Bias and confounding

R.H.H. Groenwold, MD, PhD

Bio sketch

- MD, PhD in epidemiology
- Associate professor of Epidemiology at UMC Utrecht
- Research focus on methods for causal research

- “I have no potential conflict of interest”

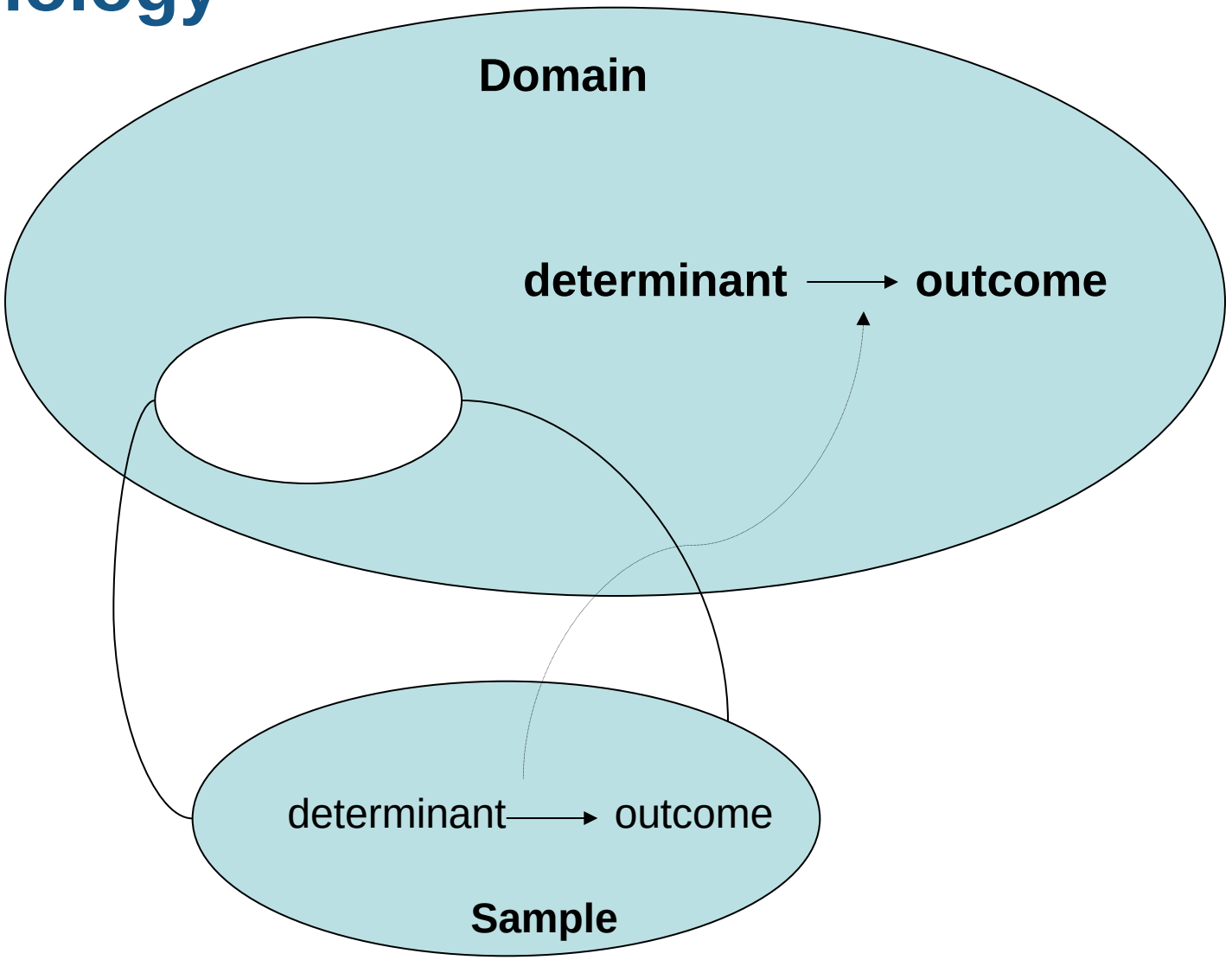
Abundant terminology in the literature!

