
# Statistical mediation analysis in cardiovascular epidemiology

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# Motivation:
# Mediators and mediation analysis (1)

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- Investigating the effect of X on Y


- **Why/how** does X exert its influence on Y?
- E.g. statins: benefical effect on coronary heart disease through lipid lowering


- Such an intermediate variable on the causal pathway of X on Y is called a **mediator**

# Motivation:
# Mediators and mediation analysis (2)

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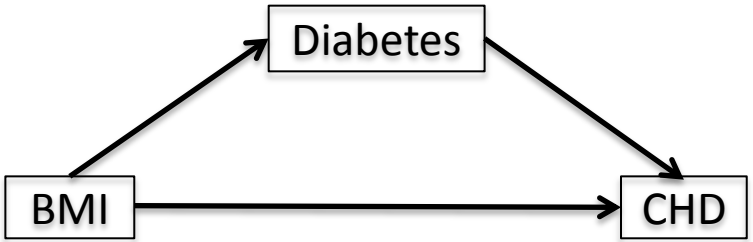
- Another example: **Effect of BMI on CHD**




- The **total** (causal) **effect** of BMI on CHD can be split up into two components:
  - The so called **indirect effect** going through diabetes
  - The so called **direct effect** (the remaining part)
- **Aim of mediation analysis:** Decompose the total effect into direct and indirect effects
- Mediation analysis **assumes the direction of causalities** to be known; other methods are needed for the study of the direction of causalities
- **Cave: Mediator ≠ confounder!!**

# Classical approaches to meditation analysis

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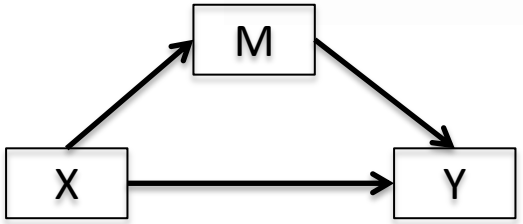
## Difference method:




1. Calculate a **model without the mediator** → **total effect**
2. Calculate another **model conditioned on the mediator** → **direct effect**
3. Subtract the direct effect from the total effect → **indirect effect**

## Product method:

1. **Outcome model** conditioned on the mediator
2. **Mediator model**
3. **Indirect effect** by **multiplying** over regression coefficients

# Difference method

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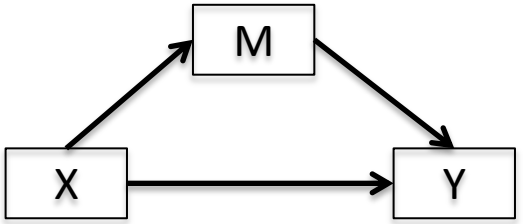
An intuitive suggestion to identify total/direct/indirect effect would be:

1. Calculate a **model without the mediator**
   → **total effect**

$$E[Y|X,C] = \beta_0 + \beta_X X + \beta_C C$$




2. Calculate another **model conditioned on the mediator**
   → **direct effect**

$$E[Y|X,C,M] = \alpha_0 + \alpha_X X + \alpha_C C + \alpha_M M$$

3. The **indirect effect** is the **difference** between total and direct effect

→ **Regression-based approach**

# Product method or "Baron and Kenny" method

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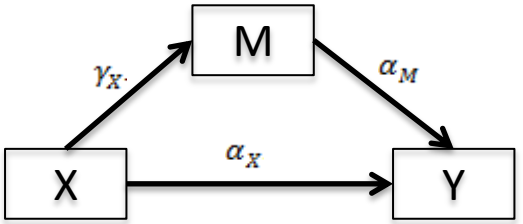
- Another regression-based approach
- Introduced by Baron and Kenny (1986)
  1. Calculate an **model for the outcome** adjusted for the mediator → **direct effect**

$$E[Y|X,C,M] = \alpha_0 + \alpha_X X + \alpha_C C + \alpha_M M$$




  2. Calculate a **model for the mediator**

$$E[M|X,C] = \gamma_0 + \gamma_X X + \gamma_C C$$

  3. The **indirect effect** is the **product** $\gamma_X * \alpha_M$ (path tracing rule)

# Limitations of the difference and product method

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**Results of the product and difference method do in general differ!** (MacKinnon and Dwyer, 1993)

