Effect estimation in the presence of a misclassified binary mediator

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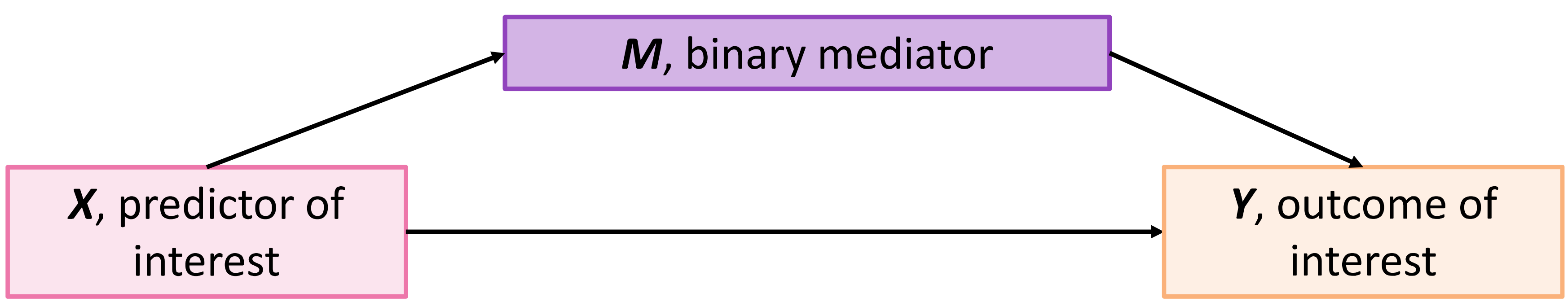
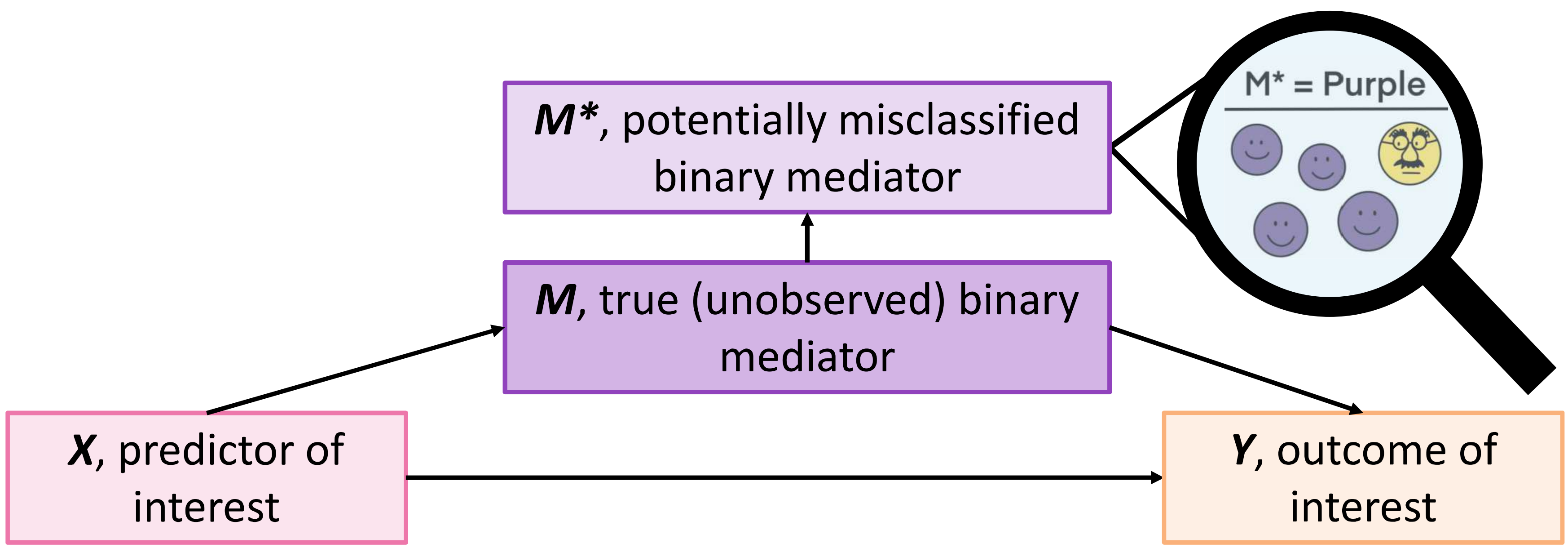
Problem setting

- **Mediation analysis** quantifies the effect of an **exposure (X)** on an **outcome (Y)**, mediated by some **intermediate (M)**.



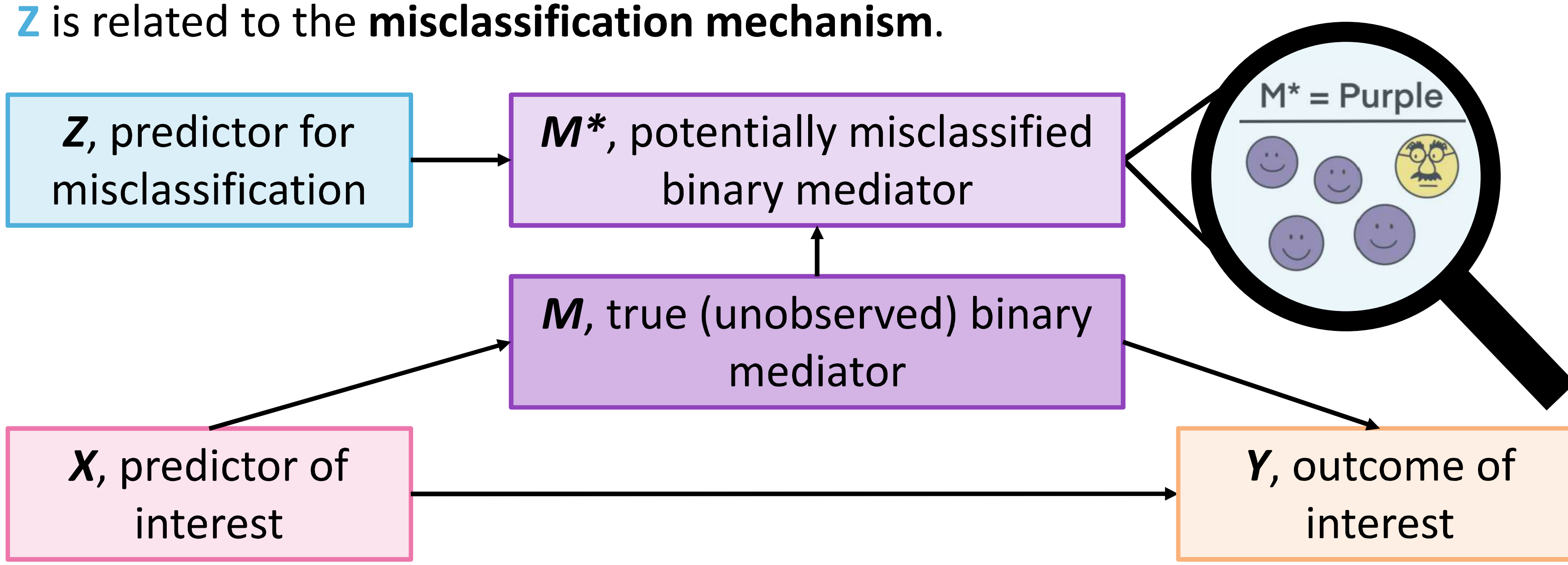
Problem setting

- **Mediation analysis** quantifies the effect of an **exposure (X)** on an **outcome (Y)**, mediated by some **intermediate (M)**.
- Measure **M** using an instrument that is not always accurate, and obtain M*.