Groenwold. NTvG 2013

- Note: confounding is just another form of bias

- **Remember:**
  1. **Confounding**
  2. **Selection bias**
  3. **Information bias**

Epidemiology



- **Bias = systematic error in the quantity you try to estimate**

- Can not be remedied by large (infinite) sample size
- Can not be remedied by pooling studies
- It is not quantified by the confidence interval (which represents random sampling variability)
- If bias, results are not valid (‘internal validity’)

- Example: broken measuring tape

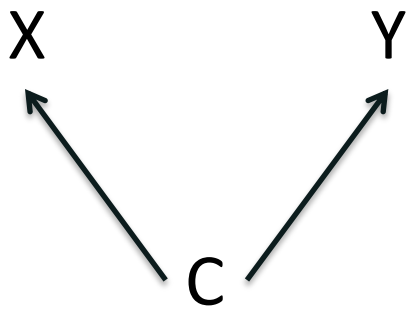
Information bias

- Bias due to misclassification (measurement error) of exposure or outcome.
- Can have huge impact, in particular when
  - Misclassification of exposure is related to outcome status
  - Misclassification of outcome is related to exposure status

Directed acyclic graphs (DAGs)

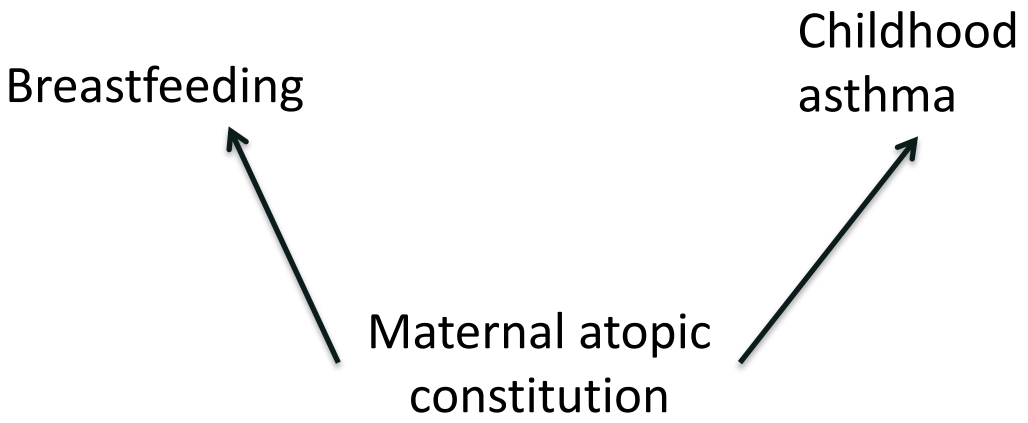
The arrow indicates that X causes Y

DAGs – common causes

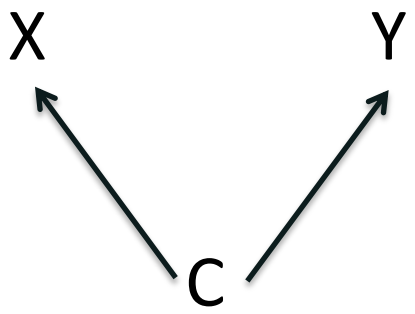


If X and Y share a common cause, it may appear that X causes Y, while in fact it does not.

Example:



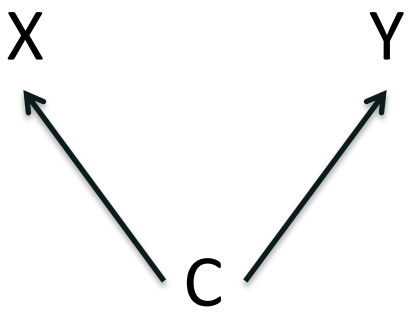
Confounding in a DAG



- If X and Y share a **common cause**, this may bias the observed association between X and Y.

