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Application of mediation analyses

Causal inference in Epidemiology

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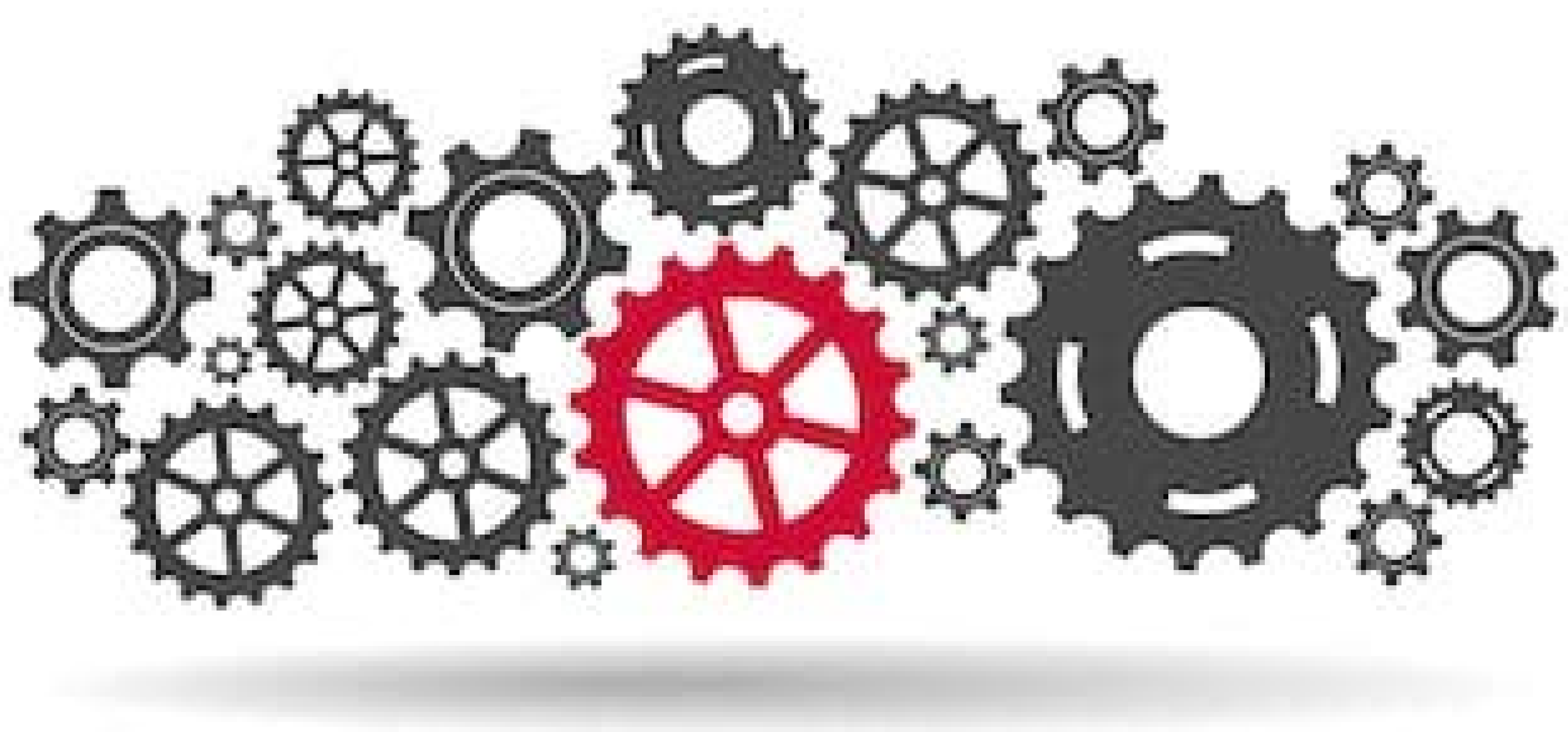
Causal inference

- There is longstanding interest in using data to gain insight into the mechanism that underlies the effect of an exposure on an outcome.



Exposure(**A**) ⟶ Outcome(**Y**)

- Mediation analyses are designed for this purpose.

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Counterfactual framework

- In “The Book of Why”, Judea Pearl quotes from Donald Rubin’s causal model theory of potential outcomes that:

- The potential outcome of a variable Y (outcome) is simply the value Y would have taken for individual *u,* had *X* (exposure) been assigned the value of *x*.

- In reality we are unable to see the outcome Y for an individual *u* given *X* or *x*, therefore we must rely on statistical modelling and assumptions for our estimates to be valid.

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Potenital outcomes and counterfactuals

	A Paracetamol	Y Headache cleared
Adam	0	0
Andrew	1	1
Lucy	1	1
Paul	1	0
Karen	1	1
Liisa	0	0
Karin	1	1

Did the paracetamol cause Karin's headache to clear?

We don't know.

To answer this we need to know what would have happened had she not taken the paracetamol?

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Potential outcomes and counterfactuals

- A is the treatment: whether or not the paracetamol was taken.
- Y is the outcome: whether or not the headache cleared.

- Y^0 and Y^1 to represent the **potential outcomes** under both treatments.

- Y^0 is the outcome we would see if the paracetamol was not taken.
- Y^1 is the outcome we would see if the paracetamol was taken.

- The outcome we do not observe is called the **counterfactual**.

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Potential outcomes and counterfactuals

	Y^0	Y^1	Causal effect?
Adam	1	1	No
Andrew	0	1	Yes (protective)
Lucy	0	1	Yes (protective)
Paul	1	0	Yes (harmful)
Karen	0	1	Yes (protective)
Liisa	0	0	No
Karin	0	1	Yes (protective)

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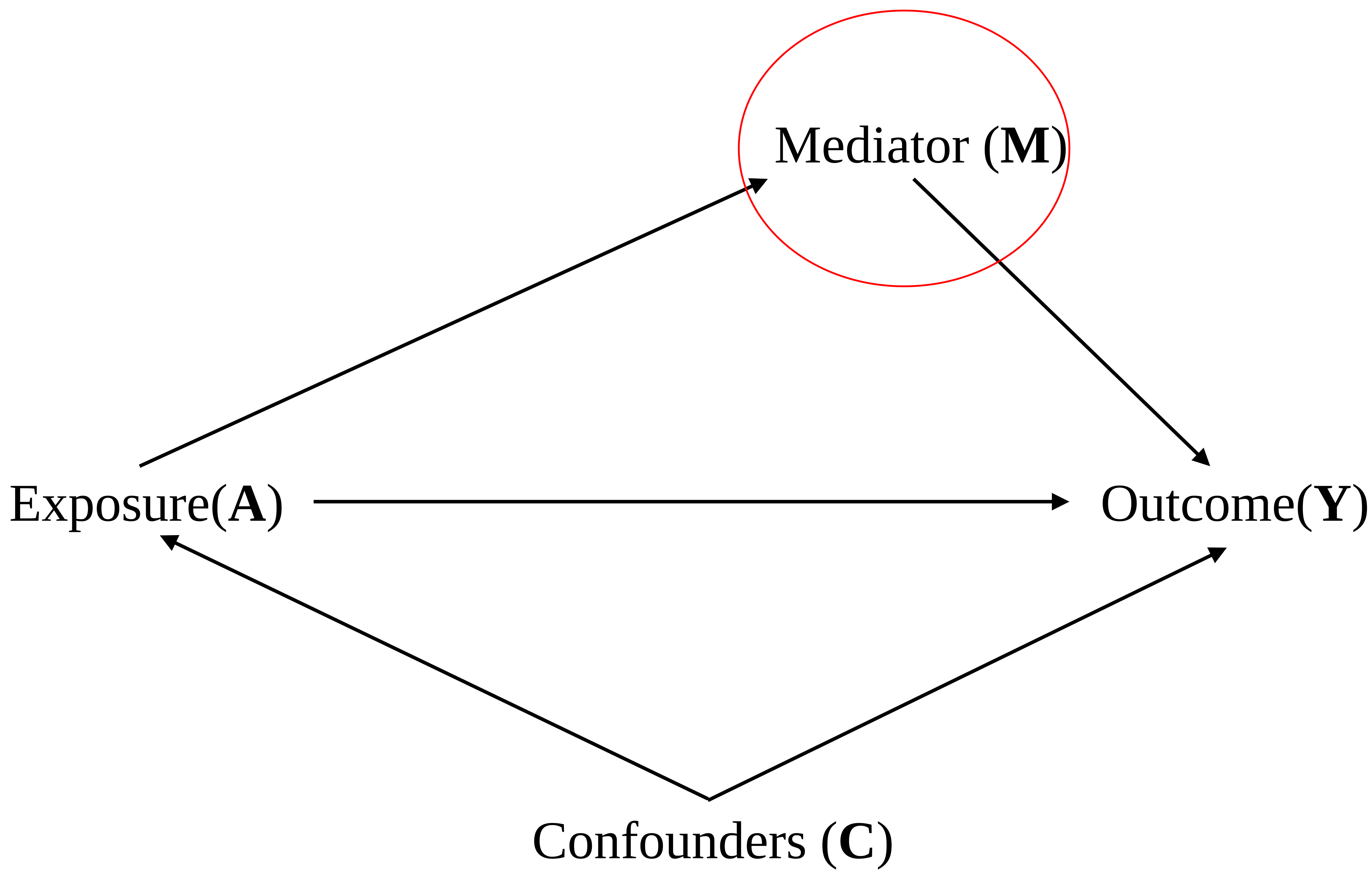
Causal Mediation Analysis

- The use of a mediator variable proposes that rather than just a direct effect between the exposure and the outcome, there exists an indirect effect.



