ISCB 2009

Estimating the Number Needed to Treat with Adjustment for Balanced Covariates in Clinical Trials

Ralf Bender, Volker Vervölgyi

Institute for Quality and Efficiency in Health Care (IQWiG), Cologne

Outline

- Introduction of NNTs
- ARD approach for adjusted NNTs
- Application in RCTs
- Simulation study
- Example: Mortality of fruit flies
- Summary
- References

Introduction

- NNT = Number Needed to Treat
- Average number of patients needed to be treated to prevent an adverse outcome in one patient
- Inverse of a risk difference (RD)
- Laupacis, Sackett & Roberts (1988)
- Cook & Sackett (1995)
- Recommended for presentation of results of RCTs (CONSORT)

Properties

- NNT scale: 2 areas (values between –1 and 1 impossible!)

  Benefit: [1,∞[, Harm:]–∞,–1]
- Practice: NNTs are estimated from data
- Documentation of estimation uncertainty via confidence intervals (CIs)
- Important: NNT scale has to be taken into account
- NNT presentation with direction of effect:

  e.g.: NNTB=7 (95%-KI: NNTB 3 to ∞ to NNTH 12)

  where

  NNTB = NNT for 1 patient to benefit

  NNTH = NNT for 1 patient to be harmed

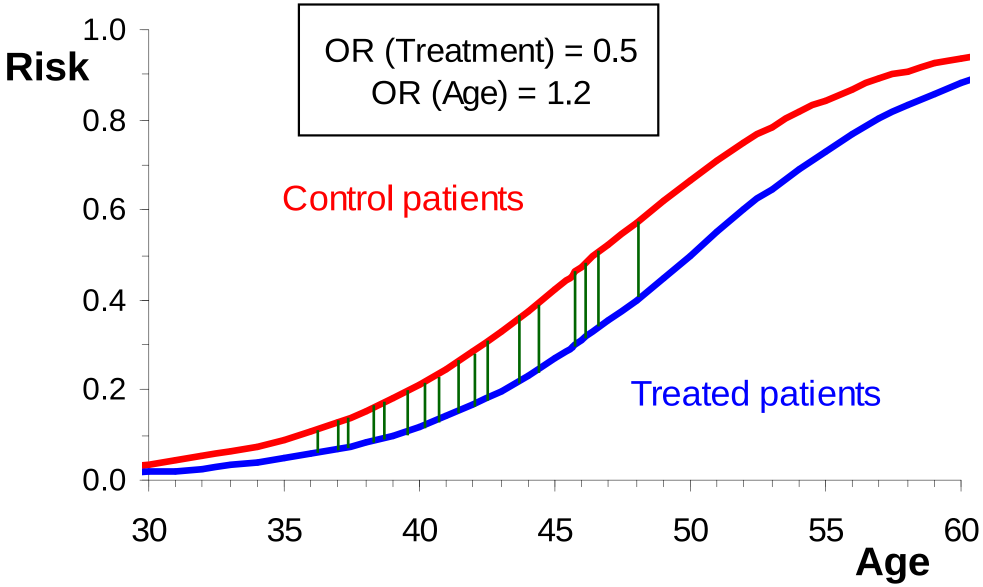
Application in Epidemiology

- RCTs:
  Crude estimation frequently sufficient
  (but not always!)
- Epidemiology:
  Confounding in most cases

⇒ Adjustment for confounders required

- Average risk difference (ARD) approach
  (Bender et al. 2007, Austin 2009, Bender & Kuss 2009)
- Main principle:
  - Estimate the risk difference via logistic regression
  - Average over appropriate population

Adjusted NNT Statistics in RCTs



ARD:

- **Appropriate population: All patients**
- **ARD for all observed patients: NNT = 1/ARD**

☞ **If patients are randomized to treatment or control: No confounding**

Confidence Intervals

- Indirect via CIs for risk difference
- ARD non-linear function of logistic regression coefficients
- Covariance matrix of estimated regression coefficients (e.g. via PROC LOGISTIC)
- Approximate confidence intervals for adjusted NNTs by means of the delta method (Bender et al. 2007)
- Alternative: Bootstrapping (Austin 2009)

Previous Results

Linear Regression

Adjustment for balanced covariates leads to

- No effect on expected value
- Gain of precision

Logistic Regression

(Robinson & Jewell 1991, Negassa & Hanley 2007)

Adjustment for balanced covariates leads to

- Correction of attenuation bias
- Loss of precision of parameter estimation
- Increase of study power to test for treatment effect