- This is called **confounding**

Textbook definition of confounding



A confounder is …

… a risk factor for the outcome

… related to exposure

… not an intermediate to the causal chain

TABLE 1 Characteristics of vaccinated and unvaccinated persons, and survivors and nonsurvivors[#]

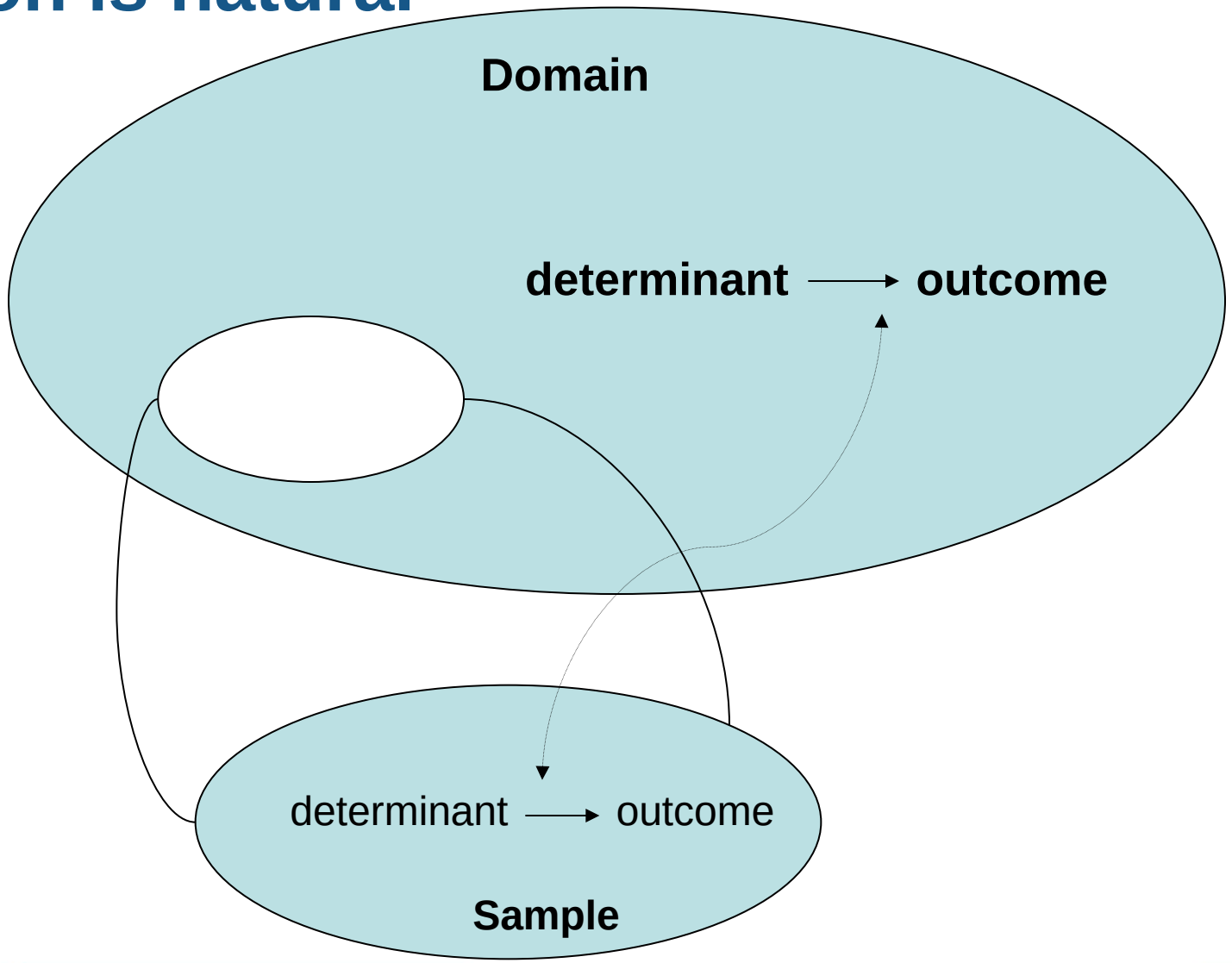
Variable	Total	Vaccinated	Unvaccinated	OR (95% CI)	Deaths	Survivors
Periods of observation n	50906	37501	13405		415	50491
Vaccinated	73.7 (37501)				70.6 (293)	73.6 (37208)
Age yrs	75 (70–80)	75 (70–81)	74 (69–80)	1.07 (1.06–1.09)[¶]	81 (74–87)	75 (70–80)
Male	38.3 (19484)	39.4 (14762)	35.2 (4722)	1.19 (1.15–1.24)	47.0 (195)	38.2 (19289)
Cardiovascular comorbidity	10.2 (5171)	10.9 (4100)	8.0 (1071)	1.41 (1.32–1.52)	33.0 (137)	10.0 (5034)
Pulmonary comorbidity	5.2 (2629)	6.0 (2254)	2.8 (375)	2.22 (1.99–2.48)	12.3 (51)	5.1 (2578)
Diabetes mellitus	6.5 (3328)	7.5 (2796)	4.0 (532)	1.95 (1.77–2.14)	11.3 (47)	6.5 (3281)
Malignancies	2.2 (1128)	2.2 (843)	2.1 (285)	1.06 (0.92–1.21)	12.5 (52)	2.1 (1076)
Cardiovascular medication use	47.4 (24112)	51.2 (19189)	36.7 (4923)	1.81 (1.73–1.88)	64.8 (269)	47.2 (23843)
Pulmonary medication use	11.4 (5809)	13.3 (4987)	6.1 (822)	2.35 (2.17–2.53)	21.7 (90)	11.3 (5719)
Diabetic medication use	7.8 (3973)	9.1 (3396)	4.3 (577)	2.21 (2.02–2.41)	14.5 (60)	7.7 (3913)
GP visits	12 (6–20)	13 (8–21)	8 (4–15)	1.21 (1.19–1.22)[+]	27 (16–41)	12 (6–19)

