Conflict of Interest Statement

Michael Schomaker: I have no conflict of interest.

Felicitas Kühne: I have no conflict of interest.

Nicholas Latimer: I am going to give an example from a recent NICE appraisal (Sodium zirconium cyclosilicate for hyperkalaemia; *NICE TA599, September 2019*). I am a member of the Appraisal Committee that considered this drug.

Workshop – Directed Acyclic Graphs in Practice: Opportunities and Challenges

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(2) Center for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa

Dr. Nicholas Latimer
(1) Reader at the School of Health and Related Research (ScHARR), University of Sheffield, United Kingdom

Why a Workshop on DAGs?

- We often use observational data to inform economic analyses about the causal effect of particular interventions
- To draw causal conclusions from observational data, we need to make assumptions about how the data was generated
- To communicate and summarize these assumptions, we can use graphs, i.e. DAGs
- Let's start to understand what DAGs are $\rightarrow$ Presentation 1 by Felicitas Kühne

Directed Acyclic Graphs
DAGs

Felicitas Kuehne

ISPOR, 19 May 2021

Dept. of Public Health, Health Services Research and Health Technology Assessment,
UMIT - University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria

UMIT TIROL
THE TYROLEAN PRIVATE UNIVERSITY

Nature and Data

- The data generating process
- Nature ("the law/code") generates data (the "footprint of nature")
- Humans draw conclusion o… nature (universal law) f… observations (data)

When drawing causal conclusions use Causal Inference Methods!

Nature and Data

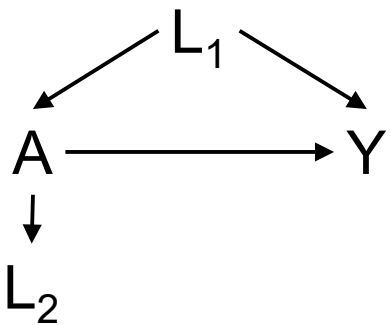
- Causal graphs or DAGs represent the data generating process
- Can be used for guiding valid causal effect estimation: finding the set of adjustment variables

When drawing causal conclusions use Causal Inference Methods!

Notation for DAGs

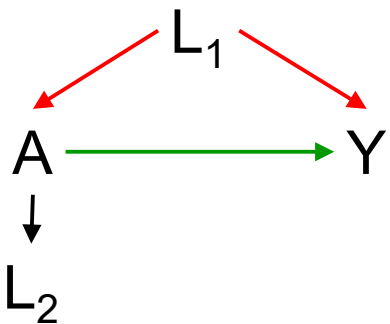
- A = Action
- Y = Outcome
- L = Other variables
- U = Unmeasured ("hidden") variables
- Any other letter for specific meaning in special cases

Directed Acyclic Graphs (DAGs)



- Letters represent variables
- Links represent associations
- Arrows represent causal relationships
- Directed: all links are arrows
- Acyclic: no loops
- Causal DAG: all common causes of any pair of variables in the DAG are also included in the DAG
- Assumptions are encoded by the absence of arrows
- Path: route between 2 variables in the graph

Directed Acyclic Graphs (DAGs)



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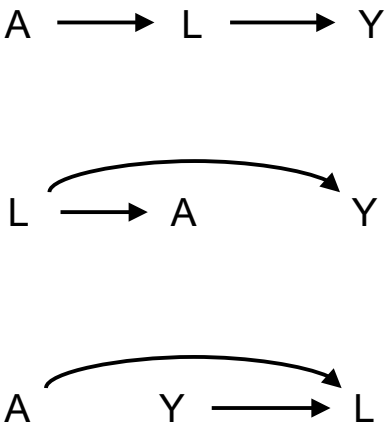
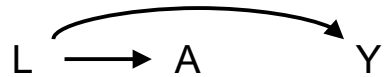
- Path: route between 2 variables in the graph
- Frontdoor and backdoor paths



3 main
DAG scenarios

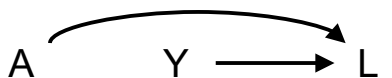
(a) Intermediate step

Causal chain



(b) Confounder

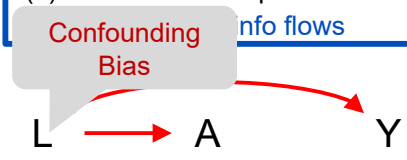
Causal fork

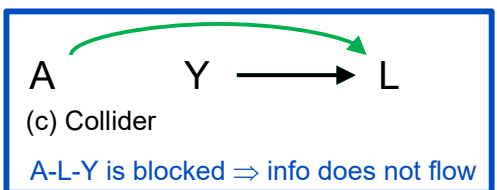


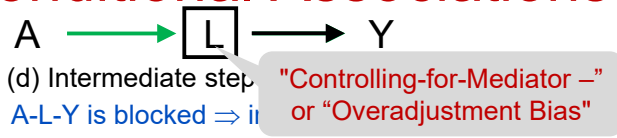
(c) Collider

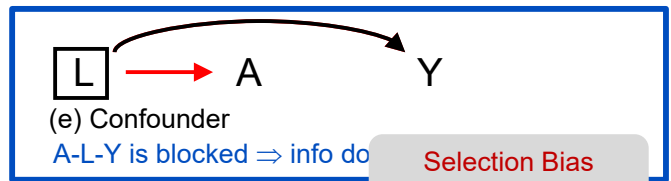
Inverted fork

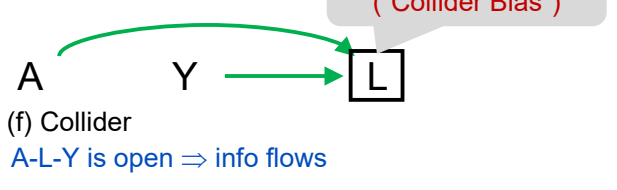
Unconditional and Conditional Associations









