Classification of exposure and outcome

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Conflict of Interest

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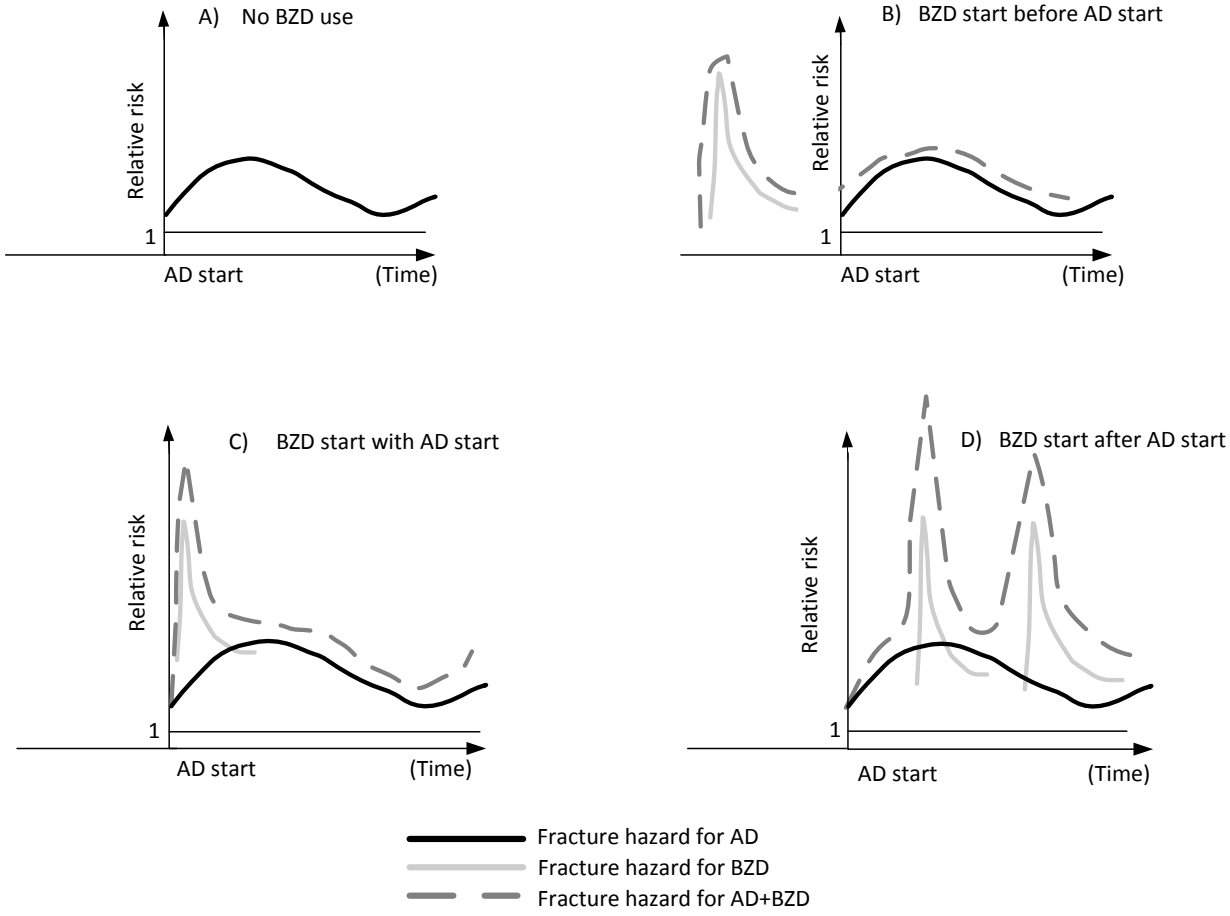
Pharmacoepidemiology

- Fundamental aspect: measuring the frequency of exposure and outcome

- However: measuring is not as straightforward as it seems…
  - Data quality/measurement errors
  - Definitions used
  - Limitations of codes