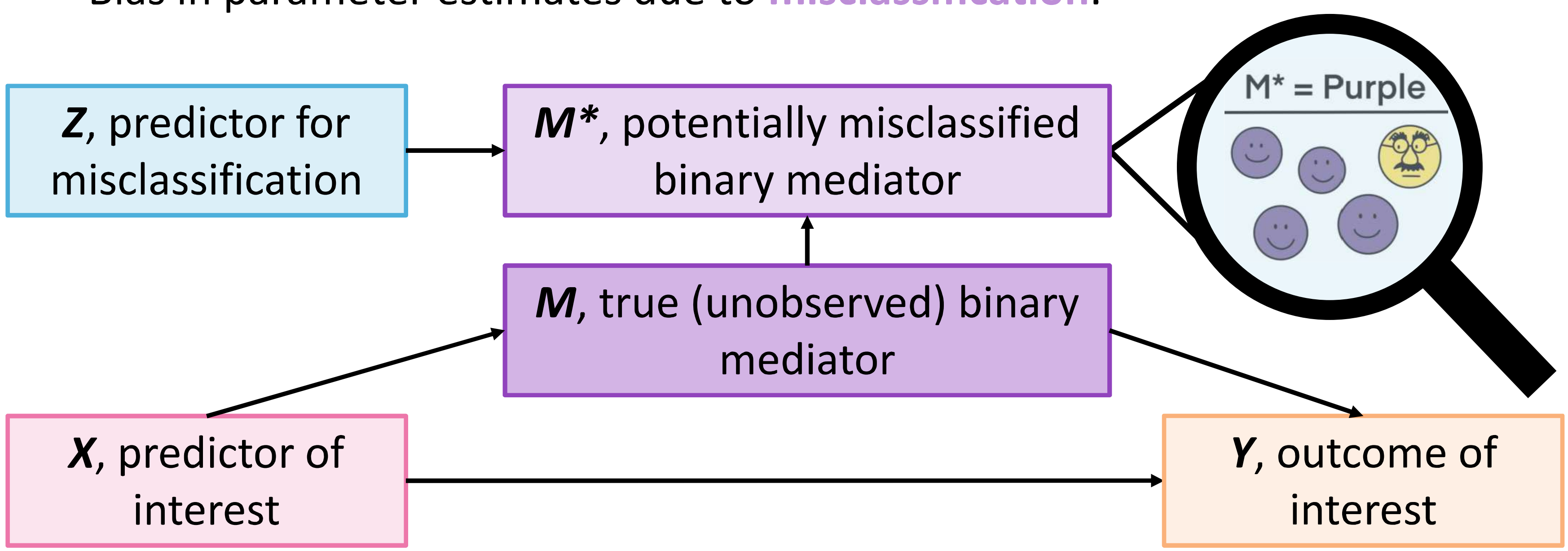
Problem setting

- **Mediation analysis** quantifies the effect of an **exposure (X)** on an **outcome (Y)**, mediated by some **intermediate (M)**.
- Measure **M** using an instrument that is not always accurate, and obtain M*.
- Z is related to the **misclassification mechanism**.



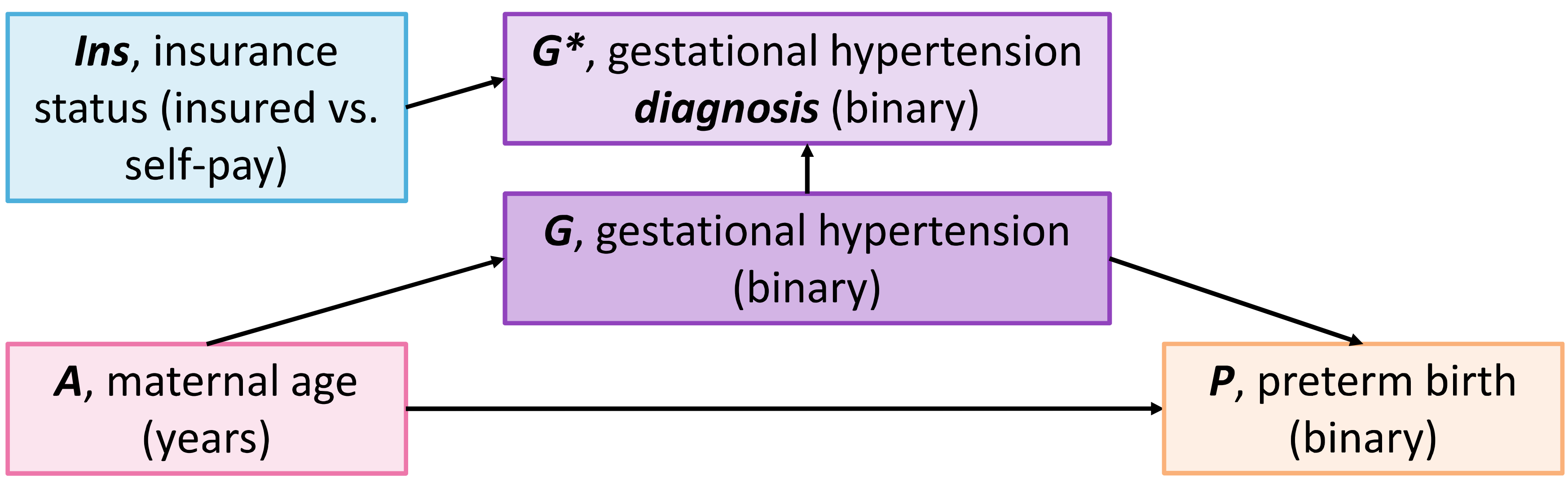
Problem setting

- **Challenges:**
  - Misclassification is **covariate-dependent**.
  - No gold standard labels.
  - Bias in parameter estimates due to **misclassification**.



Problem setting

- **Example:**
  - Does **gestational hypertension** mediate the association between **maternal age** and **preterm birth**, after accounting for potential **misdiagnosis of gestational hypertension** based on **patient insurance status**?