Standard approache's to mediation

- The standard approach to mediation analysis consists first of regressing the outcome Y on the exposure A and confounding factors C, Baron and Kenny (1986).

$$E[Y|A=a,C=c] = \phi 0 + \phi 1a + \phi 2'c$$

$$E[Y|A=a,M=m,C=c] = \theta 0 + \theta 1a + \theta 2m + \theta 4'c$$

And compare the estimate $\phi 1$ of exposure A with the estimate $\theta 1$ obtained when including the potential mediator M in the regression model

- If the coefficients $\phi 1$ and $\theta 1$ differ then some of the effect is thought to be mediated.

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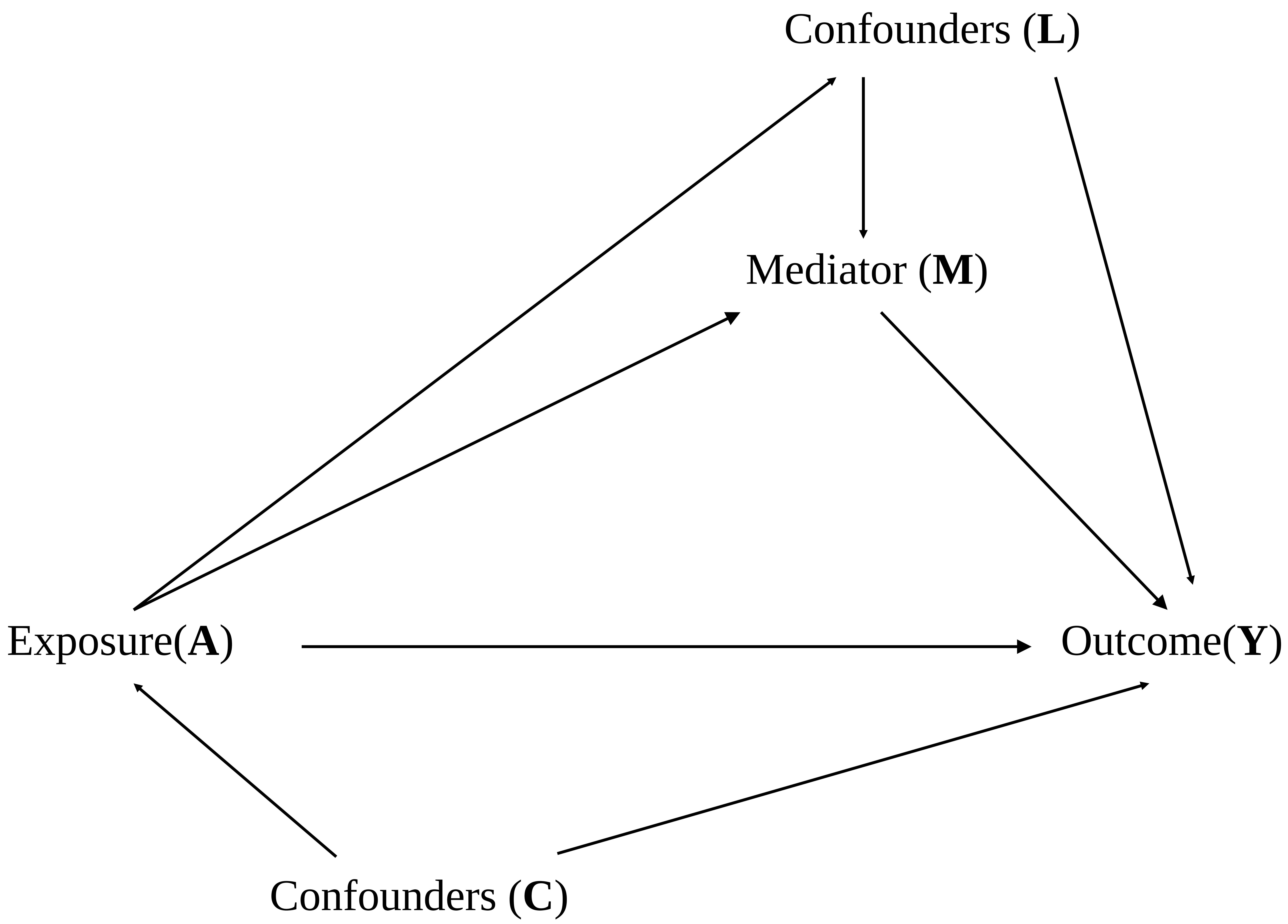
Problems with standard approach



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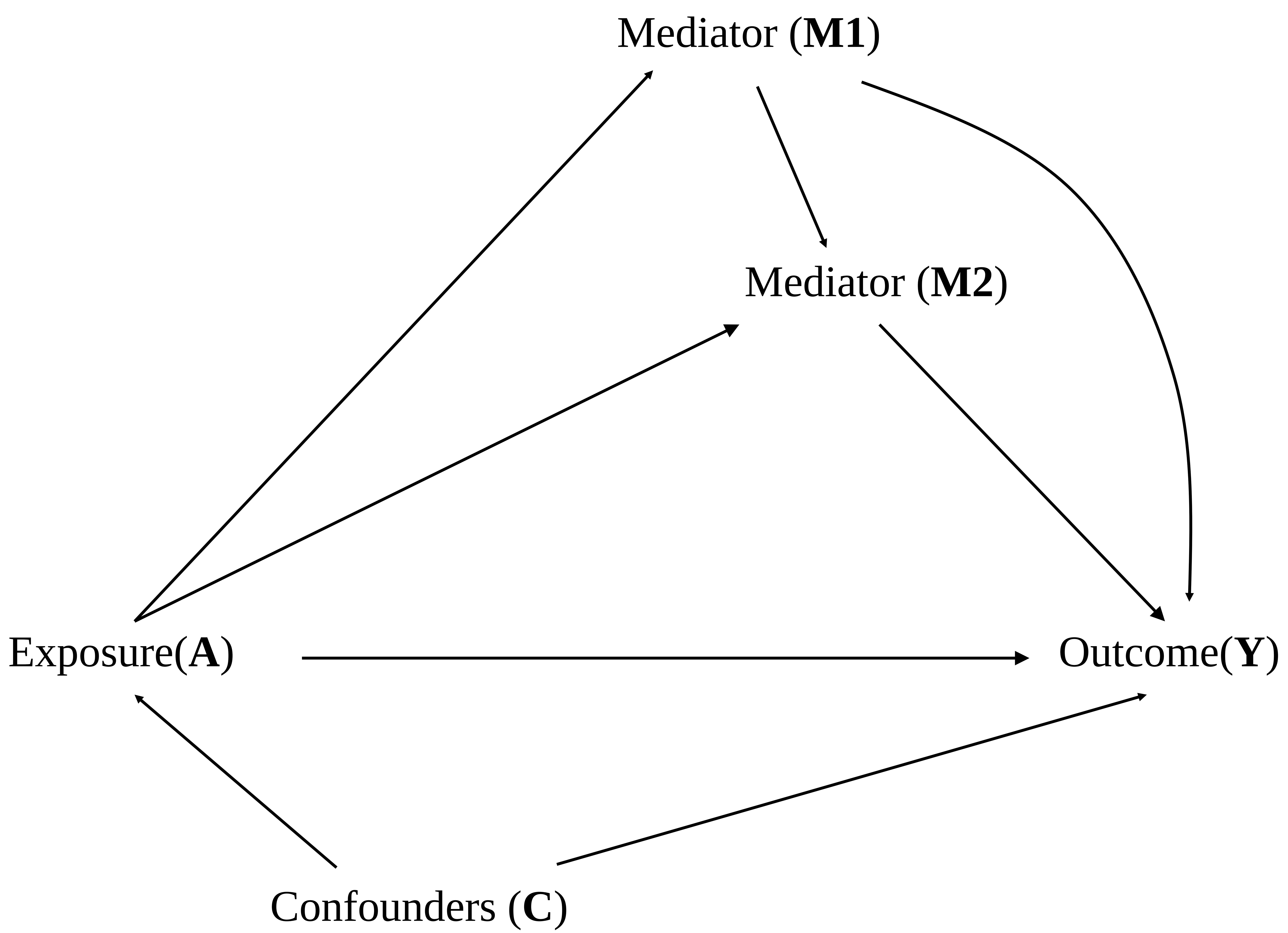
Multiple mediators



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Multiple mediators

- Repeated single mediator analyses are quite popular:
  - Single mediator analysis with mediator M1
  - Single mediator analysis with mediator M2

- The sum of the individual mediated effects may not equal the joint mediated effect, clear when the mediators influence one another.

