Causal mediation analysis of observational, population-based cancer survival data

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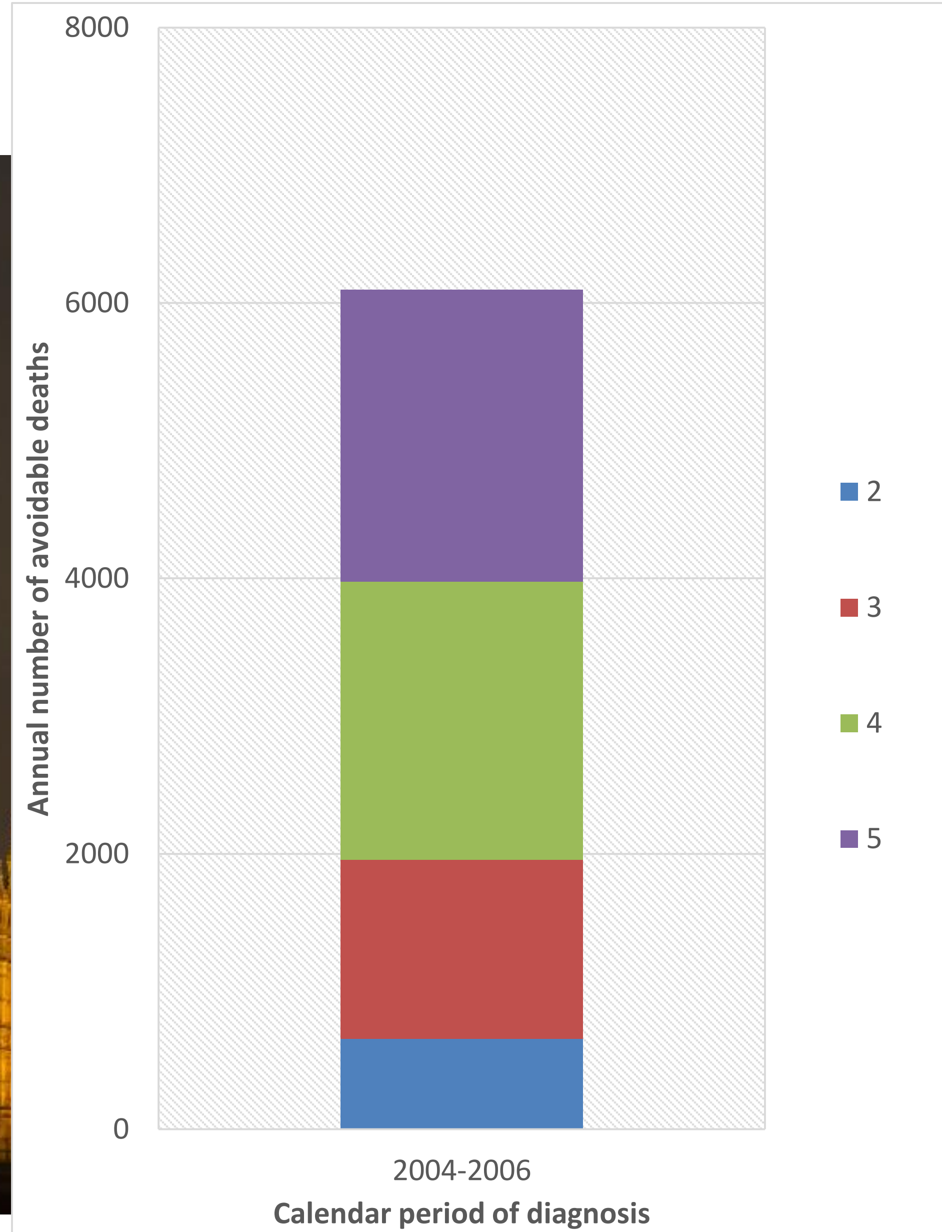
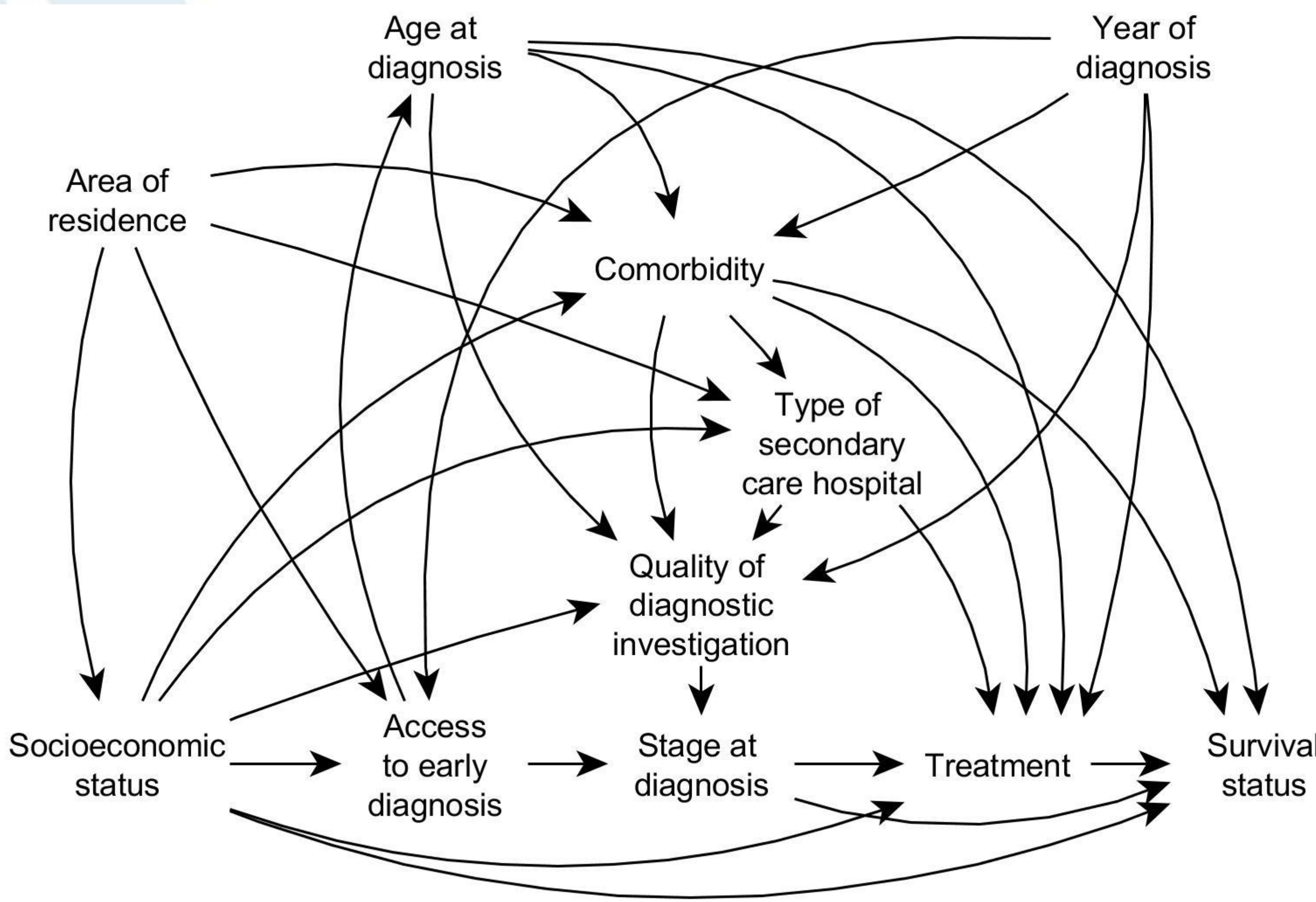
Outline