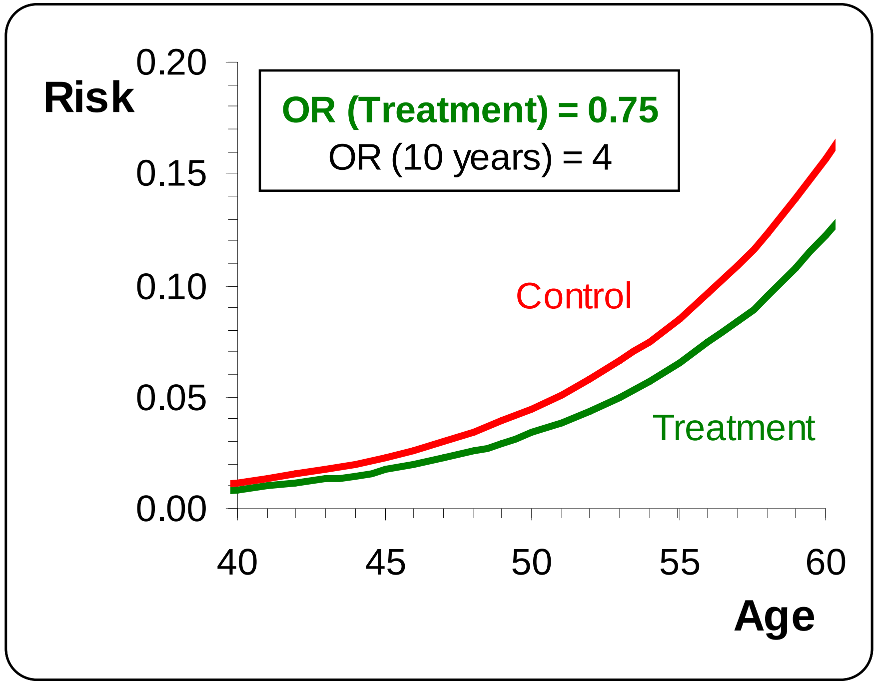
☞ Results hold for estimates of regression coefficient (i.e. OR in logistic regression)

☞ Effect of adjustment for RD and NNT ?

Simulation Study

Data Situations

- **RCT; n = 200 / 2000 / 10000; Age ~ N(50, σ²), σ = 2 / 5 / 10**
- **OR(Treat) = 0.5 / 0.75 / 0.9; OR(Age) = 2 / 4 / 8 ;**
- **3 baseline risks; 10000 simulation runs**
- **(Only a small part of the results is shown here)**



Simulation Study: Results

Results for log(OR)

We confirmed the results that adjustment for balanced covariates leads to

- **Correction of attenuation**
- **Loss of precision**

Simulation Study: Results

Relative Bias (MPE) of RD (crude / adjusted)

Sample size	Small risk (≈0.1)				Large risk (≈0.5)			
	Cov OR=2		Cov OR=8		Cov OR=2		Cov OR=8	
	SD=2	SD=10	SD=2	SD=10	SD=2	SD=10	SD=2	SD=10
Small treatment effect (OR=0.9)								
200	9.8 / **10**	4.5 / 3.8	2 / 3.1	1.2 / 1.1	-3.8 / -3.5	-1.3 / -1	-2.2 / -1.6	7.7 / 5.2
2000	-1.5 / -1.5	-0.1 / -0.1	-1.5 / -1.5	3.8 / 3.2	0.2 / 0.2	-0.1 / -0.1	-0.2 / 0	-0.4 / 0.2
10000	0.8 / 0.8	-0.6 / -0.9	-0.4 / -0.2	1.2 / 0.9	0.1 / 0.1	-0.3 / -0.2	0.2 / 0.1	-0.5 / -0.3
Large treatment effect (OR=0.5)								
200	-0.7 / -0.6	-0.5 / -0.6	0.8 / 0.8	0.3 / 0.3	-0.1 / -0.1	0.8 / 0.6	-0.7 / -0.6	0.3 / 0.8
2000	0.7 / 0.7	0.5 / 0.4	-0.2 / -0.2	-0.2 / -0.2	0.1 / 0.1	0 / 0	-0.1 / -0.1	0.3 / 0.1
10000	0 / 0	0 / 0	0 / 0	-0.1 / -0.1	0 / 0	-0.1 / -0.1	0 / 0	0.1 / 0.2

☞ **Adjustment has no relevant effect on the (negligible) bias of absolute effect estimation**

Simulation Study: Results

Precision (SE) of RD (adj-crude/crude ×100)

