The misdiagnosed mediator:
Estimating the effect of maternal age on preterm birth risk in the presence of misclassified gestational hypertension

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Joint Statistical Meetings

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Mediation analysis

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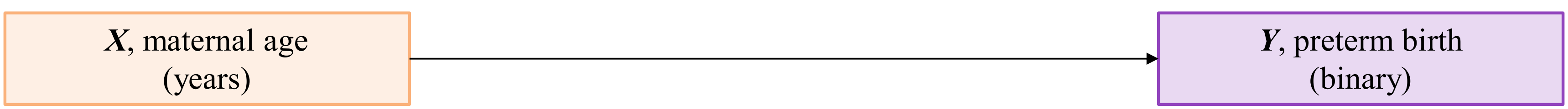

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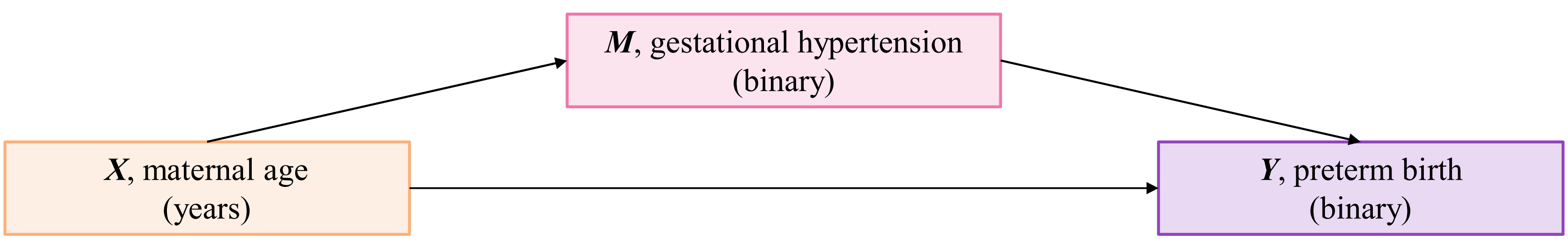

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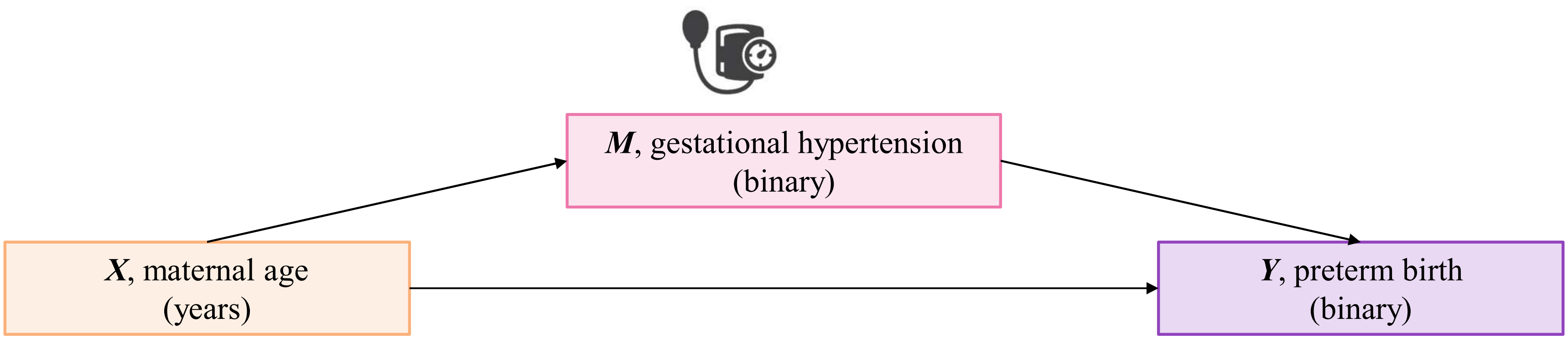

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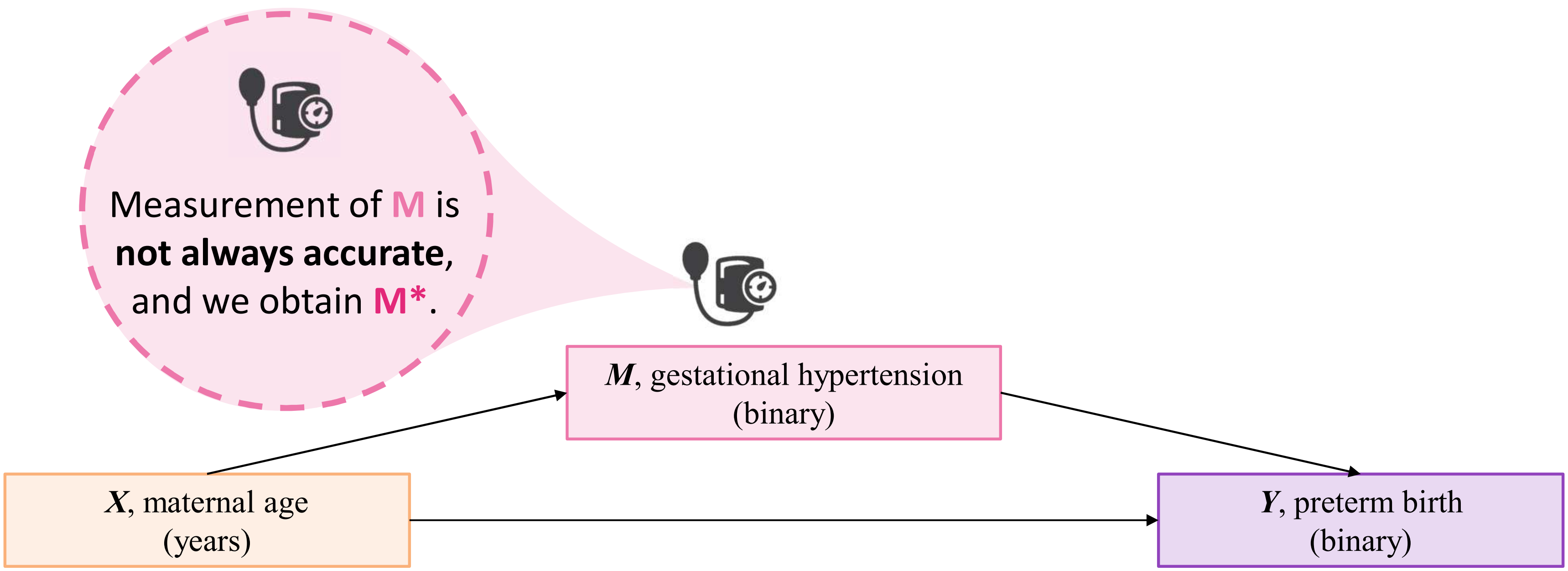