- Main questions
- Challenges with conventional approaches – results from the past
- An example of applying mediation to cancer survival data
- Challenges and discussions
  - Misclassification of mediators
    - Treatment missing for more affluent – sensitivity analysis
    - Under-staged deprived patients – sensitivity analysis
  - Biases for mediation analyses
  - Controlled and natural effects
  - Conceptual frameworks – Suggestions?

Inequalities in cancer survival



Explaining inequalities



Challenges in the past

- **More deprived patients:**
  - More comorbidity
  - More advanced cancer at diagnosis (colon, rectum, breast)
  - More often diagnosed during emergency admission
  - More often treated in non-specialised hospital and by non-specialised surgeon
  - Received more often sub-optimal and delayed treatment (colon, rectum)

- **Past conventional analysis (colon, rectum, breast)**
  - No excess mortality hazard for deprivation among those treated within one month since diagnosis
  - Adjusting for comorbidity did not modify the excess mortality hazard for deprivation
  - Adjusting for stage reduced the excess mortality hazard for deprivation by less than a third

  - Limited stage and treatment data and conventional analytic approaches did not enable identification of mechanisms underlying deprivation gap in survival

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How much of the socioeconomic differences in breast cancer patient survival can be explained by stage at diagnosis and treatment?

Application of causal mediation analysis to routine data

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Introducing breast cancer

- Most common cancer in the UK
- Screening (50-70)
- Treatment with strict guidelines

- Northern and Yorkshire Cancer Registry, population-based, covering 12% of the English population
- Women with malignant breast cancers (N=36,793)
  - Diagnosed during the period 2000–2007
  - Followed up until 31 December 2007

