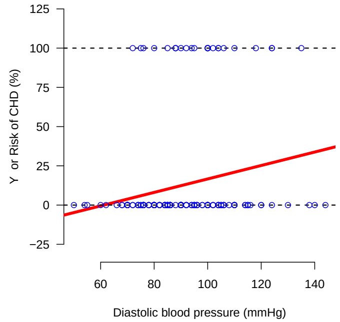
One reason is that the regression line can go below 0 and above 1.



(Univariate) logistic regression

We model the probability of the event $Y_i = 1$ for a subject with predictor variable X_i.

$$\mathrm{P}(Y_i = 1 | X_i = x_i) = p_i.$$

Instead of using a linear regression for p_i, which is bounded between 0 and 1, we apply linear regression to $\log$(odds):

$$\log\left(\frac{p_i}{1-p_i}\right) = a + bx_i$$

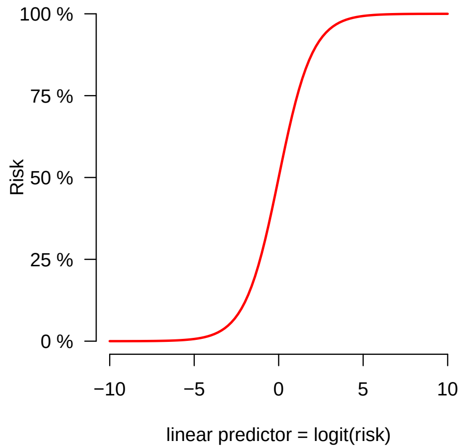
- It's a good idea as $\log\left(\frac{p_i}{1-p_i}\right)$ can be both negative and positive.
- We will see that $\exp(b)$ can be interpreted as an **odds ratio**.
- The function $p \mapsto \log\{p/(1-p)\}$ is called the "logit" function and we often write $\boxed{\mathrm{logit}(p_i) = a + bx_i}$.

Appendix: further details

Equivalently, the (univariate) logistic model is:

$$p_i = \frac{\exp(\ a + bx_i\ )}{1 + \exp(\ a + bx_i\ )}$$

- $a + bx_i$: linear predictor

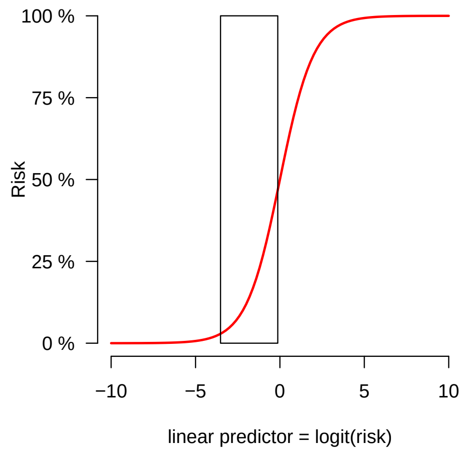


Appendix: further details

Example of model fit, with x being the diastolic blood pressure (mmHg):

$$p_i = \frac{\exp(\ -3.86 + 0.027x_i\ )}{1 + \exp(\ -3.86 + 0.027x_i\ )}$$

Here the linear predictor ranges from
$-3.86 + 0.027 \cdot 50 = -3.52$ to
$-3.86 + 0.027 \cdot 144 = -0.13$
because the pressure ranges from 50 to 144.
(box on the plot to the right)



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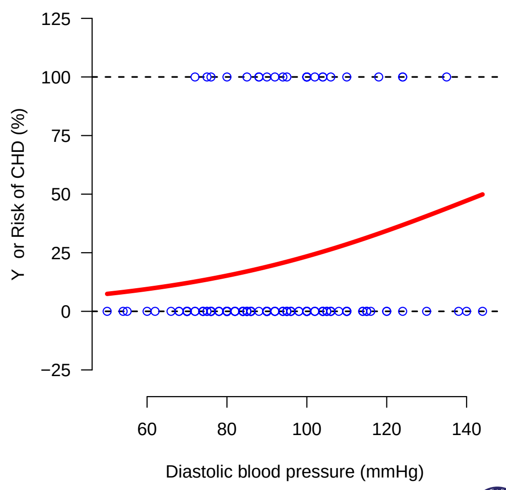

Here the linear predictor ranges from
$-3.86 + 0.027 \cdot 50 = -3.52$ to
$-3.86 + 0.027 \cdot 144 = -0.13$
because the pressure ranges from 50 to 144.
(zoom in to this range)

Outline

Research question:[4]

Do men and women have the same risk of coronary heart disease?

[4] A bit made up, just for pedagogical purpose, to illustrate the concepts.