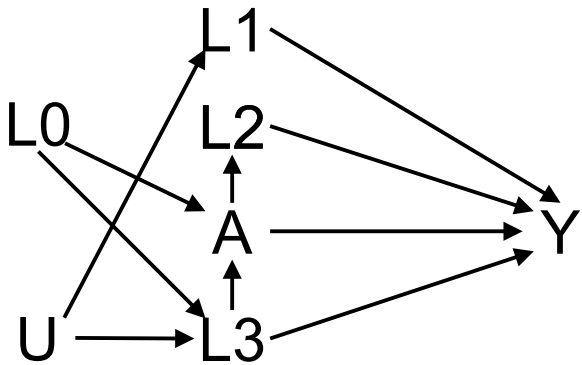


Which (controlled or uncontrolled) versions provide the causal effect?

How to Check Identifiability?

1. Identify paths between A and Y
    1. Backdoor paths
    2. Frontdoor paths
2. Check whether
    1. All backdoor paths are blocked
    2. All frontdoor paths are open
3. For each adjustment variable, check backdoor and frontdoor paths again
4. Identify variables that need to be adjusted for

Causal Effect Estimable?



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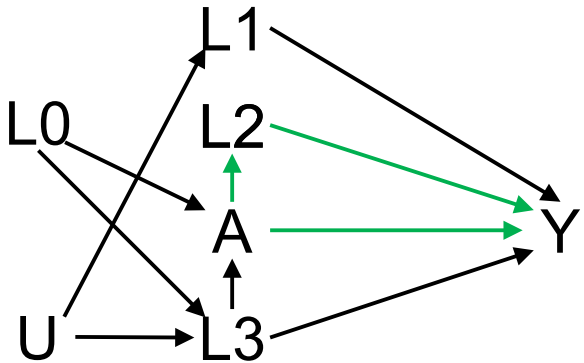

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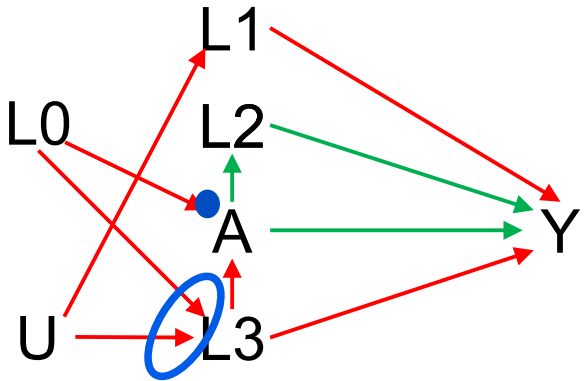

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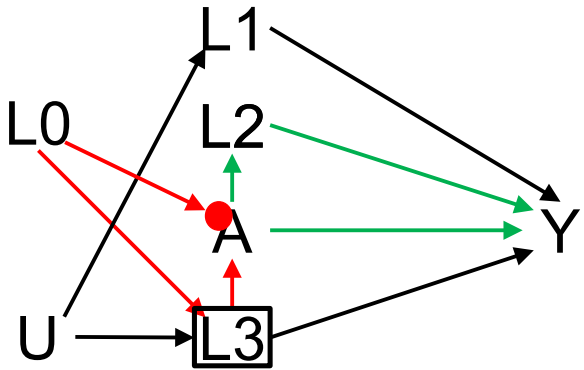

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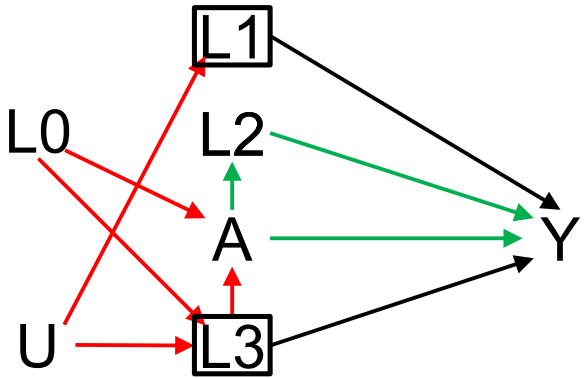
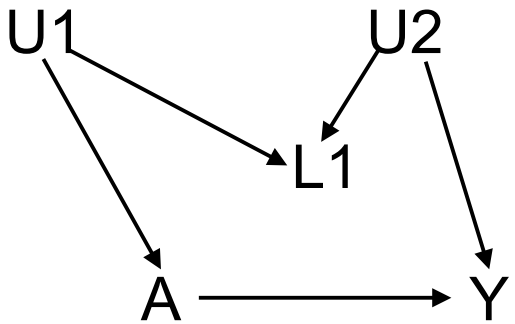


Poll (1): Causal Effect Estimable?

Is the effect estimable?

