Statistical approaches in mediation analysis: a comparison of methods for survival data

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Outline

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- Mediation / causal inference
- Mediation analysis for survival data
  - Application of methods from Baron&Kenny, VanderWeele, Lange
- Lessons learned from **two case studies**
  - Body mass index (BMI) -> coronary heart disease (CHD), mediated by blood pressure, cholesterol, and glucose
  - Sex/gender -> CHD,
    mediated by blood pressure, cholesterol, glucose, and smoking
  - With the use of own data from the Vorarlberg health examination database (VHM&PP)

Motivation (1)

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- Mediation/causal inference has arrived in the medical literature.
- We contributed VHM&PP data to a large meta-analysis:

Lancet. 2014 Mar 15;383(9921):970-83. doi: 10.1016/S0140-6736(13)61836-X. Epub 2013 Nov 22.

Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants.

Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G.

- Recently, the same working group published yet another paper:

Epidemiology. 2015 Mar;26(2):153-62. doi: 10.1097/EDE.0000000000000234.

Mediators of the effect of body mass index on coronary heart disease: decomposing direct and indirect effects.

Lu Y[1], Hajifathalian K, Rimm EB, Ezzati M, Danaei G.

Motivation (2)

- We are currently investigating the sex – CHD mortality relationship.
- With mediators blood pressure (BP), total cholesterol (TC), fasting glucose (FG), smoking status (SS).

- Paper in submission:

Mediation analysis of the relationship between sex/gender, cardiovascular risk factors and mortality from coronary heart disease

Josef Fritz, Michael Edlinger, Cecily Kelleher, Susanne Strohmaier, Gabriele Nagel, Hans Concin, Elfriede Ruttmann, Margarethe Hochleitner, Hanno Ulmer

Mediation vs. confounding

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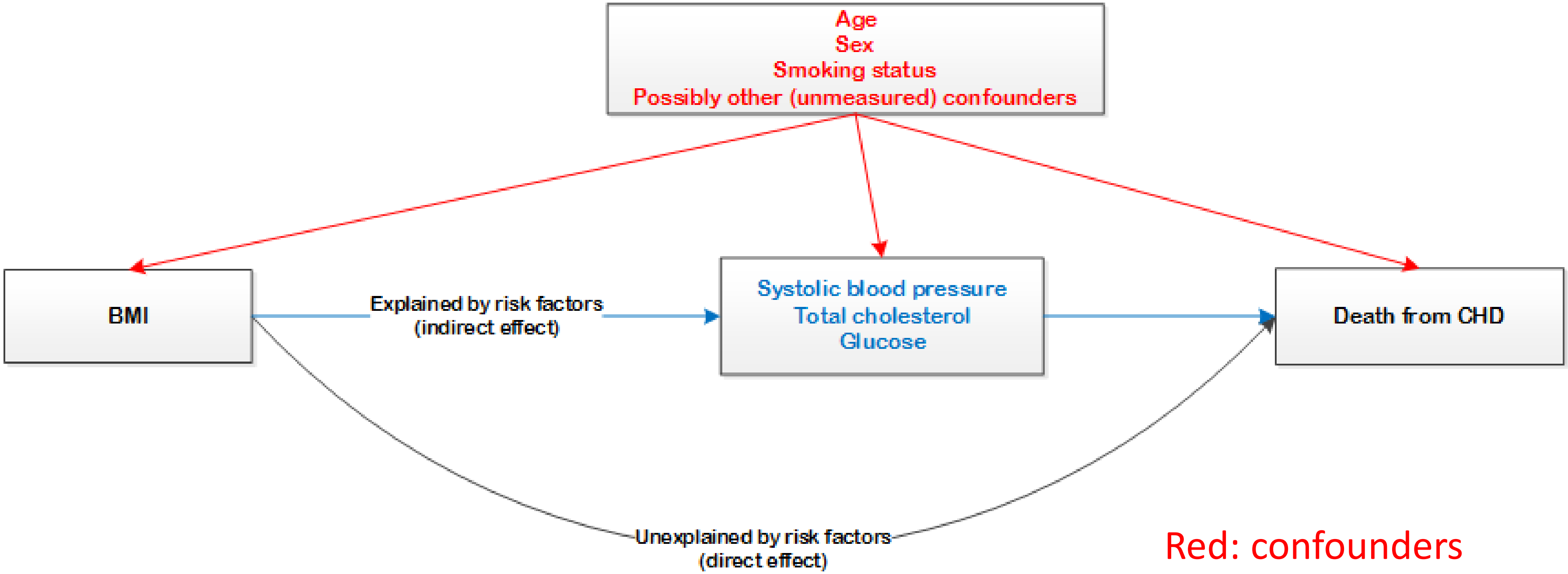
- Regression analysis allows to estimate the effect of an exposure variable on an outcome variable in the presence of one or more **‘third factors’.**
- These third factors can operate differently. They can act as **confounders**, **moderators** or **mediators**.
- A confounder is associated with the exposure and the outcome. The confounder **is not in the causal pathway** leading from the exposure to the outcome.
- Mediation occurs if factors, like confounders, are associated with the exposure of interest and the outcome, but **are in the causal pathway** leading from the exposure to the outcome.

