# Statistical Modelling

## Proportions, odds, risk and hazard ratios

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# Agenda

- Continuous outcomes (t-test, Analysis of Variance, Linear regression, Analysis of Covariance)
- Binary outcomes (Logistic regression)
- Time-to-event outcomes (Cox proportional hazard model)
- Poisson regression

# Statistical analysis of continuous outcomes

# The basic model

$$y \sim f(x_{primary}, x_i)$$

- $y$: continuous outcome variable
- $x_{primary}$: explanatory variable of primary interest (categorical or continuous)
- $x_i$: other explanatory variables that we adjust for (categorical or continuous)

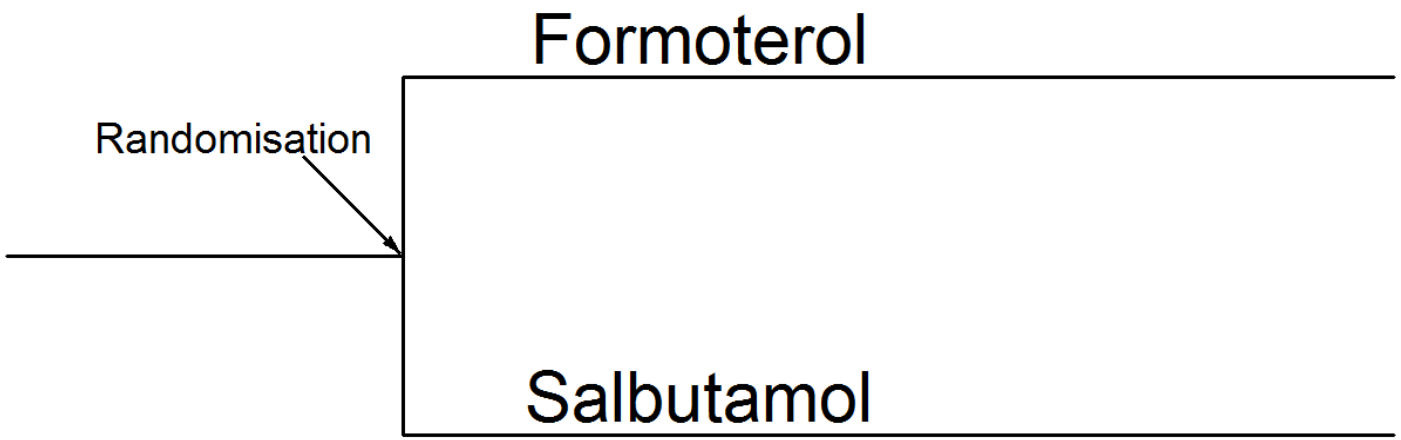
# Drug treatments of asthma

- Chronic condition
- Abnormal degree of wheezing or breathlessness
- Severity of symptoms ebbs and flows over time
- Outcome: Maximum rate at which the patient is able to exhale a fixed time after administration of the drug (PEF)
- Comparison of the two drugs Salbutamol and Formoterol for short-term relief of the symptoms

# PEF data

| Formoterol | Salbutamol |
|---|---|
| 310 | 270 |
| 310 | 260 |
| 370 | 300 |
| 410 | 390 |
| 250 | 210 |
| 380 | 350 |
| 330 | 365 |
| 385 | 370 |
| 400 | 310 |
| 410 | 380 |
| 320 | 290 |
| 340 | 260 |
| 220 | 90 |

# Design of study



# The analysis model

$$y \sim f(x_{primary}, x_i)$$

$$PEF \sim f(treatment)$$

- The $x$-variable is categorical
- This is a so-called t-test

# PEF data - some calculations

**Mean:** $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$

**Variance:** $var(x) = s^2 = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2$, measures the total squared average "distance"from the mean to the observations

**Standard deviation:** $SD = \sqrt{var(x)}$, measures the total average "distance"from the mean to the observations

**Standard error:** $SE = \frac{SD}{\sqrt{n}}$, measures the variability of the mean

**Formoterol:** Mean=341.2, variance=3559.32, SD=59.66

**Salbutamol:** Mean=295.8, variance=6865.78, SD=82.86

# PEF data - some calculations for the difference

**Mean:** $341.2 - 295.8 = 45.4$

**Pooled variance:** $(3559.32 + 6865.78)/2 = 5212.84$

**Standard error:**

$$SE = \sqrt{\frac{2 \cdot pooled\ \ variance}{n}} = \sqrt{\frac{2 \cdot 5212.84}{13}} = 28.3$$

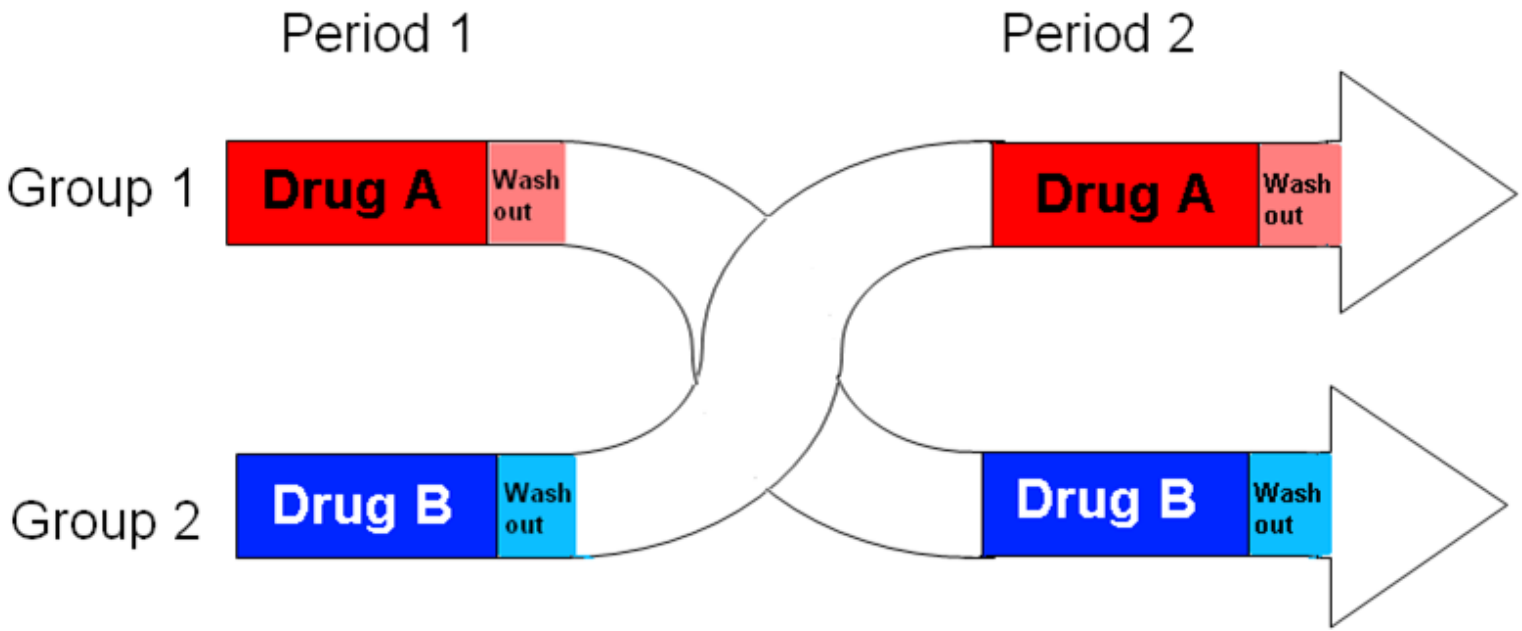
**95 % confidence interval for the difference:**