A binary explanatory variable

$$Y_i = \begin{cases} 1 & \text{subject i develops coronary heart diseased (CHD)} \\ 0 & \text{subject i does not develop CHD} \end{cases}$$

$$Z_i = \begin{cases} 1 & \text{subject } i \text{ is a man} \\ 0 & \text{if subject } i \text{ a woman} \end{cases}$$

Univariate logistic regression for $p_i = \mathrm{P}(Y_i = 1 | Z_i = z_i)$:

$$\log\left(\frac{p_i}{1 - p_i}\right) = a + b z_i = \begin{cases} a & \text{females} \\ a + b & \text{males} \end{cases}$$

A binary explanatory variable

$$Y_i = \begin{cases} 1 & \text{subject i develops coronary heart diseased (CHD)} \\ 0 & \text{subject i does not develop CHD} \end{cases}$$

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Univariate logistic regression for $p_i = \mathrm{P}(Y_i = 1 | Z_i = z_i)$:

$$\log\left(\frac{p_i}{1-p_i}\right) = a + bz_i = \begin{cases} a & \text{females} \\ a+b & \text{males} \end{cases}$$

That means,

$$b = (a+b) - a = \log(\text{odds for } ♂) - \log(\text{odds for } ♀)$$
$$= \log\left(\frac{\text{odds for } ♂}{\text{odds for } ♀}\right) = \log\left(OR_{♂\text{vs}♀}\right)$$

and $-b = \cdots = \log\left(OR_{♀\text{vs}♂}\right)$.

Note: remember that $\exp(-b) = 1/\exp(b)$.

Logistic regression in R

```
fit1 <- glm(disease~sex, data=framingham, family=binomial)
```

- disease ~ sex: tells R that disease is the outcome and sex the predictor variable.
- data=framingham: tells R where to find the variable Y and Sex.
- glm: means "generalized linear model".
- family=binomial: tells R that the outcome is binary and the that logit link function should be used.

R code: only sex variable

R code:

```
fit1 <- glm(disease~sex, data=framingham, family=binomial)
summary(fit1)
```

Output (partial):

```
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.07183    0.09047 -11.847  < 2e-16 ***
sexFemale   -0.70702    0.13937  -5.073 3.92e-07 ***
```

Note: pay attention to the default reference group ! Here it is "male", not "female" for sex, the opposite of what we had at the previous slide...

Comparison with results from the 2x2 table

```
TabSex <- table(relevel(framingham$sex,ref="Female"),
                factor(framingham$disease,levels=c(1,0)))
table2x2(TabSex,stat=c("table","or"))
```

```
2x2 contingency table
-----------------------------

             1        0      Sum
Female     104      616      720
Male       164      479      643
--          --       --       --
Sum        268     1095     1363

Odds ratio = OR = (p1/(1-p1))/(p2/(1-p2)) = 0.4931
Standard error = SE.OR = sqrt((1/a+1/b+1/c+1/d)) = 0.1394
```

And we can see the same results:

- $\widehat{OR} = \exp(-0.7070219) = 0.493$
- Standard error of log(OR)$= 0.1394$.

For this simple case with only one binary predictor variable, logistic regression is equivalent to what we have seen last week.

Confidence intervals for the odds ratio

```
library(Publish)
publish(fit1)
```

Variable	Units	OddsRatio	CI.95	p-value
Sex	Male	1.00	[1.00;1.00]	1
	Female	0.49	[0.38;0.65]	<0.0001

Note: $0.49 = \exp(-0.71)$.

Confidence intervals for the odds ratio

```
library(Publish)
publish(fit1)
```

Variable	Units	OddsRatio	CI.95	p-value
Sex	Male	1.00	[1.00;1.00]	1
	Female	0.49	[0.38;0.65]	<0.0001

Note: $0.49 = \exp(-0.71)$.

"Typical"/possible conclusion sentence:
Women have a significantly lower risk to develop coronary heart disease than men (odds ratio: 0.49, 95%-CI: [0.38; 0.65], p-value <0.0001).

Changing the reference level

```
framingham$sexF <- relevel(framingham$sex,ref="Female")
fit1a <- glm(disease~sexF, data=framingham, family=binomial)
publish(fit1a)
```


Changing the reference level

```
framingham$sexF <- relevel(framingham$sex,ref="Female")
fit1a <- glm(disease~sexF, data=framingham, family=binomial)
publish(fit1a)
```

Variable	Units	OddsRatio	CI.95	p-value
sexF	Female	1.00	[1.00;1.00]	1
	Male	2.03	[1.54;2.66]	<0.0001

Note: $2.03 = \exp(0.71)$.

"Typical"/possible conclusion sentence:
Men have a significantly higher risk to develop coronary heart disease than women (odds ratio: 2.03, 95%-CI: [1.5; 2.7], p-value <0.0001).

Outline

Research questions:[5]

Is age associated with the risk of coronary heart disease?

Are some age groups more at risk of coronary heart disease than others?

[5] A bit made up, just for pedagogical purpose, to illustrate the concepts.

Model with only one categorical explanatory variable

Assume that we want to compare several groups, e.g. four age groups.[6]

		Age				
		45-48	49-52	53-56	57-62	
Outcome	$Y=1$	51	61	64	92	268
(CHD)	$Y=0$	308	298	254	235	1095
		359	359	318	327	1363

We can either use:

- Fisher's exact test or Pearson χ^2 for the global null hypothesis H_0: "the risk is the same for all age groups" (see Lecture 5).
- or logistic regression to make all-pairwise comparisons (via OR) and use the "modern" min-P approach to efficiently account for multiple testing. If at least one adjusted p-value is significant (i.e., if min-P $\leq 5\%$), then we can reject H_0 and conclude to an association. [7]

[6] Note: we pooled the data of men and women.
[7] Rk: it also works when we "adjust" for other variables.