Exposure-outcome relations: hazard functions



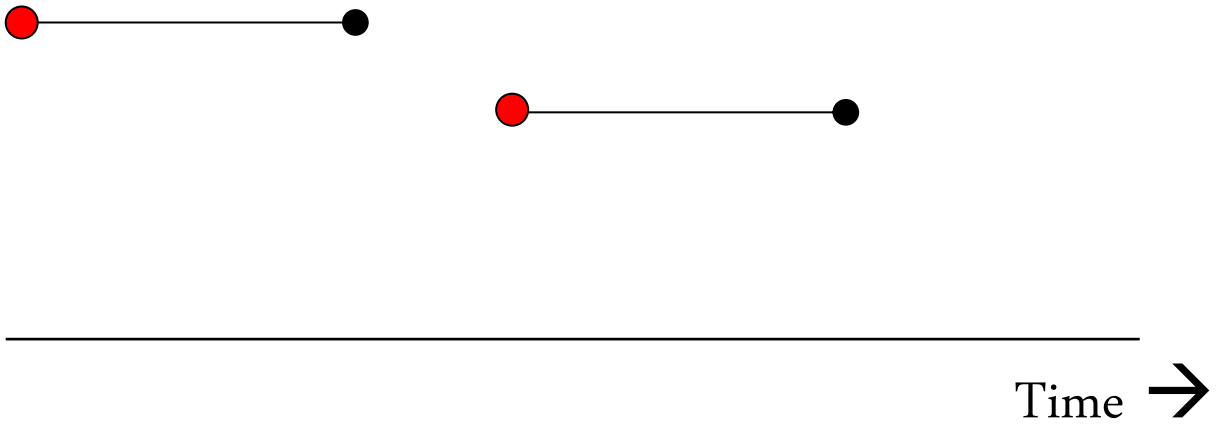
Exposure assessment

- How do we measure drug use?
  - Type of drug (classes? Individual products?)
  - Timing (current use? What does that mean?)
  - Dosage (DDD?)
  - Duration (of what?)
  - Acute effect vs long-term effect?
  - Patterns?
  - Adherence & persistence?

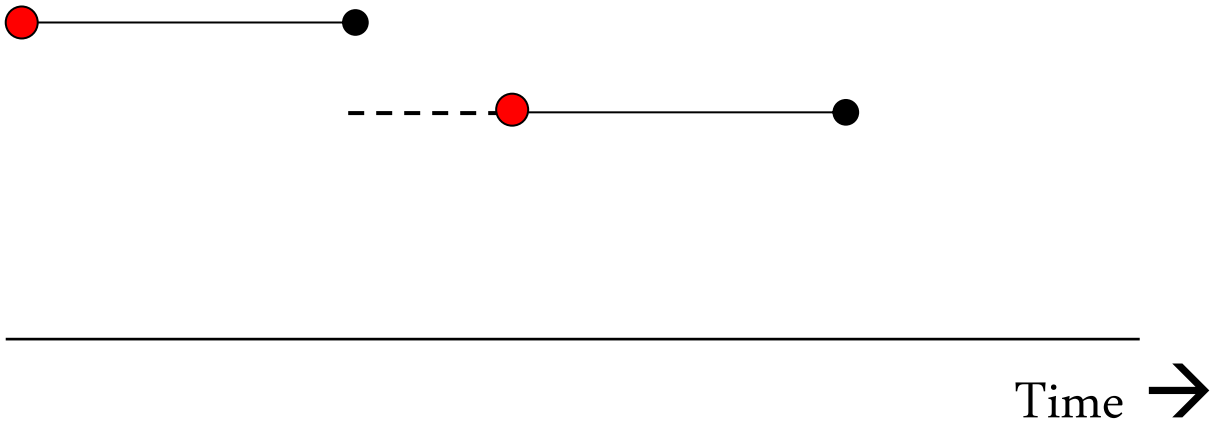
Dosage instructions

- as directed	-9
0NE PUFF TWICE A DAY OR AS DIRECTED	2000
1	1000
1 PUFF THREE TIMES A DAY	3000
1 - 2 PUFFS TWICE DAILY	3000
1 -2 DOSES ONCE OR TWICE A DAY	2500
1 -2 DOSES TWICE A DAY	3000
1 -2 DOSES TWICE DAILY	3000
1 -2 dose once or twice a day	2500
1 2 doses twice daily	3000
1 AS DIRECTED	1000
1 AT NIGHT	1000
1 BD	2000
1 BLISTER TWICE A DAY	2000
1 BLISTER TWICE DAILY	2000
1 CAP BD	2000
1 CAP FOUR TIMES DAILY	4000
1 CAP TWICE DAILY	2000
1 Cap 4 times daily	4000

