Time Dependent Exposure in Case-Control Studies

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Outline

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Motivation

- Time-dependent exposures and covariates are common in epidemiological studies
- Many examples – smoking status, medication use, blood pressure, lipid levels, etc.
- Case-control studies and logistic regression are not designed to deal with time-dependent exposure – may lead to bias
- Cox-models not designed for case-control studies

Example: Statins and AD

- Retrospective studies have shown protective effects for statins with respect to AD and Dementia (Wolozin et. al, Jick et. al., Rockwood, et. al.)
- Analysis from ACT cohort study (To appear, Li et. al.) shows no protective effect (RR=0.9 - TD Cox model)
- Naïve analysis ignoring TD exposure with age adjusted logistic regression shows a protective effect (OR = .5)
- Why? Not accounting for TD of exposure over-counts exposure, therefore underestimates RR (or OR)

A Simple TD Exposure Model

Exponential Model: λ_1 unexposed rate of disease
λ_2 exposed rate of disease

Relative Risk: λ_2/λ_1

Event times, t_i: d=1 time of disease incidence
d=0 time of last follow-up

Exposure time e_i, for those exposed

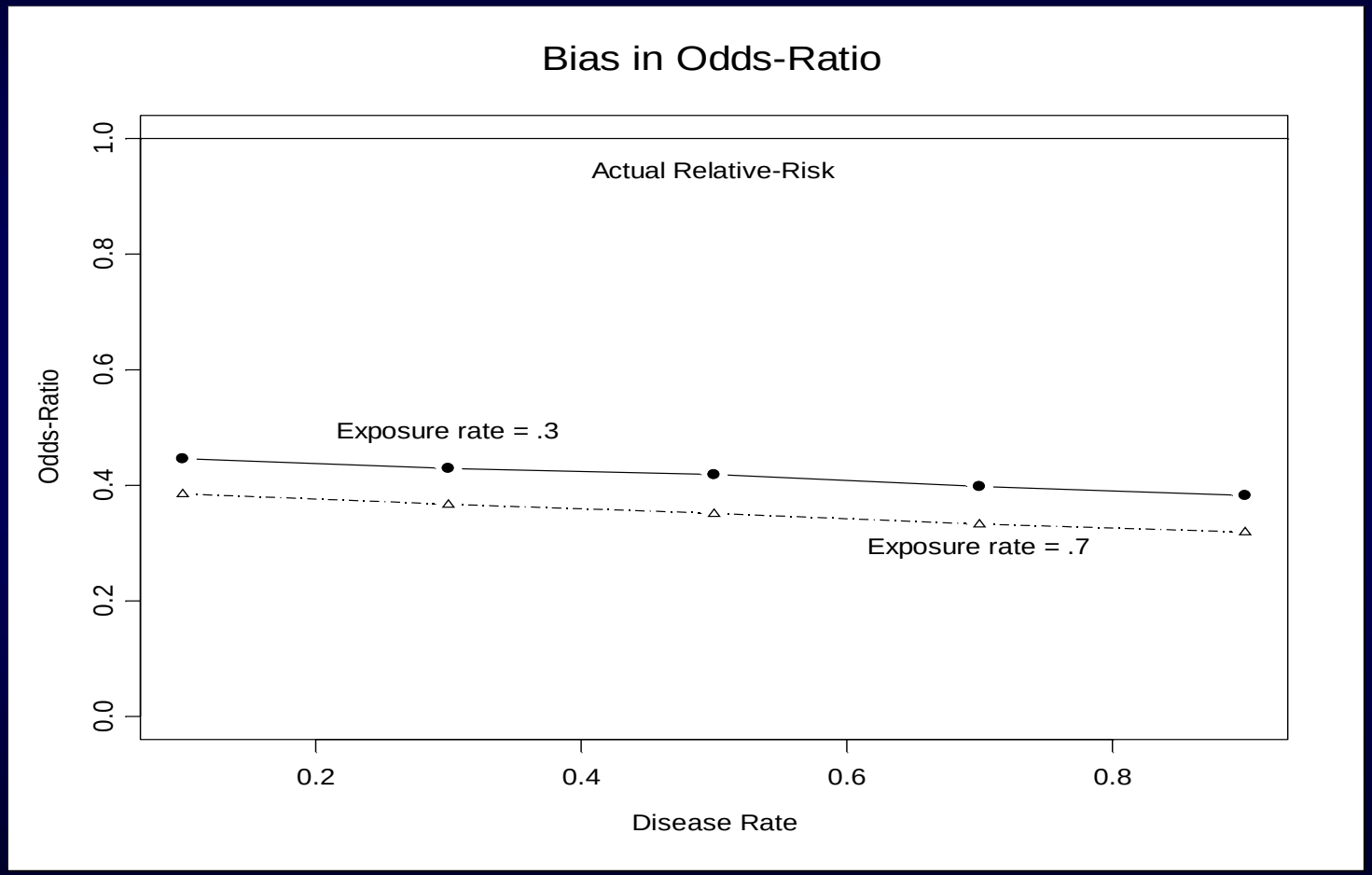
MLE: $\lambda_1 = \Sigma_{UE} d/(\Sigma_{UE} t + \Sigma_{EX} e)$