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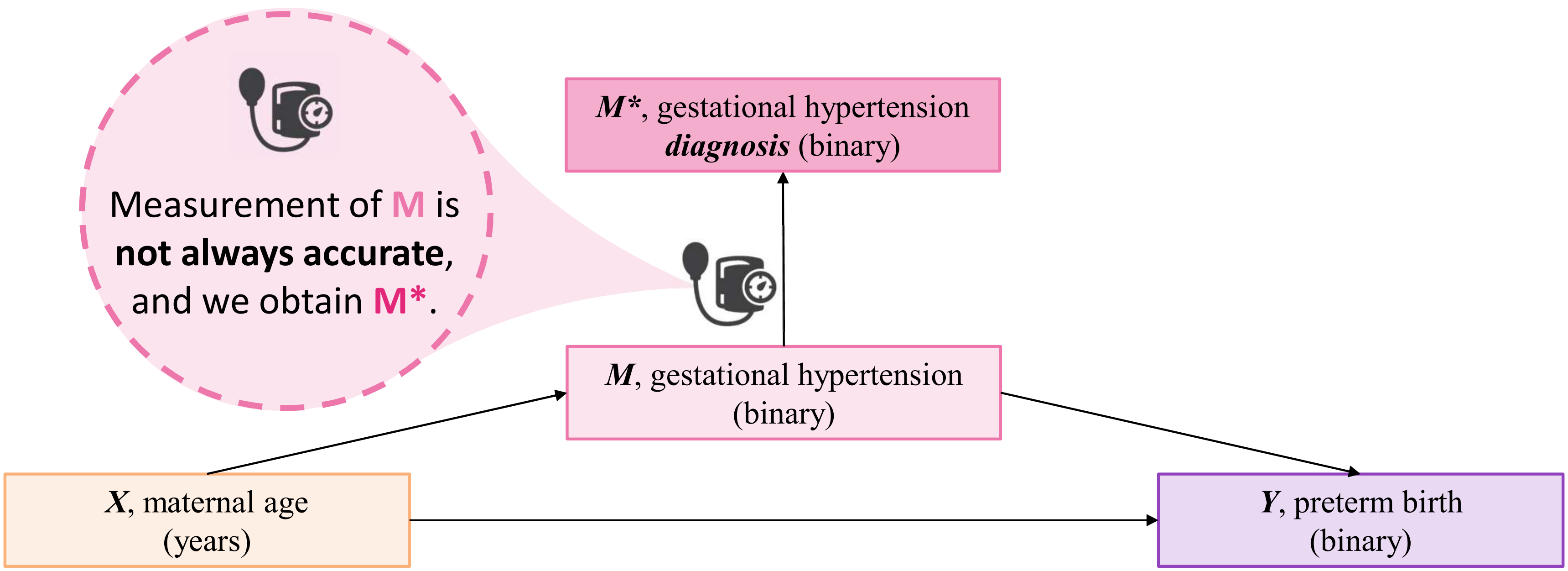