$$mean \pm 2 \cdot SE = [-11.3; 102.0]$$

# PEF data

| Subject ID | Formoterol | Salbutamol | Difference |
|---|---|---|---|
| 1 | 310 | 270 | 40 |
| 2 | 310 | 260 | 50 |
| 3 | 370 | 300 | 70 |
| 4 | 410 | 390 | 20 |
| 5 | 250 | 210 | 40 |
| 6 | 380 | 350 | 30 |
| 7 | 330 | 365 | -35 |
| 8 | 385 | 370 | 15 |
| 9 | 400 | 310 | 90 |
| 10 | 410 | 380 | 30 |
| 11 | 320 | 290 | 30 |
| 12 | 340 | 260 | 80 |
| 13 | 220 | 90 | 130 |

# Design of study



# The analysis model

$$y \sim f(x_{primary}, x_i)$$

$$PEF \sim f(treatment, subject)$$

- Both $x$-variables are categorical
- This is a paired t-test

# PEF data - revisited

**Mean:** 45.4

**SD:** 40.59

**Standard error:** $SE = \frac{SD}{\sqrt{n}} = \frac{40.59}{\sqrt{13}} = 11.26$

**95 % confidence interval for the difference:**

$$mean \pm 2 \cdot SE = [22.9; 67.9]$$

# Analysis of Variance (ANOVA)

- The $x$-variables are categorical
- The $x$-variable of primary interest has more than two levels
- Overall F-test for significance
- Pairwise tests for significance
- Analysis of means

# Linear regression

$$y \sim f(x_{primary}, x_i)$$

- All $x$-variables are continuous

# FEV1 in children - first 10 of 654 observations

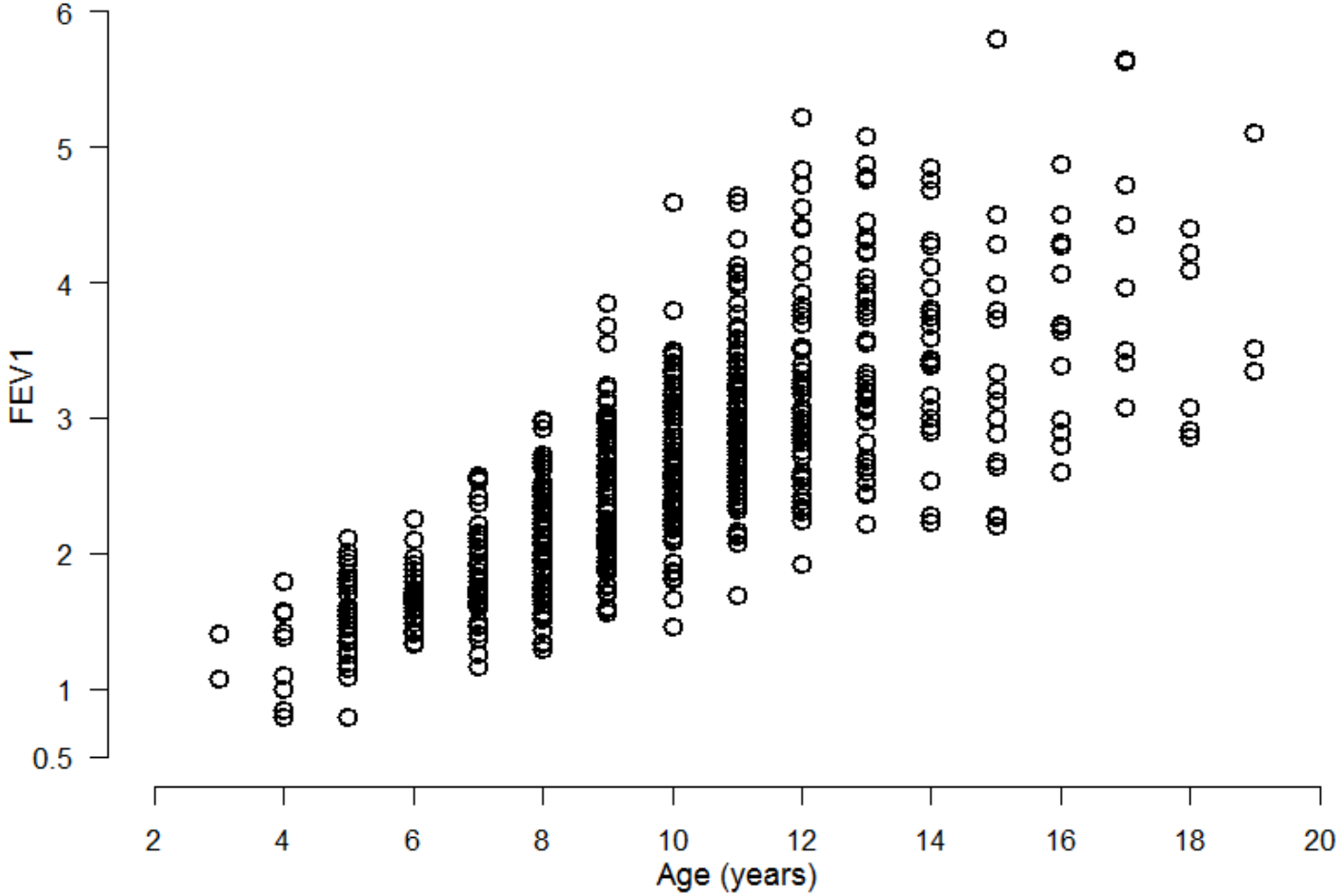
| ID | Age | FEV | Height | Sex | Smoker |
|---|---|---|---|---|---|
| 301 | 9 | 1.708 | 57 | Female | Non |
| 451 | 8 | 1.724 | 67.5 | Female | Non |
| 501 | 7 | 1.72 | 54.5 | Female | Non |
| 642 | 9 | 1.558 | 53 | Male | Non |
| 901 | 9 | 1.895 | 57 | Male | Non |
| 1701 | 8 | 2.336 | 61 | Female | Non |
| 1752 | 6 | 1.919 | 58 | Female | Non |
| 1753 | 6 | 1.415 | 56 | Female | Non |
| 1901 | 8 | 1.987 | 58.5 | Female | Non |
| 1951 | 9 | 1.942 | 60 | Female | Non |

# FEV1 in children - The influence of age

$$y \sim f(x_{primary}, x_i)$$

$$FEV1 \sim f(age)$$

# FEV1 in children - The influence of age



# FEV1 in children - The influence of age

```
summary(lm(FEV~Age,data=fev))

             Estimate  Std. Error  t value  Pr(>|t|)
(Intercept)  0.431648    0.077895    5.541  4.36e-08 ***
Age          0.222041    0.007518   29.533   < 2e-16 ***
```