- Sequential mediation analysis ‘en bloc’:
  - Mediation analysis with mediator M1
  - Mediation analysis ‘en bloc’ with mediators M1;M2

- No effect decomposition.
- Multiple mediation analysis ‘en bloc’ does not provide insight into separate pathways.

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Paper IV

Is the effect of Mediterranean diet on hip fracture mediated through type 2 diabetes and body mass index?

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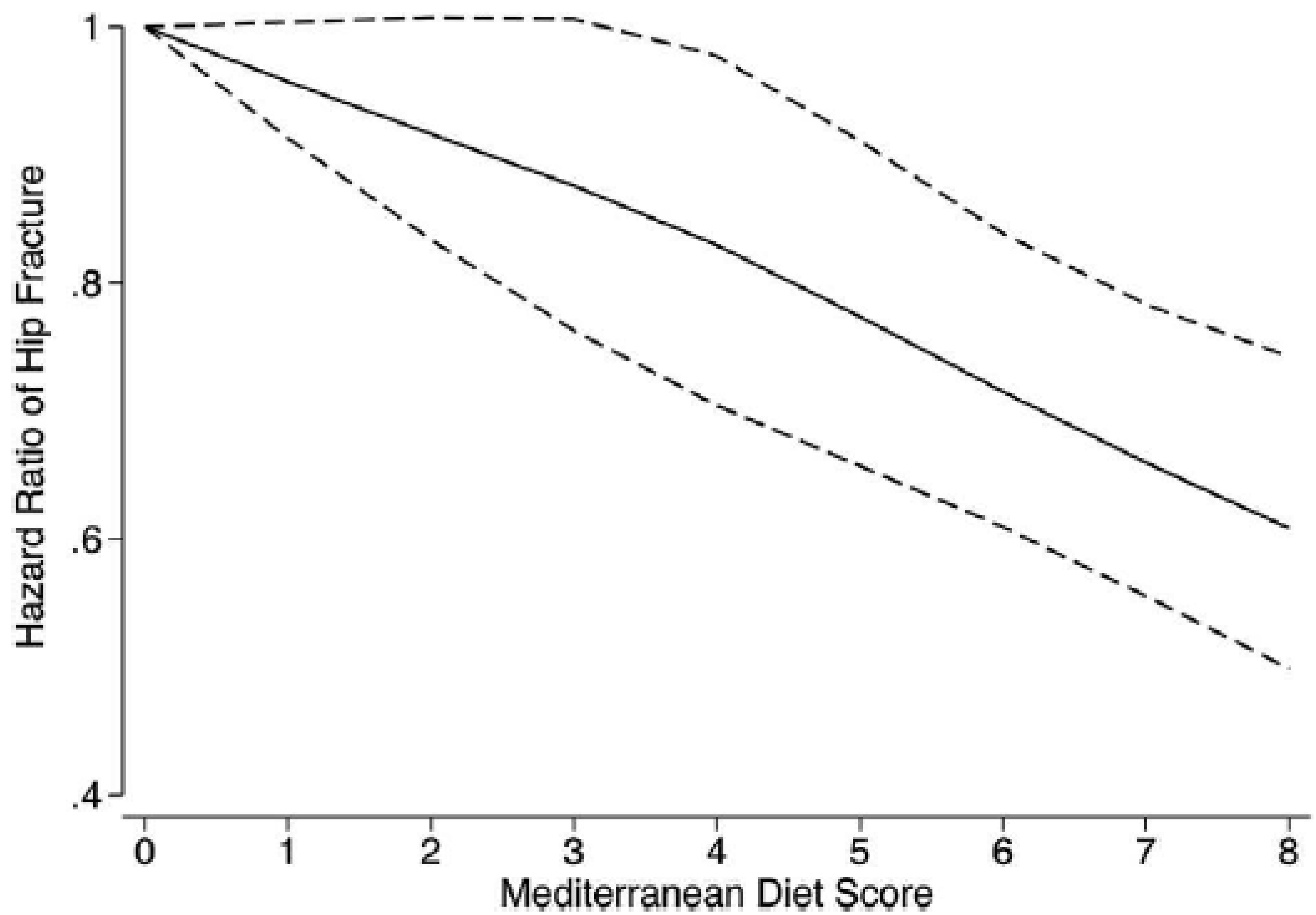
In press; International Journal of Epidemiology

Mediterranean diet and hip fracture

- Mediterranean diet associated with lower risk of hip fracture.



Byberg et al., 2016

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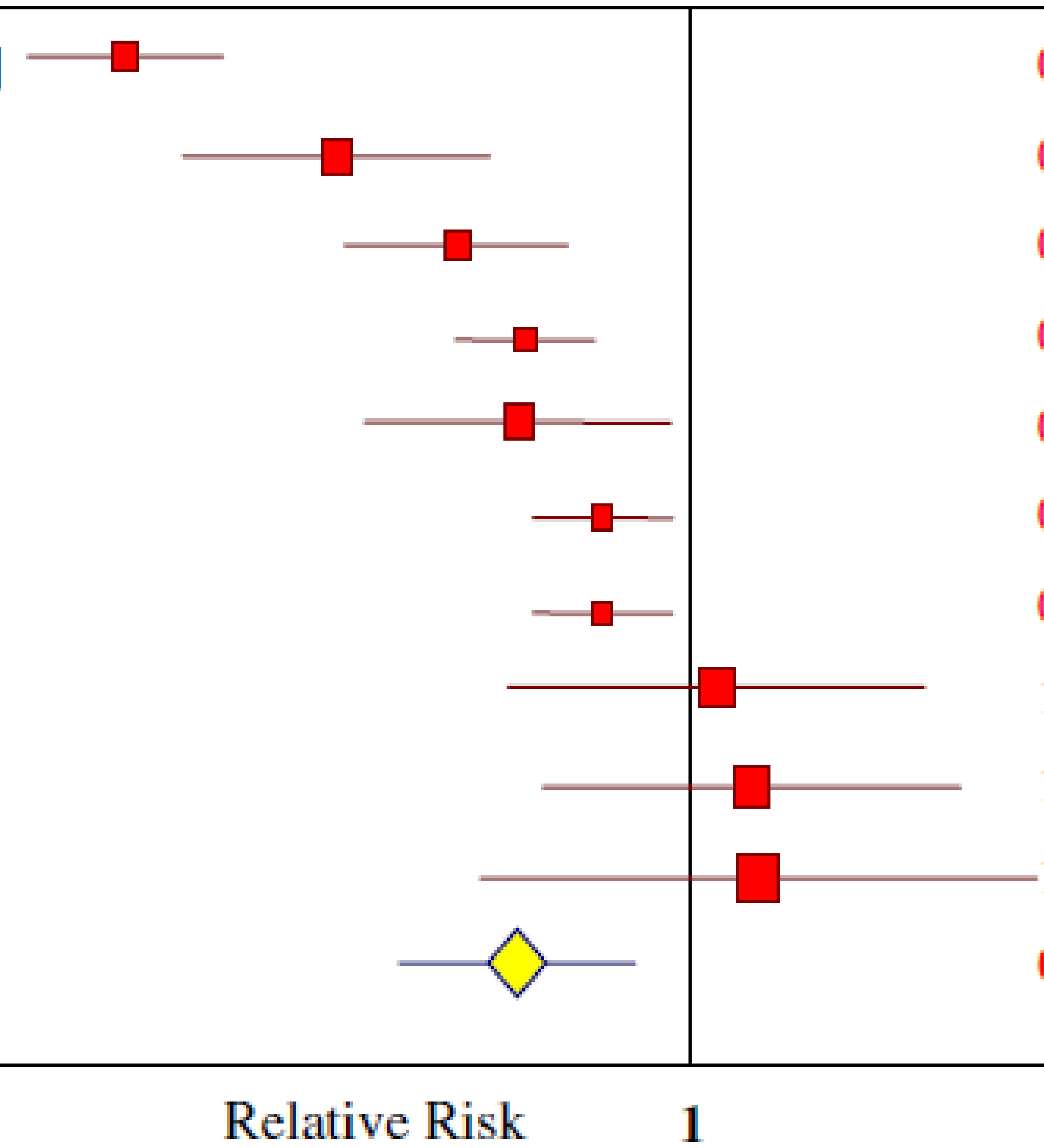
Mediterranean diet and T2DM

- Adherence to a Mediterranean-style dietary pattern associated with reduced risk of developing T2DM.