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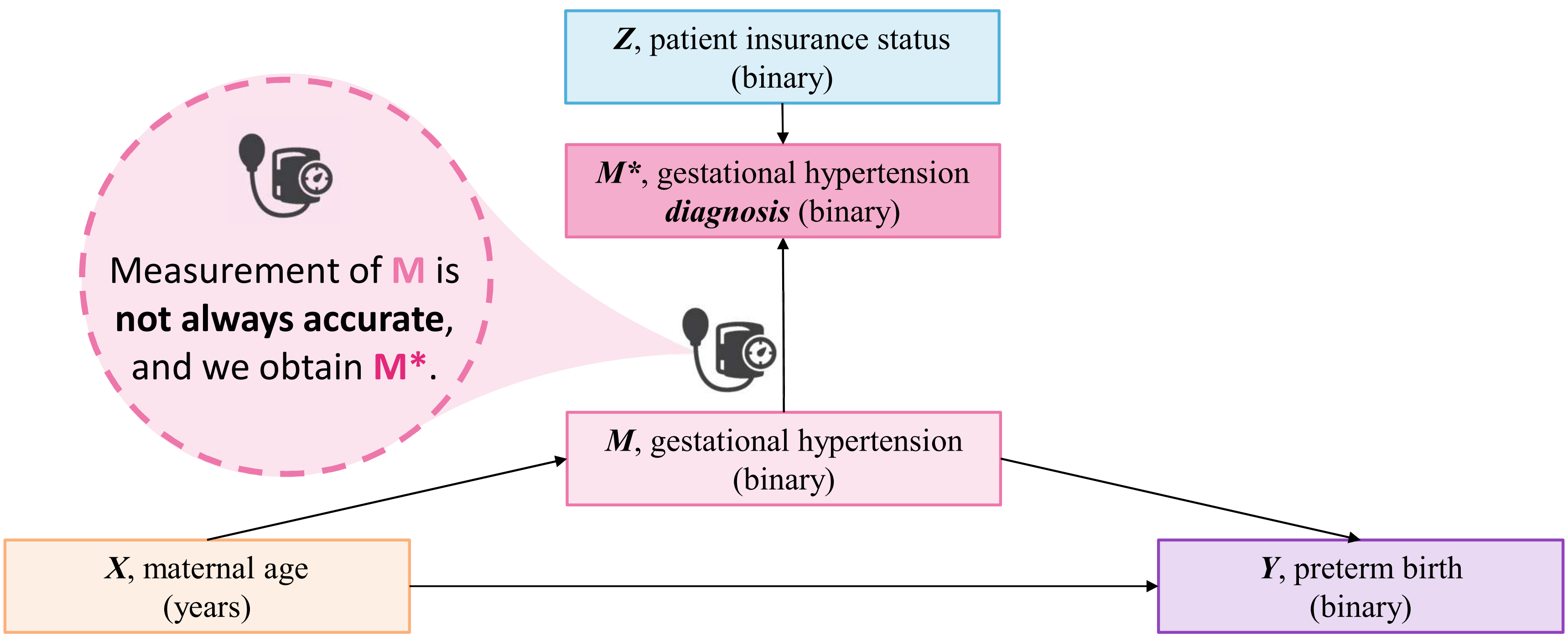