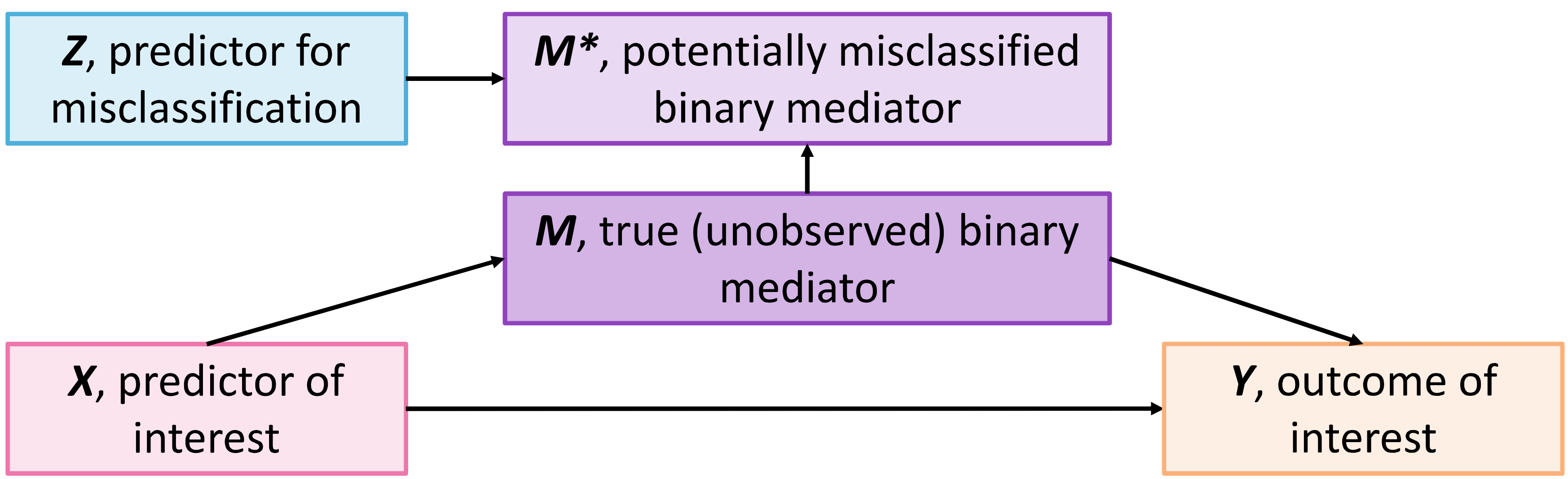


Model

True mediator model:

Observed mediator model:

Outcome model:

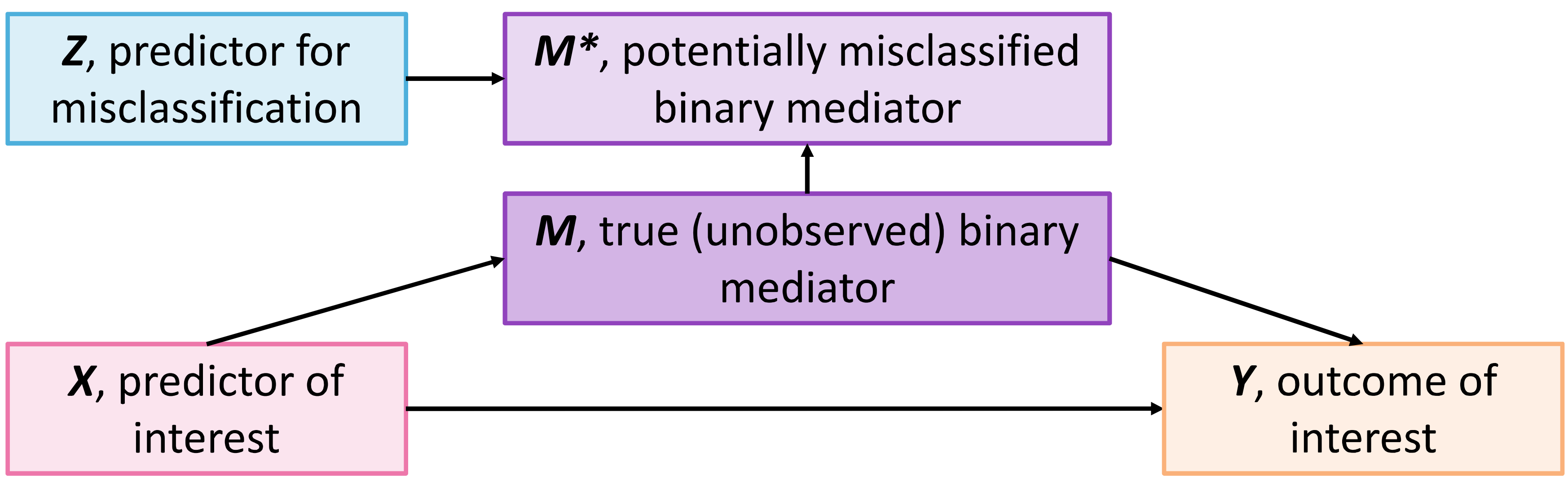


Model

True mediator model: $\text{logit}\{P(M=1|X,\boldsymbol{C};\boldsymbol{\beta})\} = \beta_0 + \beta_X X + \boldsymbol{\beta}_C \boldsymbol{C}$

Observed mediator model:

Outcome model:



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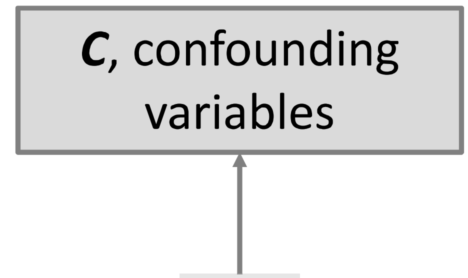

True mediator model: $\text{logit}\{P(M = 1|X, \mathbf{C}; \boldsymbol{\beta})\} = \beta_0 + \beta_X X + \beta_C C$