# FEV1 in children - Descriptive statistics by smoking status

| | Non-smoker | Smoker |
|---|---|---|
| N | 589 | 65 |
| Mean | 2.57 | 3.28 |
| SD | 0.85 | 0.75 |
| Median | 2.47 | 3.17 |
| Min | 0.79 | 1.69 |
| Max | 5.79 | 4.87 |

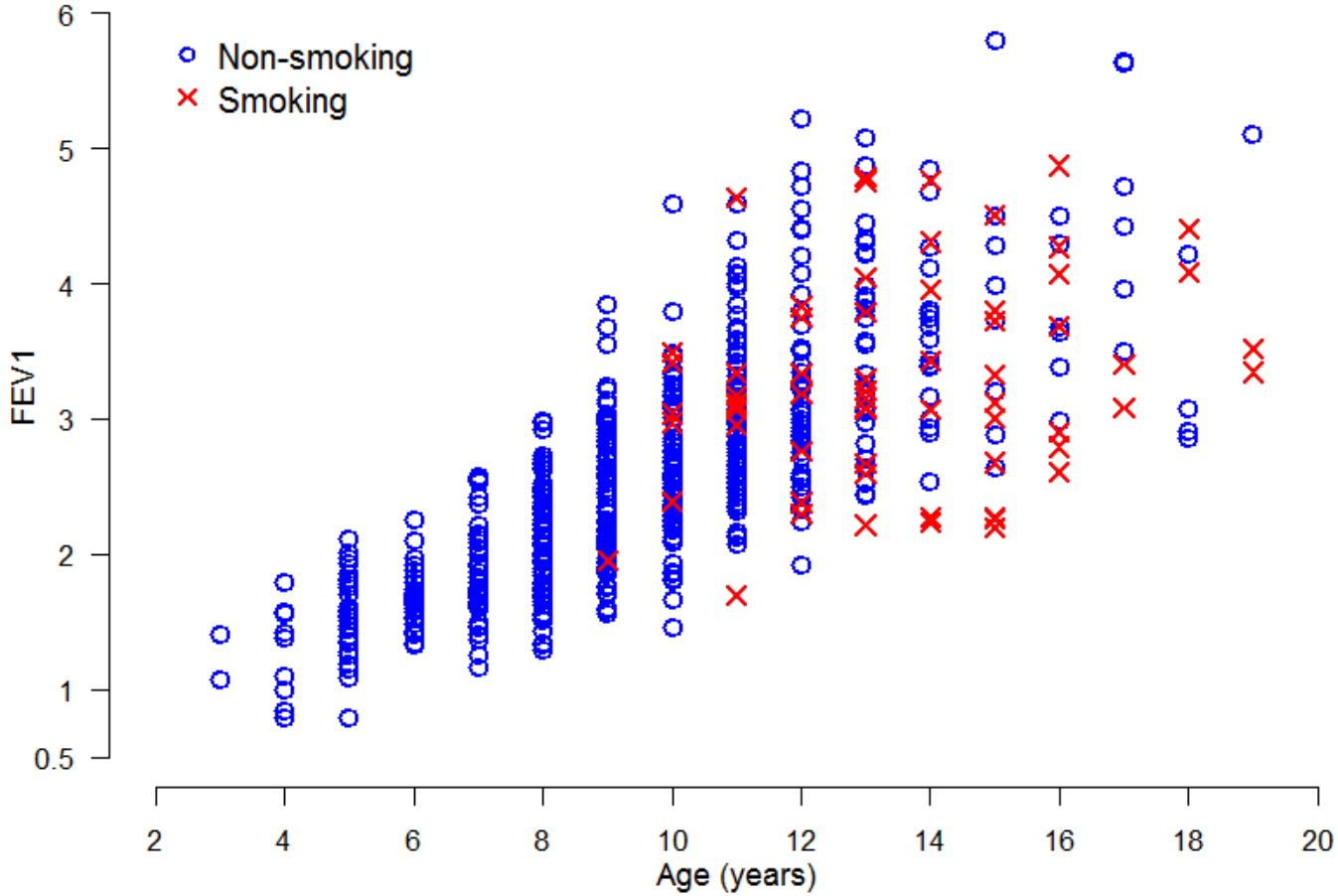
- Why do the smokers have higher lung capacity than non-smokers?
- Is it a chance finding?

# Analysis of Covariance (ANCOVA)

$$y \sim f(x_{primary}, x_i)$$

- Both continuous and categorical $x$-variables

# FEV1 in children - The influence of age and smoking status



# FEV1 in children - The influence of age and smoking status

```
summary(lm(FEV~Age+Smoker+Age:Smoker,data=fev))
```

```
                Estimate  Std. Error  t value  Pr(>|t|)
(Intercept)      2.19697     0.40596    5.412  8.78e-08 ***
Age              0.07986     0.02959    2.699   0.00713 **
SmokerNon       -1.94357     0.41428   -4.691  3.31e-06 ***
Age:SmokerNon    0.16270     0.03074    5.293  1.65e-07 ***
```

# What did we learn so far?

- For continuous outcomes the basic analysis model is the same
- Method of analysis named according to the types of *x*-variables (t-test, ANOVA, linear regression, ANCOVA)
- Ordinary least squares used for estimation
- Estimation of means, mean changes, mean differences
- The general linear model:
  $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$

# SAS terminology

- proc ttest, proc anova, proc reg
- The common procedure is proc glm

# Statistical analysis of binary outcomes

# Binary outcomes

- Two possible outcomes (e.g. dead/alive, response to treatment/no response)
- Could in general be coded as Y=0 or Y=1
- What about $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k$?
- We are interested in Prob(Y=1)
- The fitted Prob(Y=1) will be outside [0;1] for some combinations of x-variables
- Something needs to be done

# Logistic regression

Cox (1958), Walker and Duncan (1967):

$$Prob(Y = 1|X) = \frac{1}{[1 + \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k)]}$$