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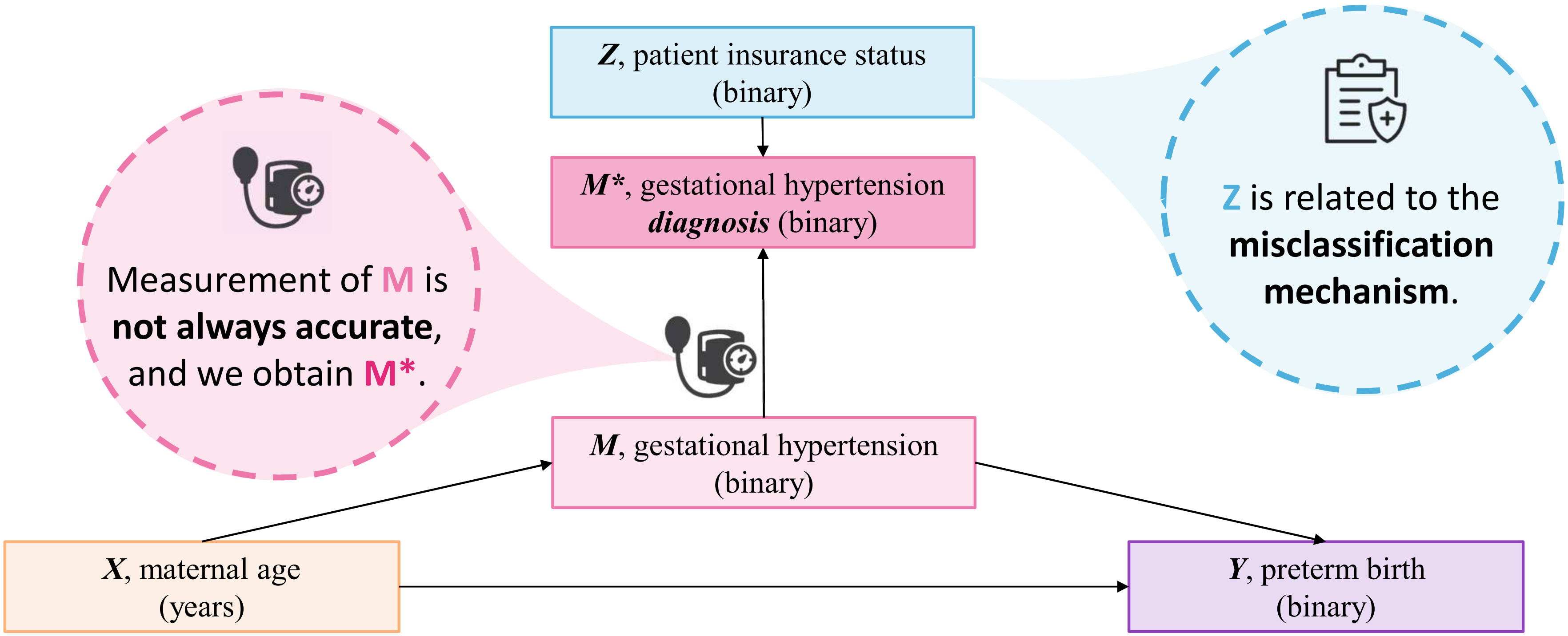
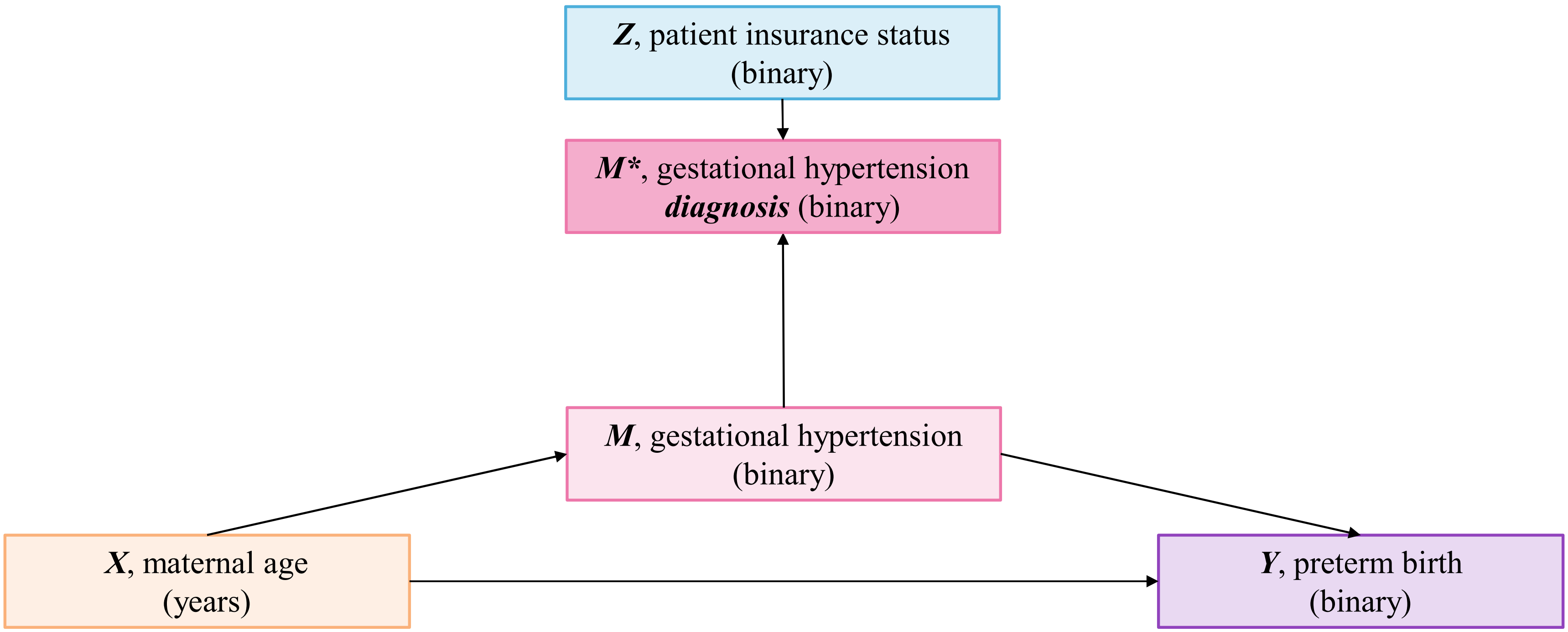


Our analysis is complicated by misdiagnosis in *M*



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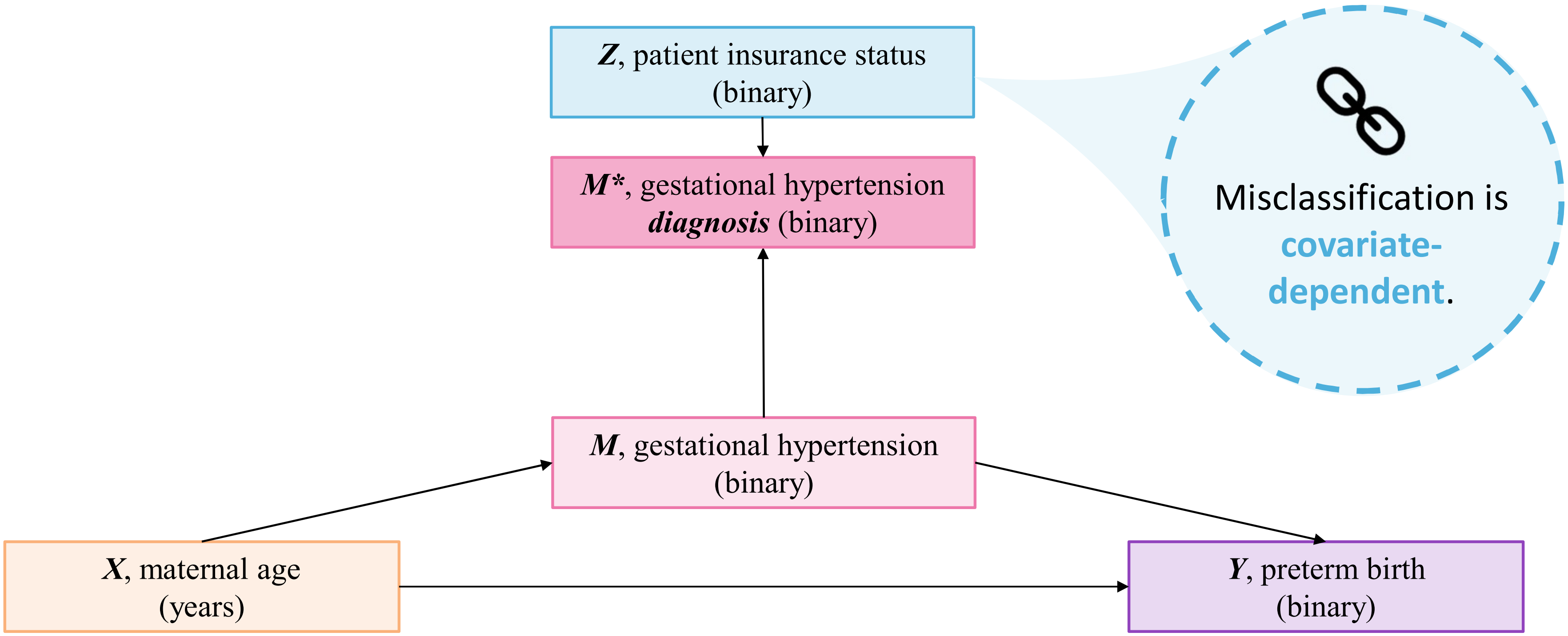