Data are presented as % (n) or median (interquartile range), unless otherwise stated. Baseline characteristics are based on the 12 months vaccination. OR: odds ratio; CI: confidence interval; GP: general practitioner. [#]: all-cause mortality; [¶]: based on 5-yr strata; [+]: based on strata o

eahp european association of hospital pharmacists

Groenwold et al. Eur Resp J 2009

Selection is natural



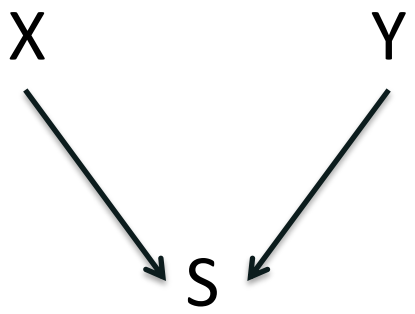
Selection does not equal selection bias

- Selection bias is a bias due to selection
- Not all selections result in a bias

- Example: RCT in which particularly severely disease patients are willing to participate…

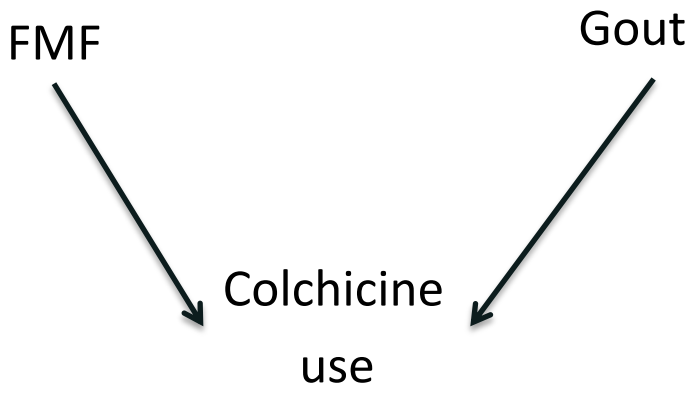
- Bias?

DAGs – colliders



If X and Y share a common effect, the observed relation between X and Y is unbiased.