$\lambda_2 = \Sigma_{EX} d/\Sigma_{EX} (t - e)$

Naïve: OR = (Odds d=1, EX)/(Odds d=1, UE)

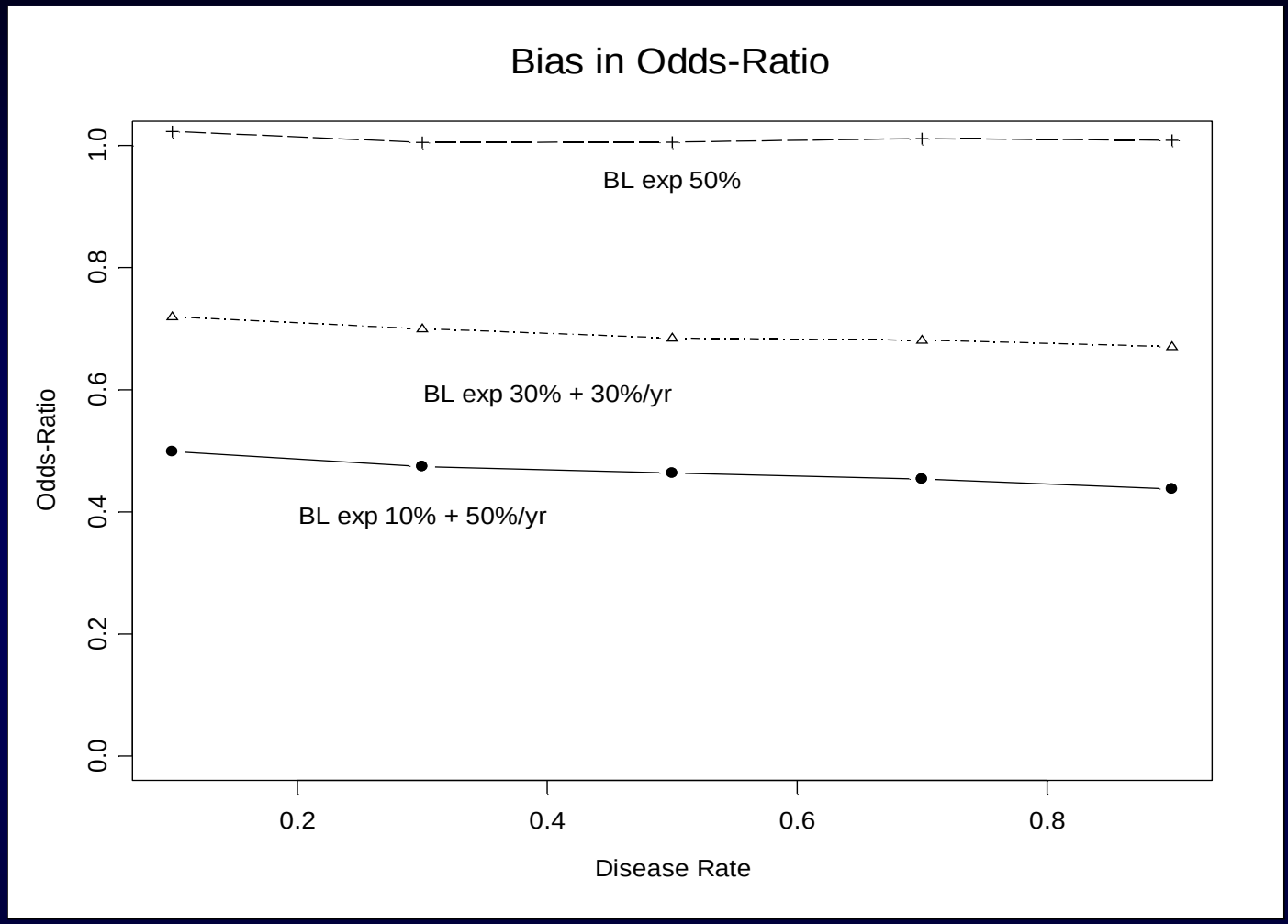
Bias of Naïve Estimator

No baseline exposure, N=1000, RR=1, 1-year follow-up



Notes about bias

- Bias approximately 50% or more of RR or more if exposure occurs after baseline
- Bias depends little on disease rate, exposure rate and what the actual RR is.
- Bias does not depend on sample size
- Bias decreases as amount of baseline exposure increases


Bias in Odds-Ratio
Odds-Ratio
0.0
0.2
0.4
0.6
0.8
1.0
BL exp 50%
BL exp 30% + 30%/yr
BL exp 10% + 50%/yr
0.2
0.4
0.6
0.8
Disease Rate

Methods for TD Exposure

- Nested Case-Control Studies (Prentice and Breslow, 1978; Langholz and Goldstein 1996)
  - Match controls to each case based on time (age) of onset for case
  - Controls should be a random sample of all subjects in the cohort at risk for disease at that time (age)
  - Exposure in controls should be ignored beyond matching time(age)
  - Conditional logistic regression can be used for analysis

- Case-Cohort Studies (Prentice, 1986; Barlow et.al 1999)
  - Take a random sample of a cohort
  - Measure exposure on the random sample and all cases in cohort
  - Analysis based on modification of Cox models.
  - Cases from outside the random sample not included in risk sets except at time of incidence
- Neither designed for Case-control studies
  - Cases excluded as controls prior to onset