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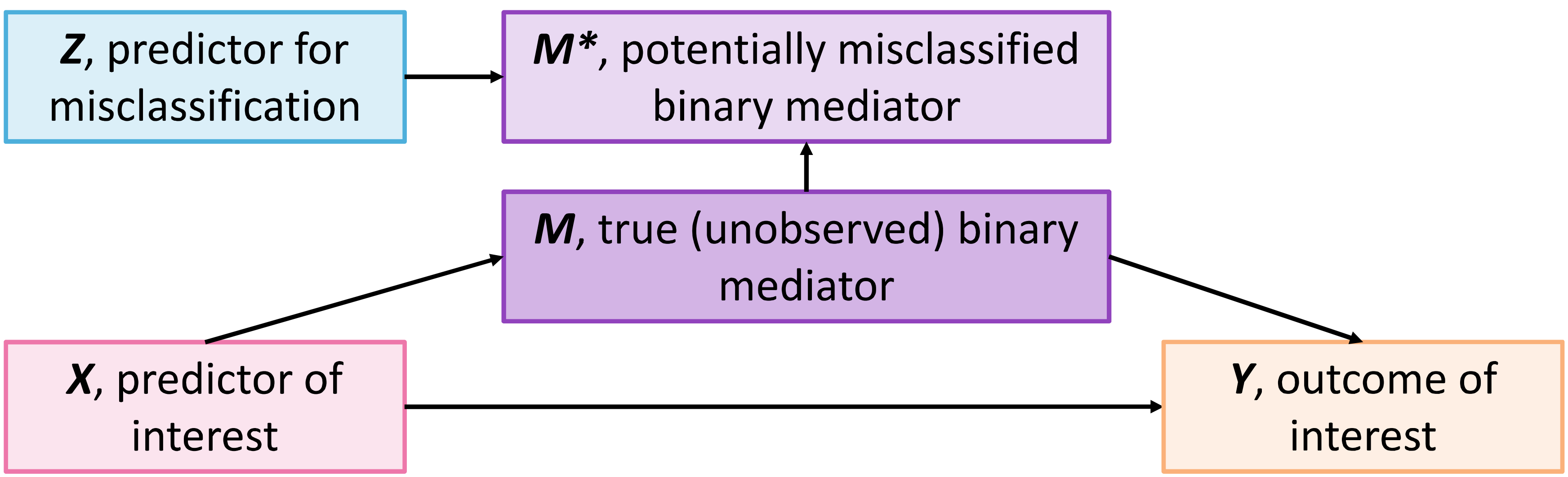
Outcome model:



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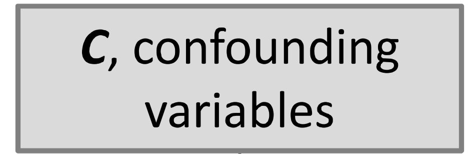

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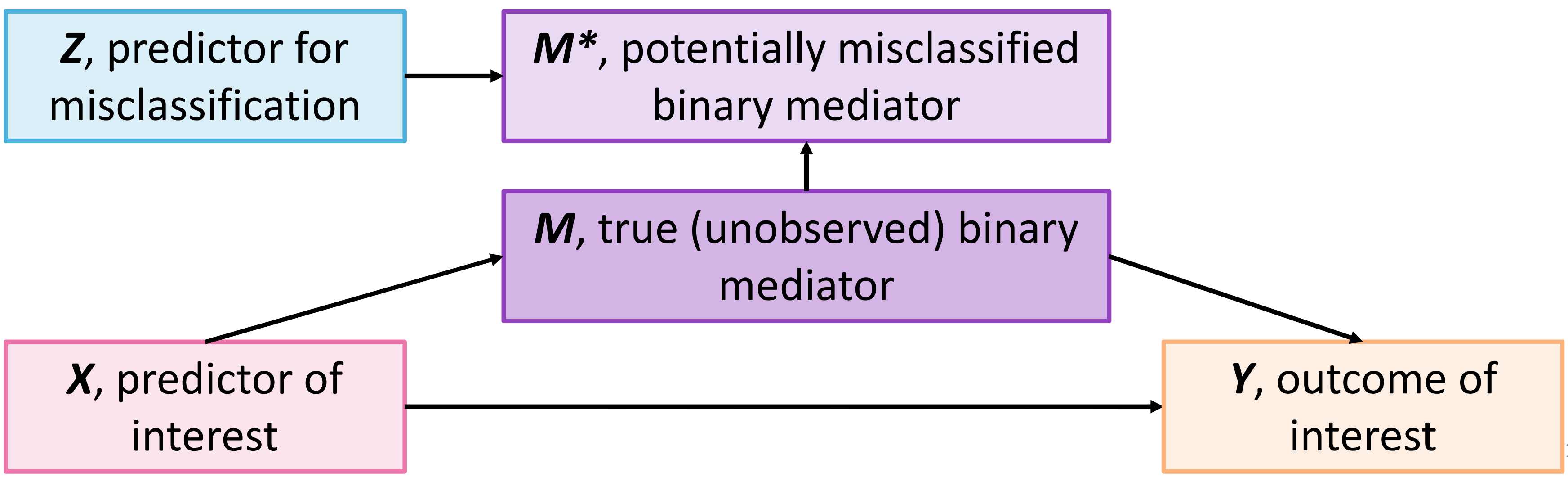

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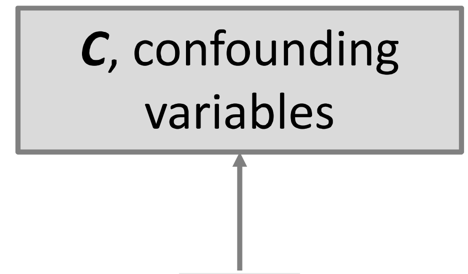

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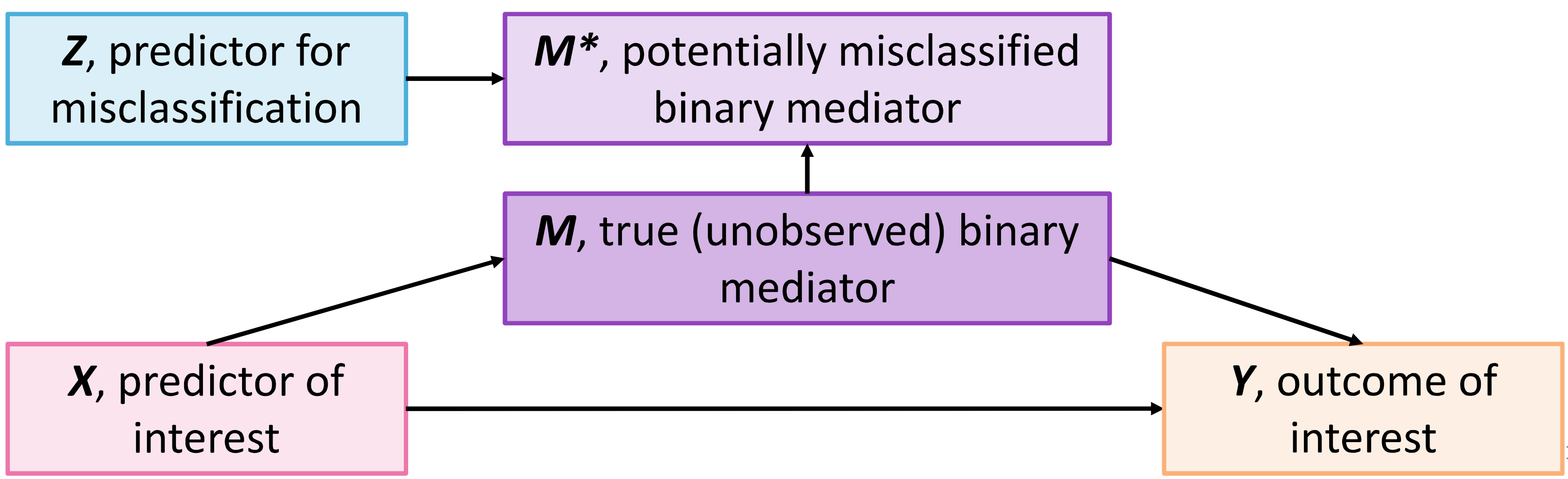

