Mediation analysis

a tool to move from estimating treatment effect to understanding treatment mechanism

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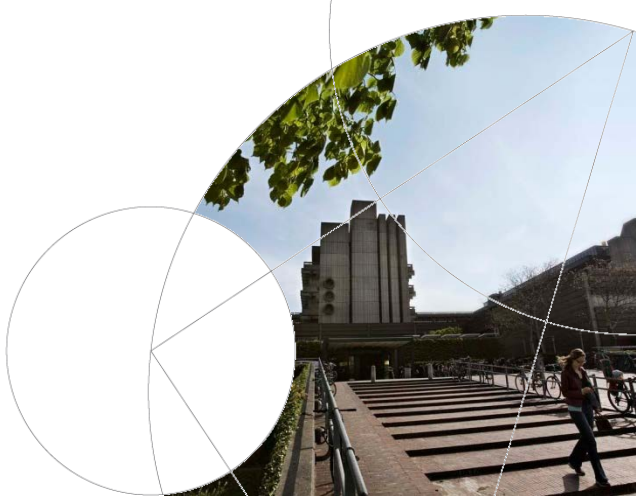
This talk was prepared with fantastic input from ALK, which is gratefully acknowledged.



There's something in the air…

Grazax - Phleum pratense

GRAZAX® er den første allergen specifikke immunterapi i tabletform, der behandler den underliggende årsag til græspollenallergi.

GRAZAX® har i studier vist signifikante reduktioner i allergi-symptomer, samtidig med at GRAZAX® mindsker behovet for anden symptomatisk behandling. GRAZAX® er en brugervenlig behandling i form af hurtigt opløselige sublinguale (under tungen) tabletter, som patienten kan tage hjemme én gang dagligt i 3 år. Tabletten indeholder 75.000 SQ-T (*Phleum pratense*).

GRAZAX® er en fordelagtig behandling for patienter som har en dominerende græs-allergi og ikke opnår tilstrækkelig god kontrol med symptomatisk behandling.

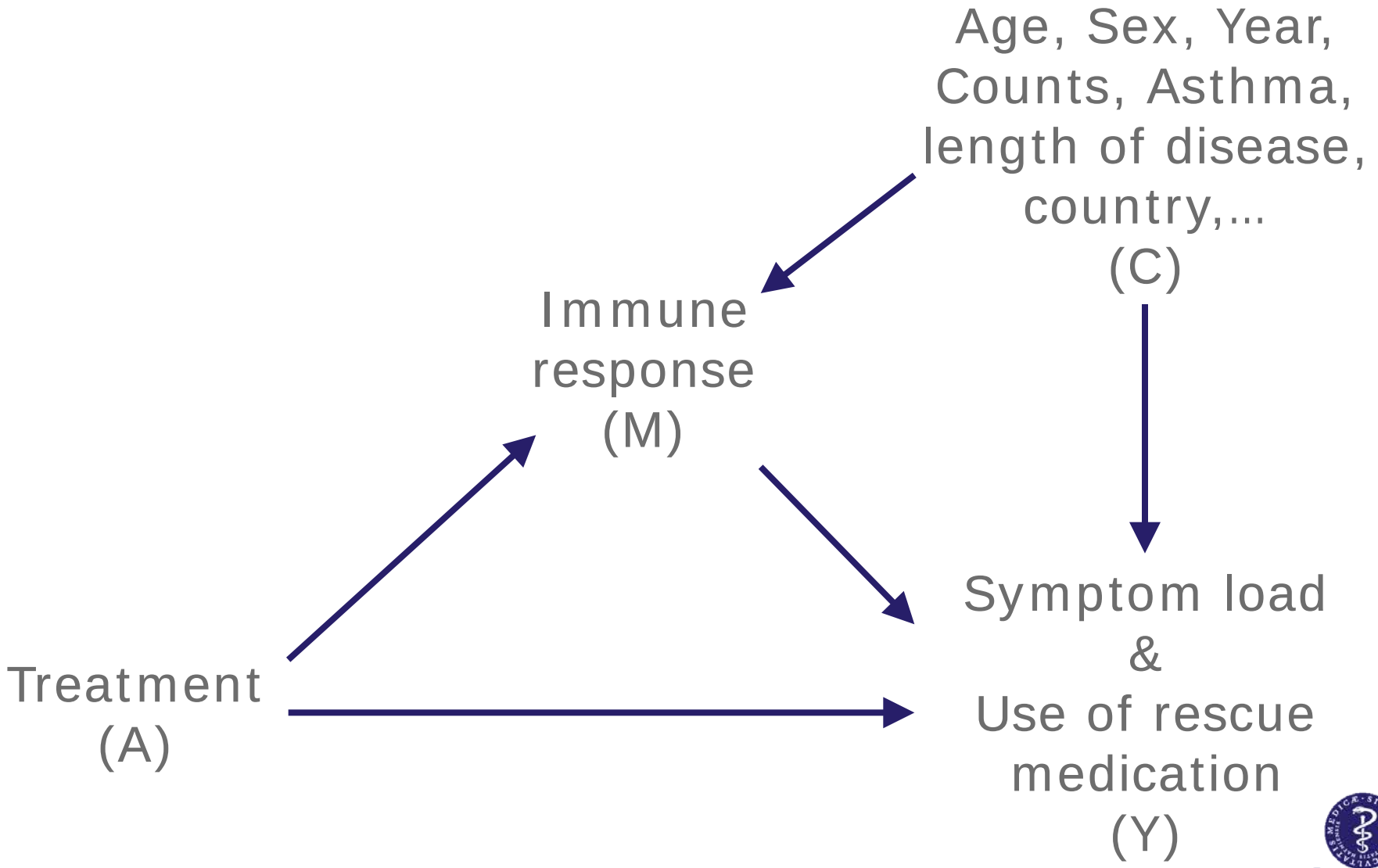
Hvis du vil vide mere om GRAZAX® kan du klikke på følgende link