Case study 1 – BMI and CHD



Red: confounders
Blue: mediators

- CHD defined as ICD-10 codes I20-I25.
- Aim: estimation of direct and indirect path.

Case study 2 – Sex/Gender and CHD

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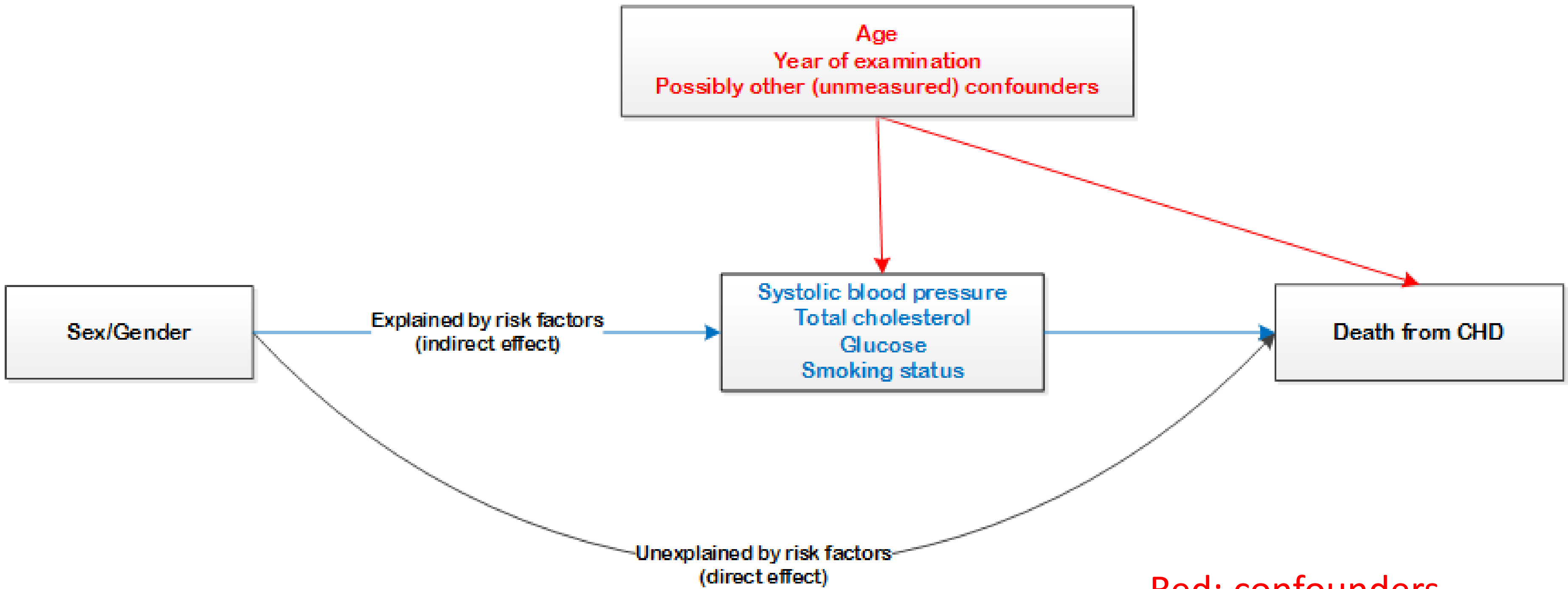

Red: confounders
Blue: mediators

Mediation analysis
Total, direct and indirect effects

- For the BMI – CHD example for Cox regression (λ - hazard)
- **Total effect** (TE): $\lambda_{T_{Overweight}} / \lambda_{T_{Normalweight}}$
- Controlled direct effect (CDE): $\lambda_{T_{Overweight,M}} / \lambda_{T_{Normalweight,M}}$
  (M - some fixed mediator level)
- **Natural direct effect** (NDE): $\lambda_{T_{Overweight,M_{Normalweight}}} / \lambda_{T_{Normalweight,M_{Normalweight}}}$
- **Natural indirect effect** (NIE): $\lambda_{T_{Overweight,M_{Overweight}}} / \lambda_{T_{Overweight,M_{Normalweight}}}$
- It can be shown: TE = NDE x NIE
- For CDE no such decomposition exists!