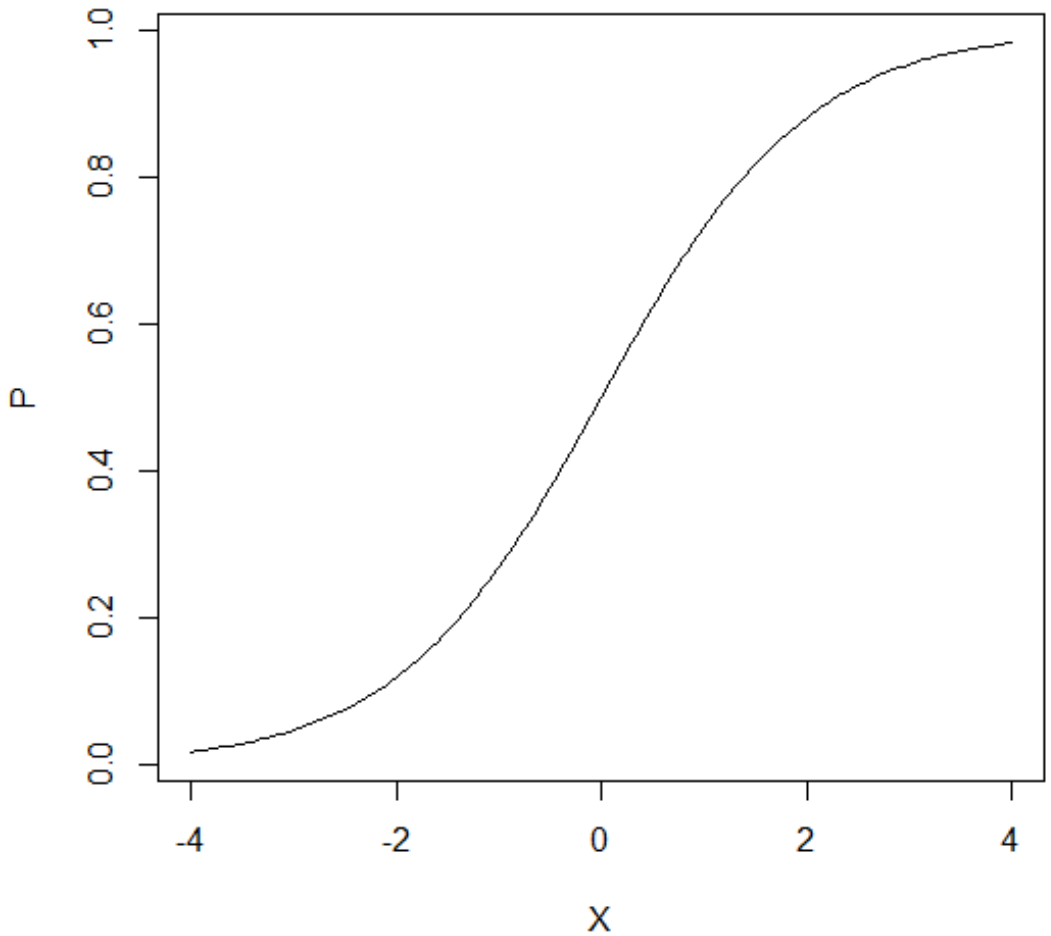
$$\begin{aligned} \text{logit}(Y = 1|X) &= \text{logit}(P) = \log(P/1 - P) = \log(\text{odds}) \\ &= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k \end{aligned}$$

A generalized linear model (in SAS: proc genmod, proc logistic)

D.R. Cox. The regression analysis of binary sequences (with discussion). Journal of the Royal Statistical Society B

S.H. Walker and D.B. Duncan. Estimation of the probability of an event as a function of several independent variables

# The logistic function



# Montgomery and Åsberg Depression Rating Scale (MADRS)

- MADRS: rating scale designed to assess the severity of depressive symptoms
- Based on a clinical interview
- Administered by trained psychiatrists
- MADRS total score is the sum of the score of the 10 individual items
- Symptoms rated on 7-point scales from 0 (no symptom) to 6 (severe symptom) with detailed anchor points
- MADRS total score goes from 0 to 60
- Response to treatment: at least 50 % reduction from baseline

# Two MADRS items

**1. Apparent sadness**

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

- ☐ 0 No sadness.
- ☐ 1
- ☐ 2 Looks dispirited but does brighten up without difficulty.
- ☐ 3
- ☐ 4 Appears sad and unhappy most of the time
- ☐ 5
- ☐ 6 Looks miserable all the time. Extremely despondent.

**4. Reduced sleep**

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

# Treatment response at week 8 in depression study

| | Responders | | | | |
|---|---|---|---|---|---|
| Treatment | N | n | (%) | OR [95% CI] | p-value |
| Placebo | 165 | 54 | (32.7) | | |
| Low dose | 174 | 88 | (50.6) | 2.10 [1.35 ; 3.27] | 0.0009 |
| High dose | 181 | 119 | (65.7) | 3.94 [2.52 ; 6.16] | <.0001 |

- Adjustment for treatment and MADRS total score at baseline
- $\beta_j$ is the change is log odds per unit change in $X_j$
- $\exp(\beta_j)$ is the relative change in odds, i.e. the odds ratio

# Probability and odds

- Probability is intuitive (range from 0 to 1)
- Odds are not intuitive (range from 0 to $\infty$)
- The probability of the event occurring divided by the probability of the event not occurring, i.e. $\text{probability}/(1 - \text{probability})$
- Probability of an event occurring is 0.05, then the odds of that event is $0.05/(1 - 0.05) = 0.053 = 1/19$

# Odds ratio and risk ratio

- Probability of outcome is 0.66 in treatment group one and 0.33 in the second treatment group
- Treatment effect: The first group is twice as likely to have the outcome as the second group

$$\text{RR} = \frac{p_1}{p_2} = 2$$

- Odds ratio = the ratio of two odds

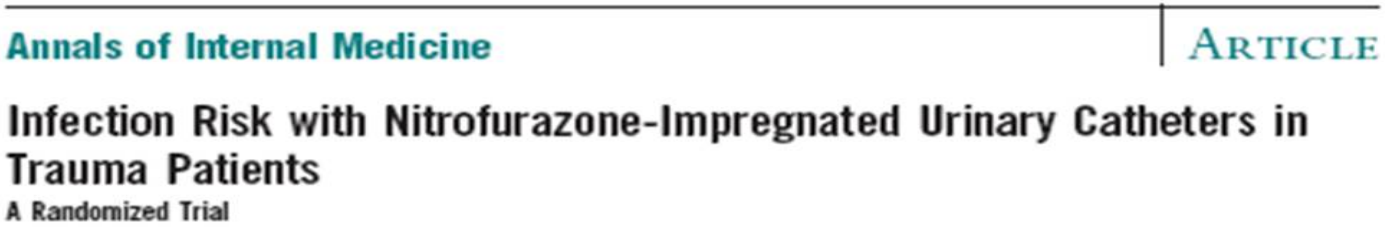
$$\text{OR} = \frac{p_1/1-p_1}{p_2/1-p_2} = \frac{p_1 \cdot (1-p_2)}{p_2 \cdot (1-p_1)} = \frac{0.66 \cdot (1-0.33)}{0.33 \cdot (1-0.66)} = 4$$

- Does not mean that the outcome is 4 times as likely in the first group as in the second group
- Odds of the outcome is 4 times higher in the first group than the second group

# Why is odds ratios so frequently reported?

- Estimated by logistic regression
- Logistic regression always produce probabilities in the range 0 to 1
- Odds have an unlimited range, and any positive odds ratio will still yield a valid probability (RR=2 can only apply to probabilities below 0.5)
- Convergence problems are rare with logistic regression

# Not all are happy about odds ratios




- A clinical trial to determine whether nitrofurazone-impregnated urinary catheters reduce the incidence of urinary tract infections in patients that were admitted directly from the accident scene to the Trauma Center in Copenhagen
- The primary endpoint was the proportion of patients developing an urinary tract infection after surgery
- Analyzed using a logistic regression model with treatment group and gender as explanatory factors
- Reviewer's comment: "We ask that you use log-binomial models because events were common, so ORs from a logistic regression model will overstate risk estimates"