Indikation
Behandling af græspollen-induceret rhinitis og konjunktivitis hos voksne patienter med klinisk relevante symptomer og diagnosticeret med en positiv hudpriktest og/eller specifik IgE-test overfor græspollen.

What was in the air?

- GT08 was placebo controlled and blinded study of the effect of GRAZAX®.
- Multi center study with 3 years of treatment (from 2005) and two additional follow-up years.
- In GT-08, trial treatment was initiated at least 16 weeks before the anticipated start of the grass pollen season.
- High-frequency recording of symptoms and use of rescue medication (logpad).
- Blood samples at end of each pollen season to assess immune response.
- **Disclaimer:** The presented analysis is post.hoc. and constitutes by no means a complete picture of mediation in connection with GRAZAX®.

The plausible causal connections



Does treatment work?

Symptoms

- Average symptom score reduced by 0.88 points.
- Highly significant (P=0.002).
- Intra-person correlation handled by GEE techniques.

Use of rescue medication

- High use of rescue medication (defined as more than one use on average) reduced in active group.
- OR of 0.57 (95% CI: 0.34-0.98).
- Intra-person correlation handled by GEE techniques.

The goal of mediation analysis

- Is the considered mediator(s) the important mechanisme linking treatment and outcome?
- How much of the effect is mediated through the selected mediator?
- How much NOT through the selected mediator?

- Note that the DAG is the key tool/assumption.
  - For instance is the causal order of mediator and outcome OK here?
  - How about the year-to-year effects?

The old way of doing mediation analysis

- The most often employed technique is to estimate models for the outcome (*Y*) both with and without the potential mediator.
- A drop in HR/OR/RR/Est. corresponding to the exposure (*A*) from the model without to the model with the mediator is taken as evidence of mediation.
- This approach was introduced in Baron and Kenny (1986), which has over 40,000 citations by now.

REF: Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. Journal of Personality and Social Psychology, 51, 1173-1182.