Mediation analysis „Classical“ methods

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- Aim of mediation analysis: decomposition of total effect into (natural) direct and indirect effect
- Classical methods: Baron&Kenny 1986
  - 2-stage regression models
  - Product method: first model for mediators, second model for outcome including exposure and mediators
  - Difference method: two models for exposure, one with and one without mediators
  - Advantage: easy to implement
  - Drawback: only mathematically consistent in “easy” settings

Mediation analysis
„New“ methods

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- 2-stage regression models
  - Refinement of product method with interactions
  - T. VanderWeele: Explanation in Causal Inference: Methods for Mediation and Interaction. Oxford University Press 2015.
- Weighting based approaches
  - T. Lange (2014): Assessing natural direct and indirect effects through multiple pathways. Am J Epidemiol. 2014.
- Inverse probability based approaches
- Applicable for more general settings, but not so easy to implement any more.

Case study 1 – BMI and CHD

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- Comparison of methods:
  - Classical product method (Baron&Kenny, 1986)
  - Classical difference method (Baron&Kenny, 1986)
  - Regression based approach developed by T. VanderWeele (refinement of product method) (2011; 2012)
  - Weighting based approach developed by T. Lange (2014)
- Classification of BMI: normal vs. overweight vs. obesity.
- Observation: BMI*Age is highly significant in a survival model on CHD.
- Therefore, stratification by age group is highly indicated!

Lu et al. (2015): Results

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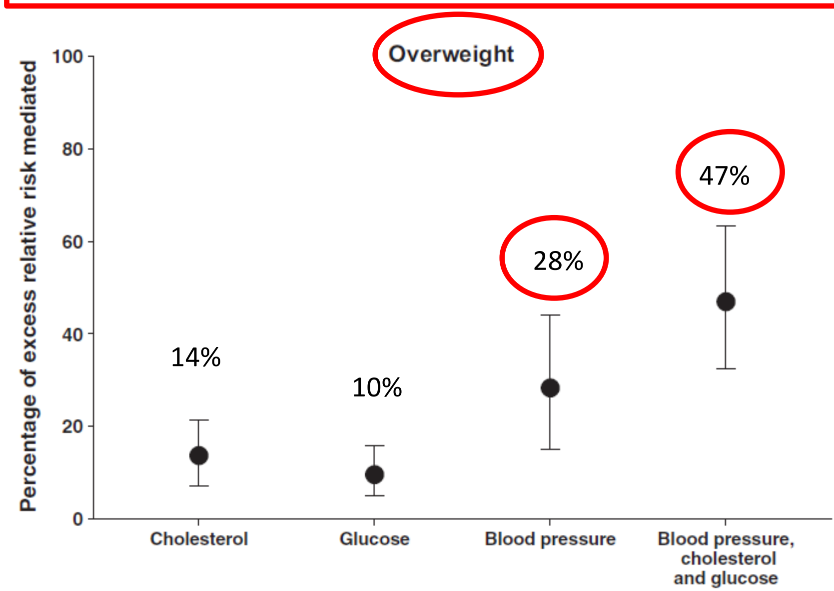
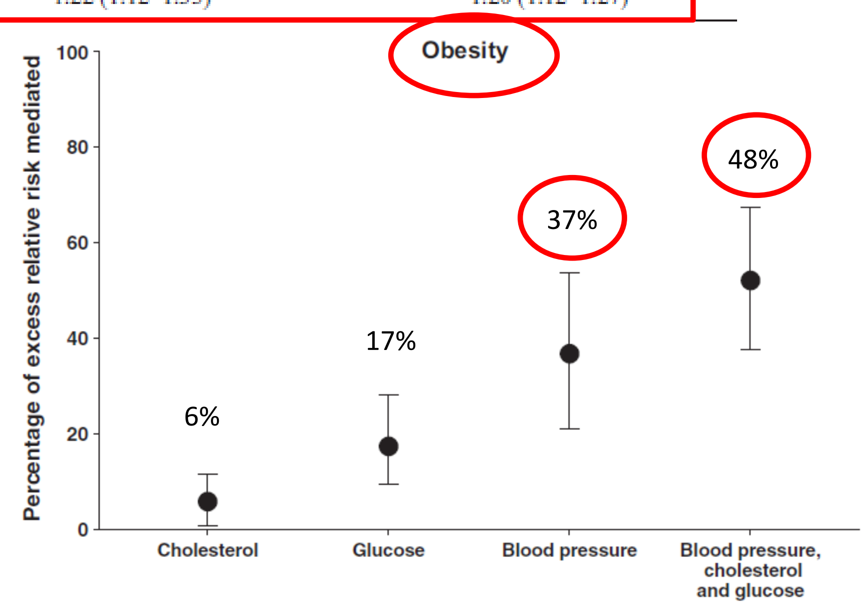
TABLE 1. Total, Direct, and Indirect Effects of Overweight and Obesity on CHD (Compared with Normal Weight) for Metabolic Mediators, 9 NHLBI Cohorts