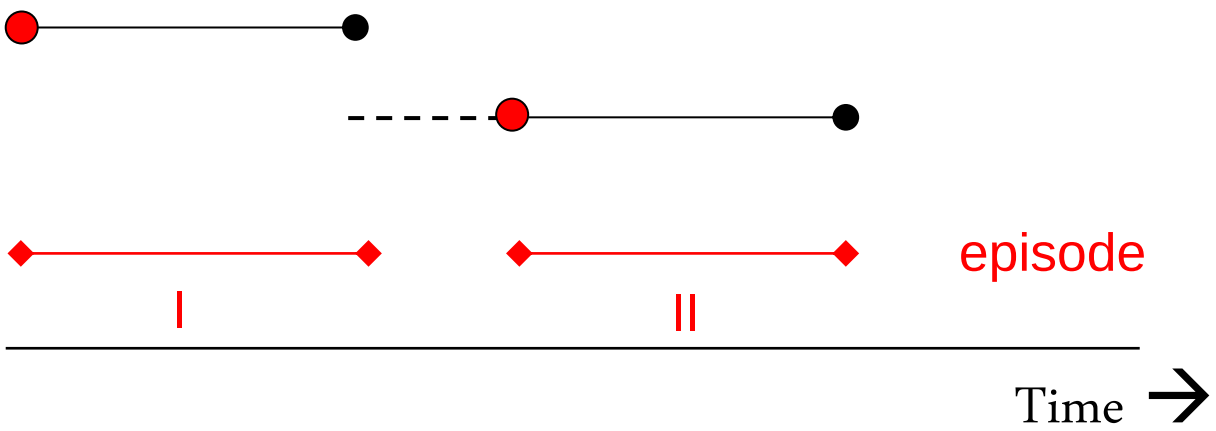
Creating exposure episodes



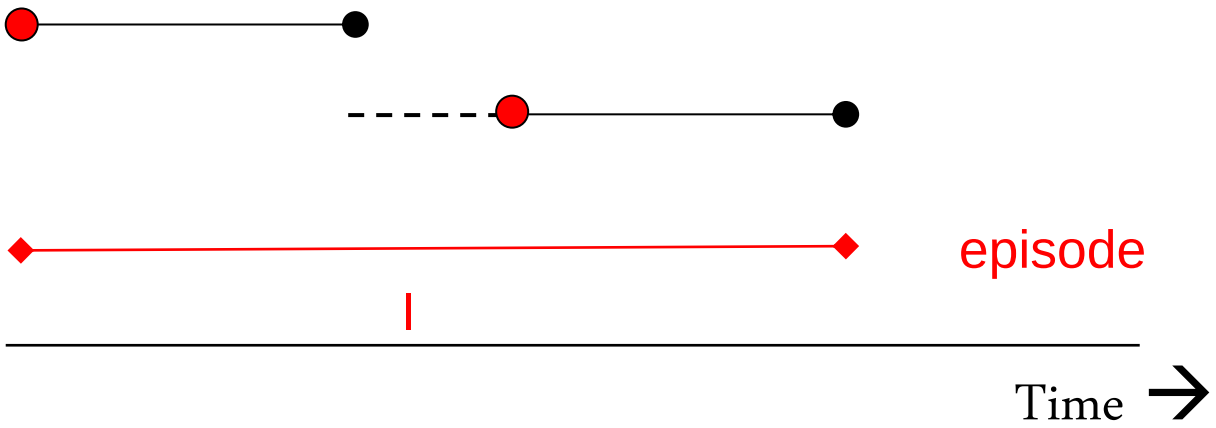
Creating exposure episodes



Creating exposure episodes



Creating exposure episodes



Problems with measuring exposure

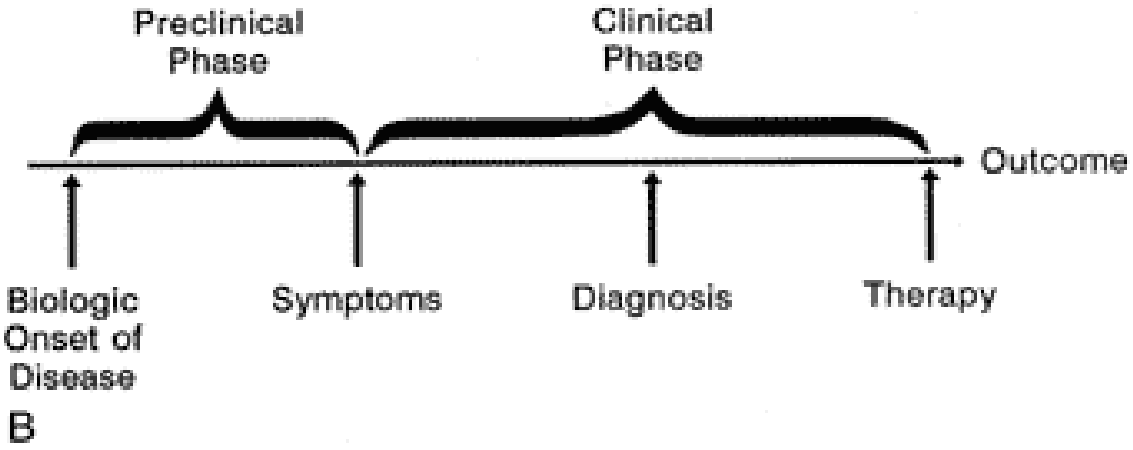
- Prescribing vs. dispensing
  - Filling the prescription?
  - Intervention by pharmacist→ substitution
- Taking
  - Compliance to prescribed regimen
  - Self management plans/as needed drugs
- Reaching adequate therapeutic levels
  - CYP polymorphisms