The new way (I/II): Counterfactuals

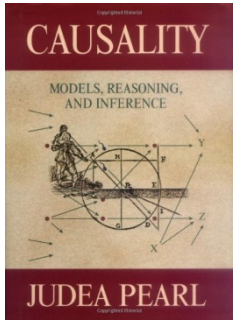
Counterfactual variables:

- $Y_{a,m}$ the outcome we would, possibly contrary to fact, have observed had exposure A been set to the value a and the mediator M set to m.
- M_a the value of the mediator if, possibly contrary to fact, exposure A was set to a.

Nested counterfactuals:

- Y_{a^*,M_a}, the outcome that would have been observed if A were set to a^* and M to the value it would have taken if A were set to a.

REF:



The new way (II/II): Natural direct and indirect effects

- **Natural direct effects (DE)** is the effect of changing the exposure relative to the direct pathway, but keeping exposure constant relative to the indirect pathway through the mediator; i.e:

$$Y_{a,M_a} \text{ vs. } Y_{a^*,M_a}$$

- **Natural indirect effects (IE)** is the effect of changing the exposure relative to the indirect pathway, but keeping exposure constant relative to the direct pathway; i.e:

$$Y_{a^*,M_a} \text{ vs. } Y_{a^*,M_{a^*}}$$

- **Total effects (TE)** denotes the effect of "simply" changing the exposure; that is comparing Y_{a,M_a} with $Y_{a^*,M_{a^*}}$.

REF: Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. *Int J Epidemiol.* 2009;38(3):838–845.

Mediation: Let us try to be precise

Following Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects *Epidemiology*. 1992;3(2):143-155.

General definition:

- The ***natural direct effect*** measures the change in outcome that would be observed if we could change the exposure, but leave the mediator at the value it naturally takes when the exposure is left unchanged.

The example:

- In the example ***natural direct effect*** is the change in symptoms that would be observed if treatment was changed without inducing any change in immune response.

Mediation: Let us try to be precise

Following Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects *Epidemiology*. 1992;3(2):143-155.

General definition:

- The ***natural indirect effect*** measures the change in outcome that would be observed if we could change the mediator as much as it would naturally change when exposure was changed without actually changing the exposure.

The example:

- In the example ***natural indirect effect*** is the change in symptoms that would be observed if immune response was changed as it would naturally change if treatment was initiated without actually doing that.

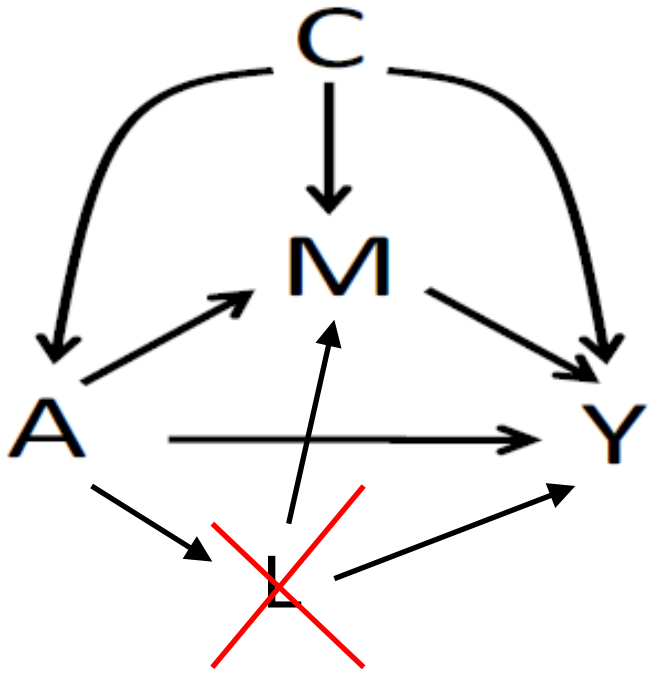
OLD vs. NEW

	OLD (Baron & Kenny)	NEW (counterfactual based)
Coding	Easy	Harder
Underlying idea	An algorithm	A defined parameter of interest.
Bias	Yes (except in purely linear models)	No (for any combination of variables types)

Assumptions for natural direct and indirect effects

1: No unmeasured confounders of:

- The exposure-outcome relation
- The exposure-mediator relation
- The mediation-outcome relation



2: No intertwined causal pathways.
(aka. Pearls identifiability condition)

3: Consistency and positivity.
(mostly technical)

REF: Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2): 143–155.