1. No
2. Yes, when controlling for L1
3. Yes, without controlling for anything

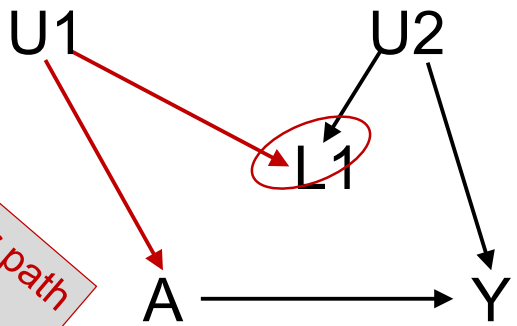


Poll (1): Causal Effect Estimable?

Is the e

1. No
2. Yes, when co
3. Yes, without con
   anything

There is no open backdoor path
Hence no adjustment
necessary for effect estimation



Presentation 2:
Challenges in constructing DAGs in realistic, sophisticated settings: a suggestion for a structured approach

Michael Schomaker

UMIT, Institut für Public Health, Medical Decision Making und HTA

19 May 2021

HIV Example

- Antiretroviral treatment (ART) is known to be highly effective in treating people living with HIV
- Treatment initiation is/was still often delayed

  (former guidelines; concerns about toxicities or non-adherence, drug resistance; logistical challenges; cost considerations)
- There was limited knowledge about the optimal timing of antiretroviral treatment initiation in children and adolescents until recently
- It was no longer ethically possible to conduct a trial
- See, e.g., Schomaker, M. et al., 2019, “Using longitudinal targeted maximum likelihood estimation in complex settings with dynamic interventions”, *Statistics in Medicine*, 38(24): 4888–4911 ... and references therein for details

HIV Example

Causal Question: what is the mean counterfactual growth (HAZ) of children aged 1-5 at the end of follow-up ($t = 30$ months) if a given treatment rule such as ART $= (1, 1, \ldots, 1)$ had been applied to *all* patients and if there had been no censoring.

We *know*: treatment decisions had been based on guidelines and decisions had been made based on CD4 count, CD4% and WHO (CDC) disease stage

It is a complex setting with many relevant variables: how can we develop the DAG?

The Concept of Time

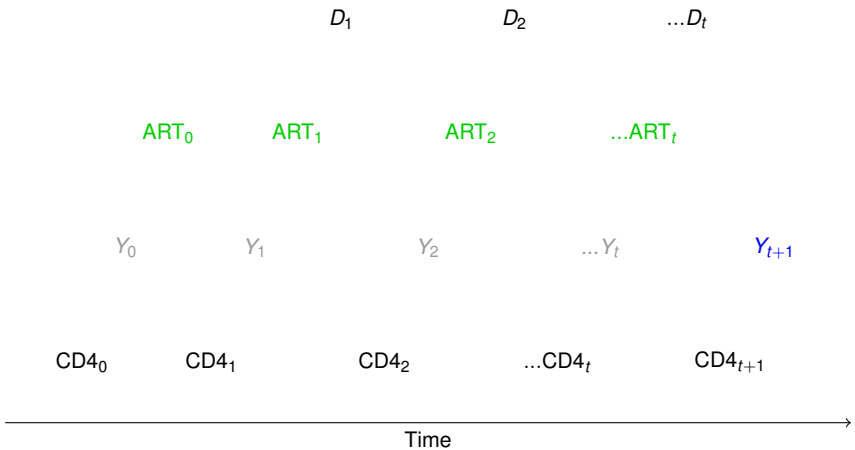
Let's start with only 4 relevant variables: HAZ (outcome), ART (treatment), CD4 count (confounder) and death (competing event)

Step 1: make an assumption about general time ordering per time interval, for example:

$\text{CD4}_t \rightarrow \text{HAZ}_t \rightarrow \text{ART}_t \rightarrow \text{Death}_t$

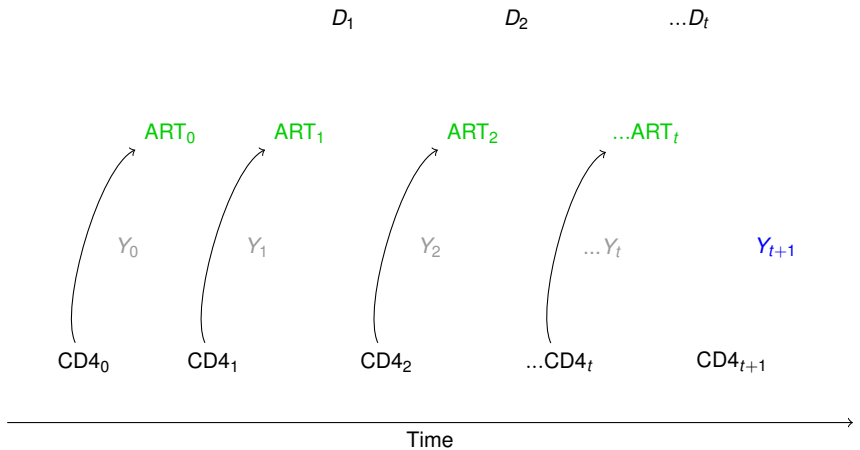
The Concept of Time

Step 2: define “time zero”, end of follow-up, relevant outcome (often at 1(!) time point) and intervention (multiple(?) time points) and order them according to assumptions made:



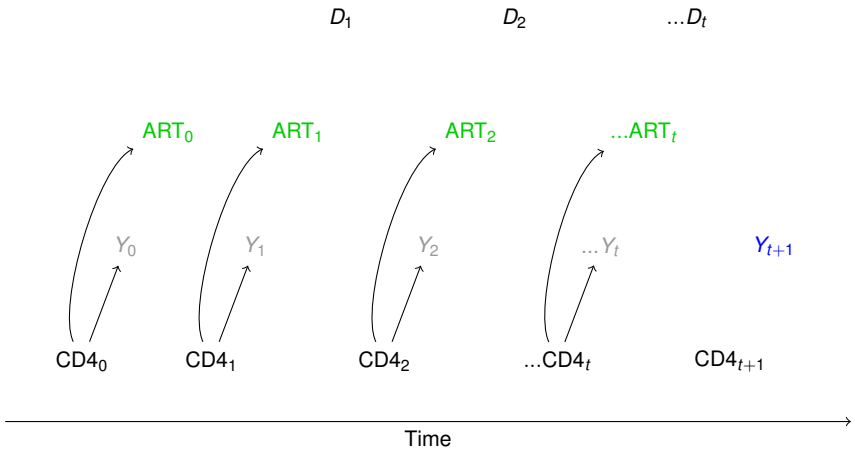
Treatment assignment

Step 3: reflect what has *determined* treatment assignment, ultimately to find confounders and back-door paths



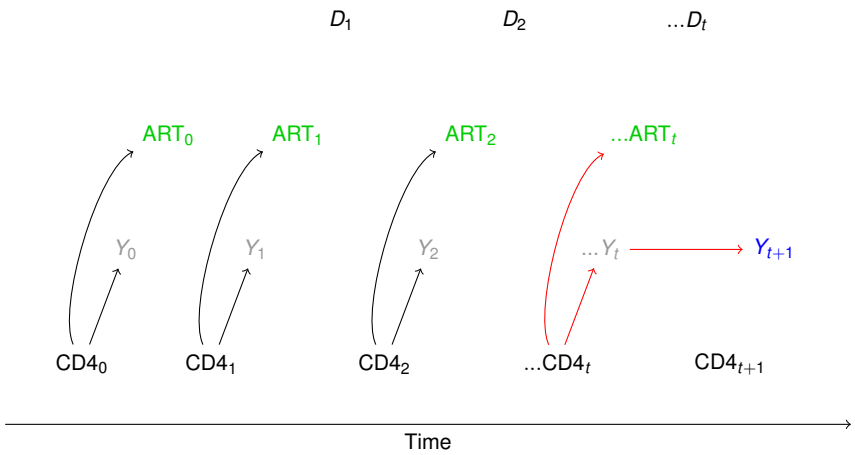
(Time-dependent) Confounders

Step 4: Of those variables that affect treatment assignment: which do also affect the outcome and are therefore confounders?



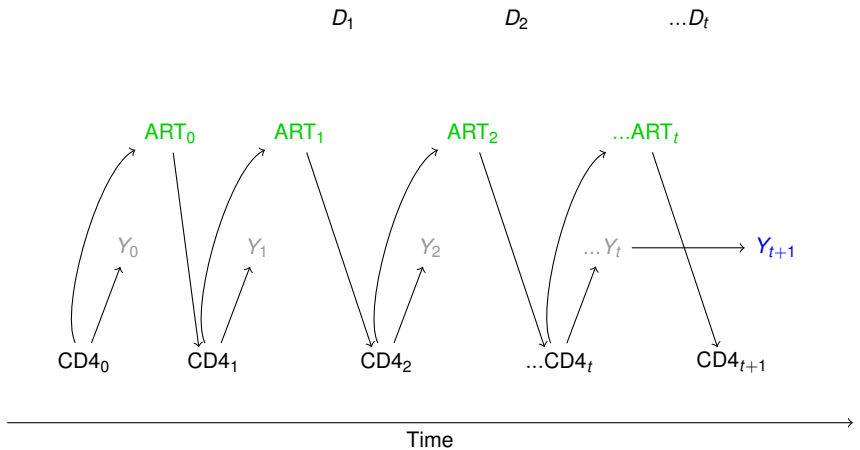
Back-door paths

Step 4 [continued]: ....this will give an indication of relevant back-door paths, for example:



Treatment-Confounder Feedback

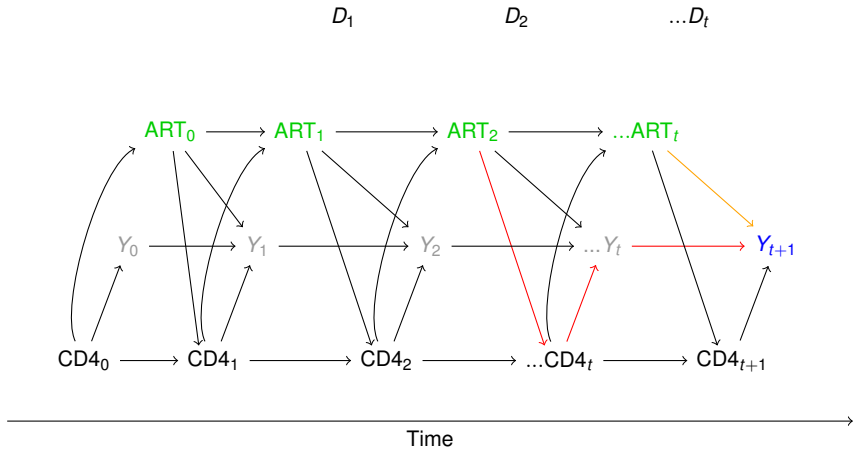
Step 5: are the confounders affected by prior treatment? If yes: regression is invalid.
$\rightarrow$ g-methods are needed, see also talk 3



Further relationships

Step 6: draw remaining relationships between outcome, intervention and confounders.