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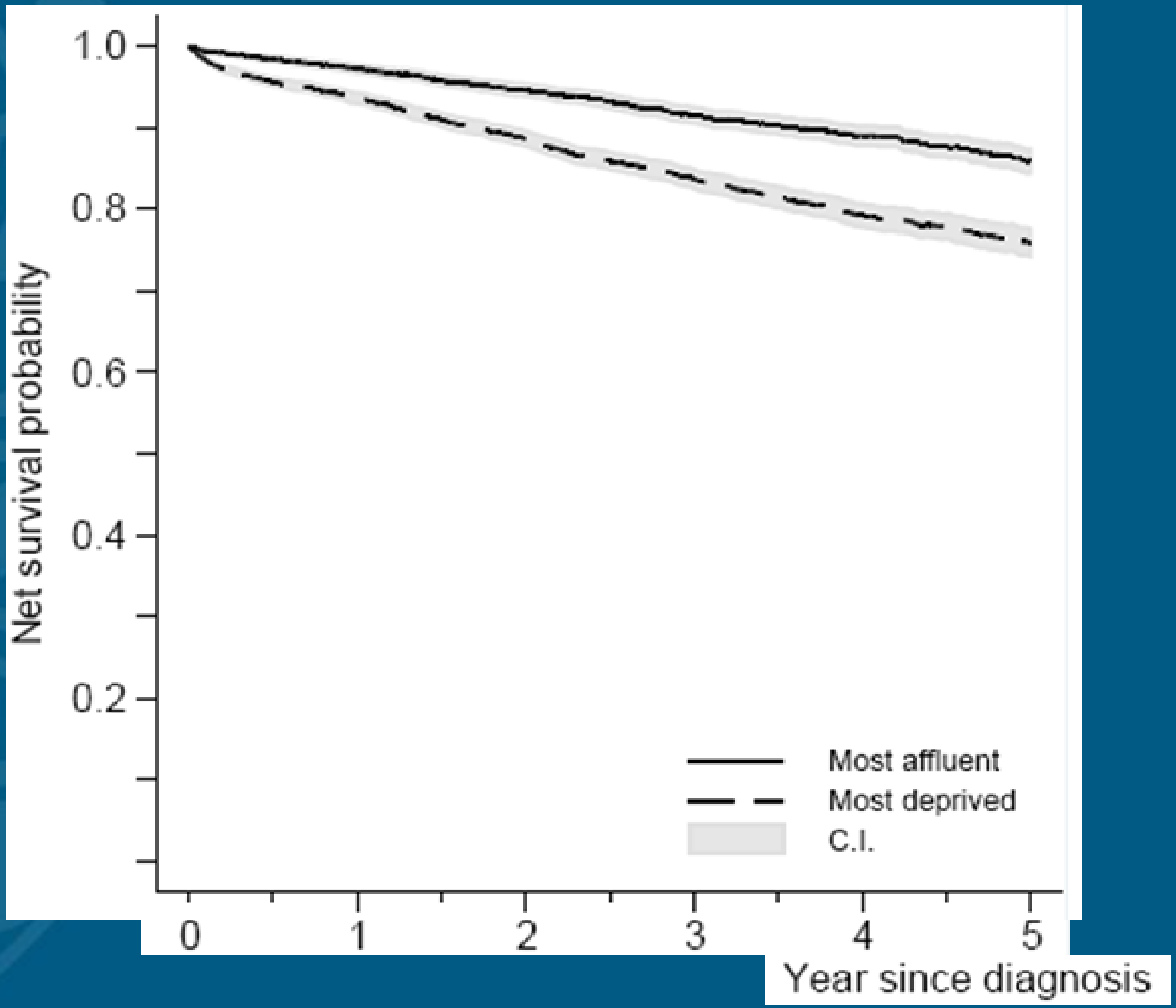
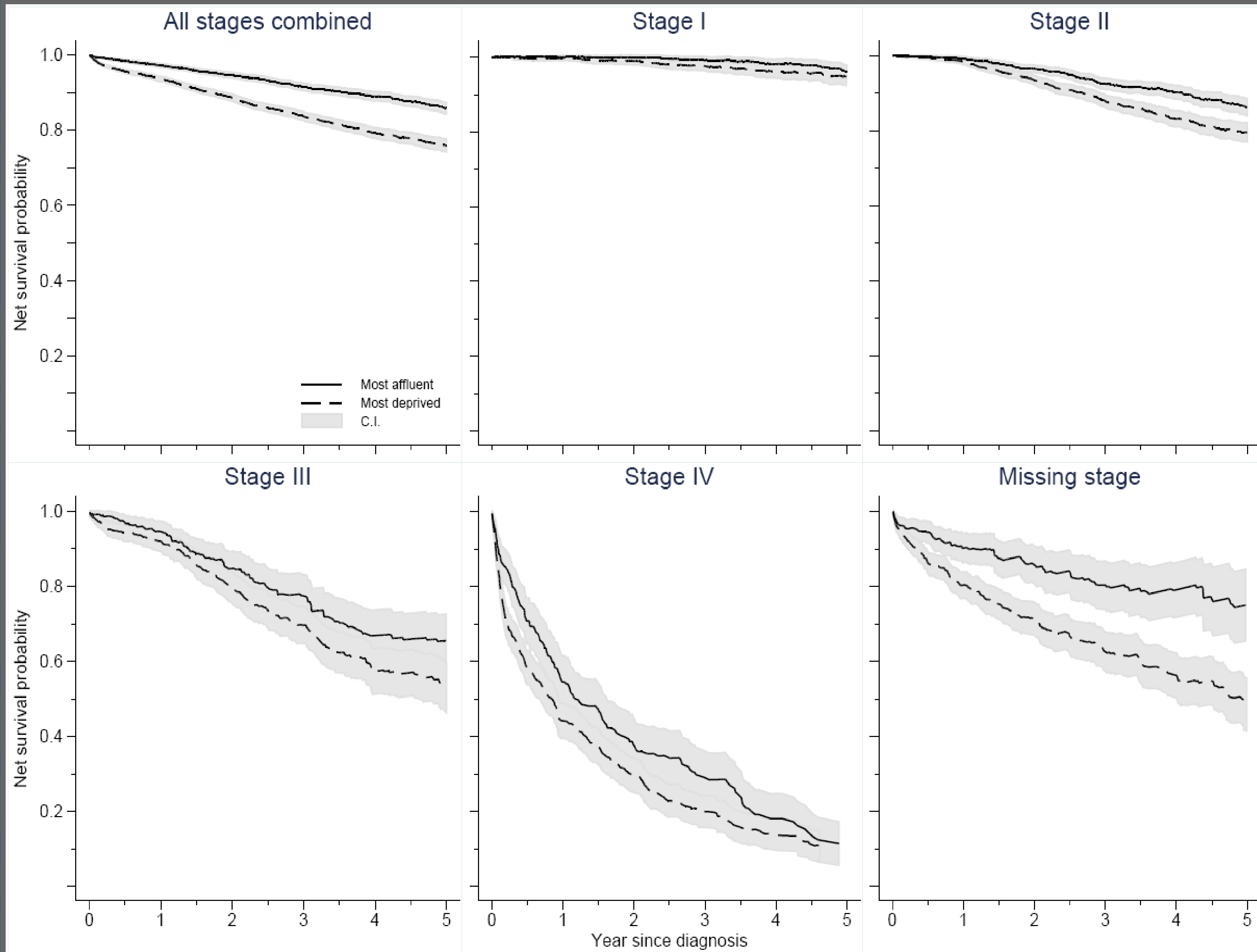
Large deprivation gap in survival from breast cancer…