So how to estimate natural direct and indirect effects

Direct and Indirect Effects in a Survival Context

(*Epidemiology* 2011;22: 575–581)

Theis Lange[a] *and Jørgen V. Hansen*[b]

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Practice of Epidemiology

A Simple Unified Approach for Estimating Natural Direct and Indirect Effects

American Journal of Epidemiology
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DOI: 10.1093/aje/kwt270

Practice of Epidemiology

Assessing Natural Direct and Indirect Effects Through Multiple Pathways

- And many more.
- Look for instance at S. Vansteelandt, Tyler VanderWeele, and Imai.

Natural effects models

- We suggest to parameterize the natural direct and indirect effects directly in a model for the (nested counterfactual) outcome:

$$g(E[Y_{a,M_{a^*}}]) = c_0 + c_1 a + c_2 a^* + c_3 a \cdot a^* \qquad (1)$$

g is a link function specifying the requested model for the outcome (e.g. logistic model) and c_3 is an interaction term.

- When $c_3 = 0$ and g is the logit link, then

$$\exp[c_1(a - a^*)] = \frac{\text{odds}[Y_{a,M_{a^*}} = 1]}{\text{odds}[Y_{a^*,M_{a^*}} = 1]}$$

captures the natural direct effect odds ratio.

Natural effects models (cont.)

- Besides all outcomes which can be modeled by generalized linear models the approach can also handle survival outcomes using either Cox or additive hazard models.

- Mediator and exposure can be of any type.

- However, we only see persons with a=a*, so we have to be clever about estimation.

Estimation procedure for natural effects models (I/II)

Under standard assumptions of no-unmeasured confounders and no exposure dependent confounding the MSMs in (1)-(3) can be estimated by the following approach:

1. Estimate a suitable model for the mediator conditional on exposure and baseline variables using the original data set.
2. Construct a new data set by repeating each observations in the original data set twice and including an additional variable A^*, which is equal to the original exposure for the first replication and equal to the opposite of the actual exposure for the second replication.

   See the paper for details regarding categorical or continuous exposures.

Estimation procedure for natural effects models (II/II)

3. Compute weights given by

$$W_i = \frac{P(M = M_i | A = A_i^*, C = C_i)}{P(M = M_i | A = A_i, C = C_i)}.$$

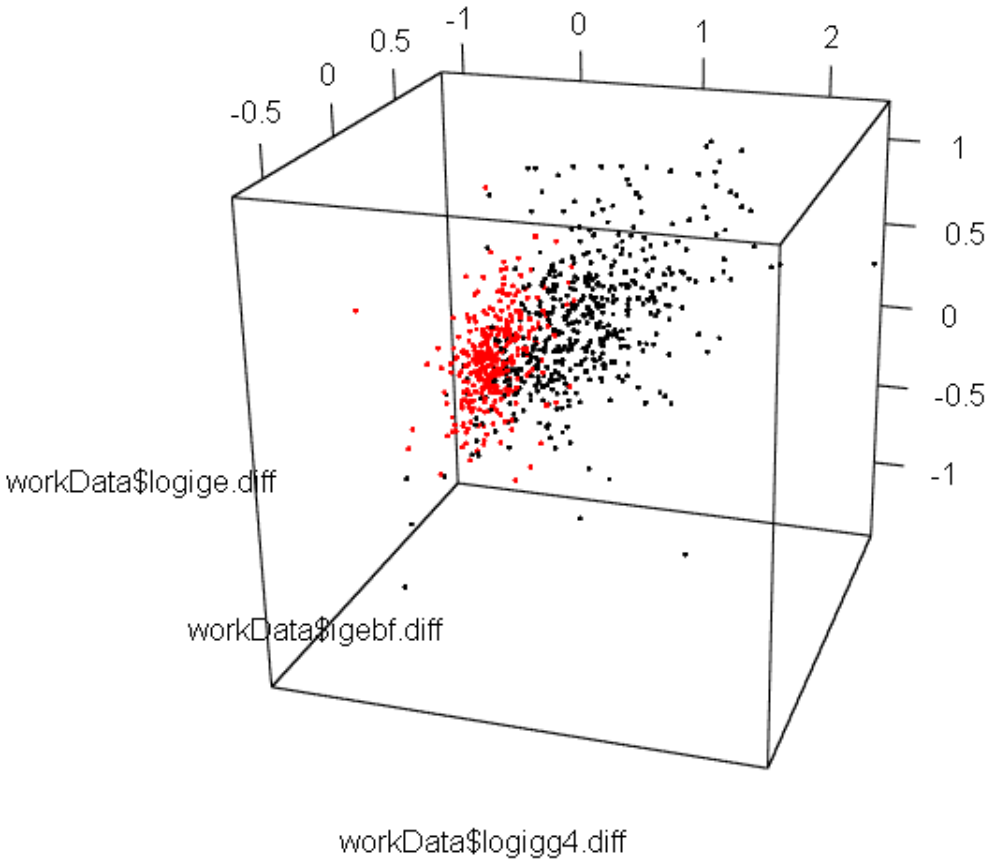
through applying the fitted model from step 1 to the new data set. In most software packages this can be done using predict-functionality.