Model

Primary interest:
Estimating β and θ

True mediator model: $\text{logit}\{P(M = 1|X, \boldsymbol{C}; \boldsymbol{\beta})\} = \beta_0 + \beta_X X + \boldsymbol{\beta}_C \boldsymbol{C}$

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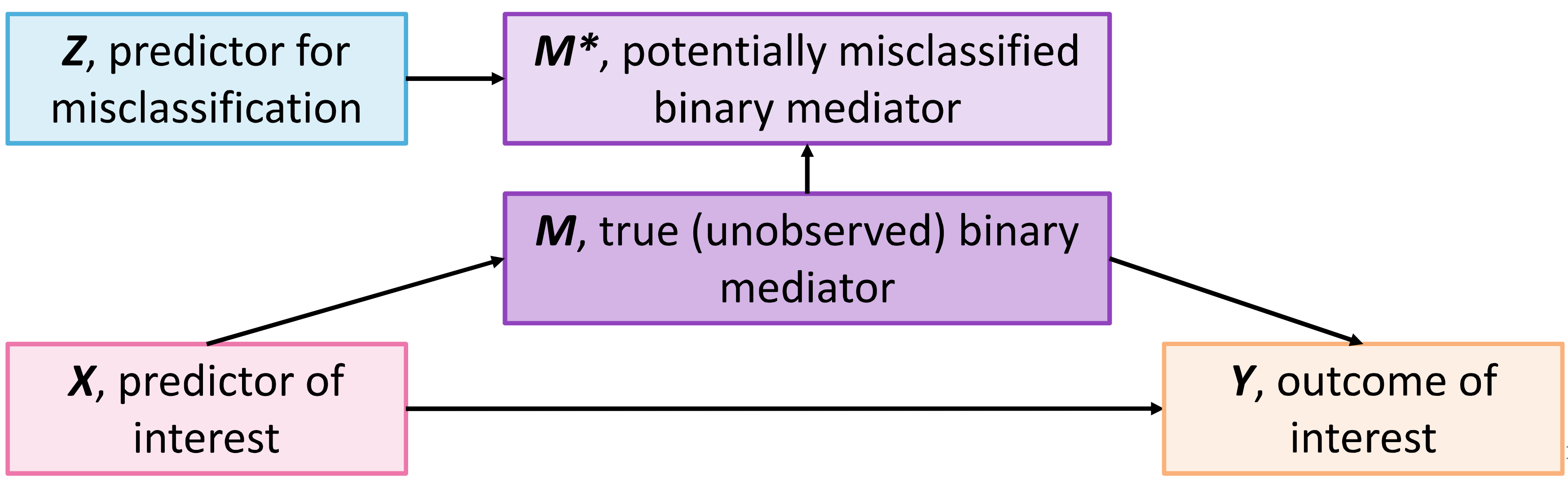

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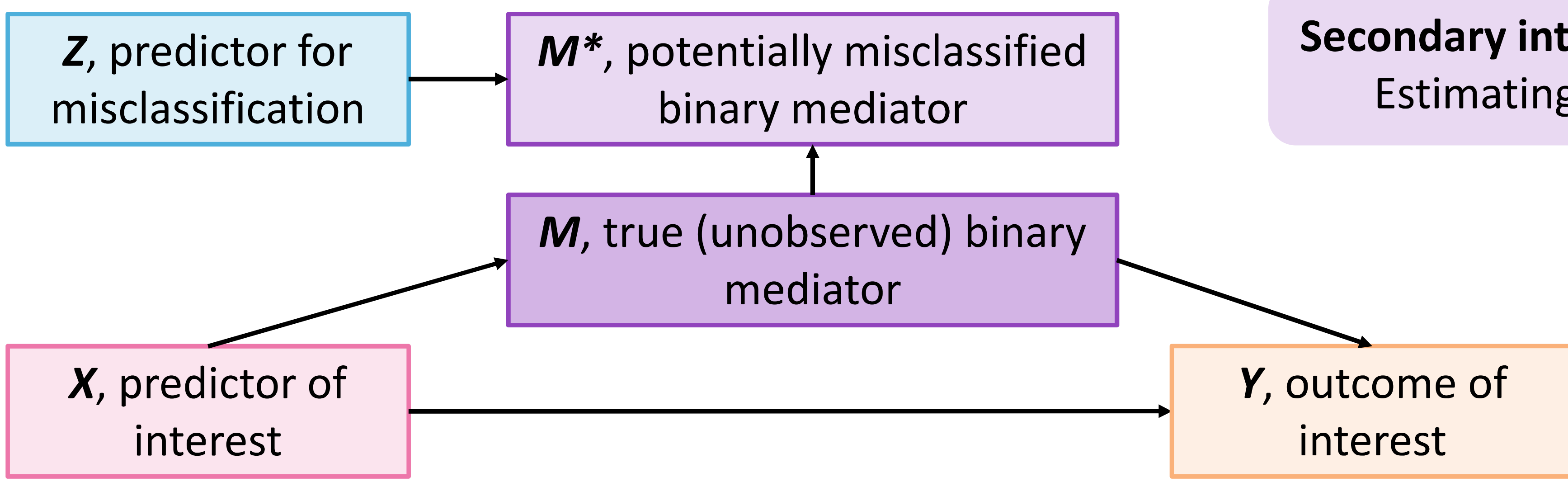
Secondary interest:
Estimating γ



Estimation

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#1: OLS Correction	#2: Predictive value weighting	#3: An EM algorithm

Estimation

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#1: OLS Correction[1]	#2: Predictive value weighting[2]	#3: An EM algorithm

Key point: We can use ***COMBO*** to estimate subject-level sensitivity and specificity, and then plug these values into existing misclassification correction procedures.

- Existing procedures relied on *known* sensitivity and specificity.

1. Extended from Nguimkeu, Rosenman, and Tennekoon (2021), "Regression with a misclassified binary regressor: Correcting for hidden bias".
2. Extended from Lyles and Lin (2010), "Sensitivity analysis for misclassification in logistic regression via likelihood methods and PVW".