Mediators	Total effect HR (95% CI)	Natural direct effect HR (95% CI)	Natural indirect effect HR (95% CI)
Overweight			
Blood pressure (per 10 mmHg)	1.22 (1.14–1.30)	1.16 (1.09–1.24)	1.06 (1.03–1.08)
Cholesterol (per 1 mmol/L)		1.18 (1.13–1.24)	1.03 (1.01–1.04)
Glucose (per 1 mmol/L)		1.20 (1.12–1.27)	1.02 (1.01–1.03)
Blood pressure, cholesterol, glucose		1.12 (1.07–1.18)	1.09 (1.06–1.13)
Obesity			
Blood pressure (per 10 mmHg)	1.42 (1.25–1.60)	1.28 (1.15–1.43)	1.13 (1.07–1.19)
Cholesterol (per 1 mmol/L)		1.39 (1.24–1.55)	1.02 (1.00–1.03)
Glucose (per 1 mmol/L)		1.34 (1.19–1.51)	1.05 (1.03–1.08)
Blood pressure, cholesterol, glucose		1.22 (1.12–1.33)	1.20 (1.12–1.27)





Case study 1
Results overweight vs. normal weight

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Effects	<50 years (454 events in 113556 individuals)		50-64 years (1571 events in 35629 individuals)		65-74 years (1687 events in 10966 individuals)		≥75 years (1045 events in 4545 individuals)	
	HR	%	HR	%	HR	%	HR	%
Difference method								
Total effect	1.50	100%	1.29	100%	1.26	100%	1.00	-
Natural direct effect	1.20	45%	1.18	65%	1.06	25%	0.94	-
Natural indirect effect	1.25	55%	1.09	35%	1.19	75%	1.06	-
Product method								
Total effect	1.48	100%	1.37	100%	1.14	100%	0.97	-
Natural direct effect	1.20	46%	1.18	52%	1.06	40%	0.94	-
Natural indirect effect	1.24	54%	1.16	48%	1.08	60%	1.04	-
Lange method								
Total effect	1.69	100%	1.32	100%	1.09	100%	0.95	-
Natural direct effect	1.22	38%	1.11	39%	1.01	8%	0.92	-
Natural indirect effect	1.39	62%	1.18	61%	1.08	92%	1.04	-
VanderWeele method								
Total effect	1.51	100%	1.35	100%	1.12	100%	0.98	-
Natural direct effect	1.24	52%	1.15	48%	1.04	36%	0.94	-
Natural indirect effect	1.22	48%	1.17	52%	1.08	64%	1.05	-

Case study 1
Results obesity vs. normal weight

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Effects	<50 years		50-64 years		65-74 years		≥75 years	
	HR	%	HR	%	HR	%	HR	%
Difference method								
Total effect	3.28	100%	1.82	100%	1.51	100%	1.18	100%
Natural direct effect	1.83	51%	1.19	29%	1.23	50%	1.14	79%
Natural indirect effect	1.79	49%	1.53	71%	1.23	50%	1.04	21%
Product method								
Total effect	2.88	100%	1.62	100%	1.46	100%	1.21	100%
Natural direct effect	1.83	57%	1.19	36%	1.23	55%	1.14	66%
Natural indirect effect	1.58	43%	1.36	64%	1.18	45%	1.07	34%
Lange method								
Total effect	4.08	100%	1.64	100%	1.46	100%	1.25	100%
Natural direct effect	1.75	40%	1.07	14%	1.21	50%	1.16	68%
Natural indirect effect	2.33	60%	1.53	86%	1.21	50%	1.07	32%
VanderWeele method								
Total effect	2.75	100%	1.6	100%	1.43	100%	1.24	100%
Natural direct effect	1.66	50%	1.20	39%	1.29	70%	1.24	101%
Natural indirect effect	1.65	50%	1.34	61%	1.12	30%	1.00	-1%

Remarks concerning methodology (1)

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- Methods deliver considerably different results. Interestingly, the new methods of VanderWeele and Lange often differ quite widely, while the classical methods deliver results in between.
- This may be due to:
  - Strict assumptions (unmeasured confounding) which may be violated.
  - Classical methods do only deliver approximate results.
  - The method by VanderWeele only delivers exact results for “rare” outcomes.
  - Lange’s method requires non-intertwined pathways.