4. Fit a suitable MSM model to the outcome including A, A^*, (perhaps their interaction) and baseline variables as covariates and weighted by the weights from the previous step.

5. Conservative confidence intervals can be obtained using robust standard errors or better yet using bootstrap.

Let us try it out on the example

Step 1: Estimate model for mediator



Let us try it out on the example

Step 1: Estimate model for mediator

- We employ a simple linear model (3-dim) including all confounders (C).
- Important point is that we can predict from this model.
- SEs are not important

R-code:

```
workData$treatmentTemp <- workData$treatment
fitM <- lm(cbind(logige.diff, igebf.diff, logigg4.diff)
       ~factor(year)+factor(treatmentTemp)+factor(country)
       +factor(sex)+counts,data=workData)
fitM.varmatrix <- var(residuals(fitM))
```

Let us try it out on the example

Step 2: Extend data set

```
myData1 <- workData
myData1$treatmentStar <- "ACT"
myData2 <- workData
myData2$treatmentStar <- "PLB"
newData <- rbind(myData1, myData2)
rm(myData1, myData2)
newData <- newData[order(newData$subject),]
```

Example:

subject	country	year	counts	treatment	treatmentStar	rhsymptoms	rhmedication	logige.diff
1	Austria	2005	42	ACT	ACT	0.384	0	0.49
1	Austria	2005	42	ACT	PLB	0.384	0	0.49

Let us try it out on the example

Step 3: Compute weights

- Idea is to compute predicted values for each row in the extended dataset
- Next evaluate normal density at the observed values of the mediator.