- The results coincide only in the case of continuous mediator and outcome in the absence of interactions.
- Which method delivers the correct results?
- We need **generic definitions** of direct and indirect effects!
- More than „standard statistics“ necessary.
- With tools and notation of the **counterfactual framework**, definitions of **controlled direct**, **natural direct** and **natural indirect effects** can be given (J. Pearl, 2001).

# Challenges in mediation

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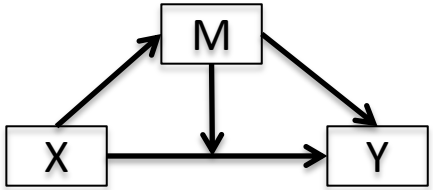
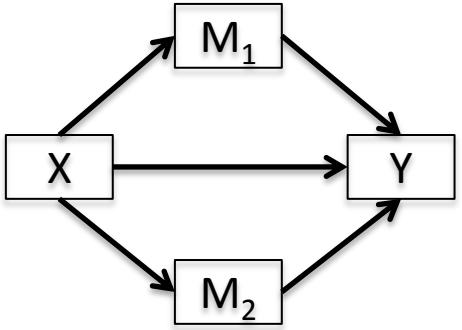
- Non-linear dependencies (binary mediators/outcomes, time-to-event outcomes)
- Interactions:

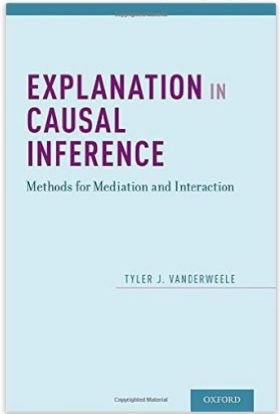



- Issues with additional confounding

- Multiple mediators:




→ Over the last decade, research based on the **causal inference theory** - and here specifically **counterfactuals (potential outcomes)** - adressed many of these issues and many new methods were developed



# Aim of our research

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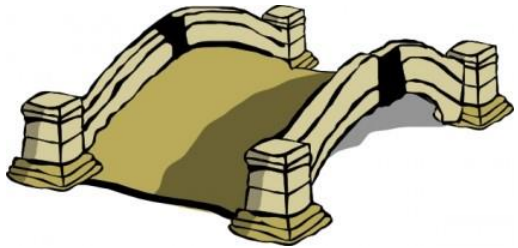
## Theoretical statistics

- New sophisticated methods
- Statistical background necessary to comprehend (counterfactual theory)
- Not so easy to implement (no handy software packages)



Cardiovascular epidemiology

Data from large cohort studies

Demonstrate feasibility of novel mediation methods

## Applied research/ epidemiology

- (Biomedical) research questions where mediation naturally appears
- Recent developments in mediation have not arrived yet

# Material and methods

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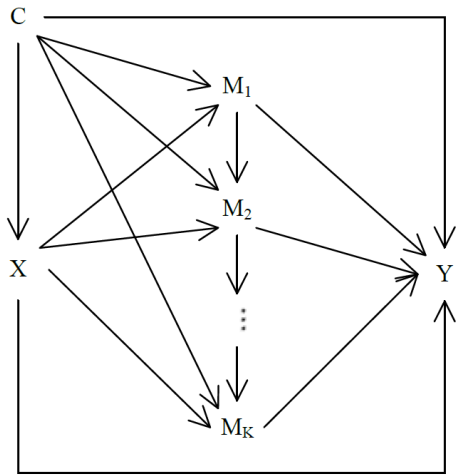
## Material:

- Malmö Diet and Cancer Study (MDCS)
  - Middle-aged men and women from Malmö
  - ~24,000 participants, more than 2,200 CHD events
- Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)
  - ~180,000 individuals, nearly 4,000 CHD deaths

## Methods:

- Regression-based approach for multiple mediators for the Cox proportional hazards model (VanderWeele, Epidemiology 2012)
- Natural effect models (Lange, Am J Epidemiol 2014)
  - Break-down of indirect effect into single mediator components



# Study 1: Mediators of sex/gender differences in CHD mortality (1)

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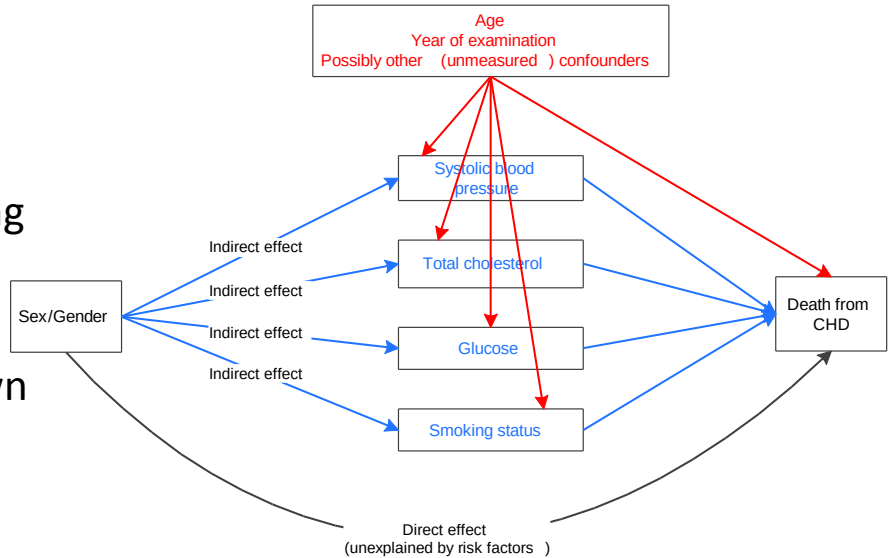
- **Can sex/gender differences in the mortality due CHD be explained by traditional cardiovascular risk factors?**
- If yes, **how much** can be explained?
- Are there **age differences**?
- No proper mediation analysis been done before (only rudimentarily tackled treating risk factors as confounders)
- **Aim**: Mediation analysis using natural effects models (Lange) allowing breakdown into single components of the indirect sex/gender effect



# Study 1: Mediators of sex/gender differences in CHD mortality (2)

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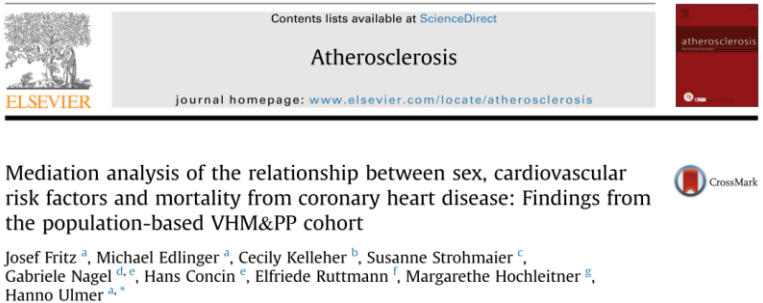
- Data of the Vorarlberg Health Monitoring and Promotion Programme
- **The extent to which risk factors contribued varied with age**
  - **<50 years**: the **4 RFs explained 41%** (95% CI: 27%-54%) of the sex effect
  - **≥50 years**: the **4 RFs explained 8%** (95% CI: 4%-12%) of the sex effect
- In younger individuals, the female survival advantage was explained to a substantial part through the pathways of the 4 major risk factors
- **Blood pressure** and **cholesterol** were the **strongest factors**