Important: understand pathways through which treatment can affect the outcome – directly and indirectly.

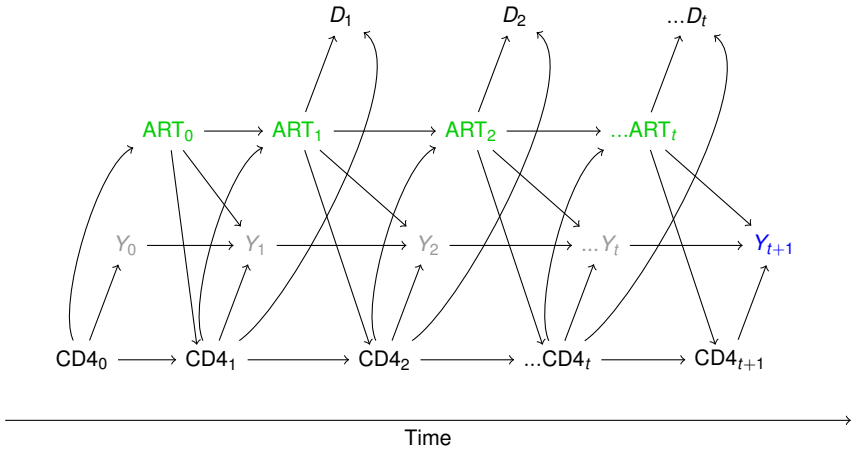


How to deal with censoring due to competing events, drop out etc?

- In our example, patients are more likely to be censored due to death *because* of higher disease severity (with consequences of more co-morbidities) or if they are/remain untreated
- $\rightarrow$ Add this knowledge to the DAG!
- Reasons for censoring are additional arrows

Censoring, Drop-out, Competing Events

Step 7: add reasons for censoring due to death



Poll Question (2)

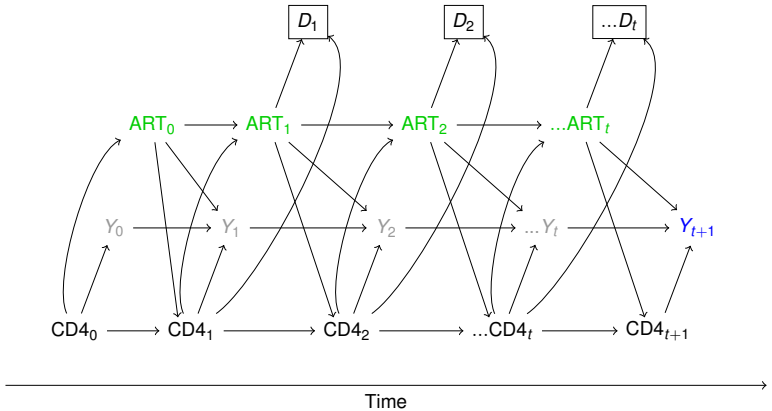
If we only evaluate children who survived, we condition on survival (see DAG). What are the consequences?

a) Confounding

b) Collider bias

c) It does not matter

d) Overadjustment bias (conditioning on a mediator)



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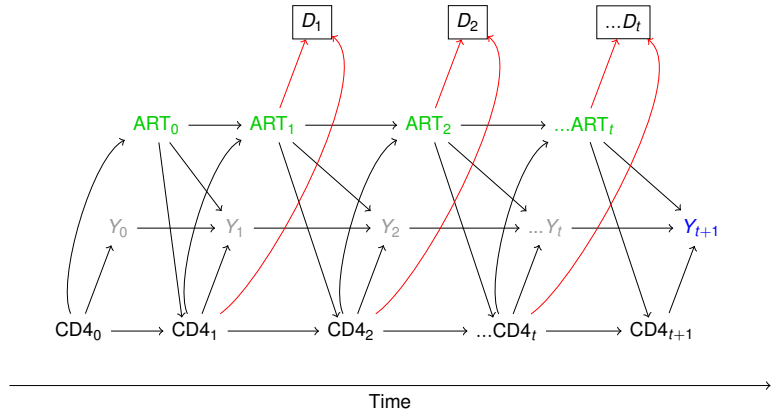


Implications of Censoring, Drop-out, Competing Events

$\rightarrow$ evaluating only uncensored patients, i.e. those without competing event, without missing data, no mortality etc., often leads to collider bias

Possible solutions: see

Schomaker, M., Kühne , F., Siebert, U., 2020, “Regarding: Effect Estimates in Randomized Trials and Observational Studies: Comparing Apples with Apples. ”, *American Journal of Epidemiology*, 89(1): 77-78

and the references therein

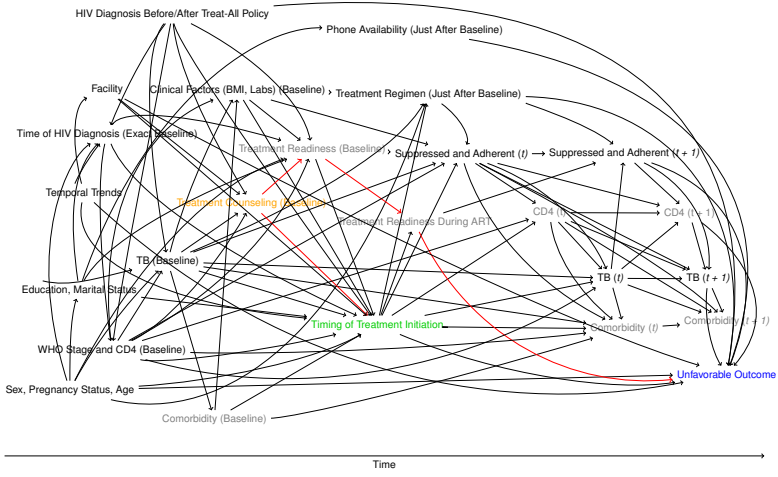
Final Steps

Step 8:

- Add other potential confounders (CD4%, stage)
- Add other censoring indicators (e.g., due to loss to follow-up)
- Think about relevant baseline variables (e.g., co-morbidities at presentation)

DAGs can be complicated in practice....[1]

→ but just use color coding and logic explained



[1] DAG from Kerschberger et al., 2021, "The impact of same-day antiretroviral therapy initiation under the WHO Treat-All policy", *American Journal of Epidemiology*, in press

Summary

- DAGs are extremely helpful in observational studies
- With a structured approach, it is feasible to work with DAGs even in sophisticated settings
- Some key concepts:
  - (time-dependent) confounders (affected by prior treatment?)
  - collider bias (also due to censoring)
  - pathways through which the treatment can affect the outcome

Directed Acyclic Graphs in Practice: Opportunities and Challenges

A Decision-Making Perspective

Nicholas Latimer, University of Sheffield, Sheffield, UK, Reader in Health Economics,
Yorkshire Cancer Research Senior Fellow

The University Of Sheffield.

Disclosures

I am going to give an example from a recent NICE appraisal (Sodium zirconium cyclosilicate for hyperkalaemia (NICE TA599, September 2019))

I am a member of the Appraisal Committee that considered this drug

But everything in this presentation is in the public domain

Introduction

- I’m going to use an example from a recently completed NICE Technology Appraisal to demonstrate how DAGs might help us:
  - Review the appropriateness of parameters / relationships / effects used in economic models
  - Decide whether model structures are appropriate
  - Decide whether new analyses are needed to inform economic models

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A Case Study: Sodium zirconium cyclosilicate for hyperkalaemia

(NICE TA599, September 2019)

- Hyperkalaemia is where people have high blood potassium levels, occurs most commonly in people with chronic kidney disease (CKD) or heart failure
- Severe hyperkalaemia can lead to cardiac arrest

Note: all details publicly available from: https://www.nice.org.uk/guidance/ta599/resources/sodium-zirconium-cyclosilicate-for-treating-hyperkalaemia-pdf-82607272135621

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- Hyperkalaemia is where people have high blood potassium levels, occurs most commonly in people with chronic kidney disease (CKD) or heart failure
- Severe hyperkalaemia can lead to cardiac arrest

- RAAS inhibitors are important treatments for hypertension, heart failure and CKD
- People often have to stop taking an optimised dose of their RAAS inhibitor because these can lead to hyperkalaemia

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- RAAS inhibitors are important treatments for hypertension, heart failure and CKD
- People often have to stop taking an optimised dose of their RAAS inhibitor because these can lead to hyperkalaemia

- **Sodium Z lowers serum potassium levels, and may allow people to stay on RAAS inhibitors for longer, leading to QALY gains**

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Sodium Z: Clinical effectiveness (NICE TA599, September 2019)

Two main trials: **ZS004** and **ZS005**

- **Trials showed that Sodium Z reduced serum potassium levels** (the primary outcome measure) **from baseline (but no comparator)**
- **ZS005 showed that most people on RAAS inhibitors continued on the same dose** (exploratory outcome measure)**, and some people not on RAAS inhibitors at the start of the trial had started them by the end of follow-up (but, no comparative evidence)**

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Sodium Z: Clinical effectiveness (NICE TA599, September 2019)

Several important limitations in the evidence which I will not address here:

- No control groups for correction phase in trials
- Eigibility criteria did not match those patients who would be treated in the NHS
- Increased risk of adverse events with low and high potassium levels (“J curve”)
- No evidence in the severe setting
- Longest trial was 52 weeks, but company assumed treatment would continue indefinitely
- Company claimed Sodium Z would prolong life and improve quality of life, but no evidence on this

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Sodium Z: Modelling (NICE TA599, September 2019)

Modelling approach

- The modelling of the long-term effect of Sodium Z was crucial in this appraisal
- The company modelled using surrogate measures. Two independent effects were modelled:

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Sodium Z: Modelling (NICE TA599, September 2019)

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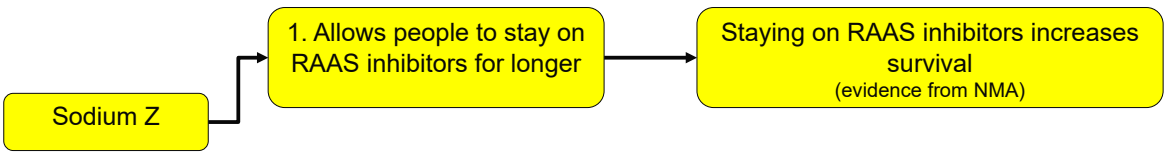