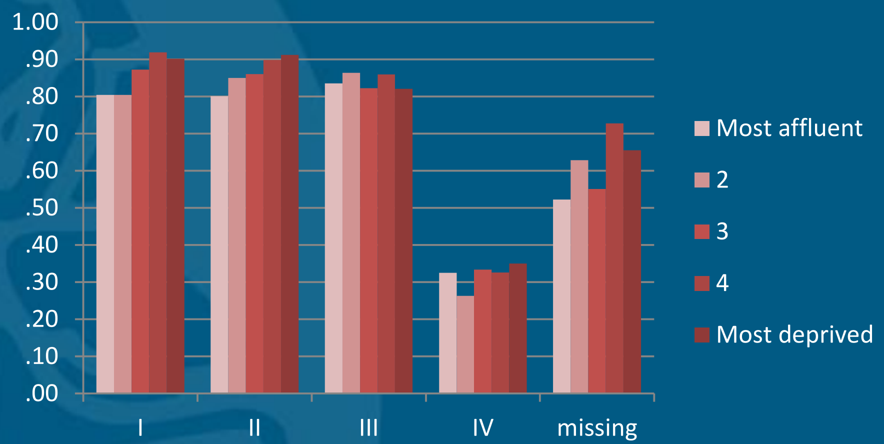
Possible explanations

- Differential stage at diagnosis?
- Differential treatment?

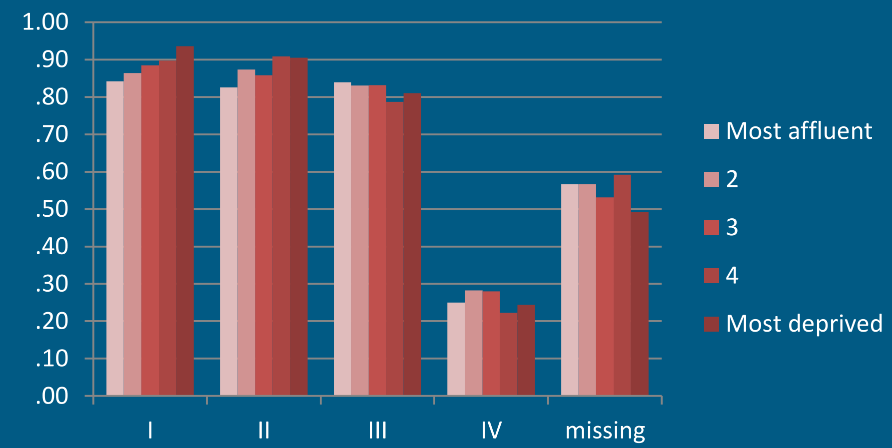

All stages combined
Stage I
Stage II
Stage III
Stage IV
Missing stage
Net survival probability
1.0
0.8
0.6
0.4
0.2
Most affluent
Most deprived
C.I.
0
1
2
3
4
5
Year since diagnosis