Case study 2 – Sex/Gender and CHD (1)

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- In general, men have a higher CHD mortality risk than women, especially at younger ages.
- Can the difference in CHD mortality risk between sexes be explained by different risk factor profiles and if yes, how much can be explained?
- New mediation **approach according to Lange et al.** (Am J Epidemiol, 2014).
- **Allows breakdown of indirect effect into single components** for non-intertwined pathways.
- Since moderating effect of age, stratification for age groups <50, 50-64, 65-74, and ≥75 years.

Case study 2 – Sex/Gender and CHD (2)

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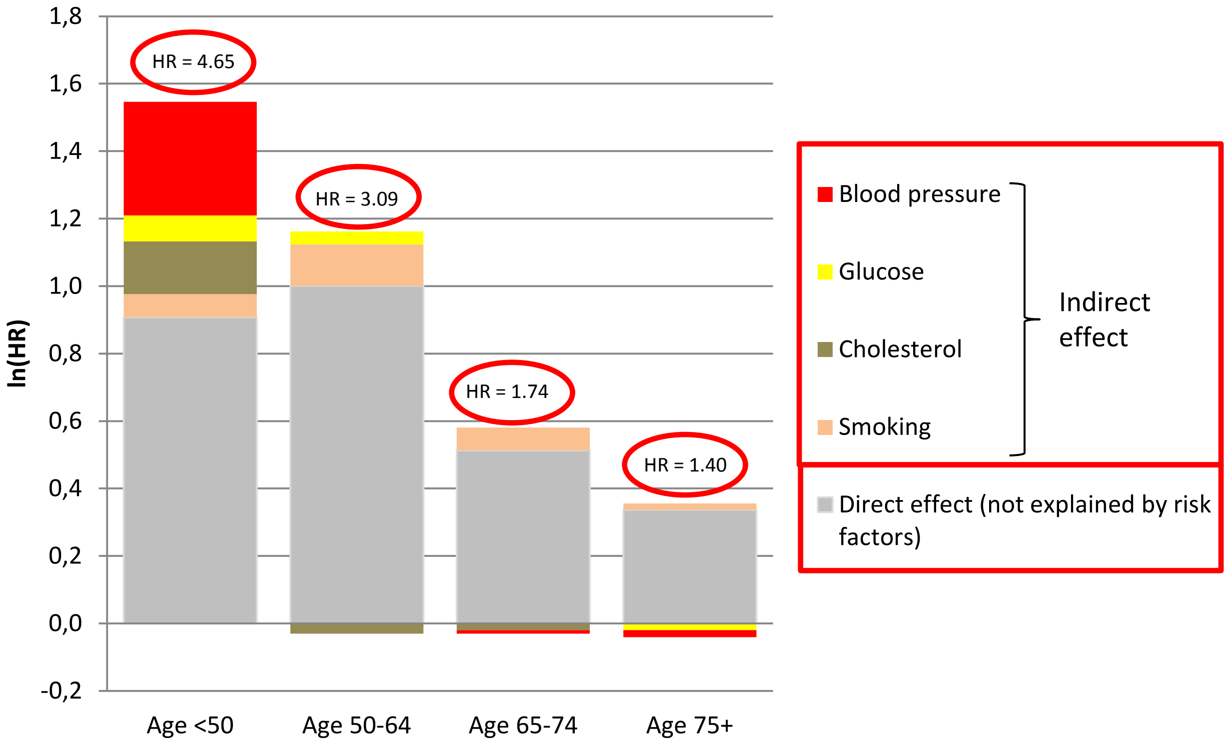
Effect decomposition, Lange et al.



Remarks concerning methodology (2)

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- Baron&Kenny: Easy, old, but reliable, product method preferable in survival setting
- VanderWeele: correction for exposure-mediator interaction possible, only for “rare” outcomes.
- Lange: computationally intensive, stringent assumptions (non-intertwined pathways), decomposition in single components possible
- There is no universally “best” method for all settings. Sensitivity analysis with different methods are recommended.