Author	RR	(95% CI)	Weight (%)	Events	Country of origin
Martinez – Gonzalez et al. [21]	0.17	(0.04, 0.72)	0.31	33	Spain
Salas- Salvado et al. [20]	0.48	(0.27, 0.86)	8.02	54	Spain
Mozaffarian et al. [22]	0.65	(0.49, 0.85)	12.11	998	Italy
de Koning et al. [30]	0.75	(0.66, 0.86)	15.30	2795	USA
Tobias et al. [29]	0.76	(0.55, 1.05)	9.46	491	USA
Rossi et al. [28]	0.88	(0.78, 0.99)	15.12	2330	Greece
Romaguera et al. [31]	0.88	(0.79, 0.97)	15.65	11994	Europe
Brunner et al. [25]	1.04	(0.75, 1.43)	6.82	410	UK
Abiemo et al. [23]	1.09	(0.80, 1.49)	6.70	412	USA
Cabrera de Leon et al. [24]	1.10	(0.70, 1.70)	4.00	146	Spain
Combined	**0.77**	**(0.66, 0.89)**	100.00		



Koloverou et al., 2014

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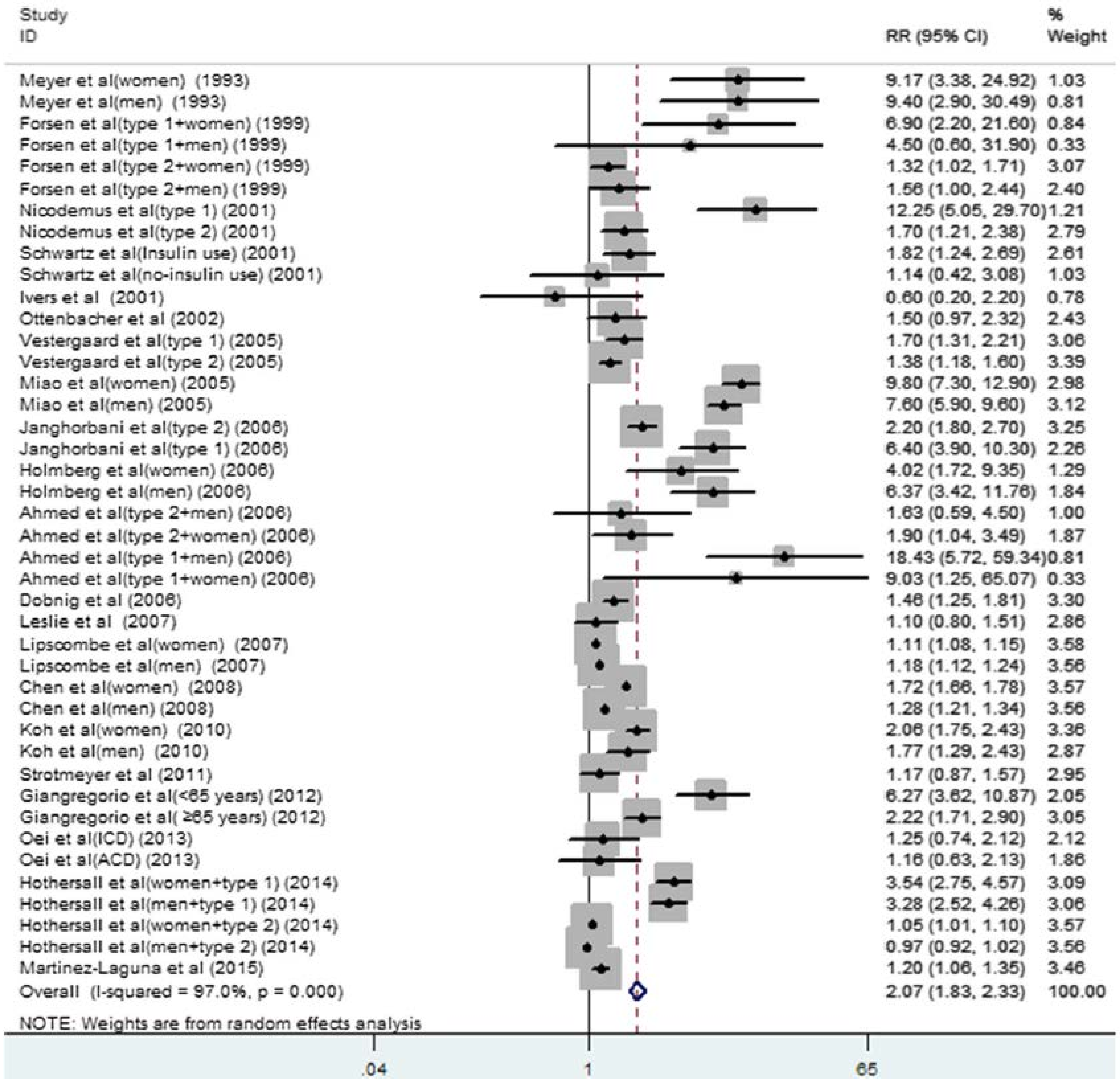
T2DM and hip fracture



Fan et al., 2016

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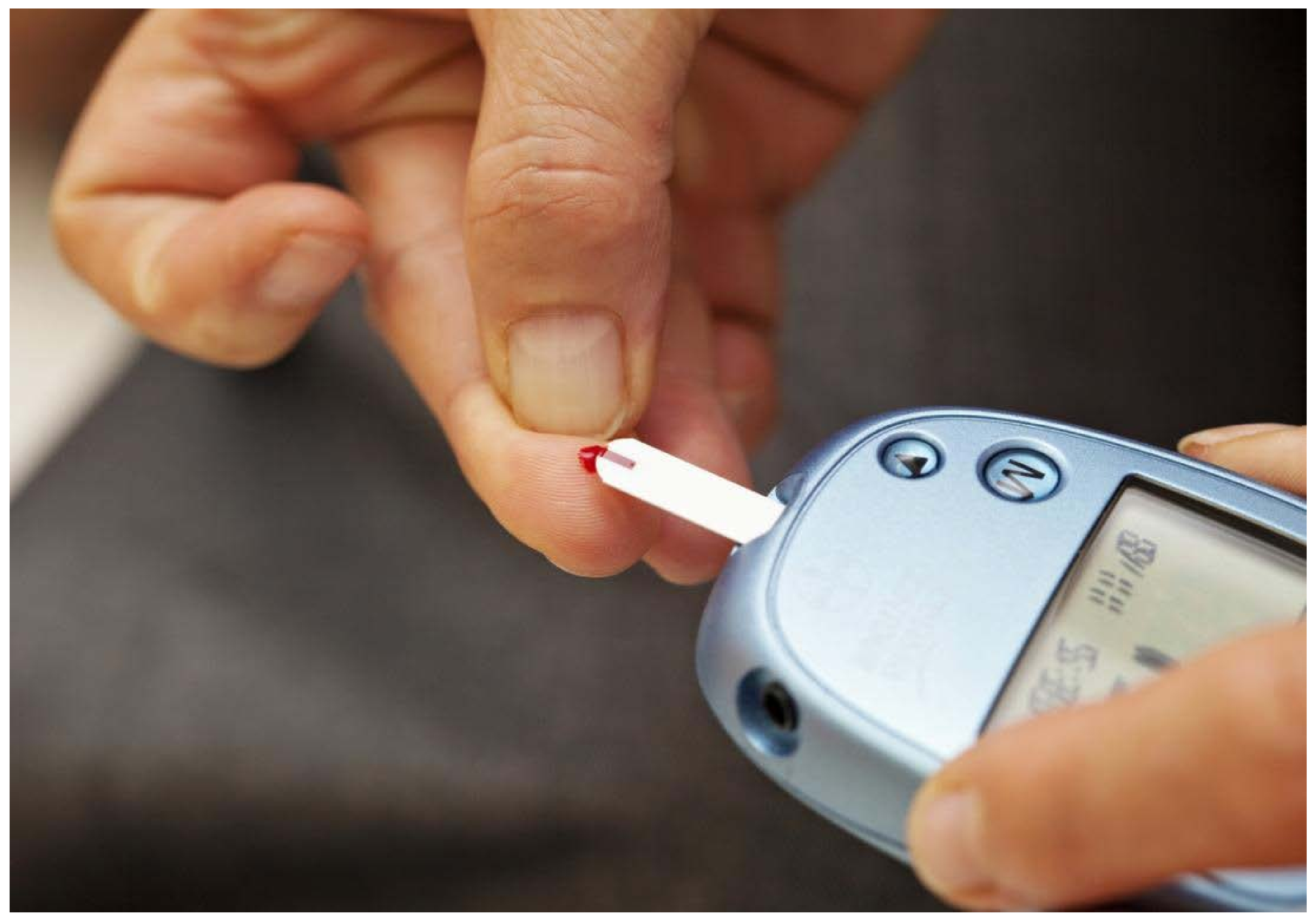