Logistic regression: categorical variable with 4 levels:

$$\log\left(\frac{p_i}{1-p_i}\right) = \begin{cases} a & \text{age} \quad 45-48 \\ a+b_1 & \text{age} \quad 49-52 \\ a+b_2 & \text{age} \quad 53-56 \\ a+b_3 & \text{age} \quad 57-62 \end{cases}$$

Reference category 45-48

$$a = \log(\text{odds}(45-48))$$

$$b1 = \log\left(\frac{\text{odds}(49-52)}{\text{odds}(45-48)}\right)$$

$$b2 = \log\left(\frac{\text{odds}(53-56)}{\text{odds}(45-48)}\right)$$

$$b3 = \log\left(\frac{\text{odds}(57-62)}{\text{odds}(45-48)}\right)$$

- Equivalent to making 3 times the 2x2 table analysis for the group 45-48 versus each of the three others .

Results: one categorical predictor variable

```
framingham$AgeCut <- cut(framingham$AGE,
                   c(40,48,52,56,99),
                   labels=c("45-48","49-52","53-56","57-62"))
fit3 <- glm(disease~AgeCut, data=framingham, family=binomial)
publish(fit3)
```

```
Variable Units OddsRatio       CI.95   p-value
  AgeCut 45-48       Ref
         49-52      1.24 [0.82;1.85]   0.30425
         53-56      1.52 [1.02;2.28]   0.04151
         57-62      2.36 [1.61;3.46]  < 0.0001
```

Remarks:

- Not all (six) comparisons are directly available from the "summary" of the model fit, for example the odds ratio for group 57-62 vs 53-56 is not.
- $\widehat{OR} = (92 \times 308)/(51 \times 235) = 2.36$ and all estimates match those of each corresponding 2 x 2 table.
- Running a similar code after changing the reference group is a convenient **"trick"** to obtain any OR estimate, with corresponding 95% CI and p-value.

Equivalent Results

```
framingham$AgeCutb <- relevel(framingham$AgeCut,"53-56")
fit3b <- glm(disease~AgeCutb, data=framingham, family=
    binomial)
publish(fit3b)
```

```
Variable Units OddsRatio       CI.95   p-value
 AgeCutb 53-56       Ref
         45-48      0.66 [0.44;0.98]   0.04151
         49-52      0.81 [0.55;1.20]   0.29468
         57-62      1.55 [1.08;2.24]   0.01798
```

As expected:

- 0.66=1/1.52, i.e. OR(45-48 vs 53-56)=1/OR(53-56 vs 45-48)
- 1.55=2.36/1.52, i.e. OR(57-62 vs 53-56)= OR(57-62 vs 45-48)/OR(53-56 vs 45-48)

All pairwise comparisons: min-P approach

Statistical methods:
Comparisons between groups were made using a logistic model. P-values and 95% confidence intervals were adjusted for multiple testing using the min-P (aka max-t test) method as implemented in the multcomp-package [ref.[8]] of the statistical software R [ref.[9]] and described in [ref.[10]].

Results (adjusted for multiple testing):

Comparison	Est. OR	95% CI	p-value
49-52 - 45-48	1.24	[0.7;2.1]	0.7329
53-56 - 45-48	1.52	[0.9;2.6]	0.1736
57-62 - 45-48	2.36	[1.4;3.9]	0.0001
53-56 - 49-52	1.23	[0.7;2.0]	0.7207
57-62 - 49-52	1.91	[1.2;3.1]	0.0028
57-62 - 53-56	1.55	[1.0;2.5]	0.0836

Note:

- Significant association between CHD and age groups, p-value= 0.0001 (the minimum of the adjusted p-values)
- Similarly, we can use the method for the **"many-to-one"** setting (as in Lecture 4).

[8] Hothorn, Bretz & Westfall (2008). Simultaneous Inference in General Parametric Models. Biometrical Journal 50(3), 346–363.
[9] R Core Team (2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
[10] Bretz, Hothorn, & Westfall (2016). Multiple comparisons using R. CRC Press.

Outline

Research questions:[11]

Is age associated with the risk of coronary heart disease?

How does age relate to the risk of coronary heart disease?

[11] A bit made up, just for pedagogical purpose, to illustrate the concepts.

Quantitative explanatory factor

It is sometimes more natural or better to include the a continuous variable (e.g. age) as a quantitative predictor in the model (i.e., *No grouping*)[12]

$$\log\left(\frac{p_i}{1-p_i}\right) = a + b \cdot \text{age}_i$$

$$a = \log(\text{odds}(\text{age}=0))$$

$$b = \log\left\{\text{odds}(\text{age}=x+1)\right\} - \log\left\{\text{odds}(\text{age}=x)\right\}$$

Interpretation: we compare two subjects, one is one year older than the other (no matter their ages, e.g. 46 vs 45 or 56 vs 55); we estimate that the odds for CHD is

$$\boxed{\exp(b) = \text{odds ratio}}$$

larger for the older subject than for the younger subject.

[12] sometimes better but not always, due to the linearity assumption or similar.

Appendix: details on inference (Est., 95% CI & p-values)

- We estimate the parameters by giving them values that makes the observations of the outcome of our data the "most likely" to be observed (again). This is called 'maximum likelihood estimation'. No simple formula, except in very specific cases.
- We compute the standard error for each the parameter by looking at how much the likelihood to observe the outcome of our data is sensitive to the parameter values. Intuition: high sensitivity= a small range of parameter values makes the data "most likely"= small standard error. No simple formula, except in very specific cases.
- 95 % confidence interval for parameters:

  $$\text{estimate} \pm 1.96 \cdot \text{standard error}.$$

- p-value for the null hypothesis H_0: "parameter=0":

  $$z = \frac{\text{estimate}}{\text{standard error}} \quad \text{and} \quad \text{p-value} = P(|Z| > |z|)\ ,$$

  with Z being a random variable with a standard normal distribution. It works well, but software can also do something slightly more precise (called "profile likelihood" inference).