Estimation

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#1: OLS Correction	#2: Predictive value weighting	#3: An EM algorithm

Complete data log-likelihood:

$$\ell_{complete}(\boldsymbol{\beta},\boldsymbol{\gamma},\boldsymbol{\gamma};X,\boldsymbol{C},\boldsymbol{Z},Y)$$

$$= \sum_{i=1}^{N}\left[\ell_{Y|X,M,C}(\boldsymbol{\theta};X_i,M_i,\boldsymbol{C}_i,Y_i) + \sum_{j=1}^{2} m_{ij}\log\{\pi_{ij}\} + \sum_{j=1}^{2}\sum_{\ell=1}^{2} m_{ij}m^*_{i\ell}\log\{\pi^*_{i\ell j}\}\right]$$

Estimation

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Outcome

Estimation

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m_{ij}: I(M_i = j)

π_{ij}: P(M_i = j)

Outcome | True mediator

Estimation

True mediator model: $\text{logit}\{P(M=1|X,\boldsymbol{C};\boldsymbol{\beta})\} = \beta_0 + \beta_X X + \boldsymbol{\beta}_C \boldsymbol{C}$

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Outcome

True mediator: m_{ij} = $\mathbb{I}(M_i = j)$; π_{ij} = $P(M_i = j)$

Observed mediator: $m^*_{i\ell}$ = $\mathbb{I}(M_i^* = \ell)$; $\pi^*_{i\ell j}$ = $P(M_i^* = \ell \mid M_i = j)$

Estimation

True mediator model: $\mathrm{logit}\{P(M=1|X,\boldsymbol{C};\boldsymbol{\beta})\} = \beta_0 + \beta_X X + \boldsymbol{\beta_C C}$

Observed mediator model: $\mathrm{logit}\{P(M^*=1|M=m,\boldsymbol{Z};\boldsymbol{\gamma})\} = \gamma_{1m0} + \boldsymbol{\gamma_{1mZ} Z}$

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Expectation Step ↔ **Maximization Step**

Estimation

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Expectation Step ↔ **Maximization Step**

$$w_{ij} = P(M_i = j | M_i^*, X_i, \boldsymbol{C}_i, \boldsymbol{Z}_i, Y_i)$$

$$= \sum_{\ell=1}^{2} \frac{m_{i\ell}^* \pi_{i\ell j}^* \pi_{ij} E[Y_i|X_i, M_i = j, \boldsymbol{C}_i, \boldsymbol{\theta}^{(t)}]}{\sum_{k=1}^{2} \pi_{i\ell k}^* \pi_{ik} E[Y_i|X_i, M_i = k, \boldsymbol{C}_i, \boldsymbol{\theta}^{(t)}]}$$

Estimation

True mediator model: $\text{logit}\{P(M=1|X,\boldsymbol{C};\boldsymbol{\beta})\} = \beta_0 + \beta_X X + \boldsymbol{\beta}_{\boldsymbol{C}}\boldsymbol{C}$

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$$Q = \sum_{i=1}^{N} \Big[\sum_{j=1}^{2} \ell_{Y|X,M,C}(\boldsymbol{\theta}; X_i, M_i = w_{ij}, \boldsymbol{C}_i, Y_i) + \sum_{j=1}^{2} w_{ij} \log\{\pi_{ij}\} + \sum_{j=1}^{2}\sum_{\ell=1}^{2} w_{ij} m_{i\ell}^* \log\{\pi_{i\ell j}^*\} \Big]$$

Estimation

$$Q_\beta = \sum_{i=1}^{N} [\sum_{j=1}^{2} w_{ij} \log\{\pi_{ij}\}]$$

model: $\text{logit}\{P(M=1|X,C;\beta)\} = \beta_0 + \beta_X X + \beta_C C$

Observed mediator model: $\text{logit}\{P(M^*=1|M=m,Z;\gamma)\} = \gamma_{1m0} + \gamma_{1mZ} Z$

$$Q_{\gamma_1} = \sum_{i=1}^{N} [\sum_{\ell=1}^{2} w_{i1} m^*_{i\ell} \log\{\pi^*_{i\ell 1}\}]$$

$(Y|X,C,M) = \theta_0 + \theta_X X + \theta_C C + \theta_M M + \theta_{XM} XM$

#1: OLS Correction

#2: Predictive value weighting

#3: An EM algorithm

$$Q_{\gamma_2} = \sum_{i=1}^{N} [\sum_{\ell=1}^{2} w_{12} m^*_{i\ell} \log\{\pi^*_{i\ell 2}\}]$$

Maximization Step

$$Q_\theta = \sum_{i=1}^{N} [\sum_{j=1}^{2} \ell_{Y|X,M,C}(\theta; X_i, M_i = w_{ij}, C_i, Y_i)]$$

$$= \sum_{\ell=1}^{2} \frac{m^*_{i\ell}\pi^*_{i\ell j}\pi_{ij} E[Y_i|X_i, M_i = j, C_i, \theta^{(t)}]}{\sum_{k=1}^{2} \pi^*_{i\ell k}\pi_{ik} E[Y_i|X_i, M_i = k, C_i, \theta^{(t)}]}$$

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Expectation Step

Apply the label switching correction from Webb and Wells (2023)