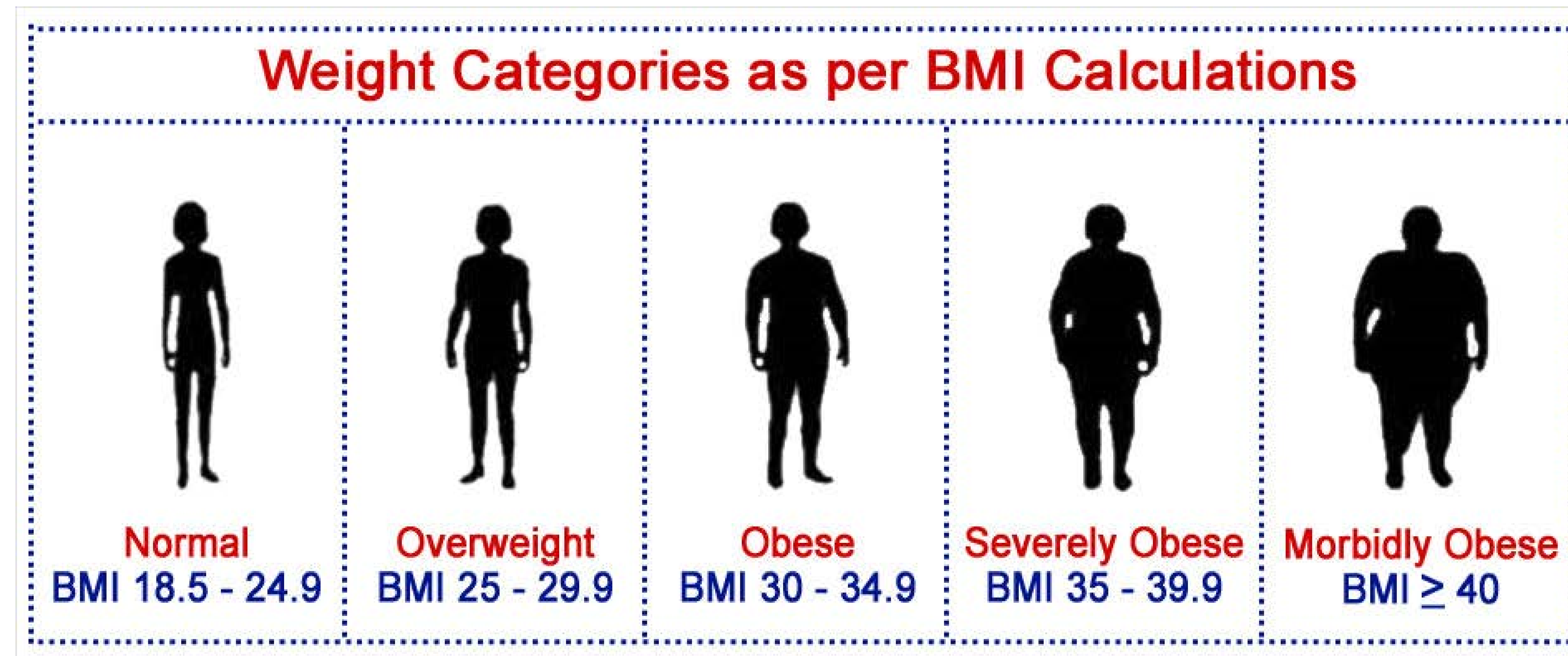

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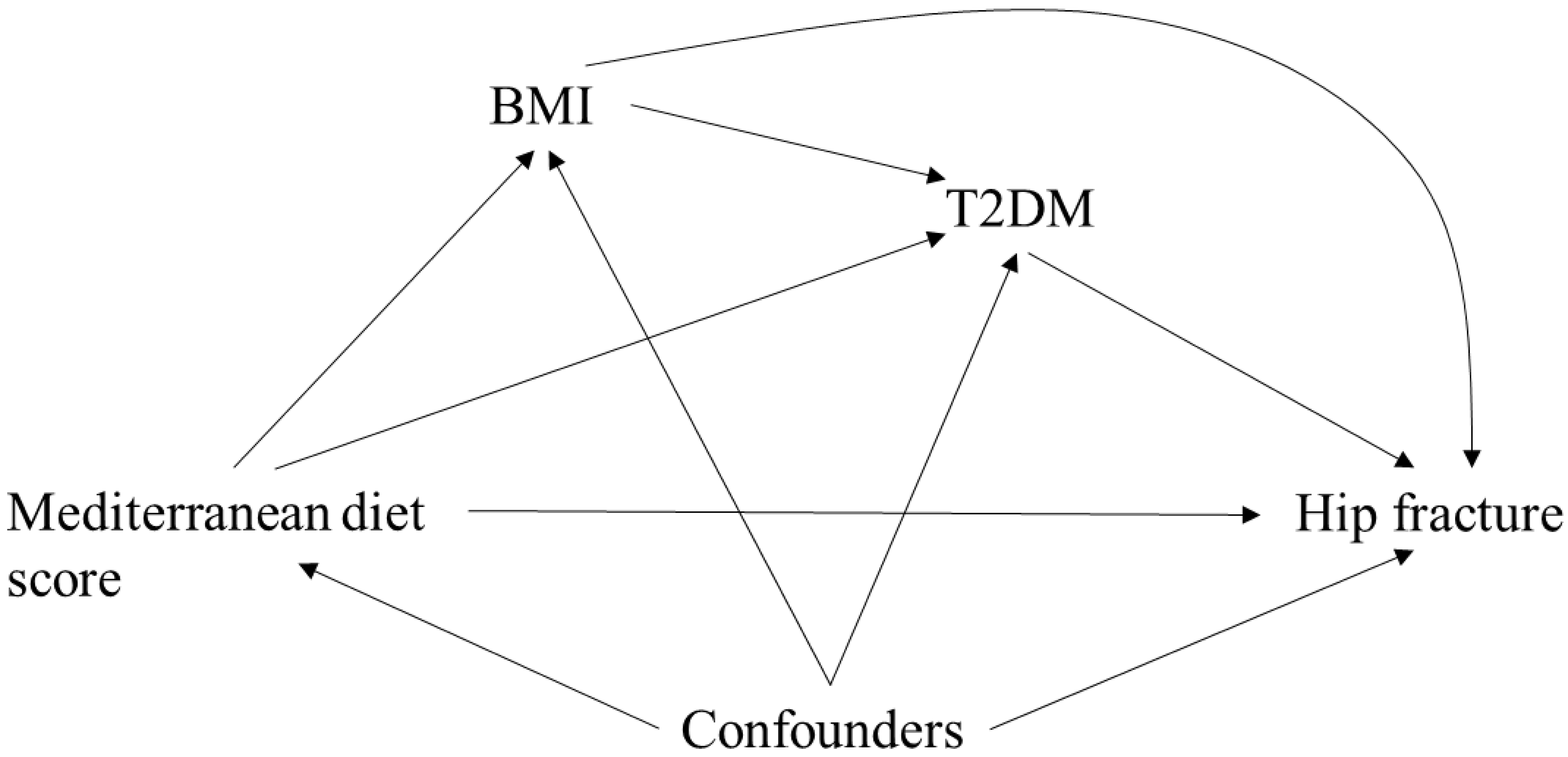

Aim

To investigate whether the inverse association between adherence to a Mediterranean diet and hip fracture risk is mediated by incident T2DM and BMI. We aimed to establish controlled direct effects, natural direct effects, natural indirect effects and partial indirect effects in 50,755 women and men from Swedish Mammography Cohort & Cohort of Swedish Men (COSM).

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Mediterranean diet score

- The Mediterranean dietary pattern was assessed by a valid and reproducible 96-item food-frequency questionnaire (FFQ) in 1997.

- Report on average, how often, they had consumed each food item in the previous year from eight possible frequency categories ranging from zero times/month to more than three times/day.

- A modified Mediterranean diet score (MDS; range, 0 to 8 points), based on a previous scale was calculated and categorized into 3 a prior determined categories.

Intakes above the median:

(1) fruit and vegetables

(2) legumes and nuts

(3) non-refined or high-fiber grains

(4) fermented dairy products

(5) fish

Intakes below the median:

(6) red and processed meat

(7) use of olive or rapeseed oil for cooking or as dressing

(8) moderate alcohol consumption with an average of 5 to 15 grams of ethanol per day

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Outcome

First incident hip fracture occurring between April 14th 2009 and December 31st 2014, (n=1386).

Mediator (s)

T2DM was defined using self-reported diabetes from questionnaires, as incident diabetes following 1st January 1998 (n=3389).