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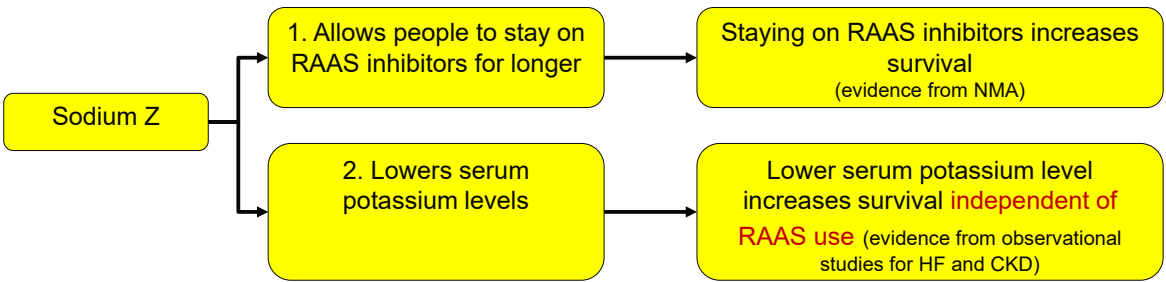

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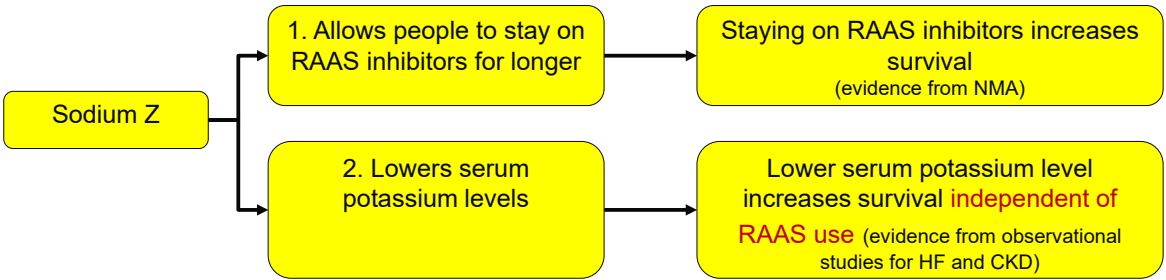
Sodium Z: Modelling (NICE TA599, September 2019)

Modelling approach

- Sodium Z increases survival because it allows people to stay on RAAS for longer, but also because having lower potassium is a good thing, independent of RAAS use
- Can we disentangle those effects?
- **Can DAGs help us?**



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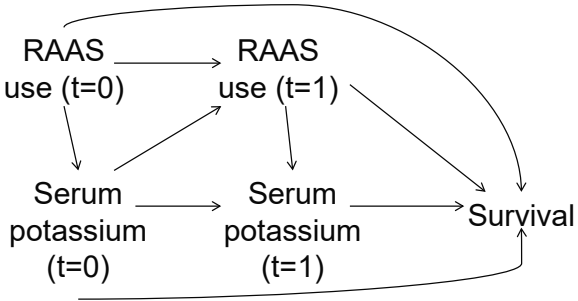
Poll

Sodium Z: How might DAGs have helped? (NICE TA599, September 2019)



Poll: For the causal effect of serum potassium on survival, should we control for RAAS use in a regression model?

- Yes ☐
- No ☐
- It's not simple ☐

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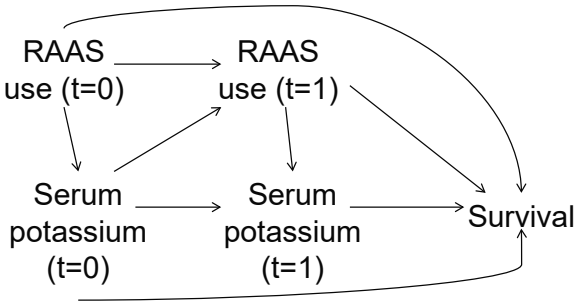
Poll - answer

Sodium Z: How might DAGs have helped? (NICE TA599, September 2019)



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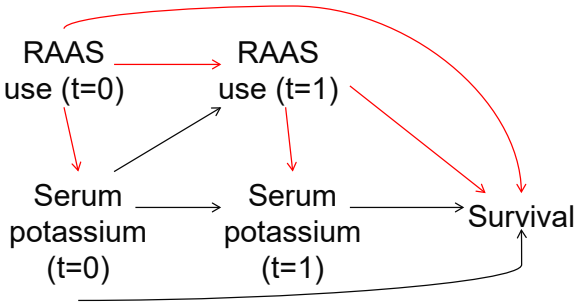
Sodium Z: How might DAGs have helped? (NICE TA599, September 2019)



If no, we have open backdoor paths

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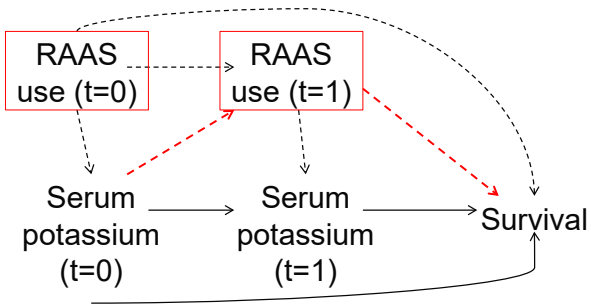

If yes (and we use standard regression), we have a blocked front-door (causal) path