Maximization Step

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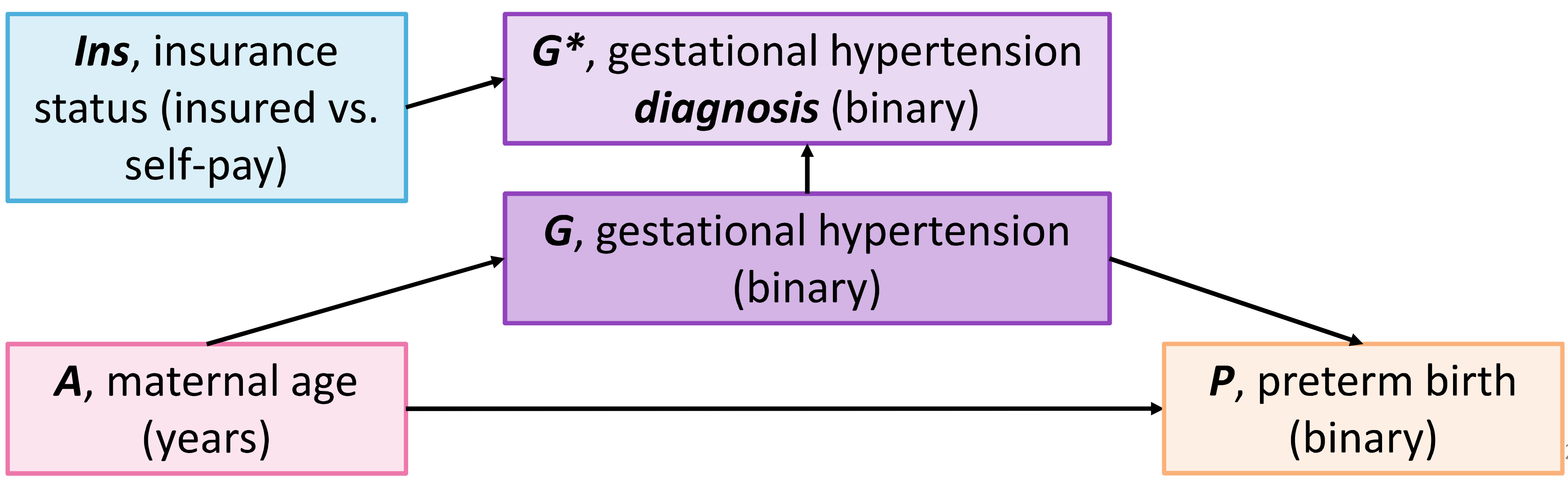
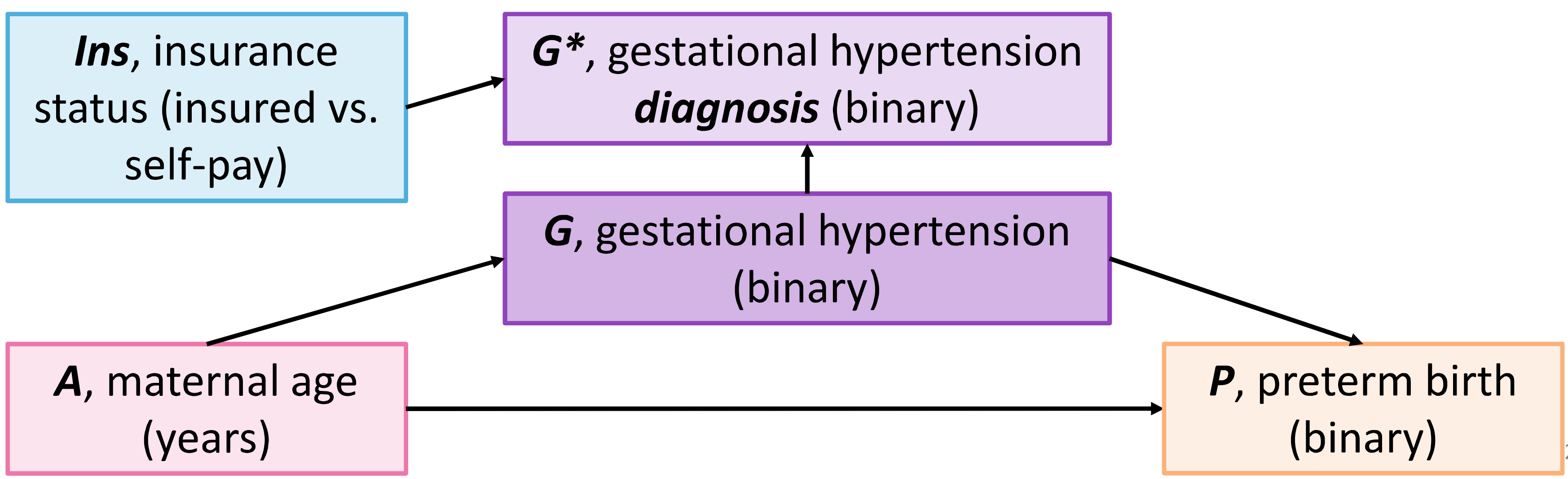
- **Example:**
  - Does **gestational hypertension** mediate the association between **maternal age** and **preterm birth**, after accounting for potential **misdiagnosis of gestational hypertension** based on **patient insurance status**?



Applied Example

Data: National Vital Statistics System of the National Center for Health Statistics

- Random sample of 20,000 observations.

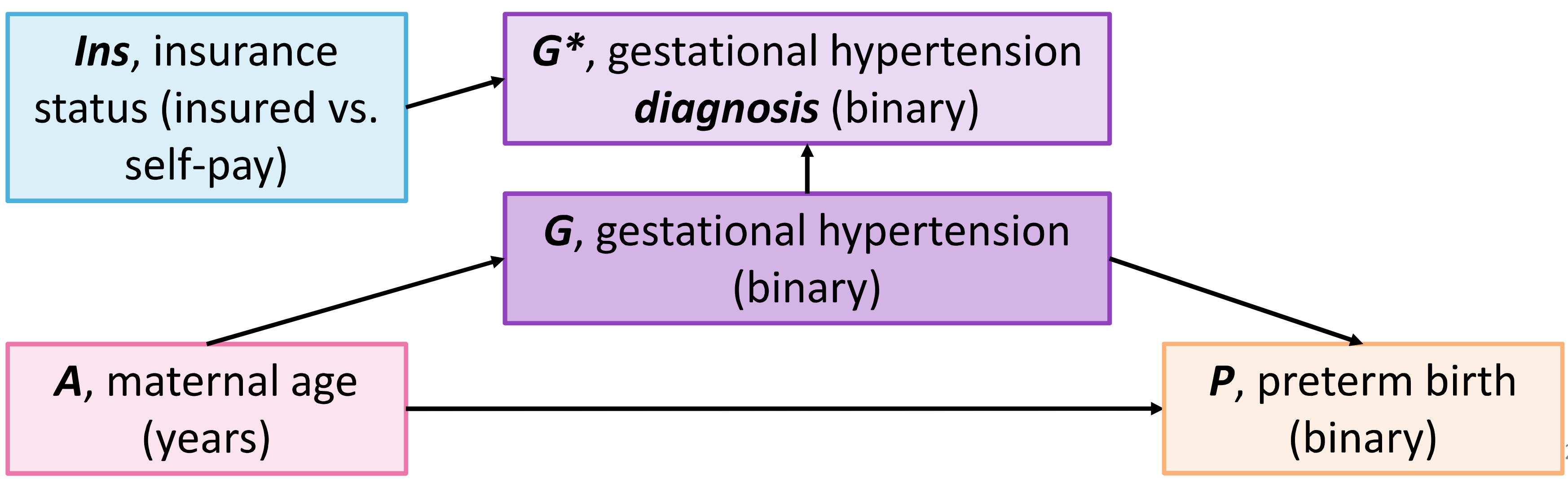


Applied Example

True mediator model: **G** ~ Age + Race + Education + Parity + Smoking + BMI

Observed mediator model: **G* | G** ~ Race + Ins

Outcome model: **P** ~ Age + Race + Education + Parity + Smoking + BMI + **G** + **G** * Age



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	EM Algorithm		Naïve Analysis	
	Est.	SE	Est.	SE
β_{age}				
$\gamma_{ins, G = 1}$				
$\gamma_{ins, G = 2}$				
θ_{age}				
θ_{G}				
$\theta_{G * age}$				

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True mediator model: G ~ Age + Race + Education + Parity + Smoking + BMI

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Outcome model: P ~ Age + Race + Education + Parity + Smoking + BMI + **G** + **G** * Age

Association between **age** and **G** unchanged, accounting for misdiagnosis

	EM Algorithm		Naïve Analysis	
	Est.	SE	Est.	SE
β_{age}	0.10	0.04	0.08	0.03
$\gamma_{ins,\, G=1}$				
$\gamma_{ins,\, G=2}$				
θ_{age}				
θ_{G}				
$\theta_{G * age}$				

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Association between **age** and **G** unchanged, accounting for misdiagnosis

Association between **G** and **P** strengthens

	EM Algorithm		Naïve Analysis	
	Est.	SE	Est.	SE
β_{age}	0.10	0.04	0.08	0.03
$\gamma_{ins,\ G=1}$				
$\gamma_{ins,\ G=2}$				
θ_{age}	0.02	0.05	0.10	0.03
θ_{G}	1.19	0.17	0.88	0.06
$\theta_{G * age}$	0.19	0.09	0.06	0.06

Applied Example

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Observed mediator model: **G* | G** ~ Race + Ins

Outcome model: **P** ~ Age + Race + Education + Parity + Smoking + BMI + **G** + **G** * Age

Association between **age** and **G** unchanged, accounting for misdiagnosis

Association between **G** and **P** strengthens

	EM Algorithm		Naïve Analysis	
	Est.	SE	Est.	SE
β_{age}	0.10	0.04	0.08	0.03
$\gamma_{ins, G=1}$	-1.01	0.40	-	-
$\gamma_{ins, G=2}$	2.09	8.81	-	-
θ_{age}	0.02	0.05	0.10	0.03
θ_{G}	1.19	0.17	0.88	0.06
$\theta_{G * age}$	0.19	0.09	0.06	0.06

Use γ estimates to compute sensitivity and specificity.