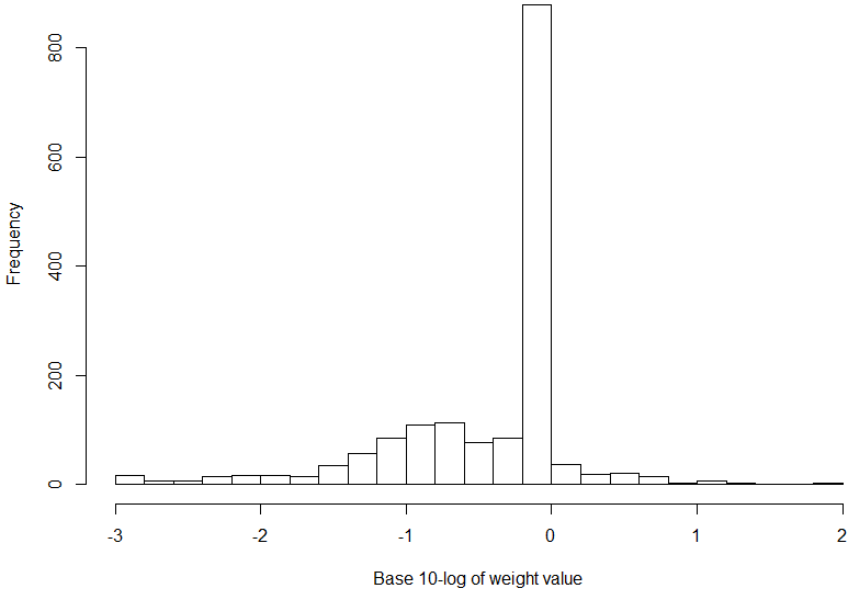
R-code:

```
newData$treatmentTemp <- newData$treatment
temp <- predict(fitM, newdata=newData)
denumWeight <- dmvnorm2(mediatorsMatrix, mean=temp,
   sigma=fitM.varmatrix)

newData$treatmentTemp <- newData$treatmentStar
temp<-predict(fitM, newdata=newData)
numWeight <- dmvnorm2(mediatorsMatrix, mean=temp,
   sigma=fitM.varmatrix)

newData$weightM <- numWeight/denumWeight
```

Let us try it out on the example

Step 3: compute weights

```
> summary(newData$weightM)
       V1
 Min.   :  0.0010
 1st Qu.:  0.1872
 Median :  1.0000
 Mean   :  1.1892
 3rd Qu.:  1.0000
 Max.   : 75.9022
```



- Weights a bit to extreme. This rarely happens, but is due to the extreme separation of treatment groups.
- I am not perfectly happy with model for mediator.

Let us try it out on the example

Step 4 and 5: Compute natural direct and indirect effects

R-code:

```
fitNEM <-
   geeglm(I(rhmedicationBinary=="High")~(treatment+treatmentStar)+fac
   tor(year)+country+age+sex+counts,  data=newData, weight=weightM,
   family="binomial", id=newData$subject)
summary(fitNEM)
```

Results:

```
 Coefficients:
                 Estimate   Std.err  Wald Pr(>|W|)
(Intercept)      0.009052  0.733329  0.00   0.9902
treatmentPLB     0.000353  0.301346  0.00   0.9991
treatmentStarPLB 0.610462  0.196594  9.64   0.0019 **
...
```

Let us try it out on the example

Step 4 and 5: Compute natural direct and indirect effects

- Other quantities, such as mediated proportion, can be conducted as part of bootstrap procedure or in Excel sheet.

Type input here:		
	Est	SE
Direct effect	0,000353	0,301346
Indirect effect	0,610462	0,196594
Covariance b/w ests	-0,0189	

Results:	
Implied correlation b/w estimates	-0,32
Implied SE for Total effect	0,302752

	Direct effect			Indirect effect			Total effect			Mediated proportion***		
	Est	CI		Est	CI		Est	CI		Est	CI	
On linear scale*	0,000	-0,590	0,591	0,610	0,225	0,996	0,611	0,017	1,204	0,999	0,337	3,938
On exp(est) scale**	1,000	0,554	1,806	1,841	1,252	2,707	1,842	1,018	3,334	0,999	0,247	4,793

Conclusion: The estimates indicate that the reduction in rescue mediation use can almost entirely be attributed to mediation. However, confidence intervals show a different story.

Conclusions/perspectives/discussion (not the last slide!)