  - Lubin and Gail, 1984 and Greenland and Thomas, 1982 show bias in estimates for case control sampling
  - Chen and Lo, 1999 and Chen, 2001 modify methods for case-control if overall prevalence of cases in cohort is known

Comparison of Estimators

All cases and random sample of controls (equal to number of cases) from the previously used exponential model, Exposure rate = 50%/year

RR	Disease Rate	Naïve CC est.	MLE for cohort	Nested CC est.	Case-cohort
1.0	0.1	0.42	1.14	1.09	1.10
	0.3	0.40	1.09	1.03	1.06
0.5	0.1	0.21	0.65	0.53	0.54
	0.3	0.20	0.60	0.49	0.51
2.0	0.1	0.86	1.96	2.22	2.32
	0.3	0.85	1.97	2.28	2.44

Additional Comments

- Both the case-cohort and nested (matched) case-control method worked well in example
- Lubin and Gail showed they are biased, and bias is worse with higher prevalence, bigger RR's, and is not based on TD exposure
- Case-cohort estimator can be estimated with Cox model software but need custom variance estimates
- Have not addressed how inference may be effected by the situations

Conclusions

- Issue of time dependent exposure needs to be addressed in case-control studies
- Case-cohort and nested case-control methods may be reasonable to apply to these situations
- Further study may be warranted as to when and when not to use these estimators
- Work needs to be done on how whether modifications for case-control sampling can be applied to specific situations