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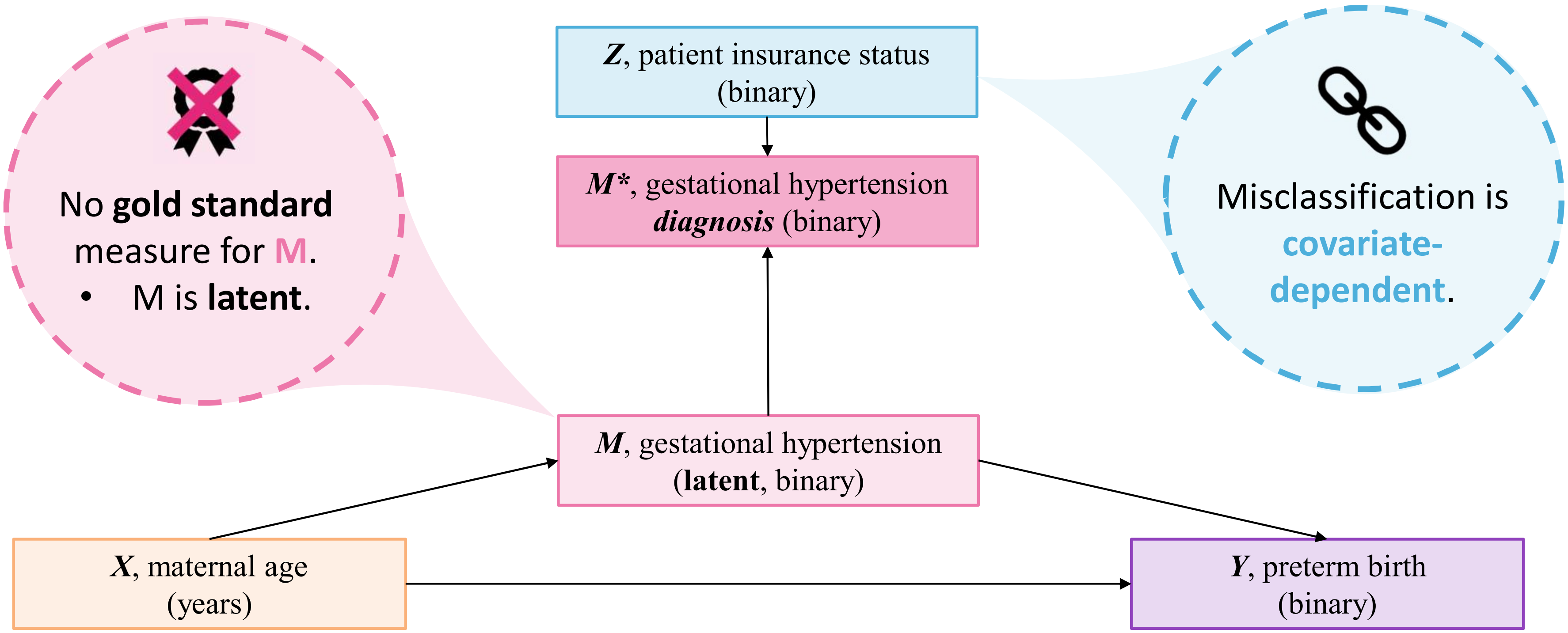