# What is the problem?

- Risk ratios has a natural interpretation. The odds ratios has not
- Many examples of researchers misinterpreting the odds ratio as a risk ratio
- Holcomb et al. (2001) report that 26% of authors in top-tier medical journals explicitly misinterpret odds ratios as though they were risk ratios
- Thomas Lumley: *Most people don't have any feel for the meaning of an odds ratio (and those that do mostly can't communicate it to those who don't)*
- If the outcome is common ($> 10\%$ with event) the odds ratio becomes a poor approximation of the relative risk
- In this case the odds ratio overestimates the relative risk

# Example (Schulman et al., 1999)

Primary care physicians were shown videotaped interviews with an actor portraying a patient with chest pain, and given data on cardiac risk factors and results of thallium stress test. There were 18 scenarios, and each was portrayed by 8 actors (race $\times$ sex $\times$ age combinations). The outcome was whether the doctors recommended referral to cardiac catheterization.

| | Odds ratio 95 % CI |
|---|---|
| White | 1 |
| Black | 0.6 (0.4-0.9) |
| Men | 1 |
| Women | 0.6 (0.4-0.9) |

So the odds of referral were 40% lower for women than for men and for blacks than for whites.

# Example (Schulman et al., 1999)

**Nightline** "In our main analysis we found that blacks were 40 % less likely to be referred for cardiac catheterization compared to whites"

**USA Today** "Heart Care Reflects Race and Sex, not Symptoms"

**Washington Post** "Doctors are far less likely to recommend sophisticated cardiac tests for blacks and women than for white men with identical complaints"

**LA Times** "Authors suggest the differences are the consequences of race and sex bias"

**NY Times** "Doctors are only 60 % as likely to order cardiac catheterization for women and blacks as for men and whites"

# Example (Schulman et al., 1999)

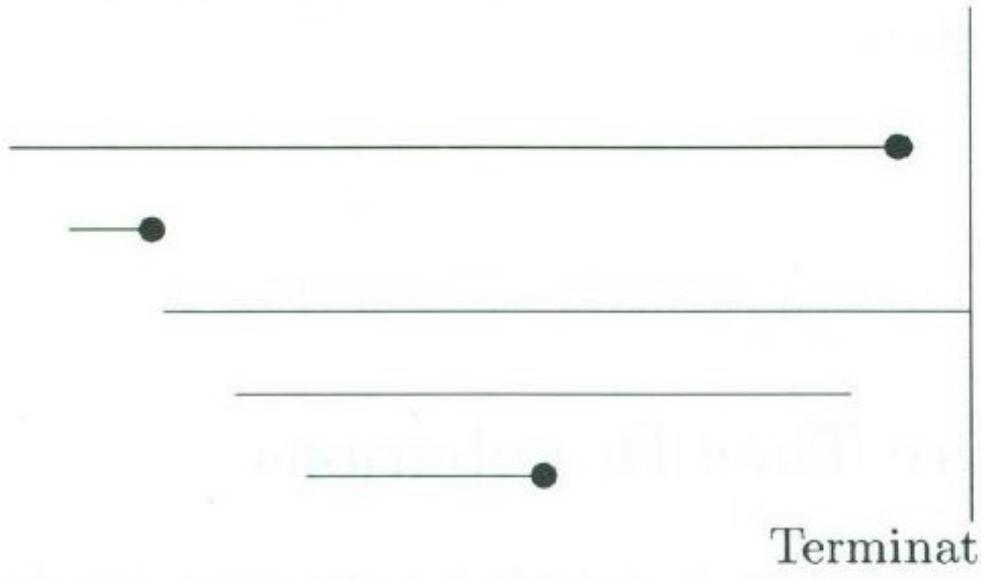
- After many readers pointed out that a relative risk of 0.93 isn't a 40 % reduction the New England Journal of Medicine and many of the news sources carried a revision of the story. The original article is still being cited as evidence of widespread and serious racial bias in medicine.
- This was a particularly public and embarrassing example, but the underlying problem is much more common.

# Statistical analysis of time-to-event outcomes

# Logistic regression or survival analysis?

- If time until the occurence of the event is not important $\longrightarrow$ binary endpoint $\longrightarrow$ logistic regression
- If time until the occurence of the event is important $\longrightarrow$ time until event endpoint $\longrightarrow$ survival analysis (Cox proportional hazards model)