Differential treatment?
– probability of getting major surgery

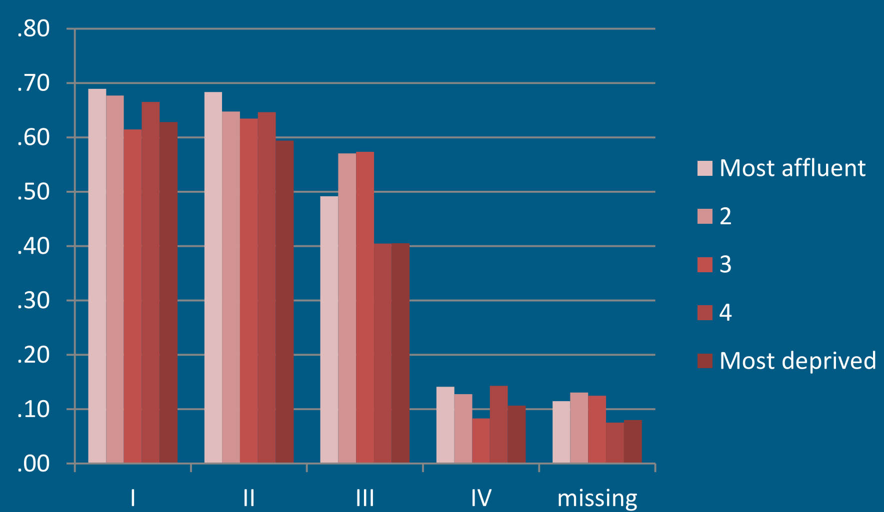
15-49 pre-screening



50-69 screening



70+
post-screening



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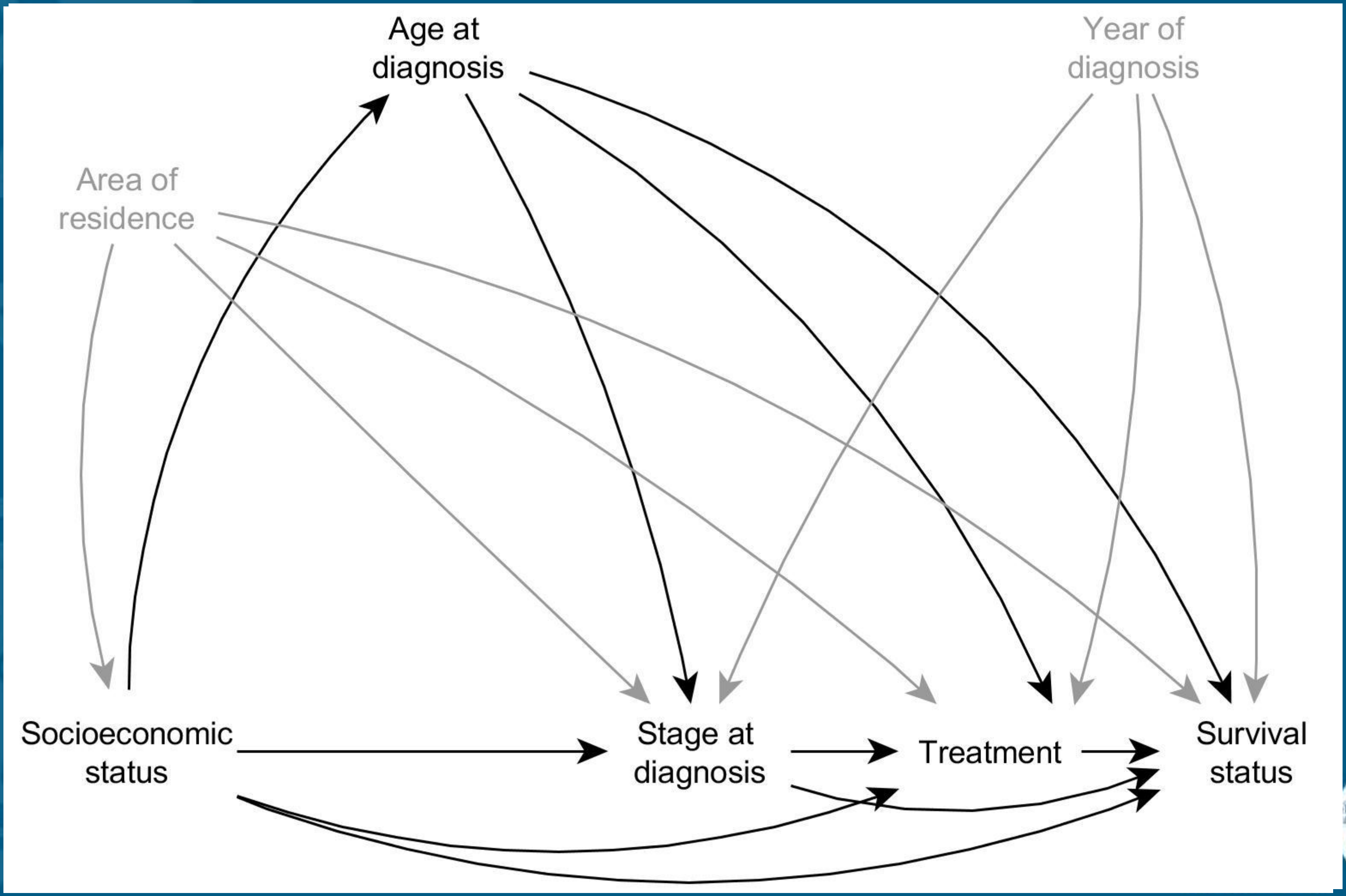
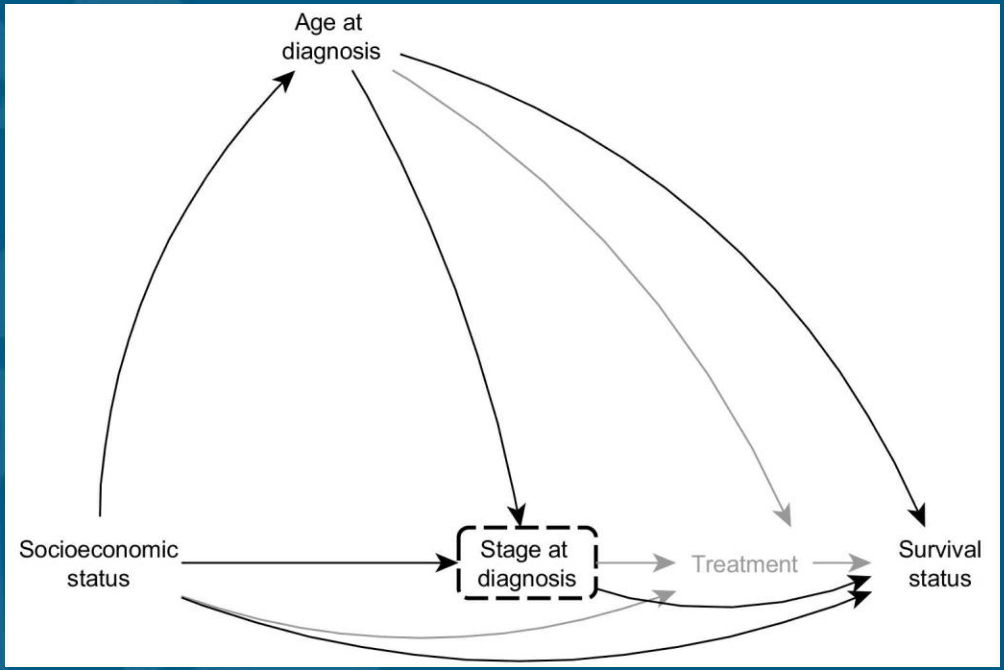
Linking to the conceptual diagram...