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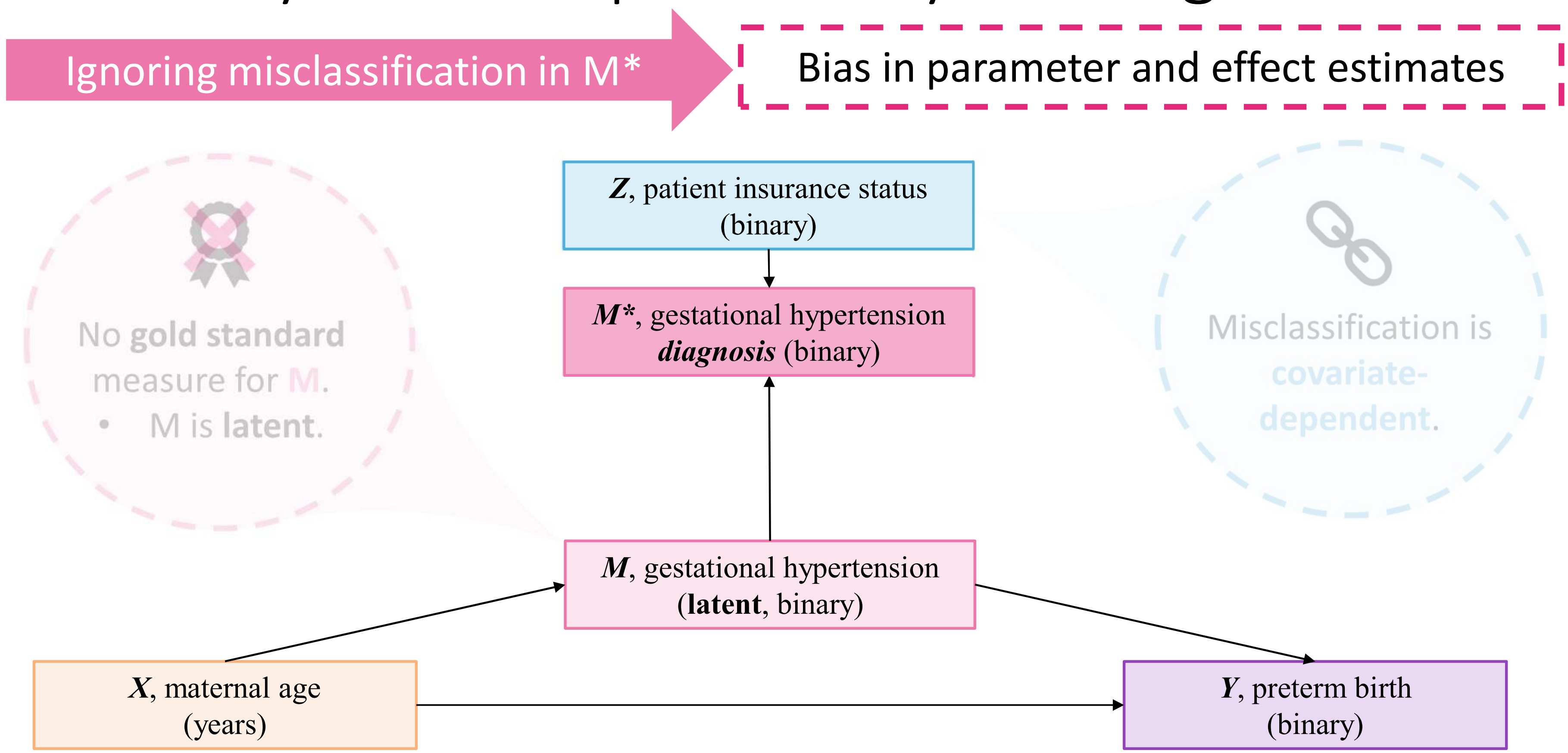