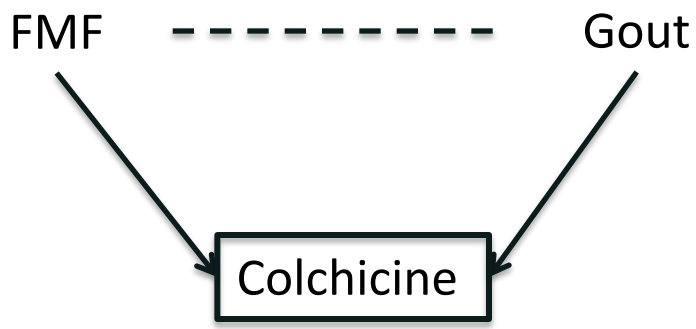
Example:



Selection bias in a DAG

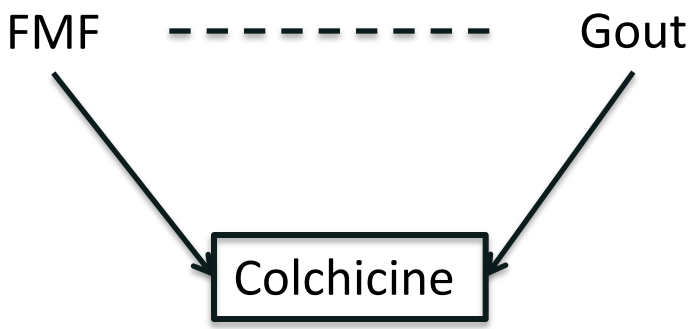
- If X and Y share a **common effect**, the overall association between X and Y is unbiased.
- In a DAG a common effect is called a collider.
- Conditioning (e.g. stratification) on a collider will bias the relation between X and Y.
- This is called **selection bias**.

Selection bias – example



- In general, no association between FMF and gout.
- Among those who use colchicine…
- … negative association is observed.
- This is **selection bias**.

Selection bias – informal



Among those who use colchicine…

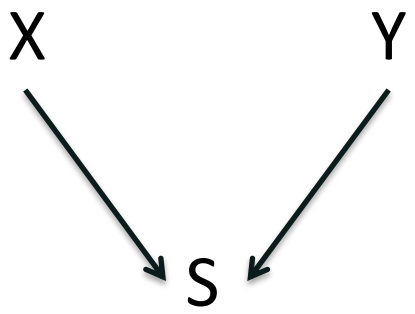
… there must be a reason why they use it

If a subject does not have gout ….

… it very likely (s)he has FMF,

and vice versa

Selection bias – it takes two …



- Conditioning on S will only result in a bias if **both** X and Y are related to S.
- Hence, selection based on outcome status only (case-control study) or exposure status only (e.g. matching in cohort study) will not induce a selection bias.

Selection vs. selection bias

- Selection bias is due to selective inclusion of subjects in the study population.
- However, selective inclusion of subjects in the study population does not necessarily result in selection bias!!!
- Example: case-control study
  - Inclusion in study population is strongly related to outcome status, but does not result in bias
- Example: RCT in which half of placebo group drops out
  - Inclusion in analysis is strongly related to treatment status, but does not results in bias

Selection does not equal selection bias[2]

- Example: RCT in which particularly severely disease patients are willing to participate…
- Bias?

- Probability of being ‘selected’ for the study depends on risk of the outcome…
- Probability of being ‘selected’ does not depend on treatment status…
- So, … no selection bias!

Selection bias vs. confounding

- Is it a common cause or a common effect?
  - Hard to derive from data
  - Think about chronological order!

- DAGs may help you to identify variables to control for in your analysis (confounders) and variables that you should not control for (colliders).

- Bias classification:
  - Information bias
  - Confounding
  - Selection bias

Generalizability

- External validity (outdated term)
- To whom do the results of my study apply?
- Generalizability does not require representativeness
- Use clinical knowledge!

Generalizability

- Example: antibiotics for acute otitis media
  1. Study among 50 boys, 50 girls
  2. Study among 100 boys, no girls
  3. Study among 100 girls, no boys

- Which study would you prefer in terms of generalizability of results?

Further reading:

- Hernan et al. A structural approach to selection bias. *Epidemiology* 2004;15:615-25.