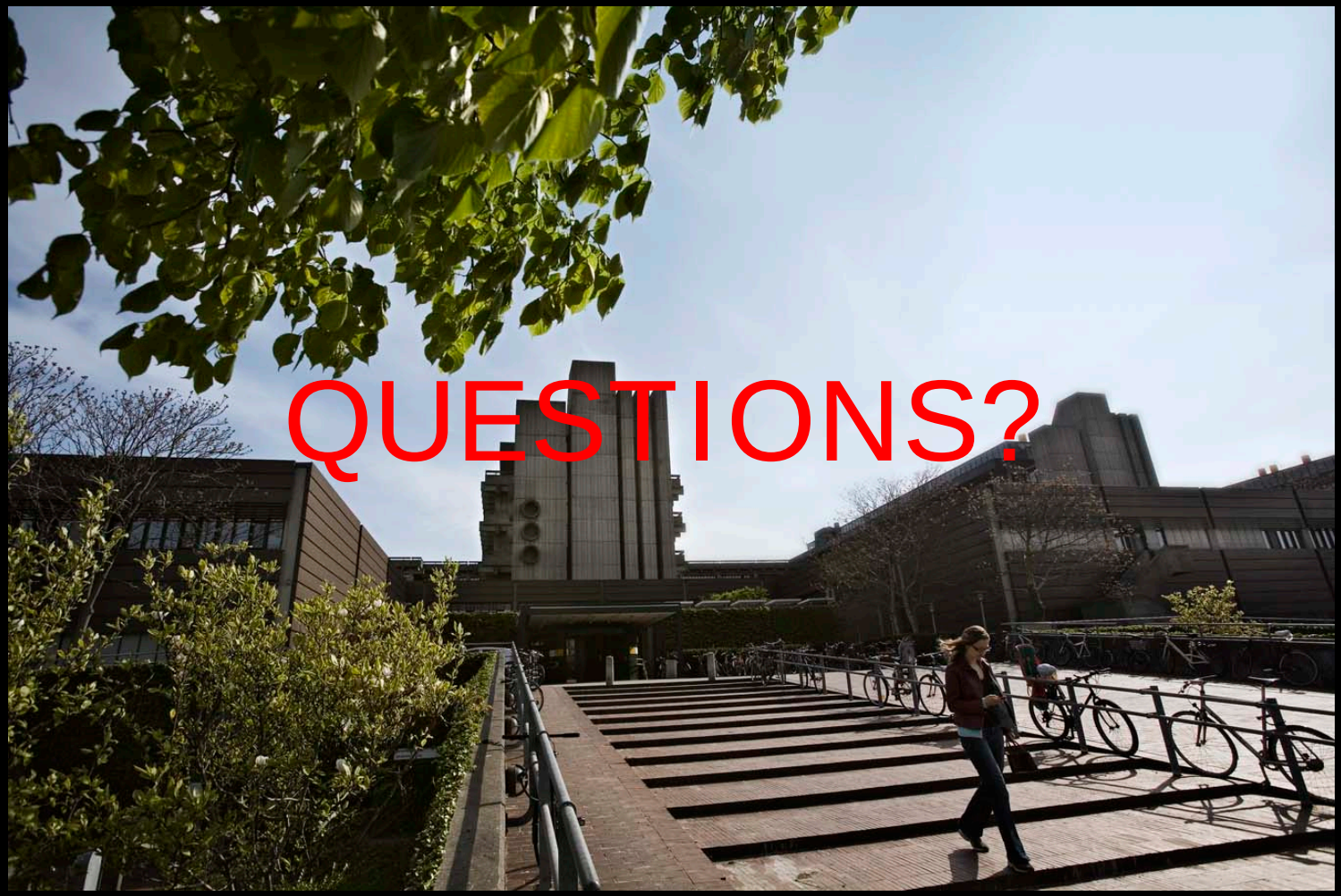
- Mediation analysis offers a way of opening the black box of treatment mechanisms.
- If both outcome and mediator can be modeled by linear models B&K is the best you can do.
- Natural effect models (as suggested by Lange et al) can also handle non-linear models and multiple mediators.
  - Code available in web-appendix.
  - Software package is under development.
- The ALK example highlights the need for
  - Good models for the mediator
  - High-temporal resolution of measurements.
  - Should mediation analyses be protocolled in advance?

Other potential uses of causal inference

Observation: The more complex sampling/question the more need for causal inference.

Examples:

- Causal effects of dynamic treatment strategies from observational studies or trials not specifically aimed at this.
- Handling non-complience using instrumental variables techniques.
- Extracting dosage information without/before dedicated dose finding trials by using doctor initiated dose changes.
- Caulsal inference modelling should not replace traditional analysis, but supplement them.


QUESTIONS?