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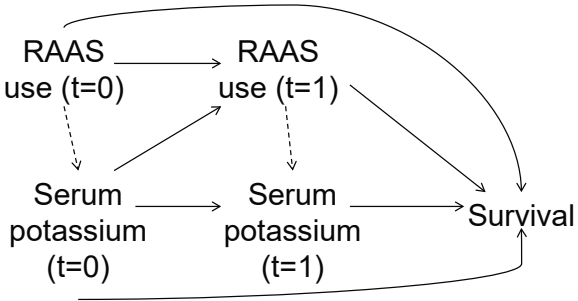

DAGs show we need g-methods to estimate the causal effect of serum potassium, because RAAS use is a confounder that is affected by prior serum potassium levels – it is a time-dependent confounder

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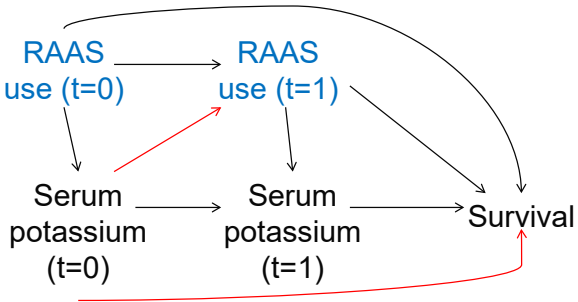

We could ask the same questions about the estimates of the causal effect of RAAS use on survival: was serum potassium dealt with appropriately?

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Sodium Z: What happened? (NICE TA599, September 2019)

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    - But did not use g-methods

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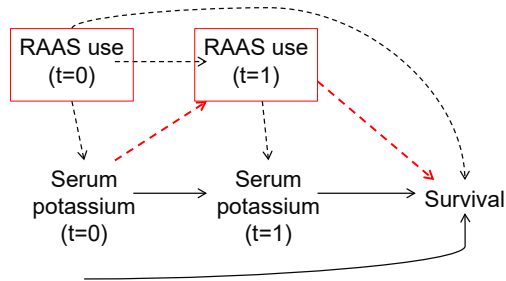
    - **Blocked front-door causal path?**



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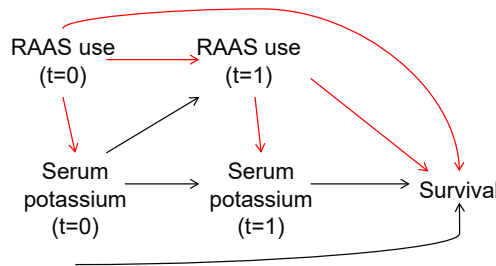

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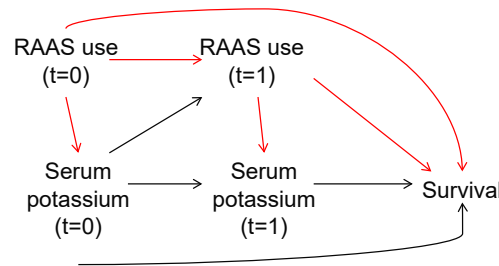
  - **So can we trust these analyses, for use in the economic modelling?**



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Sodium Z: What happened? (NICE TA599, September 2019)

- NICE Appraisal Committee noted that:
  - Observational data on the association between serum potassium levels and death **did not guarantee an independent causal effect** and **authors the studies cautioned against assuming a causal effect**
  - Noted the **potential for unmeasured confounding**
  - Were **concerned about time-dependent confounding**

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  - Were concerned about time-dependent confounding

- Company stated in response to the ACD:
  - RAAS was a time-dependent confounder
  - Including RAAS as a time-updated covariate is appropriate to isolate the effect of serum potassium on survival (?)
    (page 18, https://www.nice.org.uk/guidance/ta599/documents/committee-papers-3)
  - No new analyses presented for the estimation of these model parameters

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Sodium Z: What happened? (NICE TA599, September 2019)

Scenarios

- In addition to their base case, dual effect, analysis, the company presented scenario analyses where reduced potassium levels only had an effect through one of the modelled routes:
  - Scenario 1: Benefit of Sodium Z only though lowering potassium level, not also through longer RAAS use
  - Scenario 2: Benefit of Sodium Z only though longer RAAS use, not also through lower potassium level

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- Sodium Z likely to be cost-effective in the chronic setting, even removing the association between serum potassium and mortality (with a Patient Access Scheme) → positive recommendation
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Would the recommendations (or the nature of the PAS) have been different if more appropriate causal analyses had been undertaken to estimate values for the key parameters in the economic model?

Summary

- Evidence used in economic models often come from a range of sources, including observational data
- These models inform healthcare decision making

- Are the inputs to our models always estimated appropriately?
- Can DAGs help with this?

Q & A

Do you have any questions about the content of the presentations before we have a last short poll?

Poll (4)

After attending this workshop, would you consider using DAGs in the (causal) analysis of your observational data?

a) yes
b) only in simple examples
c) no
d) only in complicated examples

Discussion

Acknowledgements

- Prof. Uwe Siebert, UMIT - University for Health Sciences, Medical Informatics and Technology, for sharing his slides and giving valuable feedback
- Igor Stojkov, UMIT - University for Health Sciences, Medical Informatics and Technology, for valuable feedback
- Bernhard Kerschberger, Médicins Sans Frontiéres, Mbabane, Eswatini, for DAG

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