Sample size	Small risk (≈0.1)				Large risk (≈0.5)			
	Cov OR=2		Cov OR=8		Cov OR=2		Cov OR=8	
	SD=2	SD=10	SD=2	SD=10	SD=2	SD=10	SD=2	SD=10
Small treatment effect (OR=0.9)								
200	0.1	-1.7	-0.5	**-19.3**	0	-4.9	-1.2	**-22.2**
2000	-0.1	-2.3	-0.8	**-19.6**	-0.2	-4.9	-2.2	**-22.7**
10000	-0.1	-2.2	-0.7	**-20.3**	-0.3	-4.9	-2.2	**-23.2**
Large treatment effect (OR=0.5)								
200	0.2	-0.6	-1.5	**-18.5**	-0.2	-4.7	-1.8	**-22.3**
2000	-0.1	-2.1	-0.6	**-19.0**	-0.2	**-5.0**	-1.8	**-22.9**
10000	0	-1.9	-0.8	**-19.7**	-0.2	-4.1	-2.3	**-22.7**

☞ **Adjustment leads to a GAIN in precision for absolute effect estimation**

Simulation Study: Results

Further Results

- Coverage probability close to 95% in all cases (crude and adjusted estimation of RD and NNT)
- Power of treatment effect in almost all cases higher in the adjusted analysis
- Considerable gain in power only in the case of a very strong predictor

Example: Fruit Flies

- Sexual activity and mortality of male fruit flies (Hanley & Shapiro 1994, Negassa & Hanley 2007)
- Original experiment: 5 randomized groups
- Only 2 groups used here:
  - Intervention group (n=25): 1 receptive female fly every 2 days
  - Control group (n=25): 1 newly inseminated female fly every 2 days
  - Study duration: about 100 days (all male flies deceased)
  - Binary outcome: mortality within 60 days (mortality rate about 50%)
  - Strong predictor: thorax length

Example: Fruit Flies

- Thorax length represents balanced covariate:
  - IG: mean 0.84 mm (SD=0.07)
  - CG: mean 0.83 mm (SD=0.07)
- Events: IG: n=17 (68%), CG: n=10 (40%)
- Crude analysis:
  - OR=3.2 (95% confidence interval: 0.99 to 10.2)
  - Fisher test: $p = 0.088$, logistic regression: $p = 0.0502$
  - RD = 0.28 (SE=0.1353), 95% CI: 0.015 to 0.55
  - NNT = 3.6, 95% CI: 1.8 to 67.4
- Adjusted analysis:
  - OR=6.2 (95% confidence interval: 1.4 to 27.5), $p = 0.004$
  - RD = 0.32 (SE=0.113), 95% CI: 0.102 to 0.55
  - NNT = 3.1, 95% CI: 1.8 to 9.8

☞ **In adjusted analysis SE(RD) 16.5% smaller**

Summary

- NNTs useful to present study results
- ARD approach required in epidemiology for estimation of adjusted NNT measures to take confounding into account
- In RCTs with balanced covariates ARD approach leads to gain in precision of absolute effect measures (risk difference, NNT)
- In RCTs ARD approach useful especially in the case of strong predictors
- The need to adjust for important covariates should be considered in the design and analysis of RCTs

References

- Austin, P.C. (2009): Absolute risk reductions, relative risks, relative risk reductions, and numbers needed to treat can be obtained from a logistic regression model. *J. Clin. Epidemiol.* **62** (in press).
- Bender, R. & Kuss, O. (2009): Methods to calculate relative risks, risk differences, and numbers needed to treat from logistic regression (Letter). *J. Clin. Epidemiol.* **62** (in press).
- Bender, R., Kuss, O., Hildebrandt, M. & Gehrmann, U. (2007): Estimating adjusted NNT statistics in logistic regression analysis. *Stat. Med.* **26,** 5586-5595.
- Cook, R.J. & Sackett, D.L. (1995): The number needed to treat: A clinically useful measure of treatment effect. *BMJ* **310**, 452-454.
- Hanley, J.A. & Shapiro, A.P. (1994): Sexual activity and the lifespan of male fruitflies: A dataset that gets attention. *J. Stat. Educ.* **2**, 1.
- Laupacis, A., Sackett, D.L. & Roberts, R.S. (1988): An assessment of clinically useful measures of the consequences of treatment. *N. Engl. J. Med.* **318**, 1728-1733.
- Negassa, A. & Hanley, J.A. (2007): The effect of omitted covariates on confidence interval and study power in binary outcome analysis: A simulation study. *Contemp. Clin. Trials* **28**, 242-248.
- Robinson, L.D. & Jewell, N.P. (1991): Some surprising results about covariate adjustment in logistic regression models. *Int. Stat. Rev.* **59**, 227-240.