# Censoring



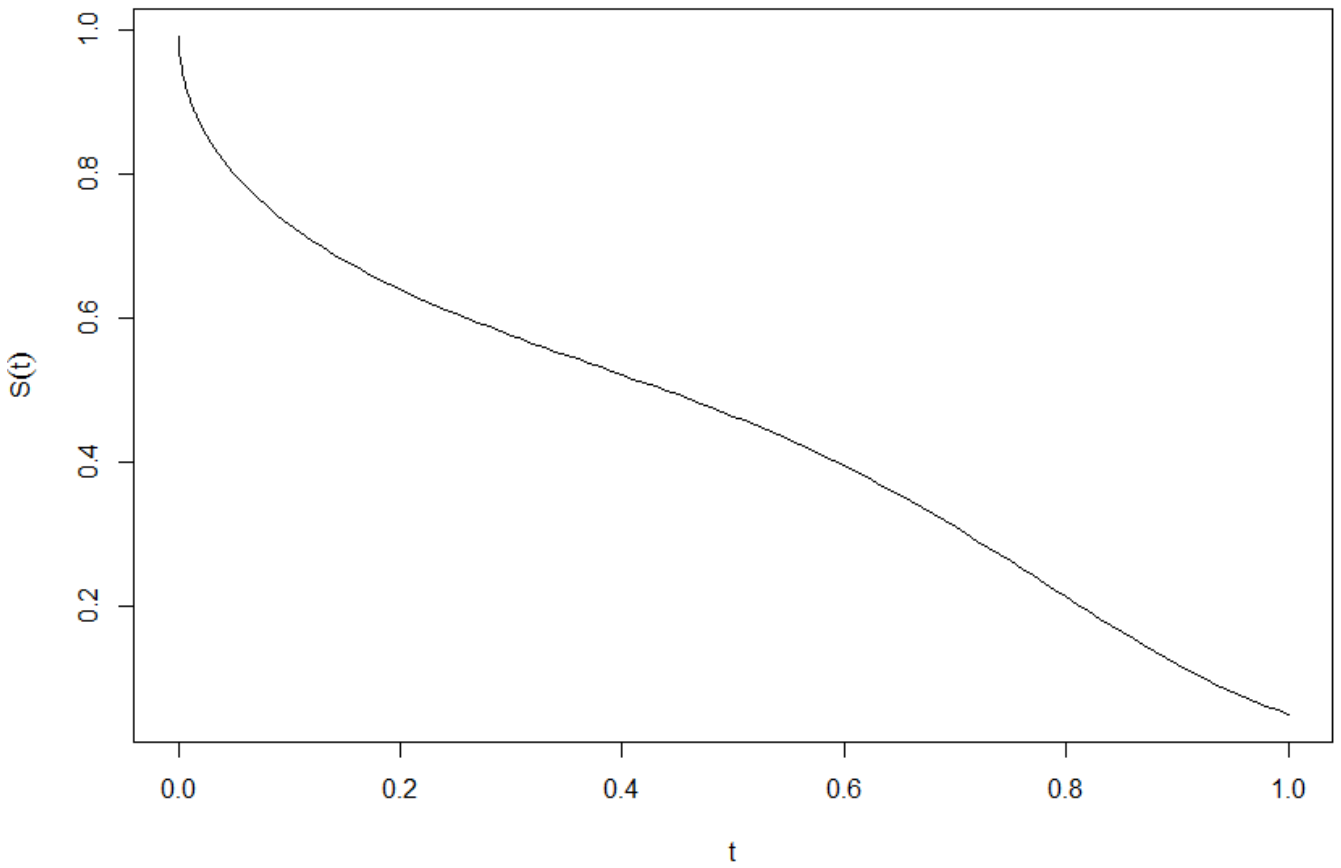

| $T_i$ | $C_i$ | $Y_i$ | $e_i$ |
|---|---|---|---|
| 75 | 81 | 75 | 1 |
| 7 | 76 | 7 | 1 |
| 68+ | 68 | 68 | 0 |
| 52+ | 52 | 52 | 0 |
| 20 | 56 | 20 | 1 |

- Censored data: The time to event is only known to exceed some time $t$
- No responses censored $\longrightarrow$ standard regression models could be applied

# Survival function

The probability that an event occurs after some time $t$:

$$S(t) = \text{Prob}\{T > t\}$$



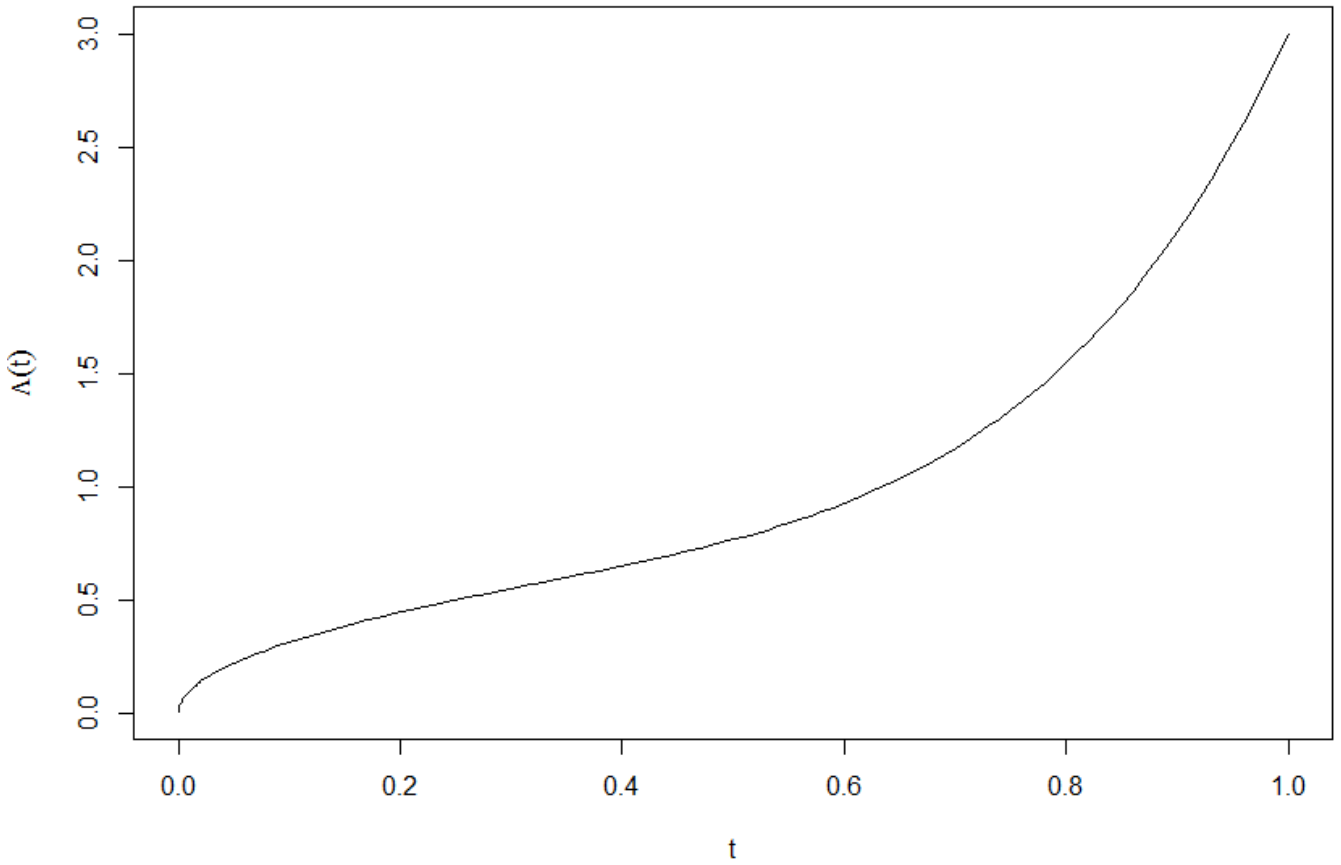
# Survival function

- $S(t) = 1$ for $t = 0$, i.e. all subjects survived at least to time zero
- $S(t)$ is nonincreasing as $t$ increases

- Very high risk of event in the beginning
- $S(t)$ flat for $0.1 \leq t \leq 0.6 \longrightarrow$ low risk of event
- For $t > 0.6$ the risk increases again