Applied Example

True mediator model: **G** ~ Age + Race + Education + Parity + Smoking + BMI

Observed mediator model: **G* | G** ~ Race + Ins

Outcome model: **P** ~ Age + Race + Education + Parity + Smoking + BMI + **G** + **G** * Age

	Estimated Specificity P(no G* | no G)	**Estimated Sensitivity** P(G* | G)
Insured	99.9%	43.1%
Self-Pay	99.4%	21.7%

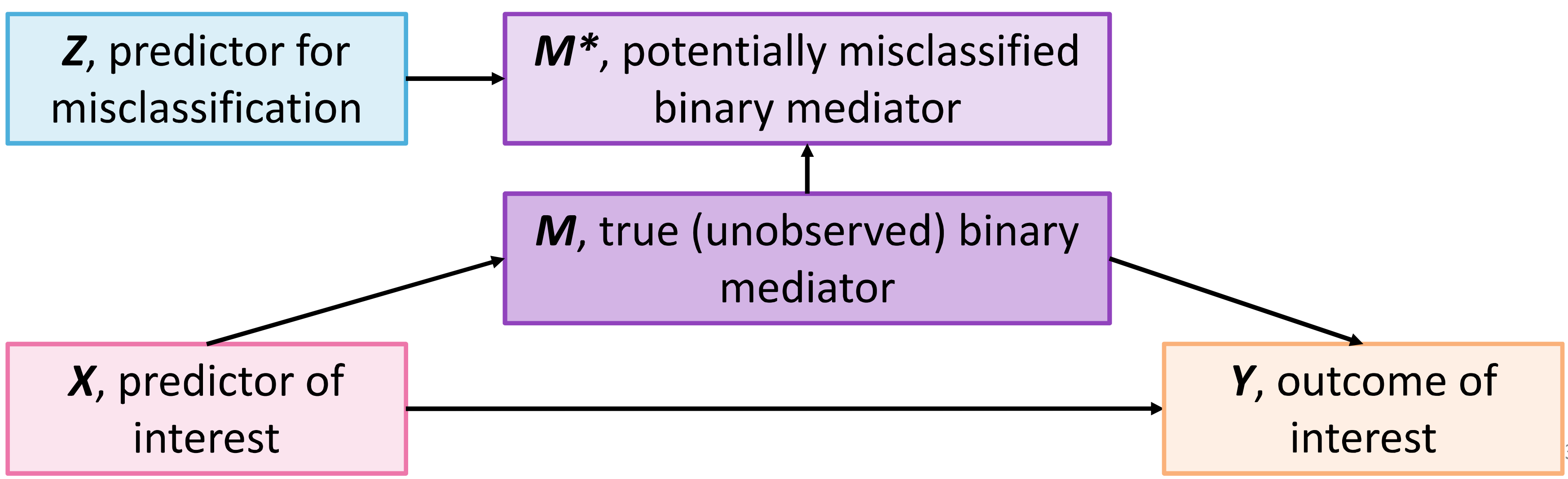
Code is available!

- Sample function and simulation code at:

bit.ly/enar2024-code-webb

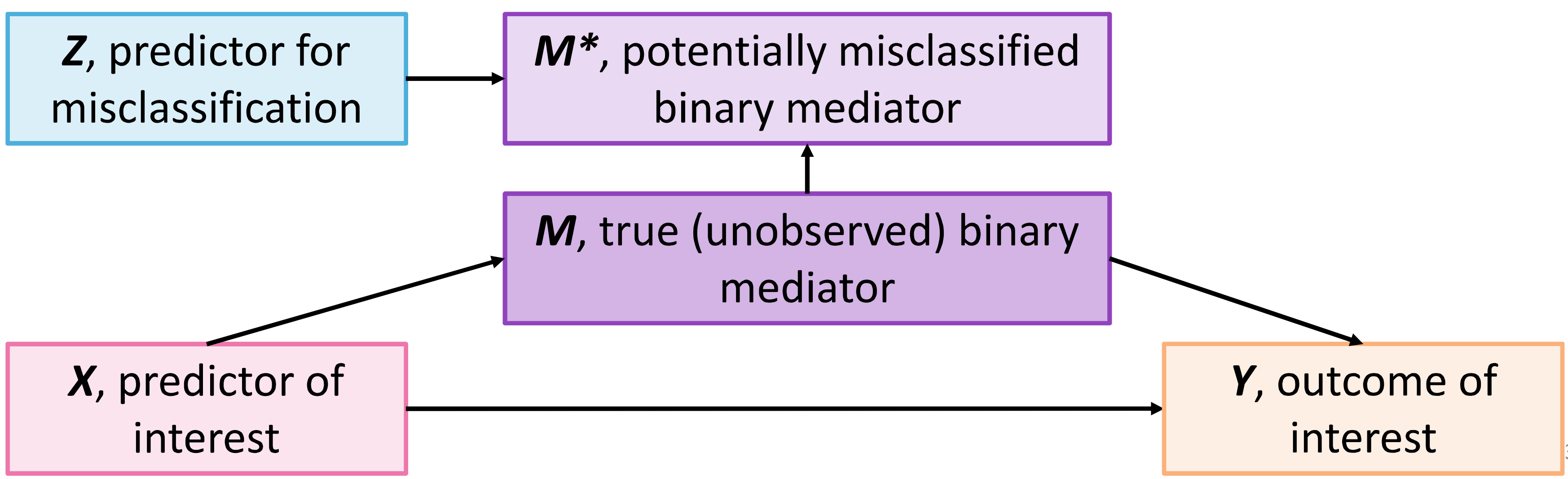
Conclusions and Next Steps

- We can use the proposed methods to **estimate associations** when a **binary mediator is potentially misclassified**.



Conclusions and Next Steps

- We can use the proposed methods to **estimate associations** when a **binary mediator is potentially misclassified**.
- **Next steps:** Incorporate other variables measured with error.



Thank you!

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