BMI which was collected at baseline (1997) was calculated as weight (kg) divided by the height (m) squared.

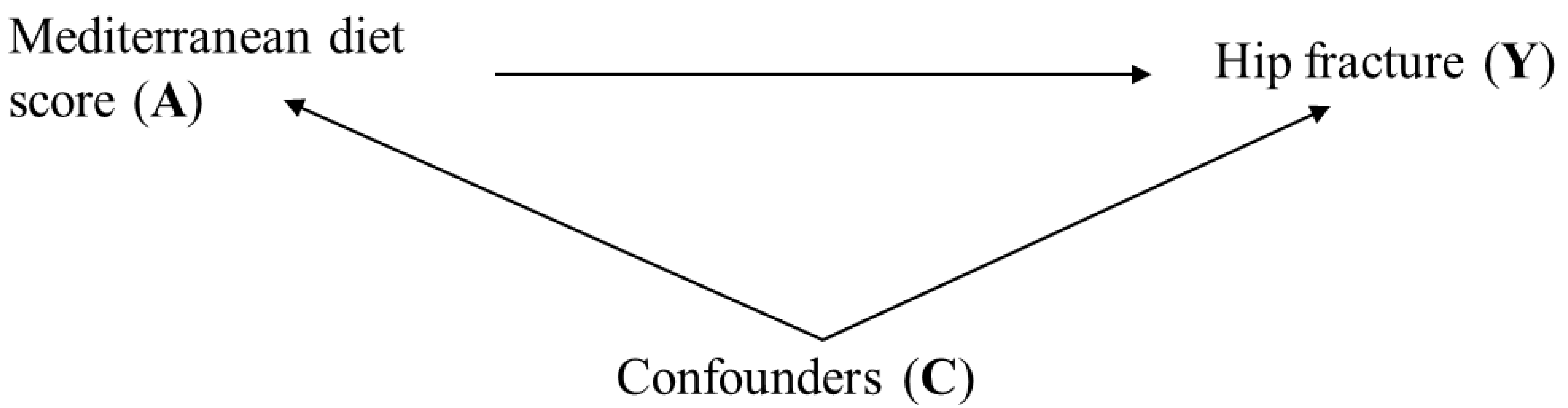
Baseline confounders

- age
- education
- physical activity
- smoking status
- living alone status
- calcium supplement use
- vitamin D supplement use
- total energy intake
- Charlson comorbidity index