If we look at stage



We can **decompose** the total effect (TCE) of socioeconomic status (deprivation) on mortality into…

- Those mediated by stage (The indirect effect, NIE)

- Those not mediated by stage (The direct effect, NDE)

TCE = log(odds(Y(Dep=*most*, Stage(Dep=*most*)))) – log(odds(Y(Dep=*least*, Stage(Dep=*least*))))

NIE = log(odds(Y(Dep=*most*, Stage(Dep=*most*)))) – log(odds(Y(Dep=*most*, Stage(Dep=*least*))))

NDE = log(odds(Y(Dep=*most*, Stage(Dep=*least*)))) – log(odds(Y(Dep=*least*, Stage(Dep=*least*))))

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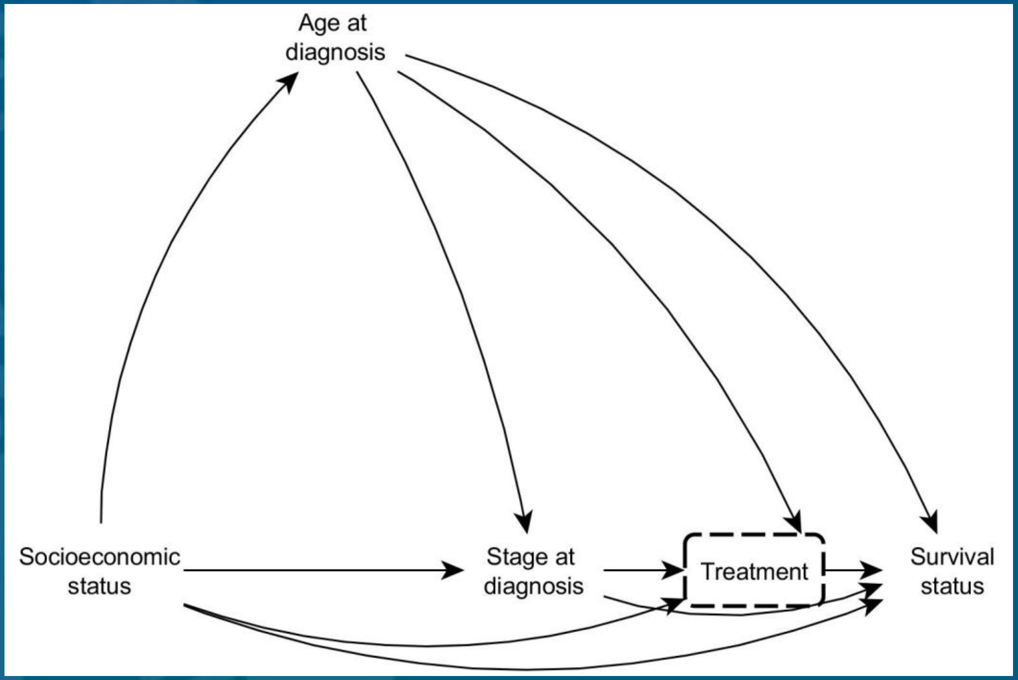
If we look at treatment



We can **decompose** the total effect (TCE) of deprivation on mortality into…

- Those mediated by treatment (The indirect effect, NIE)

- Those not mediated by treatment (The direct effect, NDE)

TCE = log(odds(Y(Dep=*most*, Treat(Dep=*most*)))) – log(odds(Y(Dep=*least*, Treat(Dep=*least*))))

NIE = log(odds(Y(Dep=*most*, Treat(Dep=*most*)))) – log(odds(Y(Dep=*most*, Treat(Dep=*least*))))

NDE = log(odds(Y(Dep=*most*, Treat(Dep=*least*)))) – log(odds(Y(Dep=*least*, Treat(Dep=*least*))))