Raw results

```
fit5 <- glm(disease~AGE,data=framingham,family=binomial)
summary(fit5)
```

```
Coefficients:
             Estimate Std. Error z value       Pr(>|z|)
(Intercept) -4.88431    0.77372  -6.313 0.000000000274 ***
AGE          0.06581    0.01446   4.550 0.000005374208 ***
```

- $\widehat{OR} = \exp(0.06581) = 1.07$

Good reporting practice

1-year change in age (not very good)

```
fit5 <- glm(disease~AGE,data=framingham,family=binomial)
publish(fit5)
```

```
Variable Units OddsRatio       CI.95  p-value
     AGE             1.07 [1.04;1.10] < 0.0001
```

10-year change in age (probably better)

```
framingham$age10 <- framingham$AGE/10
fit5b <- glm(disease~age10,data=framingham,family=binomial)
publish(fit5b)
```

```
Variable Units OddsRatio       CI.95  p-value
   age10             1.93 [1.45;2.56] < 0.0001
```


Good reporting practice

1-year change in age (not very good)

```
fit5 <- glm(disease~AGE,data=framingham,family=binomial)
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Variable Units OddsRatio       CI.95  p-value
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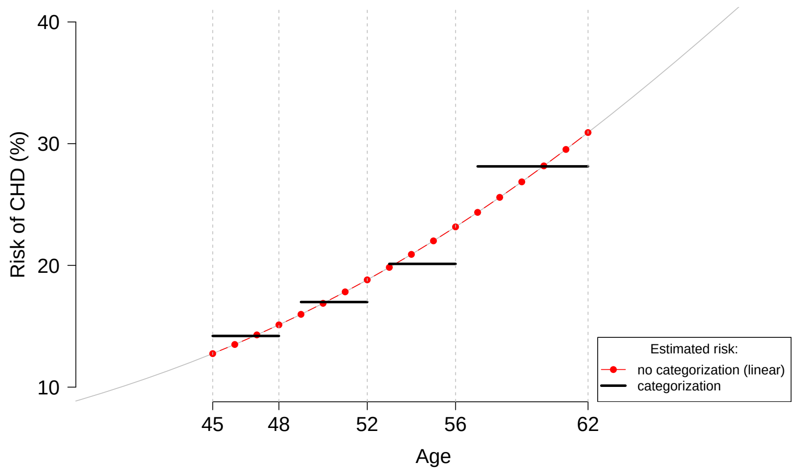
10-year change in age (probably better)

```
framingham$age10 <- framingham$AGE/10
fit5b <- glm(disease~age10,data=framingham,family=binomial)
publish(fit5b)
```

```
Variable Units OddsRatio       CI.95  p-value
   age10             1.93 [1.45;2.56] < 0.0001
```


These results are completely equivalent: $1.93 = 1.07^{10}$. The fitted models are the same, but the "default" way of presenting the results is different.

Visualizing and checking the linearity assumption



- We compare the "flexible" model which uses the categorized variable to the "less flexible" model (but "nicer" if correct!) which uses the continuous variable (together with a "linearity" assumption).

Outline

Multiple logistic regression

Additive effects of several explanatory variables:

$$\log\left(\frac{p_i}{1-p_i}\right) = a + b_1 z_i + b_2 x_i + \dots$$

with $p_i = \mathrm{P}(Y_i = 1 | X_i = x_i, Z_i = z_i, \dots)$.

- Multiple logistic regression is a way to control for confounding / unbalanced design.
- Makes it possible to estimate odds ratios to compare the risks of two groups of subjects who are similar with respect to all predictor variables except one.

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$$\log\left(\frac{p_i}{1-p_i}\right) = a + b_1 z_i + b_2 x_i + \dots$$

with $p_i = \mathrm{P}(Y_i = 1 | X_i = x_i, Z_i = z_i, \dots)$.

- Multiple logistic regression is a way to control for confounding / unbalanced design.
- Makes it possible to estimate odds ratios to compare the risks of two groups of subjects who are similar with respect to all predictor variables except one.
- We often say that the effect (via the odds ratio) on the outcome of each predictor variable under study (e.g. "exposure"), is adjusted for the other explanatory variables (e.g. age, sex, comorbidity).
- Without interaction, the model assumes that the effect (odds ratio) of z on Y is the same for all values of x.

Research question:[13]

Are smokers more at risk of coronary heart disease than non-smokers?

Background (that we need to take into account):
It is known that men smoke more than women.

Hence the aim of the statistical analysis:
We want to compare the risk of two subjects, one smokes, the other doesn't, who are similar with respect to sex (i.e. either both men or both women).

[13] A bit made up, just for pedagogical purpose, to illustrate the concepts.

Example of two binary variables

$$Z_i = \begin{cases} 1 & \text{if male} \\ 0 & \text{female} \end{cases} \quad \text{and} \quad V_i = \begin{cases} 1 & \text{if smokes} \\ 0 & \text{otherwise} \end{cases}$$

Data can be summarized as two 2 by 2 tables **in two ways**, but usually, one option is more interesting than the other for the research question.

	Males (Z=1)			Females (Z=0)	
	$Y=1$	$Y=0$		$Y=1$	$Y=0$
Smoker: $V=1$	107	288	$V=1$	27	192
Non Smoker: $V=0$	57	191	$V=0$	77	423

Here it is less interesting to look at the two 2 by 2 tables showing the association between Y (disease) and Z (Sex) given V (Smoking) because it is less related to our research question.

Model with two binary variables (without interaction)

$$\log\left(\frac{p_i}{1-p_i}\right) = a + b_1 Z_i + b_2 V_i = \begin{cases} a & \text{Female} \quad \text{non-smoker} \\ a+b_1 & \text{Male} \quad \text{non-smoker} \\ a+b_2 & \text{Female} \quad \text{smoker} \\ a+b_1+b_2 & \text{Male} \quad \text{smoker} \end{cases}$$

Note: $b_1 = (a+b_1) - a$ (comparison among non-smoker)

$= (a+b_1+b_2) - (a+b_2)$ (comparison among smoker)

$= \log OR($♂ vs ♀ for given smoking status $)$

and $b_2 = (a+b_2) - a$ (comparison among female)

$= (a+b_1+b_2) - (a+b_1)$ (comparison among male)

$= \log OR$ (smokers vs. non-smokers for given sex)

Note: this is similar to the ANOVA model (lecture 4).

Logistic regression results