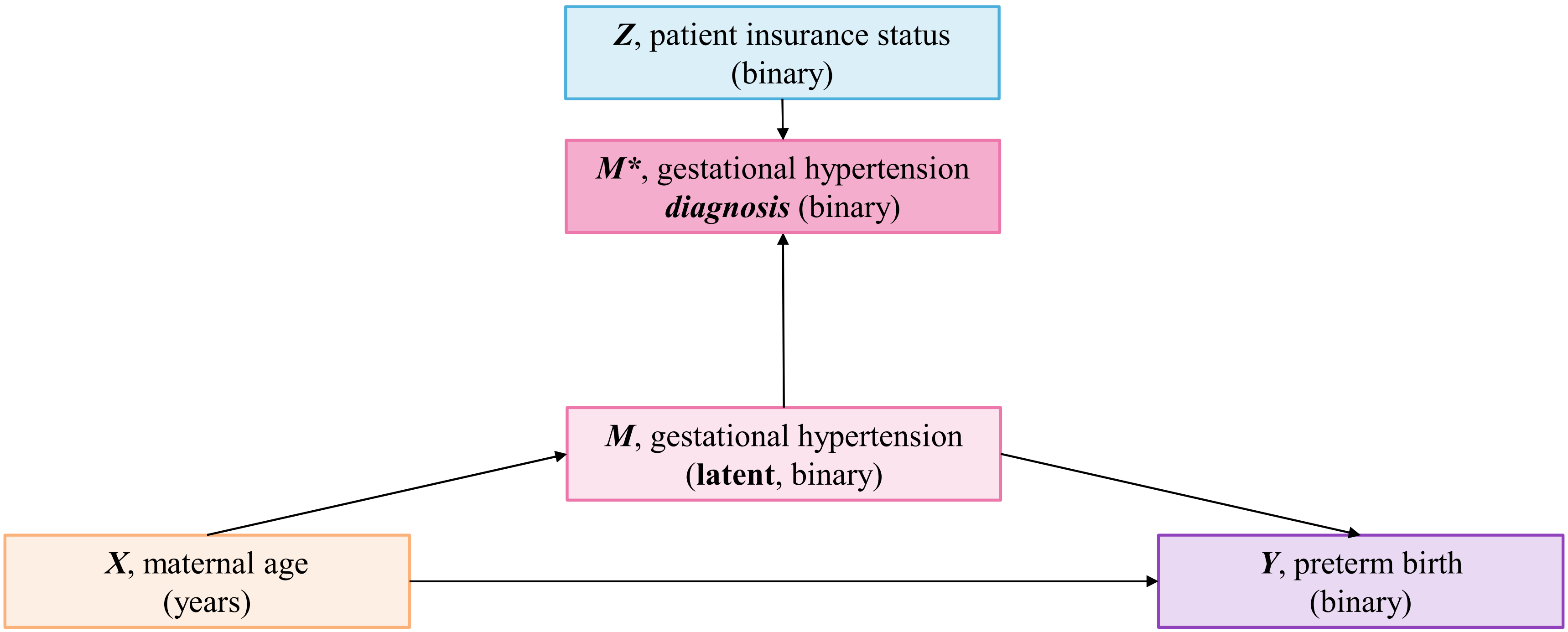
Analysis Plan

1. Define the **misclassification model**

2. Develop **estimation methods** for parameters of interest

3. Use parameter estimates to compute **(in)direct effects and misclassification rates**

Our model accounts for misdiagnosis in *M*



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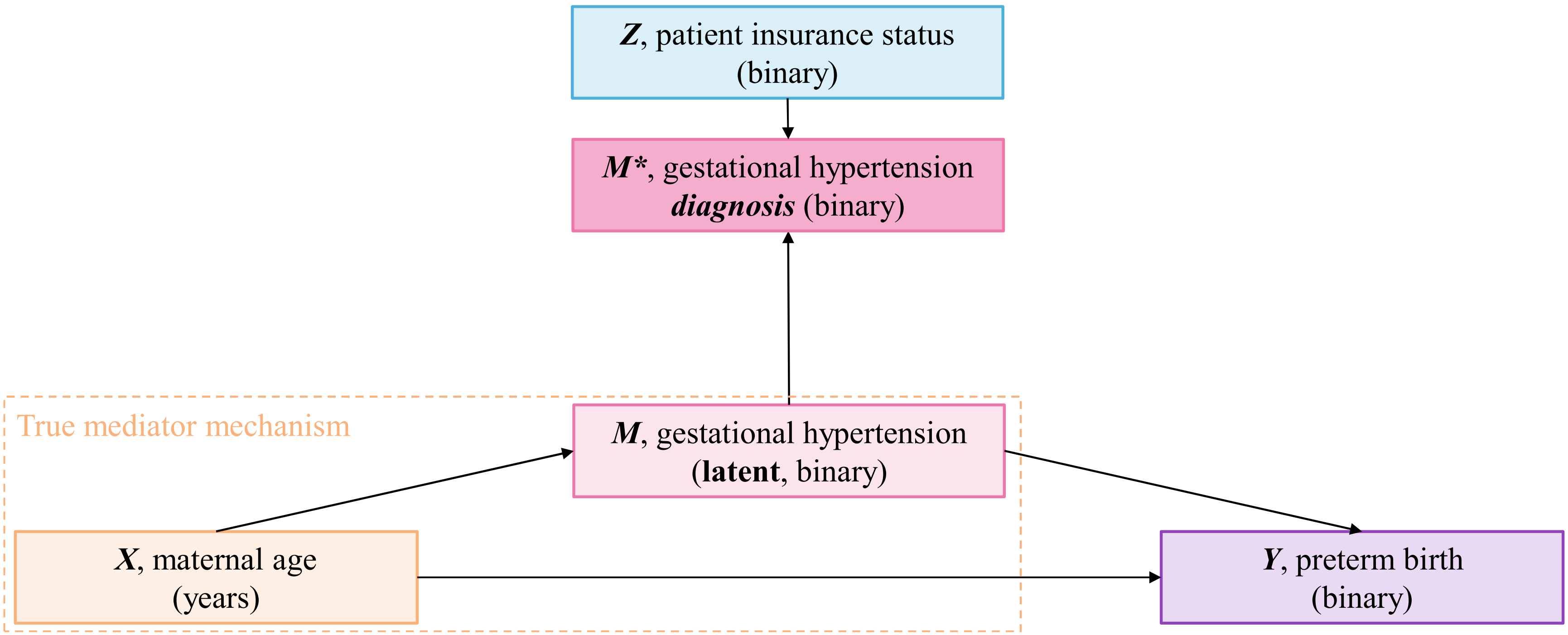