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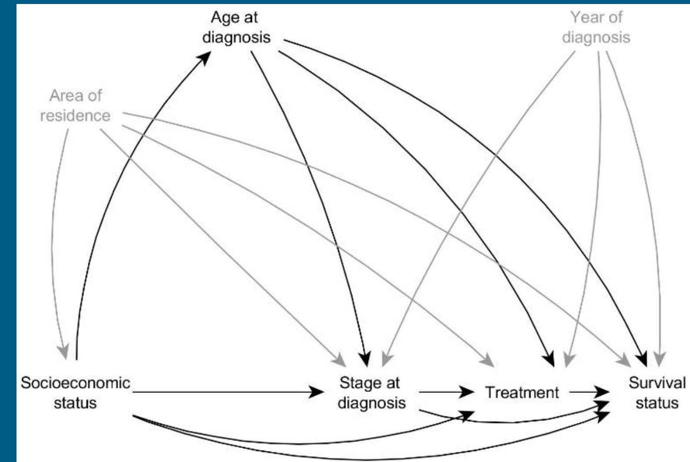
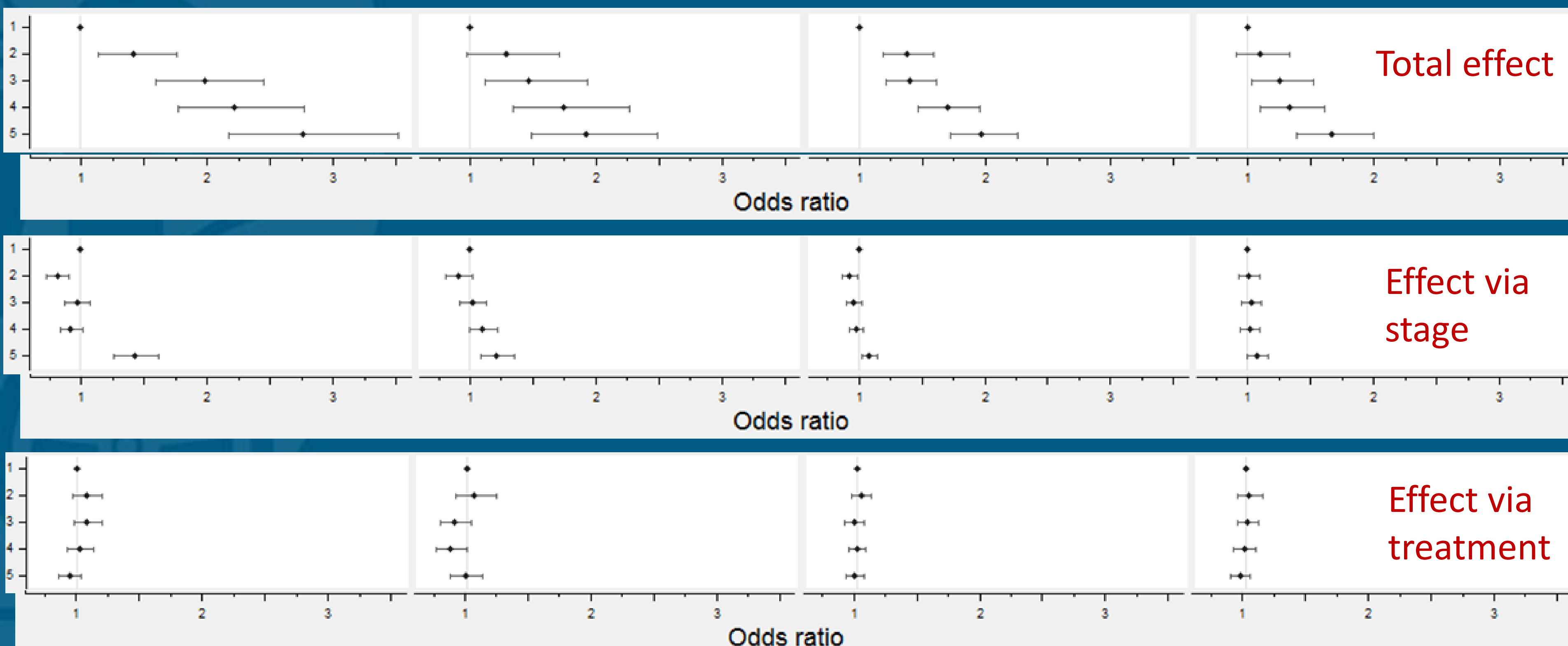
G-formula results



6 months | 12 months | 3 years | 5 years



Preliminary conclusions

- Breast cancer survival differed between the most deprived and most affluent patients

- Effect of deprivation on mortality:
  - Large total effect **FOR ALL DEPRIVATION CATEGORIES**:
    - Increasing with deprivation
    - Decreasing with time since diagnosis
  - Mediated via stage **ONLY FOR MOST DEPRIVED CATEGORY**:
    - One third of at six months
    - One tenth at three/five years since diagnosis
  - Mediated via treatment:
    - None

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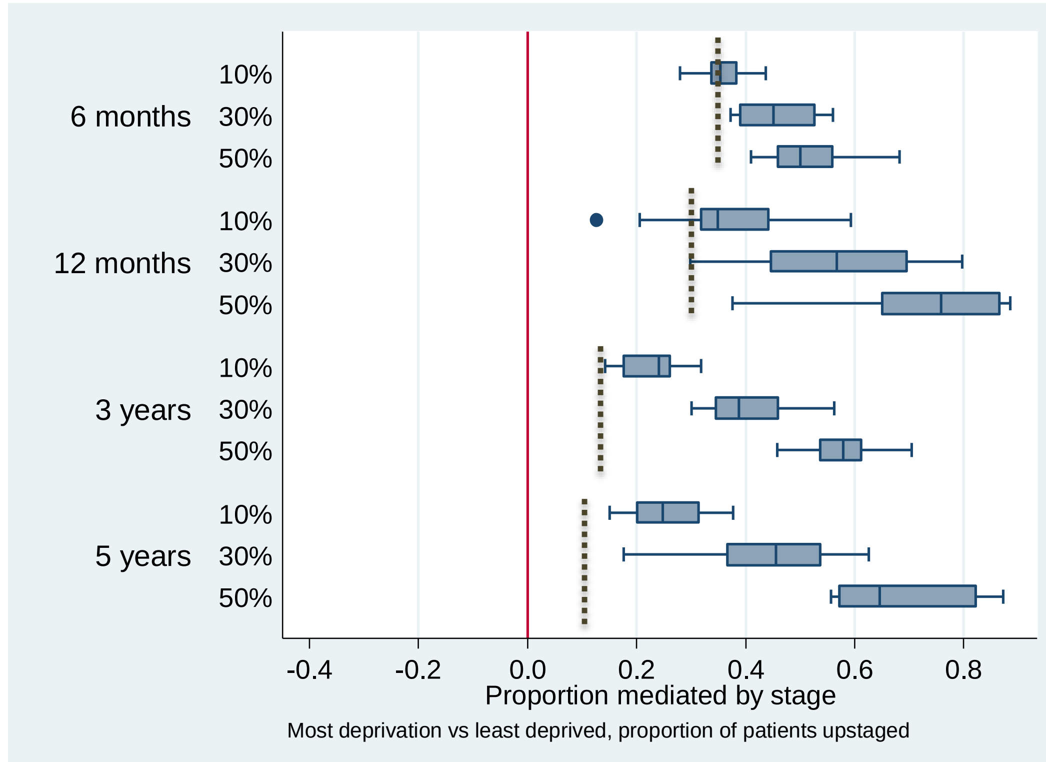
Misclassification of stage