```
fit2 <-glm(disease~sex+Smoke,data=framingham,family=binomial)
summary(fit2)
```

```
Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.09215    0.12717  -8.588  < 2e-16 ***
sexFemale   -0.69521    0.14635  -4.750 2.03e-06 ***
SmokeYes     0.03296    0.14457   0.228     0.82
```


Extracting odds ratios with confidence intervals

```
publish(fit2)
```

```
 Variable  Units OddsRatio       CI.95  p-value
      sex   Male       Ref
          Female      0.50 [0.37;0.66]   <1e-04
    Smoke     No       Ref
             Yes      1.03 [0.78;1.37]   0.8196
```


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Extracting odds ratios with confidence intervals

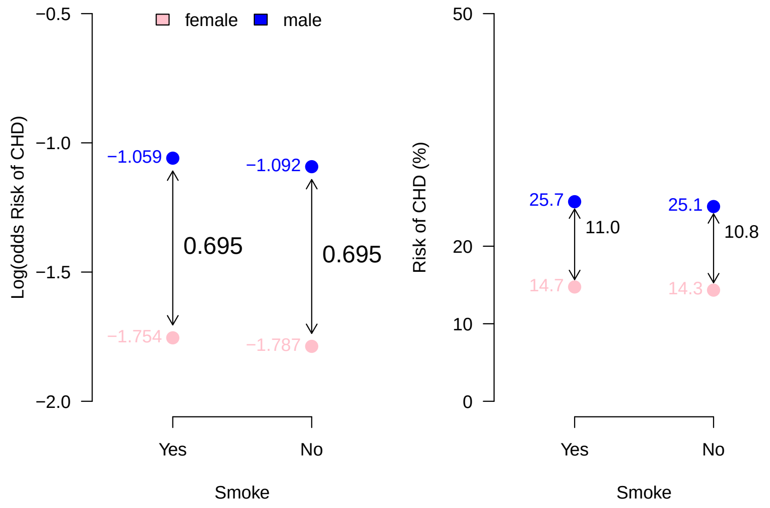
```
publish(fit2)
```

```
 Variable  Units OddsRatio       CI.95  p-value
      sex   Male       Ref
          Female      0.50 [0.37;0.66]   <1e-04
    Smoke     No       Ref
             Yes      1.03 [0.78;1.37]   0.8196
```


"Typical"/possible conclusion sentence:

Logistic regression adjusted for sex did not show an increase in odds of CHD in smokers compared to non-smokers (OR=1.03, 95% CI: [0.78;1.37], p=0.82).

Visual interpretation



Note: additivity is on the logit scale (i.e. log(odds)), not on the risk scale

Outline

Research question:[14]

Do men and women have the same risk of coronary heart disease?

Background:
It is known that aging increases the risks of coronary heart disease. We could not collect the data in a way that necessarily makes the distribution of age similar for men and women.

Hence the aim of statistical analysis:
We want to compare the risk of two subjects, one is a man, the other a woman, both are similar with respect to age.

[14] A bit made up, just for pedagogical purpose, to illustrate the concepts.

Another multiple regression example

Additive model (no statistical interactions)

$$\log\underbrace{\left(\frac{p_i}{1-p_i}\right)}_{=\text{odds}_i} = a + b_1 z_i + b_2 x_i$$

Effect of sex z_i (0 = female, 1 = male) adjusted for age (x_i)

$$\frac{\text{odds(age=50, male)}}{\text{odds(age=50, female)}} = \frac{\exp(a + b_1 + b_2 50)}{\exp(a + b_2 50)}$$
$$= \exp(a + b_1 + b_2 50 - a - b_2 50)$$
$$= \exp(b_1).$$

The result is the same for age 46 and age 61 and all other ages.

Effect of age (x_i) for males:

$$\frac{\text{odds(age=51, male)}}{\text{odds(age=50, male)}} = \frac{\exp(a + b_1 + b_2 51)}{\exp(a + b_1 + b_2 50)}$$
$$= \exp(a + b_1 + b_2 51 - a - b_1 - b_2 50)$$
$$= \exp(b_2).$$

The result is the same for females:

$$\frac{\text{odds(age=51, female)}}{\text{odds(age=50, female)}} = \frac{\exp(a + b_2 51)}{\exp(a + b_2 50)}$$
$$= \exp(a + b_2 51 - a - b_2 50)$$
$$= \exp(b_2).$$

Linearity means that the result is the same for a comparison of age 63 and age 62 and all other one year differences.

Results (raw)