Outcome assessment

- What is the type of outcome?
  - Hard clinical endpoint?
  - Diagnosis?
  - Test result?

- Validity and completeness of outcome event recorded in your data resource?

Problems with measuring outcomes



Problems with measuring outcomes

- Diagnosis vs. onset of disease
  - What is the actual ‘index date’ ?
  - What is the relevant exposure period when disease has long asymptomatic phase (cancer, dementia, BPH)

- Effect of clinical decision making process (initial diagnosis cough vs final diagnosis of a more serious outcome)

Measuring in electronic health care databases

- Health care system knowledge
  - Gatekeeper function, referrals, how is medication dispensed
- Consistency of data collection/coding principles over time
- Event date vs. event registration date

Consequences of measurement errors

- Incorrect classification of subjects with respect to exposure and/or outcome

→ Information bias

Misclassification

- Non-differential: the amount of misclassification is equal in the groups that are compared
- Differential: the amount of misclassification is not equal in the groups that are compared
- Has impact on risk estimates

Non-differential misclassification: example

- Proportion of truly exposed subjects that are classified as exposed: sensitivity
- Proportion of truly non-exposed subjects that are classified as non-exposed: specificity
- Exposure prevalence

Non-differential misclassification: example

	Cases	Controls
Exposed	80	50
Non-exposed	20	50

True Odds Ratio = (80/20)/(50/50) = 4

Non-differential misclassification: example

	Cases	Controls
Exposed	80	50
Non-exposed	20	50

Sensitivity = 80%

Specificity = 90%

Non-differential misclassification: example

	Cases	Controls
Exposed	80	50
Non-exposed	20	50

Sensitivity = 80%

Specificity = 90%

Sensitivity and specificity?

Truth: / Classified	Exposed	Unexposed
Exposed	a	b
Non-exposed	c	d

Sensitivity → probability of being classified as exposed when subject is ‘truly’ exposed (a/a+c)

Specificity → probability of being classified as non-exposed when subject is ‘truly’ non-exposed (d/b+d)

Non-differential misclassification: example

	Cases	Controls
Exposed	80	50
Non-exposed	20	50

Cases:

80 * 90% = 72

20 * 80% = 16

Controls:

50 * 90% = 45

50 * 80% = 40

Non-differential misclassification: example

	Cases	Controls
Exposed	~~80~~ 72+4	~~50~~ 45+10
Non-exposed	~~20~~ 16+8	~~50~~ 40+5

Cases:

80 * 90% = 72

20 * 80% = 16

Controls:

50 * 90% = 45

50 * 80% = 40

Non-differential misclassification: example

	Cases	Controls
Exposed	76	55
Non-exposed	24	45

Observed Odds Ratio = (76/24)/(55/45) = 2.6

→ underestimation of the true effect

Non-differential misclassification: example

Magnitude of bias on the Odds Ratio, true OR=4.0

Sensitivity	Specificity	Exposure prevalence	Observed OR
0.90	0.85	0.20	2.6
0.60	0.85	0.20	1.9
0.90	**0.95**	0.20	3.2
0.90	**0.60**	0.20	1.9
0.90	0.90	**0.368**	3.0
0.90	0.90	**0.20**	2.8
0.90	0.90	**0.077**	2.2

Non-differential misclassification: example

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Non-differential misclassification

- Expected effect is that it results in bias toward the null, i.e. underestimation of the true effect

- But….. as misclassification occurs in individuals there is some probability it may bias away from the null

Differential misclassification

- Difference in proportion of misclassification between groups that are compared
- Classic example: recall bias of exposure which is more likely to be remembered among cases then among controls
- Direction of bias can be either way

Conclusion

- Classification errors are common in epidemiological research
- Standard research practices minimize differential misclassification
- When extent of classification errors (e.g., sensitivity and specificity) are known, it is possible to back-calculate to truth
- If exact classification errors are not known, it is possible to perform sensitivity analyses to estimate a range of study results given a range of possible classification errors