- More deprived patients may be under-staged?
- Randomly "up-staging" 10%, 30% and 50% of most deprived patients…

- 10% up-staging did not change results much
- After 30%-50% upstaging, stage would mediate more than half of the survival differences
- Longer-term survival is more affected …



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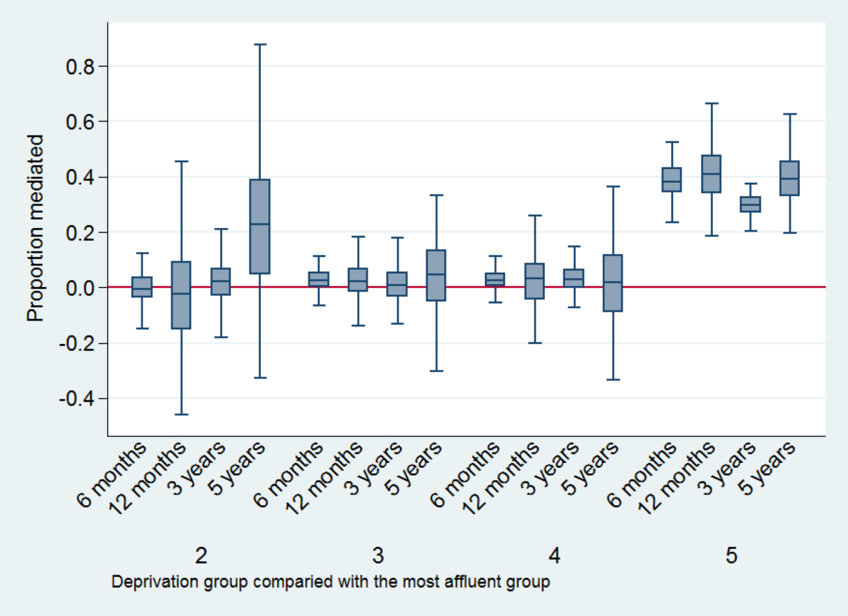
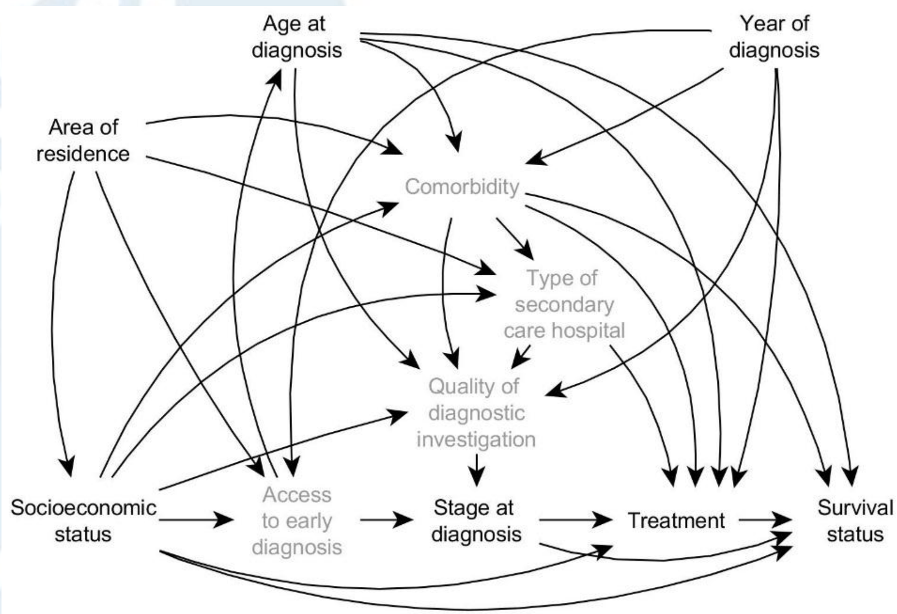
Misclassification of treatment

- One report showed that 4% of surgical treatment for breast cancer were made in private hospital
- Sensitivity analysis:
  – Assumption: all missing surgery is among most affluent patients
  – Randomly adding “major surgery” to 4% of women, all from the most affluent category
- Now treatment mediates survival differences for the most deprived!



Biases for mediation analysis



- Unmeasured or poorly measured confounders, e.g. between mediator and outcome?
- Presence of confounder(s) between mediator and outcome affected by exposure?

Summary

- First application of the causal mediation tool in study of cancer registry data
- Population-based data
- Drawbacks
  - Data quality and detail
  - Unmeasured confounder, e.g. comorbidity
- Useful for answering questions related to causality
  - Resource allocation

References

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- Daniel, R. M., De Stavola, B. L., and Cousens, S. N. 2011. gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. The Stata Journal 11(4):479-517.
- Hernán M. A., Robins J. M. Causal Inference. Part II Causal inference with models http://www.hsph.harvard.edu/miguel-hernan/files/2013/10/hernanrobins_v2.15.02.pdf [updated 15 October 2013]

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Questions for you

- How to deal with the potential biases, due to unmeasured/poorly measured confounders?
- Controlled *vs.* natural effects?
- How to deal with stage misclassification?
- Suggestions on the research questions or the frameworks?

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