# Cumulative hazard function

Corresponding to survival function in previous slide

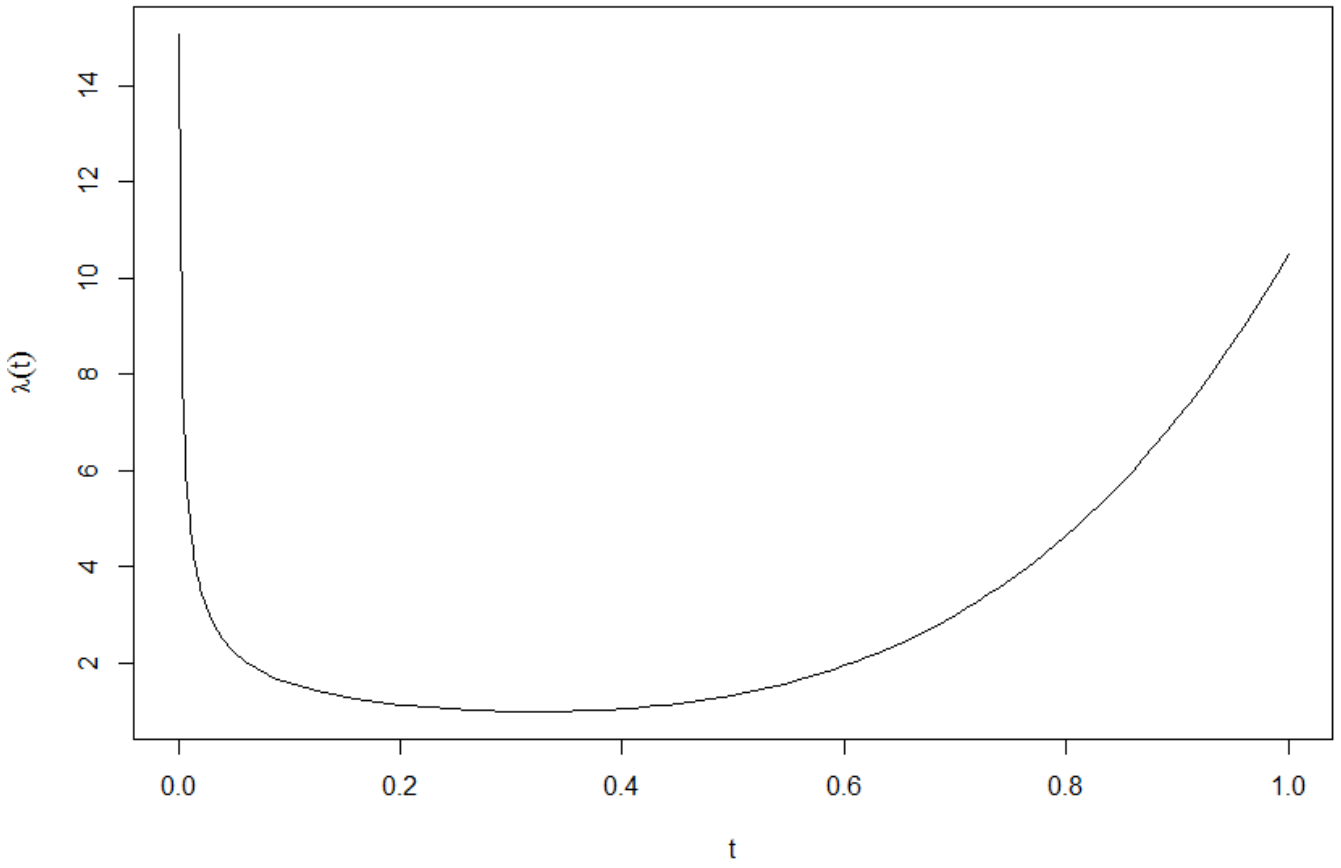


# Cumulative hazard function

- $\Lambda(t)$ describes the accumulated risk up until time $t$
- $\Lambda(t)$ is nondecreasing as $t$ increases
- $\Lambda(t) = -\log\{S(t)\}$

# Hazard function

Corresponding to survival function in previous slide



# Hazard function

- The hazard at time $t$ is the probability that the event will occur in a small interval around $t$ given that the event has not occurred before time $t$

# The Kaplan-Meier estimator

- Estimation of survival function $S(t)$
- $S_{km}(t) = \prod_{i:t_i<t}(1 - d_i/n_i)$
- $d_i$: number of events at time $t_i$
- $n_i$: number at subjects at risk at time $t_i$

# The Kaplan-Meier estimator

Event times: 1, 3, 3, $6^+$, $8^+$, 9, $10^+$

| $i$ | $t_i$ | $n_i$ | $d_i$ | $(n_i - d_i)/n_i$ |
|---|---|---|---|---|
| 1 | 1 | 7 | 1 | 6/7 |
| 2 | 3 | 6 | 2 | 4/6 |
| 3 | 9 | 2 | 1 | 1/2 |

$$
\begin{aligned}
S_{km}(t) &= 1, \quad 0 \leq t < 1 \\
&= 6/7 = 0.85, \quad 1 \leq t < 3 \\
&= (6/7)(4/6) = 0.57, \quad 3 \leq t < 9 \\
&= (6/7)(4/6)(1/2) = 0.29, \quad 9 \leq t < 10
\end{aligned}
$$

# The Cox proportional hazards model

Stated in terms of the hazard function:

$$\lambda(t|X) = \lambda(t)\exp(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k)$$

- No assumption about specific shape of $\lambda(t)$
- No interest in estimating it

# The Cox proportional hazards model

- The form of the true hazard is unknown $\longrightarrow$ Cox PH does not assume any particular form for the hazard function
- The form of the true hazard is usually not of primary interest $\longrightarrow$ Cox PH allows the analyst to ignore the hazard function
- In the Cox PH the explanatory variables are linearly related to the hazard function
- Hazard ratio = risk ratio obtained by exponentiating parameter estimates
- The survival functions for subjects with different values of $X$ are powers of each other

# Evaluating the proportional hazards assumption

Three graphical approaches:

- Plot survival curves for different levels of an explanatry variable $X$. The curves should not cross each other at any point in time
- Plot the cumulative hazard functions for different levels of an explanatory variable $X$. For all time points one should get from the lower curve to the upper by multiplication with the same constant: $\Lambda(level1) = C \cdot \Lambda(level2)$.
- Plot the logarithm of the cumulative hazard functions for different levels of an explanatory variable $X$. The curves should be parallel, i.e. for all time points one should get from the lower curve to the upper by adding the same constant: $\log(\Lambda(level1)) = C + \log(\Lambda(level2))$.

# Night shift work and incidence of diabetes in the Danish Nurse Cohort

Objective:

- To study the association between shift work and incidence of diabetes in Danish nurses

Methodology:

- Data from the Danish Nurse Cohort with 28731 participating female nurses recruited in 1993 (19898) or 1999 (8833)
- Self-reported baseline information on diabetes prevalence, lifestyle and working time
- Self-reported whether they worked night, evening, rotating or day shifts
- Followed-up in the Danish Diabetes Register for incidence of diabetes until 2013
- The association between working time and diabetes incidence was analysed using a Cox proportional hazards model adjusted for diabetes risk factors, separately with and without adjustment for body mass index (BMI) which might be an intermediate variable
- 19873 nurses worked and were diabetes-free at recruitment

# Night shift work and incidence of diabetes in the Danish Nurse Cohort

| | Total N=19 837 | No diabetes N=19 000 | Diabetes N=837 |
|---|---|---|---|
| Person-years | 308 078 | 298 541 | 9536 |
| Baseline age, mean (SD) | 51.4 (5.4) | 51.4 (5.3) | 53.6 (5.8) |
| Shifts | | | |
| Day shifts, n (%) | 12 414 (62.4) | 11 905 (62.6) | 509 (58.3) |
| Evening shifts, n (%) | 2022 (10.1) | 1918 (10.1) | 104 (11.9) |
| Night shifts, n (%) | 1098 (5.5) | 1014 (5.3) | 84 (9.6) |
| Rotating shifts, n (%) | 4339 (21.8) | 4163 (21.9) | 176 (20.1) |
| BMI | | | |
| Underweight (<18.5 kg/m$^2$), n (%) | 401 (2.0) | 393 (2.1) | 8 (0.9) |
| Normal (18.5–25 kg/m$^2$), n (%) | 14 124 (71.0) | 13 775 (72.5) | 349 (39.9) |
| Overweight (25–30 kg/m$^2$), n (%) | 4320 (21.7) | 3991 (21.0) | 329 (37.7) |
| Obese (>30 kg/m$^2$), n (%) | 1028 (5.1) | 841 (4.4) | 187 (21.4) |
| Smoking status | | | |
| Never smoked, n (%) | 7185 (36.1) | 6891 (36.2) | 294 (33.7) |
| Currently smoker, n (%) | 6854 (34.4) | 6501 (34.2) | 353 (40.4) |
| Previously smoked, n (%) | 5834 (29.3) | 5608 (29.5) | 226 (25.9) |
| Smoking intensity* (g/day), mean (SD) | 7.7 (9.0) | 7.6 (8.9) | 9.4 (10.2) |
| Alcohol consumption (g/week), mean (SD) | 119.5 (125.8) | 119.7 (124.8) | 116.0 (144.6) |