- The study was published in Atherosclerosis in September 2015


Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

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Mediation analysis of the relationship between sex, cardiovascular risk factors and mortality from coronary heart disease: Findings from the population-based VHM&PP cohort

Josef Fritz [a], Michael Edlinger [a], Cecily Kelleher [b], Susanne Strohmaier [c], Gabriele Nagel [d, e], Hans Concin [e], Elfriede Ruttmann [f], Margarethe Hochleitner [g], Hanno Ulmer [a, *]

# Study 2: Age, metabolic mediators of BMI and CHD mortality (1)

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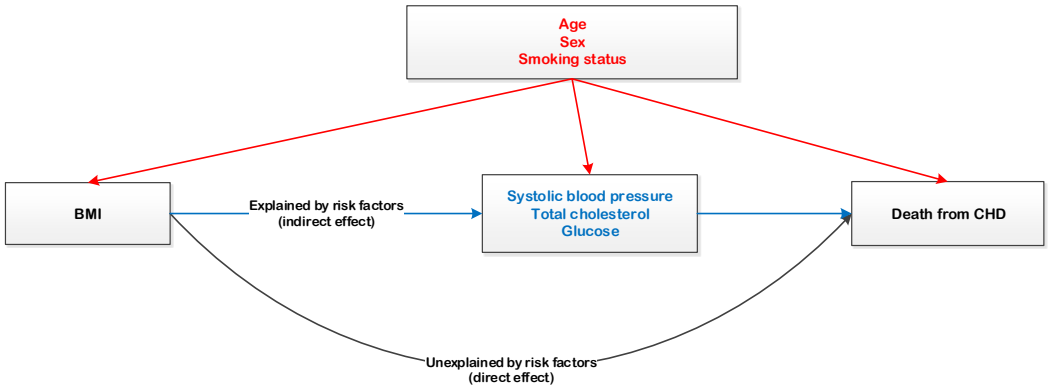
- Previous studies by Lu et al. (Lancet, 2014; Epidemiology, 2015) showed that about **half of the risk of BMI on CHD is mediated by metabolic risk factors**
- Age only as confounder, not as effect moderator
- Our additional question: Are there **age dependencies** in metabolic mediation of body mass index (BMI) on CHD mortality?
- **Aim**: Mediation analysis using the regression-based mediation analysis approach by VanderWeele



# Study 2: Age, metabolic mediators of BMI and CHD mortality (2)

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- Our results indicate that **metabolic risk factors may play different roles in explaining the risk of increased BMI on CHD between the younger and the elderly**

- Published in Epidemiology in May 2016 as an extended letter referring to the original article by Lu et al.