```
fit6 <- glm(disease ~ AGE + sex, family = binomial,
        data = framingham)
summary(fit6)
```

```
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.59208    0.78019  -5.886 3.96e-09 ***
AGE          0.06672    0.01458   4.575 4.75e-06 ***
sexFemale   -0.71613    0.14052  -5.096 3.46e-07 ***
```


Results (formatted for publication)

```
fit6 <- glm(disease ~ AGE + sex, family = binomial, data =
    framingham)
publish(fit6)
```

```
 Variable  Units OddsRatio       CI.95 p-value
      AGE               1.07 [1.04;1.10]  <1e-04
      sex   Male         Ref
          Female        0.49 [0.37;0.64]  <1e-04
```

Possible conclusion sentences:
Logistic regression was used to investigate gender differences in odds (risks) of CHD adjusted for age.

The age adjusted odds ratio was 0.49 (95%-CI: [0.37;0.64]) showing that the risks of CHD were significantly lower for women compared to men (p<0.0001).

Predicted risks based on logistic regression model

A logistic regression model can be used to predict "personalized"/conditional risks, since

$$\log\left(\frac{p_i}{1-p_i}\right) = a + b_1 z_i + b_2 z_i + \dots$$

is equivalent to

$$p_i = \frac{\exp(a + b_1 z_i + b_2 x_i + \dots)}{1 + \exp(a + b_1 z_i + b_2 x_i + \dots)}$$

We can predict a risk for any value of the covariates Z, X,... once we have estimated the model parameters. We just need to plug the estimated parameter values into the equations. [15]

Note: the risks (and risk ratios) depend on all predictor variables simultaneously.

[15] However, upmost caution is needed when using covariate values beyond the range of those observed (e.g. age=110). Usually we do not want to extrapolate beyond the observed data. Same remark as in Lecture 3.

Visualization of predicted risks

- For men:

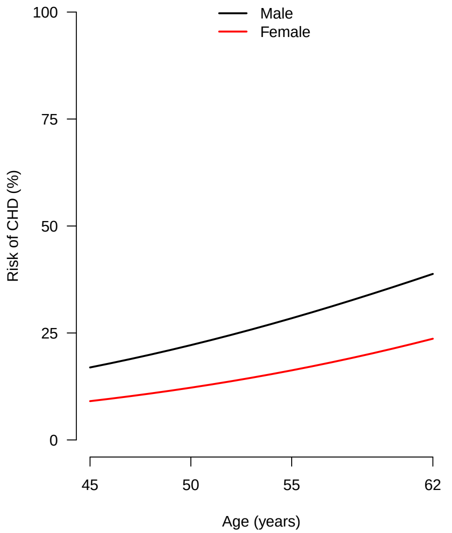
$$\frac{\exp(-4.59208 + 0.06672 \cdot \text{age})}{1 + \exp(-4.59208 + 0.06672 \cdot \text{age})}$$

- For women:

$$\frac{\exp(-4.59208 - 0.71613 + 0.06672 \cdot \text{age})}{1 + \exp(-4.59208 - 0.71613 + 0.06672 \cdot \text{age})}$$

Because we have seen:

```
             Estimate
(Intercept) -4.59208
AGE          0.06672
SexFemale   -0.71613
```



Note: $\widehat{OR}$(male vs female given age) $= e^{-0.71613} = 0.489$ but $\widehat{RR}$ varies from 0.535 to 0.610. Remember lecture 5, the large the risks and the more different RR from OR.

Outline

Overview
ILO: to outline what the (univariate) logistic model is about

One binary covariate
ILO: to interpret the model fit when using only one binary covariate

One categorical (non binary) covariate
ILO: to interpret the model fit when using only categorical binary covariate
ILO: to use the model to perform a powerful multiple testing adjustment

One continuous covariate
ILO: to interpret and check the model, when using only one continuous covariate

Multiple regression: two binary covariates
ILO: to interpret the fit of a multiple regression (i.e. an adjsuted model)

Multiple regression: one continuous and one binary covariate
ILO: to interpret the fit of a multiple regression (i.e. an adjsuted model)

Multiple regression: interaction
ILO: to interpret interactions and explain their meaning to others

Statistical interaction = Effect modification

The effect of X on Y depends on Z

Example: the effect of age (X) on coronary heart disease (Y) depends on the sex (Z).

Effect modification

Setting: 3 variables.

- two predictor variables X and Z
- one outcome Y

Meaning

In logistic regression, an interaction means that the odds ratio which describes the effect of X on the odds of $Y = 1$ depends on the value of Z.

Symmetry

If the effect of variable X on Y is modified by Z then also the effect of Z on Y is modified X.

Research question:[16]

What are the risk of coronary heart disease for men and women at any age?

How different is the consequence of aging on the risk of coronary heart disease between men and women?

[16] A bit made up, just for pedagogical purpose, to illustrate the concepts.

Interaction between a continuous and a binary variable

To model the **interaction** we add "$b_3 x_i \cdot z_i$" in the model, i.e.,

$$\log\underbrace{\left(\frac{p_i}{1-p_i}\right)}_{=\text{odds}_i} = a + b_1 z_i + b_2 x_i + b_3 x_i \cdot z_i$$

- The effect of sex z_i (0 = female, 1 = male) depends on age (x_i).

$$\frac{\text{odds(age=50, male)}}{\text{odds(age=50, female)}} = \frac{\exp(a + b_1 + b_2 50 + b_3 50)}{\exp(a + b_2 50)} = \exp(b_1 + b_3 50).$$

When $\left\{\begin{array}{l} b_3 > 0 \\ b_3 < 0 \end{array}\right\}$, then OR(♂ vs ♀ given age) $\left\{\begin{array}{l} \text{increases} \\ \text{decreases} \end{array}\right\}$ with age.

- The effect of age (x_i) depends on sex z_i.

$$\frac{\text{odds(age=50, male)}}{\text{odds(age=45, male)}} = \frac{\exp(a + b_1 + b_2 50 + b_3 50)}{\exp(a + b_1 + b_2 45 + b_3 45)} = \exp(b_2 5 + b_3 5).$$

$$\frac{\text{odds(age=50, female)}}{\text{odds(age=45, female)}} = \exp(b_2 5).$$

Note: $\exp(b_2)$ describes the odds ratio for age in the reference group for sex (female) only, while it is $\exp(b_2 + b_3)$ in the other group (male).

Statistical interaction in R

First option (more transparent):

```
glm(disease ~ AGE + sex + AGE:sex, family = binomial,
    data = framingham)
```

Shorter syntax (less transparent):

```
glm(disease ~ AGE * sex, family = binomial,
    data = framingham)
```

Raw R output

```
fit7 <- glm(disease ~ AGE + sex + AGE:sex, family = binomial,
     data = framingham)
summary(fit7)
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.45290    1.00008  -3.453 0.000555 ***
AGE            0.04523    0.01883   2.402 0.016288 *
sexFemale     -3.54459    1.60431  -2.209 0.027146 *
AGE:sexFemale  0.05297    0.02987   1.773 0.076194 .
```

Note: pay attention to the default reference group ! Here it is “male”, not “female” for sex, the opposite of what we had at the previous slide...

Interpretation: some details

- `(Intercept):` est. log of the odds in the reference group (male, AGE=0). Not meaningful here!
- `(AGE):` est. log of the OR, when comparing the risks of two males (the reference group for `sex`), one being 1 year older than the other. The value is `0.04523`. Because it is positive, it means that OR>1 and thus that aging increases the risk of disease.
- `(sexFemale):` est. log of the OR, when comparing the risk of a female to that of a male, the two being `AGE`=0. Not meaningful here!
- `(AGE:sexFemale):` est. log of the ratio of two ORs. The first OR (numerator) is the OR to compare the the risks of two males (the reference group for `sex`), one being 1 year older than the other. The second is the OR to compare the the risks of two females one being 1 year older than the other. The value is `0.05297`. Because it is positive, it means that the ratio is > 1 and thus that aging is "worse" for females than males. I mean, the association between age and the risk of disease is stronger in females than in males.

Formatted results