# Night shift work and incidence of diabetes in the Danish Nurse Cohort

| | | | |
|---|---|---|---|
| Physical activity | | | |
| Low, n (%) | 1057 (5.3) | 972 (5.1) | 85 (9.8) |
| Medium, n (%) | 13 105 (65.9) | 12 510 (65.9) | 595 (68.1) |
| High, n (%) | 5711 (28.7) | 5518 (29.0) | 193 (22.1) |
| Consume vegetables and fruit regularly, n (%) | 19 452 (97.8) | 18 601 (97.9) | 849 (97.2) |
| Avoid fatty meat, n (%) | 18 097 (91.0) | 17 337 (91.2) | 760 (87.0) |
| Hypertension, n (%) | 1970 (9.9) | 1734 (9.1) | 236 (27.1) |
| AMI, n (%) | 60 (0.3) | 54 (0.3) | 6 (0.7) |
| Employment status | | | |
| Employed, n (%) | 19 725 (99.2) | 18 873 (99.3) | 852 (97.5) |
| Retired, n (%) | 99 (0.5) | 83 (0.4) | 16 (1.8) |
| Unemployed, n (%) | 6 (0.03) | 5 (0.03) | 1 (0.11) |
| In rehabilitation, n (%) | 43 (0.2) | 39 (0.2) | 4 (0.4) |
| Marital status | | | |
| Married, n (%) | 14 827 (74.6) | 14 218 (74.8) | 609 (69.7) |
| Separated, n (%) | 359 (1.8) | 345 (1.8) | 14 (1.6) |
| Divorced, n (%) | 2319 (11.6) | 2197 (11.5) | 122 (13.9) |
| Unmarried, n (%) | 1553 (7.8) | 1471 (7.7) | 82 (9.3) |
| Widow, n (%) | 815 (4.1) | 769 .0) | 46 (5.2) |

*In ever smokers.
AMI, acute myocardial infarction; BMI, body mass index.

# Night shift work and incidence of diabetes in the Danish Nurse Cohort

| Work shift | Person years<br>Years | Cases<br>N | Crude* model<br>HR (95% CI) | Fully adjusted† model<br>HR (95% CI) | Fully adjusted† model+BMI<br>HR (95% CI) |
|---|---|---|---|---|---|
| Day shifts | 193 624 | 509 | 1.00 | 1.00 | 1.00 |
| Evening shifts | 31 619 | 104 | 1.24 (1.01 to 1.53) | 1.21 (0.98 to 1.50) | 1.29 (1.04 to 1.59) |
| Night shifts | 17 118 | 84 | 1.84 (1.46 to 2.31) | 1.73 (1.37 to 2.19) | 1.58 (1.25 to 1.99) |
| Rotating shifts | 65 716 | 176 | 1.04 (0.87 to 1.23) | 1.06 (0.89 to 1.26) | 1.08 (0.91 to 1.28) |

*Adjusted for age.
†Adjusted for age, smoking status, smoking intensity, physical activity, alcohol consumption (g/week), intake of fatty meat, marital status, employment status, acute myocardial infarction, hypertension, fruit and vegetables intake.
BMI, body mass index.

# Poisson Regression

# Statistical models for different outcomes

- The General Linear Model for continuous outcomes
- Logistic regression for binary outcomes
- Cox proportional hazards model for time-to-event outcomes
- Poisson regression for count data

# The Poisson regression model

Count data given by a rate:

$$\log(\mu/t) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

- $\mu$: expected number of events
- $t$: length of time at risk

$$\begin{aligned} \log(\mu) - \log(t) &= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k \Longrightarrow \\ \log(\mu) &= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + \log(t) \end{aligned}$$

- Modelling the number of events
- $\log(t)$: offset. Allows for different time at risk for each subject

# Effect of drug treatment on exacerbation rate in patients with COPD

Objective:

- Investigate the effect of drug treatment on exacerbation rate and pulmonary function in patients with chronic obstructive pulmonary disease (COPD)

Methodology:

- Primary endpoint: Mean rate of moderate to severe COPD exacerbations per patient per year
- Secondary endpoint: Time to first COPD exacerbation
- Active drug versus placebo
- Analysis of primary endpoint: Poisson regression model with adjustment for treatment, age, sex, smoking status, concomitant treatment with LABA, country and baseline post-bronchodilator FEV1
- Analysis of secondary endpoint: Cox proportional hazards model with adjustment for treatment, age, sex, smoking status, concomitant treatment with LABA and country

# Results

## Primary endpoint:

| Active | | Placebo | | Ratio Active/placebo | | |
|---|---|---|---|---|---|---|
| N | Rate [95% CI] | N | Rate [95% CI] | Risk ratio [95 % CI] | Change (%) | p-value |
| 772 | 1.210 [1.074 ; 1.364] | 796 | 1.485 [1.333 ; 1.655] | 0.815 [0.710 ; 0.935] | -18.5 | 0.0035 |

## Secondary endpoint:

| Active | Placebo | Patients with event | | | | Cox PH model | |
|---|---|---|---|---|---|---|---|
| n | n | Active | % | Placebo | % | HR [95 % CI] | p-value |
| 772 | 796 | 373 | 48.3 | 432 | 54.3 | 0.894 [0.778 ; 1.027] | 0.1132 |

# Poisson regression versus the Cox proportional hazards model

- For time to first event a Poisson model can be formulated to give similar results as the Cox proportional hazards model (the situation in which each cell of the cross-classification of person-time and events includes a single event)
- The Poisson model gives interpretable rate estimates by group
- No proportional hazards assumption for the Poisson model
- The Poisson model can handle subjects switching from exposed to not-exposed and vice versa several times in the study

# Poisson regression versus the Cox proportional hazards model

**Table 3** Comparison of estimated regression beta coefficients* and standard errors for brain cancer and cumulative magnetic field exposure in the electrical worker cohort

| | Ungrouped Poisson | Proportional hazards | Grouped Poisson | |
|---|---|---|---|---|
| Model | β (SE) | β (SE) | β† (SE) | β‡ (SE) |
| Model 1: age, exposure | 0.0842 (0.0375) | 0.0842 (0.0375) | 0.1483 (0.0503) | 0.1123 (0.0392) |
| Model 2: age, calendar time, race, exposure | 0.0910 (0.0380) | 0.0910 (0.0380) | 0.1479 (0.0508) | 0.1183 (0.0396) |