# Study 3: Metabolic mediators and CHD genetics (1)

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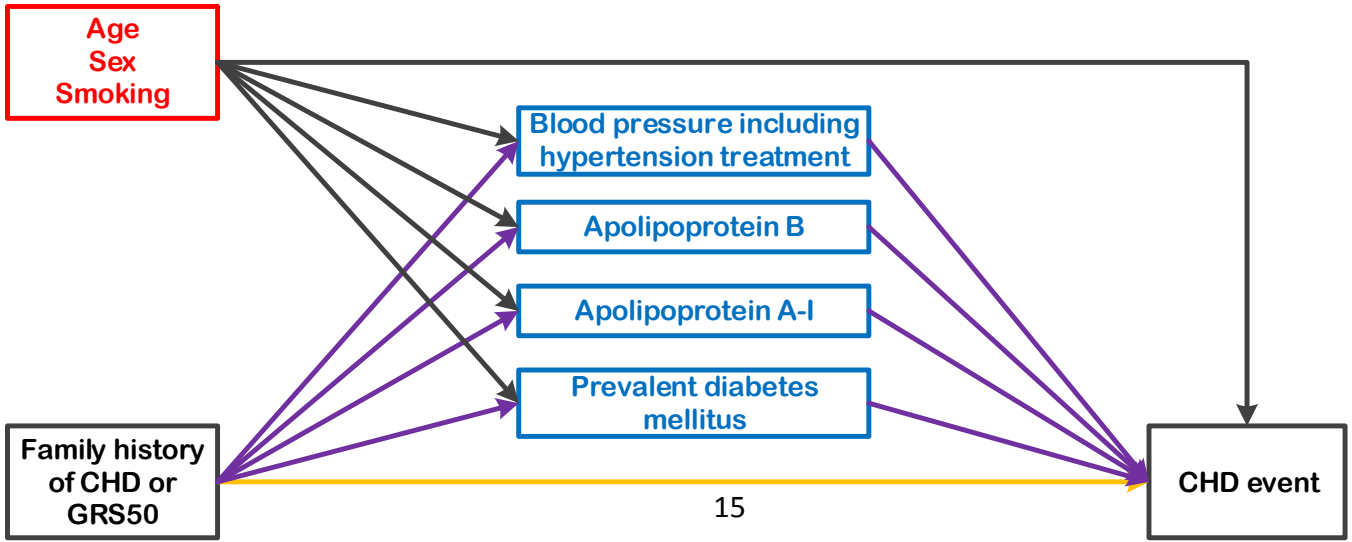
- **Guidelines on CVD/CHD prevention** acknowledge that conventional CV risk factors can **"partly explain the impact of genetic risk"**
- Otherwise very unspecific
  - How much exactly is explained?
  - By which risk factors exactly?



# Study 3: Metabolic mediators and CHD genetics (2)

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- Data of the Malmö Diet and Cancer Study
- Genetical CHD risk measured as
  - Self-reported **family history of CHD**
  - genetic risk scored based on 50 CHD related SNPs **(GRS50)**
- The data indicates that a fraction of the CHD risk associated with family history or with GRS50 is mediated through dyslipidaemia and hypertension, but not through diabetes.
- However, it seems that the major part (≥80%) of the genetic effect operates independently from the established metabolic risk factors.

- The study was published in JAHA in March 2017

American Heart Association | American Stroke Association

Metabolic Mediators of the Effects of Family History and Genetic Risk Score on Coronary Heart Disease—Findings From the Malmö Diet and Cancer Study

Josef Fritz, MSc; Dov Shiffman, PhD; Olle Melander, MD, PhD; Hayato Tada, MD, PhD; Hanno Ulmer, PhD

# Study 3: Model dependencies of the results


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| | Family history (yes vs. no) | | | GRS50 (high vs. low/intermediate) | | |
|---|---|---|---|---|---|---|
| **Effects** | **Natural effects model[1]** | **Regression-based approach[2]** | **Difference method** | **Natural effects model[1]** | **Regression-based approach[2]** | **Difference method** |
| **Total effect** | 1.52 | 1.55 | 1.52 | 1.53 | 1.55 | 1.53 |
| **Direct effect** | 1.40 (80%) | 1.44 (83%) | 1.43 (86%) | 1.45 (87%) | 1.48 (89%) | 1.49 (93%) |
| **Indirect effect, combined** | 1.09 (20%) | 1.08 (17%) | 1.06 (14%) | 1.06 (13%) | 1.05 (11%) | 1.03 (7%) |
| **Indirect effect, through systolic blood pressure** | 1.04 (9%) | - | - | 1.02 (4%) | - | - |
| **Indirect effect, through apoA-I** | 1.01 (2%) | - | - | 1.01 (1%) | - | - |
| **Indirect effect, through apoB** | 1.04 (8%) | - | - | 1.04 (8%) | - | - |
| **Indirect effect, through diabetes mellitus** | 1.01 (1%) | - | - | 1.00 (0%) | - | - |

Effects given as HR (Proportion explained)

[1]Lange, Am J Epidemiol 2014

[2]VanderWeele, Epidemiology 2012

# Thanks to / Acknowledgements

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