Can we identify effects from micronutrients in nutritional epidemiology studies?

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INTRODUCTION

It has been argued that effects from micronutrients are unidentifiable because they lay in a food matrix and this can also affect the outcome of interest, and therefore it is not possible to separate one effect from the other.
When designing target trial interested in the effect of a micronutrients (i.e., sodium), we can imagine we randomize people to

a_0 Unprocessed meat
a_1 Processed meat
Y Hypertension

$$E(Y^{a_1} = 1|L, C=0) - E(Y^{a_0} = 1|L, C=0)$$

to estimate the per-protocol effect of a point isocaloric intervention (full adherence, no loss to follow-up).

Two limitations for identification in observational data:
a) Foods used as a comparison may not be fully equivalent exept for the micronutrient of interest (unprocessed meat + salt ≠ processed meat)
b) Unmeasured confounding by past diet and participants' characteristics

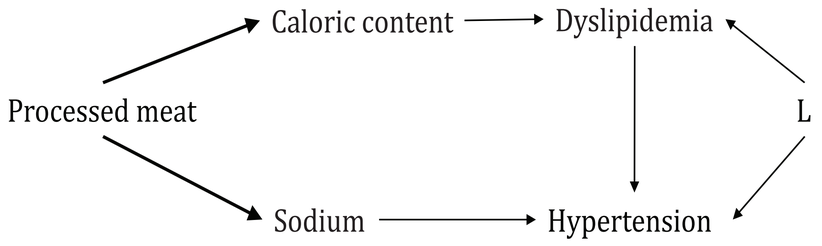
AIM: Propose identification potentially overcoming these two limitations.

METHODS

a) Separable effects (conditional separable direct effect)

a_c caloric content in processed meat (fats, carbohydrates)
a_s sodium

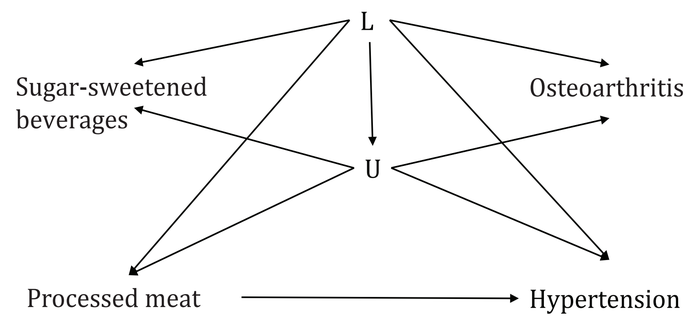
$$E(Y^{ac,as=1} = 1 |W^{ac,as=1}, L, C=0) - E(Y^{ac,as=0} = 1|W^{ac,as=0}, L, C=0)$$



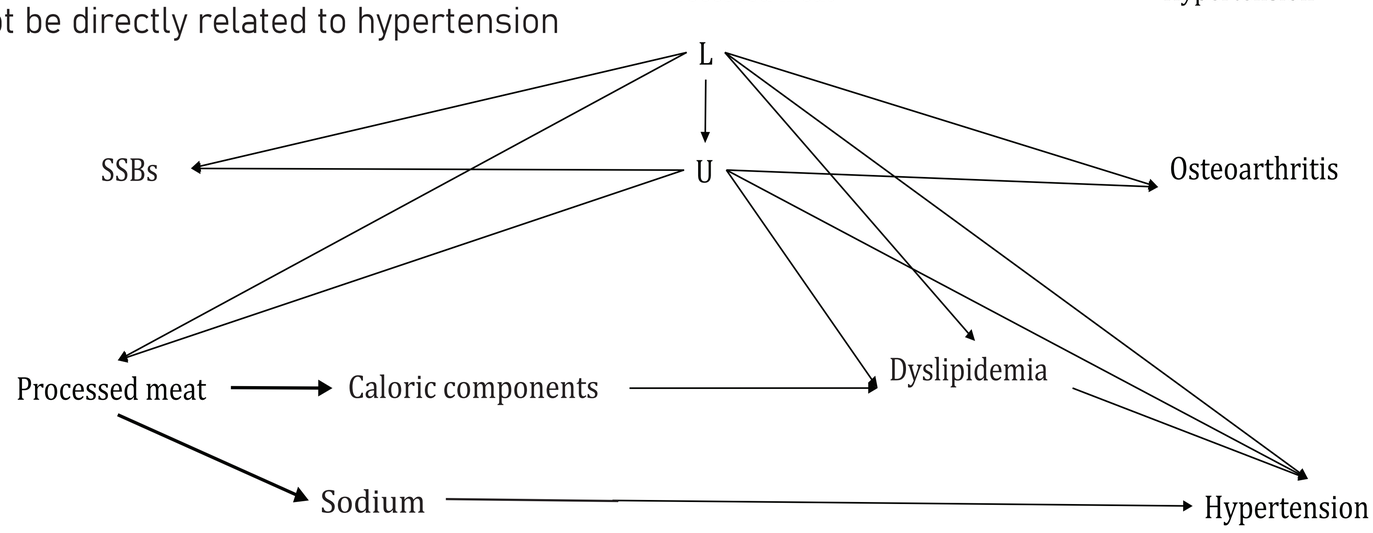
Assumptions: modified treatment, isolation and no unmeasured common causes between hypertension and dyslipidemia

b) Double negative controls (average causal effect)

$$E[Y^{a_1} = 1|Z,W,U] - E[Y^{a_0} = 1|Z,W,U]$$



Assumptions: i.i.d, sugar-sweetened beverages (SSBs) must not be directly related to hypertension given L and U
Estimation for binary exposure-outcome:
$Y \sim A + \text{logit}(Pr(W=1|A,Z,Y=1)) + W$



a+b) Proximal conditional separable effects

$$E[Y^{ac,as=1}|D^{ac,as=1} = 0, L, C=0] - E[Y^{ac,as=0}|D^{ac,as=0} = 0, L, C=0]$$

ESTIMATION STRATEGY

- Inclusion criteria: meat eaters in Rotterdam Study (n=11k) - non-naïve to the treatment
- Threshold intervention a_0 replace all processed for unprocessed maintaining all the diet the same.
  a_1 replace all unprocessed for processed maintaining all the diet the same.
- Replacements require two observations of the diet to define treated vs. control leading to immortal time bias.
- Population specific effect depending on their baseline consumption.

CONCLUSION

- Effect of removing sodium from processed food, not the effect of sodium overall
- Crazy assumptions
  Time-varying nature of the exposure - treatment-confounder feedback under realistic assumtions
  Time-varying confounding
  Positivity: not likely to observe complete replacements
- Methods that can accomodate a suitable for a number of exposures/outcomes

References
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