Standard regression approach to mediation

Model 1

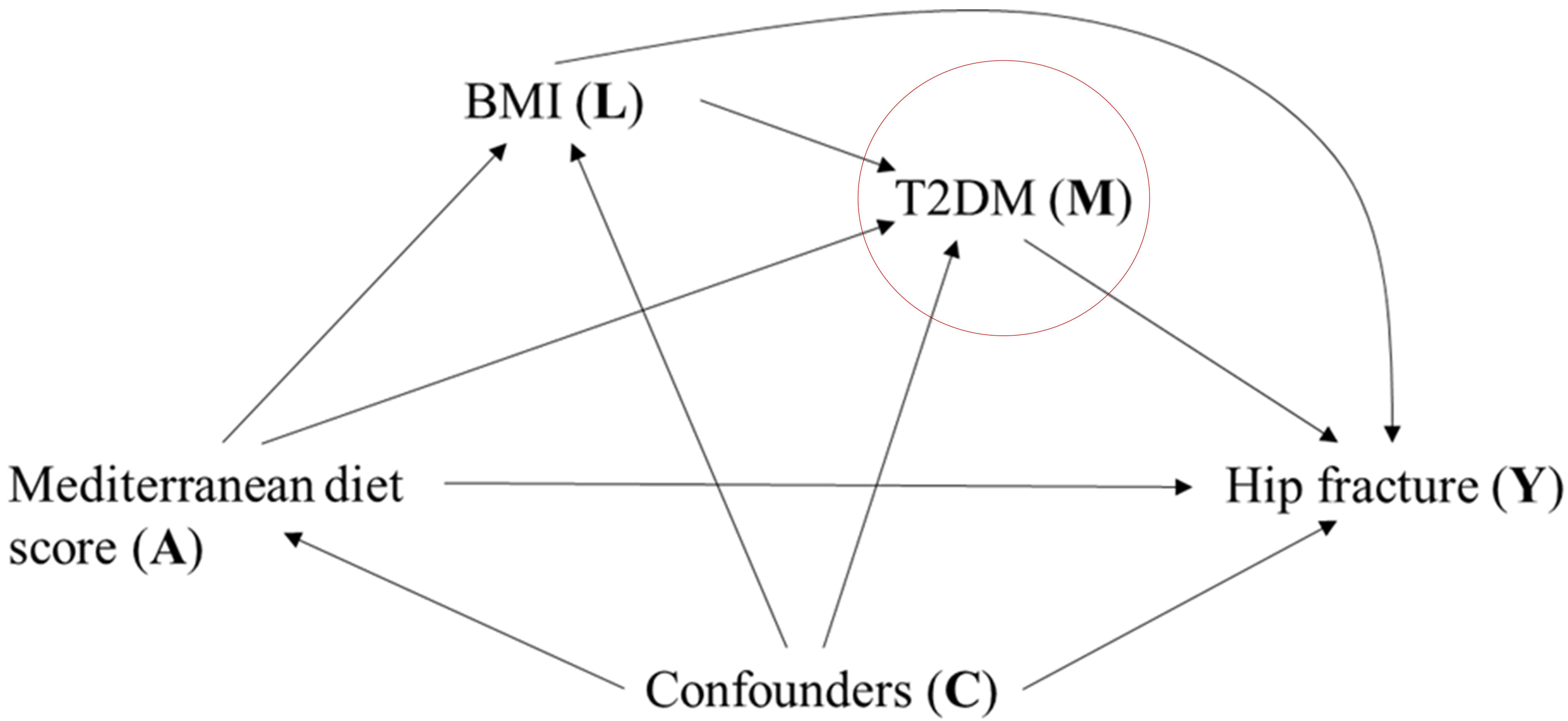
$P(Y=1|A = a, C=c)$



Standard regression approach to mediation

Model 2

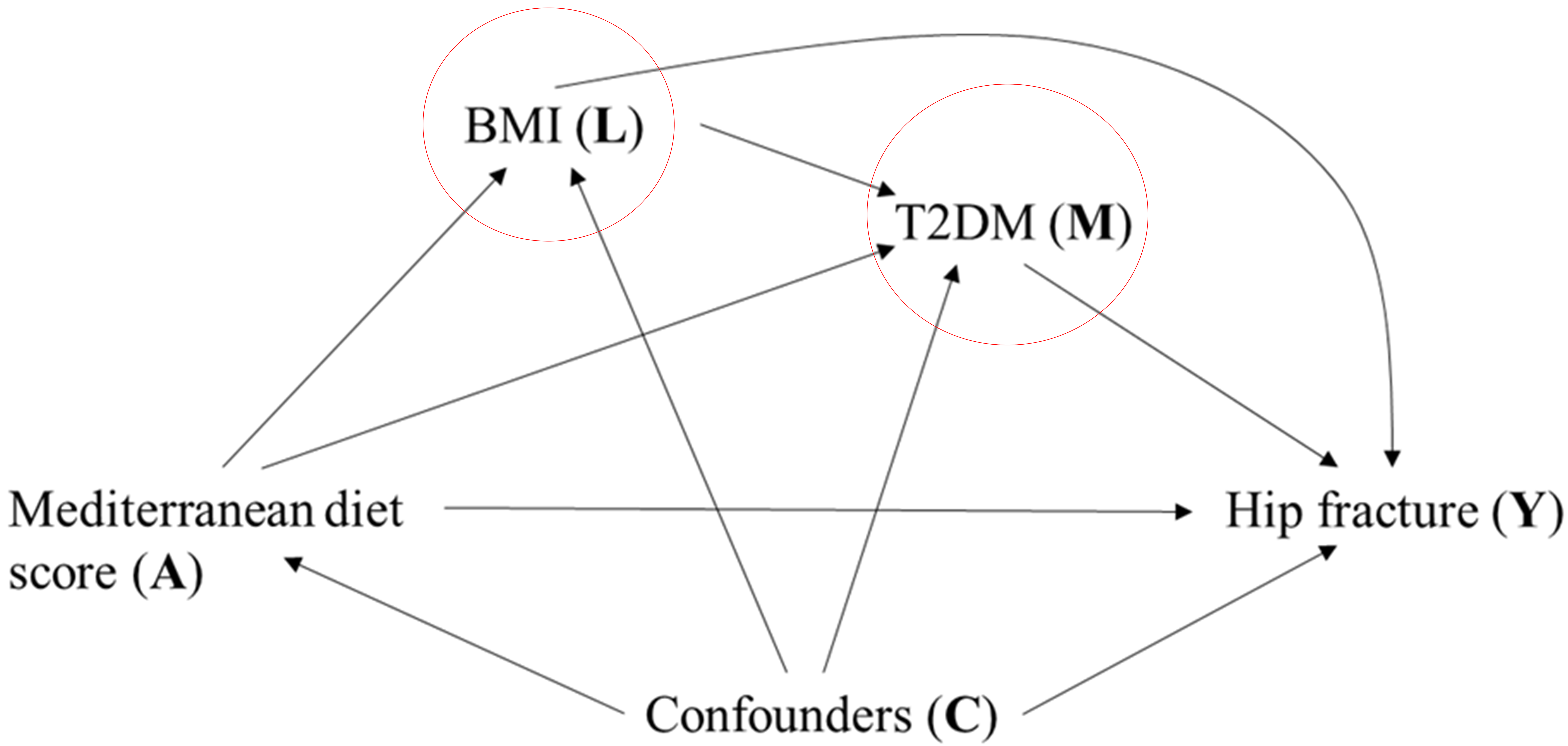
$P(Y=1|A = a, M=m, C=c)$



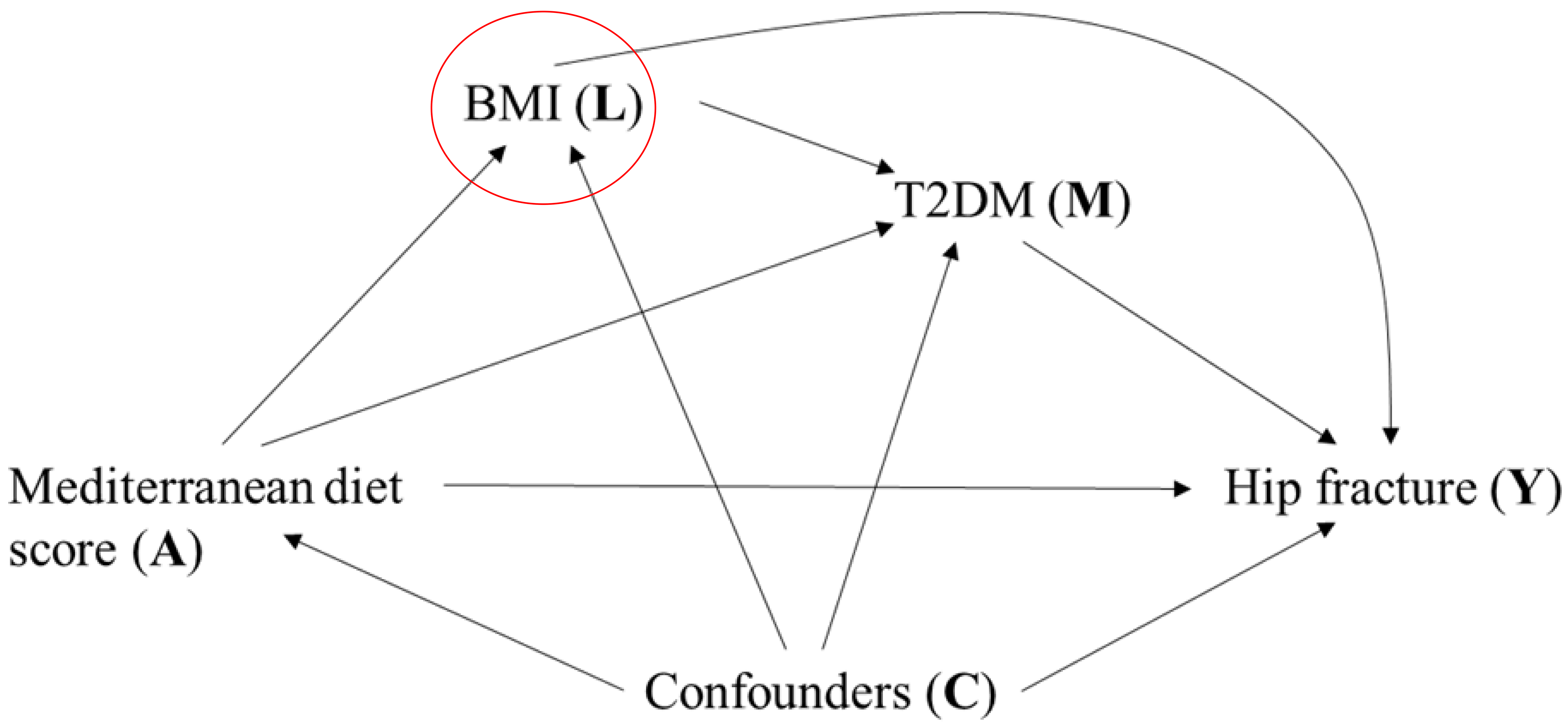
Standard regression approach to mediation

Model 3

$P(Y=1|A = a, M=m, C=c, L=r)$



Marginal structural model (MSM)



Nandi et al., Epidemiology, 2012 & Vanderweele, 2015

Marginal structural model (MSM) which allows for the identification of controlled direct effects (CDE) when conventional approaches are biased due to exposure induced mediator outcome confounding.

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Method - Inverse probability weighting (IPW)

We estimated the controlled direct effect using a marginal structural model with stabilised inverse probability weights for the mediator T2DM (including the exposure-induced confounder BMI), conditional on confounders C.

$$w_M = \frac{P(M_i = m|A_i = a)}{P(M_i = m|A_i = a, C_i = c, L_i = l)}$$

$$\text{logit } \hat{P}(Y_i = 1|A_i=a, M_i=m, C_i=c) = \hat{\eta}_0 + \hat{\eta}_1 A_i + \hat{\eta}_2 M_i + \hat{\eta}_3 C_i$$

Each individual is weighted by w_M

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Results – Conditional Controlled direct effect (CDE)

	Total effect	Conditional controlled direct effect with respect to T2DM as a mediator		
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Mediterranean diet score (mMED)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 (reference) (lowest adherence)	1.00	1.00	1.00	1.00
1	0.82 (0.71, 0.95)	0.82 (0.71, 0.95)	0.82 (0.71, 0.94)	0.82 (0.71, 0.95)
2 (highest adherence)	0.75 (0.62, 0.91)	0.75 (0.62, 0.91)	0.73 (0.61, 0.90)	0.73 (0.60, 0.88)

Model 4

Conditional controlled direct effect of Mediterranean diet on the risk of hip fracture independent of T2DM and controlling for exposure inducued confounding caused by BMI.

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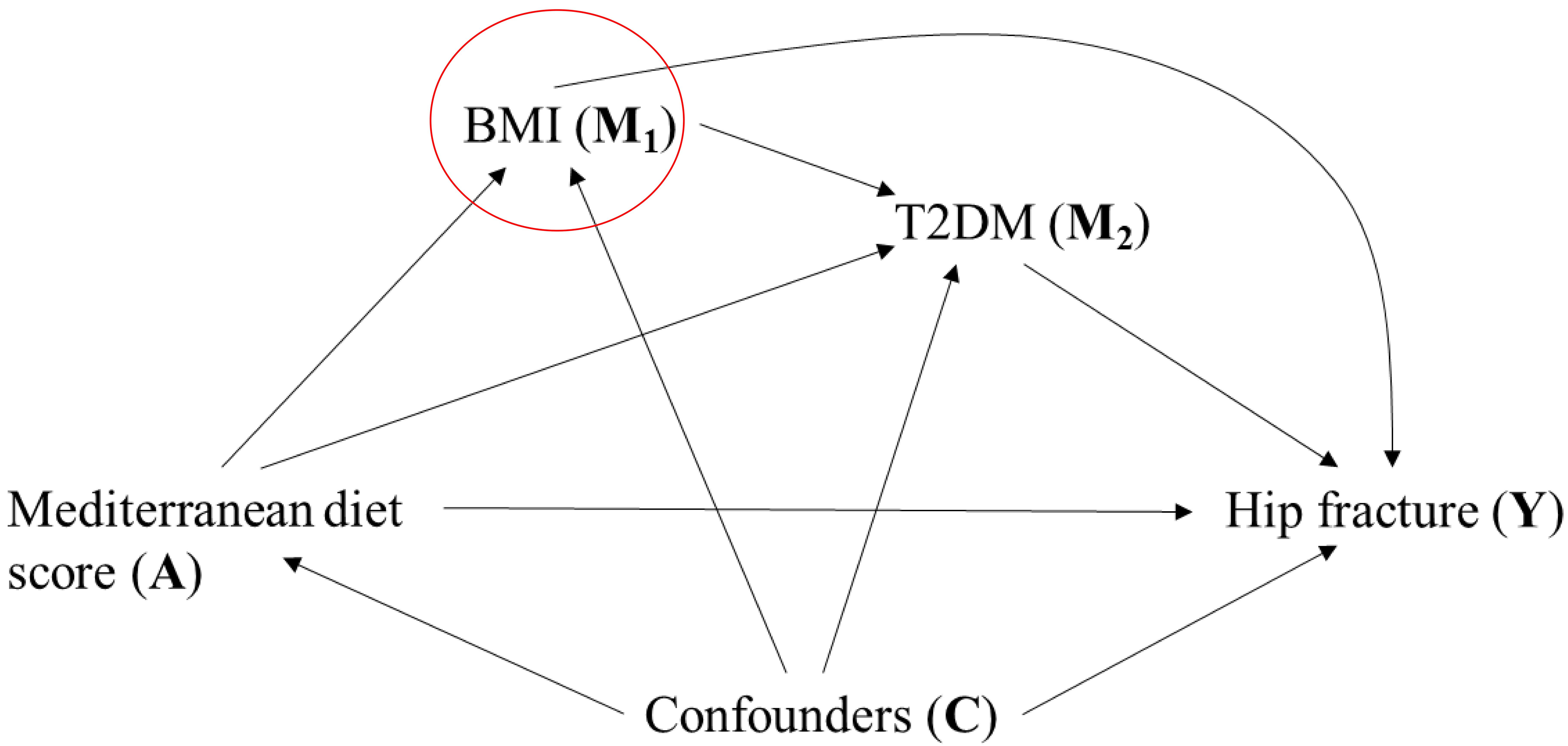
Multiple mediators