```
fit7 <- glm(disease ~ AGE + sex + AGE:sex, family = binomial,
     data = framingham)
publish(fit7)
```

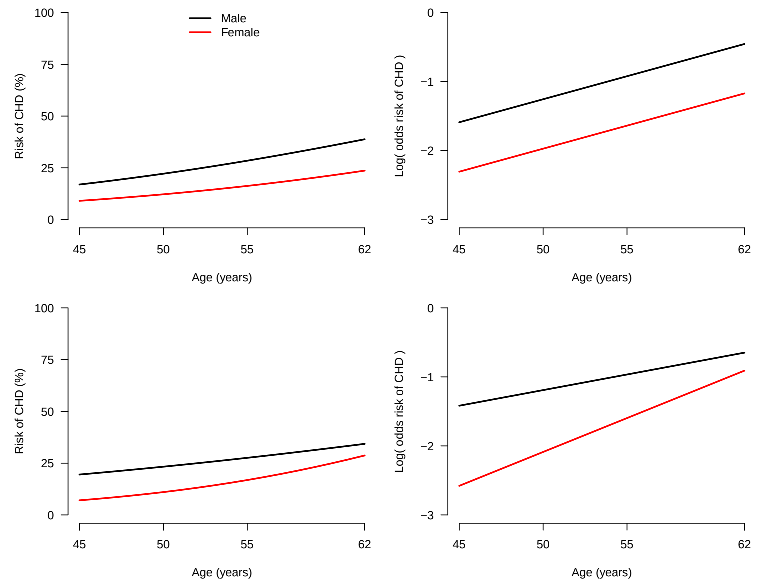
```
        Variable Units OddsRatio       CI.95   p-value
    AGE: sex(Male)          1.05 [1.01;1.09]   0.01629
  AGE: sex(Female)          1.10 [1.05;1.15]   < 1e-04
```

Interpretation

- One year more in age increases the odds by 5% (95% CI=[1;9]) in males and by 10% (95% CI=[5;15]) in females.[17]
- However, note that the difference in the increase in odds between men and women is not significant (p-value=0.076).

[17] $1.05 = \exp(0.04523)$ and $1.10 = \exp(0.04523 + 0.05297)$

Predicted risk with or without interaction



Note: without an interaction (top), the curves cannot cross. With (bottom), they can.

When using models with interaction?

- When it makes sense in the context of your study[18].
  - Because of the research question.
  - To better "adjust".
  - When subgroup analyses could be interesting.
- To check that the corresponding model without interaction seems "reasonable", i.e. to challenge your modeling assumptions.

[18] But you should have enough data... the more flexible the model the more data you need to estimate it accurately.

Two binary variables revisited: with interaction

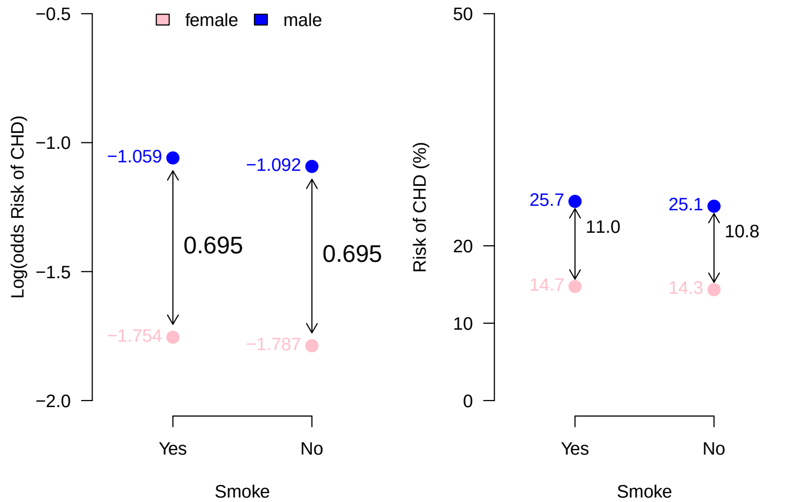
```
fit8 <-glm(disease~sex*Smoke,data=framingham,family=binomial)
summary(fit8)
```

```
Coefficients:
                  Estimate Std. Error z value Pr(>|z|)
(Intercept)        -1.2092     0.1509  -8.012 1.13e-15 ***
sexFemale          -0.4943     0.1953  -2.532   0.0114 *
SmokeYes            0.2191     0.1887   1.161   0.2456
sexFemale:SmokeYes -0.4772     0.3053  -1.563   0.1180
```

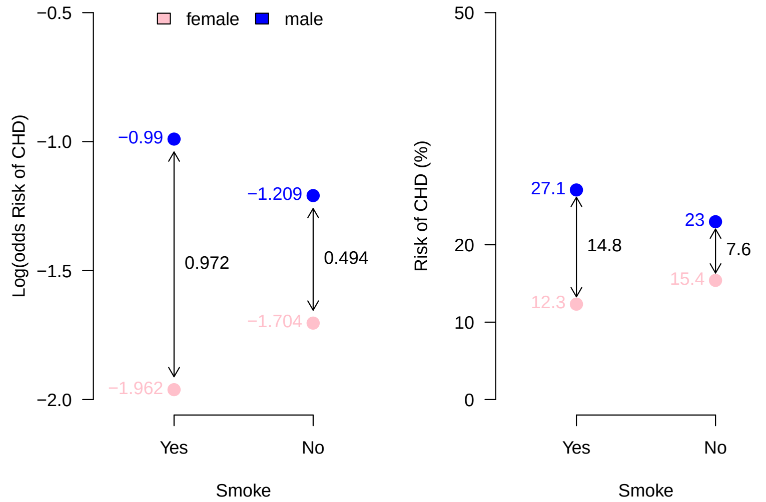
```
publish(fit8)
```

```
                  Variable Units OddsRatio       CI.95   p-value
    sex(Male): Smoke(Yes vs No)       1.24 [0.86;1.80]   0.24555
  sex(Female): Smoke(Yes vs No)       0.77 [0.48;1.24]   0.28219
   Smoke(No): sex(Female vs Male)     0.61 [0.42;0.89]   0.01135
  Smoke(Yes): sex(Female vs Male)     0.38 [0.24;0.60]   < 1e-04
```


Reminder: results without interaction



Reminder: results with interaction



- Estimates are simply those obtained by stratifying, i.e. they match those of the two 2x2 tables of slide 39, e.g. 27.1% =107/(107+288).

Take home messages

- (Multiple) logistic regression describes associations between one or several explanatory variables and the risk of an event (binary outcome), via odds ratio.
- The analysis of an exposure of interest can be adjusted for potential confounders.
- In an additive model (no interactions), the odds ratio for each explanatory variable does not depend on the other explanatory variables.
- Risks and risk ratios predicted by the model depend on the other explanatory variables.
- Linearity and absence of interaction are assumptions which might need to be checked.
- Models with interactions are flexible and useful but need more concentration to be interpreted correctly and more data to be fitted.
- Many models can be fitted from the same data, but some are more relevant than others for a given research question (e.g. in terms of adjustments and interactions).