Steen et al., American Journal of Epidemiology, 2017

We used nested counterfactuals to estimate:

Natural direct effects (NDE) mMED → hip fracture

Natural indirect effects (NIE) mMED → BMI → hip fracture mMED → BMI → T2DM → hip fracture

Partial indirect effects (PIE) mMED → T2DM → hip fracture

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Flexible Multiple mediator Method

1. We predicted the probability of T2DM (M_2) conditional on mMED (A), BMI (M_1) and confounders (C).

2. We predicted the risk of hip fracture (Y), given mMED (A), BMI (M_1), T2DM (M_2) and confounders (C).

3. We created three auxiliary variables (a, a', a") and extended the dataset by sequential replications to then fit the counterfactual models.

Based on our three-level exposure we first created three copies of the dataset where a was set to the observed mMED level in the first copy, to the first counterfactual in the second copy, and to the second counterfactual in the third copy. Repeated for each level of exposure.

Each exposure level of mMED thus has two counterfactual levels.

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Methods cont.

4. For each row of the final extended dataset

$$w_{NE} = \frac{\hat{P}(M_{2i} = m_2 | A_i = a", m_1, c)}{\hat{P}(M_{2i} = m_2 | A_i = a, m_1, c)}$$

5. Use the fitted values from the natural effects outcome model in step 2.

$$E\{Y(a, M_{1i}(a'), M_{2i}(a", M_{1i}(a')))|C\}$$

To impute nested counterfactuals from step 3.

6. Run a logistic regression model on the imputed counterfactuals, given confounders

Estimated by:

$$\text{logit } \hat{P}(\hat{E} \,|\, a, a', a'', C) = \hat{\theta}_1 a + \hat{\theta}_2 a' + \hat{\theta}_3 a'' + \hat{\theta}_4 C$$

Methods cont.

$$\frac{\mathrm{E}\left\{Y\left(1, M_1(\mathrm{a}'), M_2\left(\mathrm{a}'', M_1(\mathrm{a}')\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(1, M_1(\mathrm{a}'), M_2\left(\mathrm{a}'', M_1(\mathrm{a}')\right)\right\}\right)}{\mathrm{E}\left\{Y\left(0, M_1(\mathrm{a}'), M_2\left(\mathrm{a}'', M_1(\mathrm{a}')\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(0, M_1(\mathrm{a}'), M_2\left(\mathrm{a}'', M_1(\mathrm{a}')\right)\right\}\right)}$$

Estimated by the component $E_{A \rightarrow Y}$ (a', a") = θ_1

$$\frac{\mathrm{E}\left\{Y\left(a, M_1(1), M_2\left(\mathrm{a}'', M_1(1)\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(a, M_1(1), M_2\left(\mathrm{a}'', M_1(1)\right)\right\}\right)}{\mathrm{E}\left\{Y\left(a, M_1(0), M_2\left(\mathrm{a}'', M_1(0)\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(a, M_1(0), M_2\left(\mathrm{a}'', M_1(0)\right)\right\}\right)}$$

Estimated by the component $E_{A \rightarrow M1 \rightarrow Y}$ (a, a") = θ_2

$$\frac{\mathrm{E}\left\{Y\left(a, M_1(\mathrm{a}'), M_2\left(1, M_1(\mathrm{a}')\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(a, M_1(\mathrm{a}'), M_2\left(1, M_1(\mathrm{a}')\right)\right\}\right)}{\mathrm{E}\left\{Y\left(a, M_1(\mathrm{a}'), M_2\left(0, M_1(\mathrm{a}')\right)\right\} / \left(1 - \mathrm{E}\left\{Y\left(a, M_1(\mathrm{a}'), M_2\left(0, M_1(\mathrm{a}')\right)\right\}\right)}$$

Estimated by the component $E_{A \rightarrow M2 \rightarrow Y}$ (a, a') = θ_3

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Results - Natural direct effect (NDE) Natural indirect effect (NIE) & Partial indirect effect

mMED	Natural direct effect (a)[a]	Natural indirect effect (a′)[b]	Partial indirect effect (a″)[c]
	mMED → hip fracture	mMED → BMI → hip fracture mMED → BMI → T2DM → hip fracture	mMED → T2DM → hip fracture
Mediterranean diet score (mMED)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0 (reference) (lowest adherence)	1.00	1.00	1.00
1	0.819 (0.710, 0.945)	1.006 (0.994, 1.017)	0.998 (0.989, 1.007)
2 (highest adherence)	0.737 (0.609, 0.893)	1.022 (1.004, 1.040)	0.989 (0.977, 1.002)

Natural direct effect (NDE) odds ratio of Mediterranean diet on risk of hip fracture through neither BMI or T2DM.

Natural indirect effect (NIE) odds ratio mediated by Mediterranean diet induced changes in BMI.

Partial indirect effect (PIE) odds ratio mediated solely by Mediterranean diet induced changes in T2DM.

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Controlled effects vs Natural effects

- Controlled direct effects are generally closer to interventional scenarios where intermediates can be intervened upon (intervening to make everyone T2DM or not), making them of greater interest in planning for public health policy.

- Whereas natural direct and indirect effects are of greater interest in evaluating the mechanisms of action between and exposure and an outcome via any potential mediators as values take on their natural state in the population under study.

Strengths

- The application of two recently developed mediation methods applied to a three-level categorical exposure.
- Control for mediator outcome confounding
- Handle multiple causally ordered mediators
- Effect decomposition
- Longitudinal design allowing temporal ordering of exposure, mediator and outcome variables, a prerequisite for mediation analysis.

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Limitations

- Assumptions.
- We cannot completely exclude the possibility of residual confounding.
- We assume that our models were correctly specified and that the consistency assumption holds.
  - An individual's potential outcome under his or her observed exposure history is the outcome that will actually be observed for that person.
- Marginal structural models and inverse-probability- weighting require a positivity assumption that the probabilities in the denominator of the weights are nonzero.
  - In all covariate strata some individuals are exposed while others are unexposed. Low, Moderate or High mMED.

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Limitations

- Restricting the duration of T2DM to incident cases in 1997-2009, may limit our power to detect possible mediating effects, which is an inherent limitation of the available data.

- Repeat exposure and mediator assessments would be desirable for time updated analysis.

- Even if the counterfactual framework allows for analysis and interpretation of mediation effects, the combination of counterfactuals assessed in our mediation analyses are constructs that can never be observed in reality.

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Things to consider

- The research question of interest will first require the graphical illustration of causal effects in a DAG which will be constructed through background knowledge and previous evidence.
- This will then lead to the effect estimate of particular interest which will require different methods of application.
- In this study we used traditional methods of mediation analysis with simple covariate adjustment, marginal structural models with IPW to estimate controlled direct effects and flexible multiple mediation using counterfactual notation to estimate natural direct, indirect and partial indirect effects.

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Conclusion

- Evidence of a direct effect of Mediterranean diet on hip fracture risk not mediated via T2DM and BMI.

- The reduced risk of hip fracture with high adherence to a Mediterranean diet may be mediated via the diets effect on other biological processes:

- Reduced inflammation
- Antioxidant effect
- Bone formation > bone resorption

- We cannot rule out mediation or counteracting effects but what we can say is that there is an effect of Mediterranean diet on hip fracture that does not go through T2DM and BMI.

- Further work is therefore needed to establish casual pathways between Mediterranean diet and hip fracture risk.

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- Karl Michaëlsson
- Tove Fall
- Håkan Melhus

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