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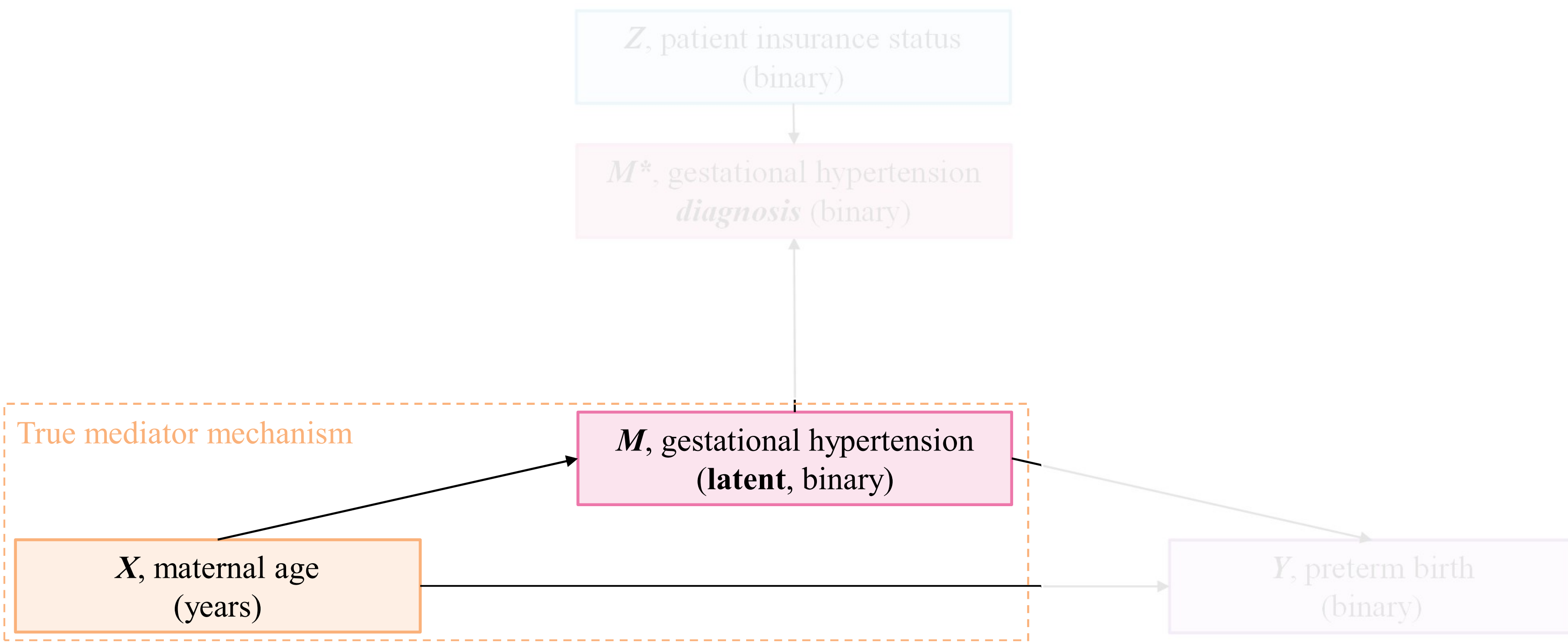

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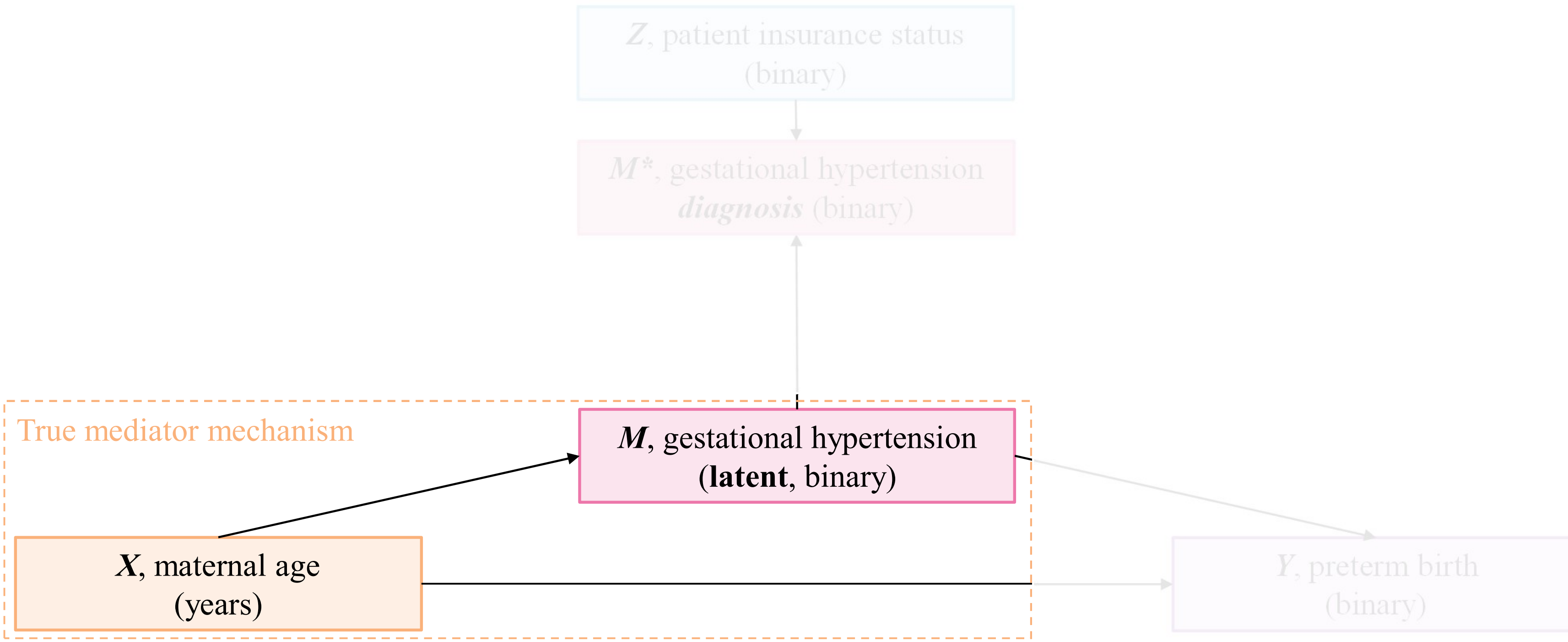

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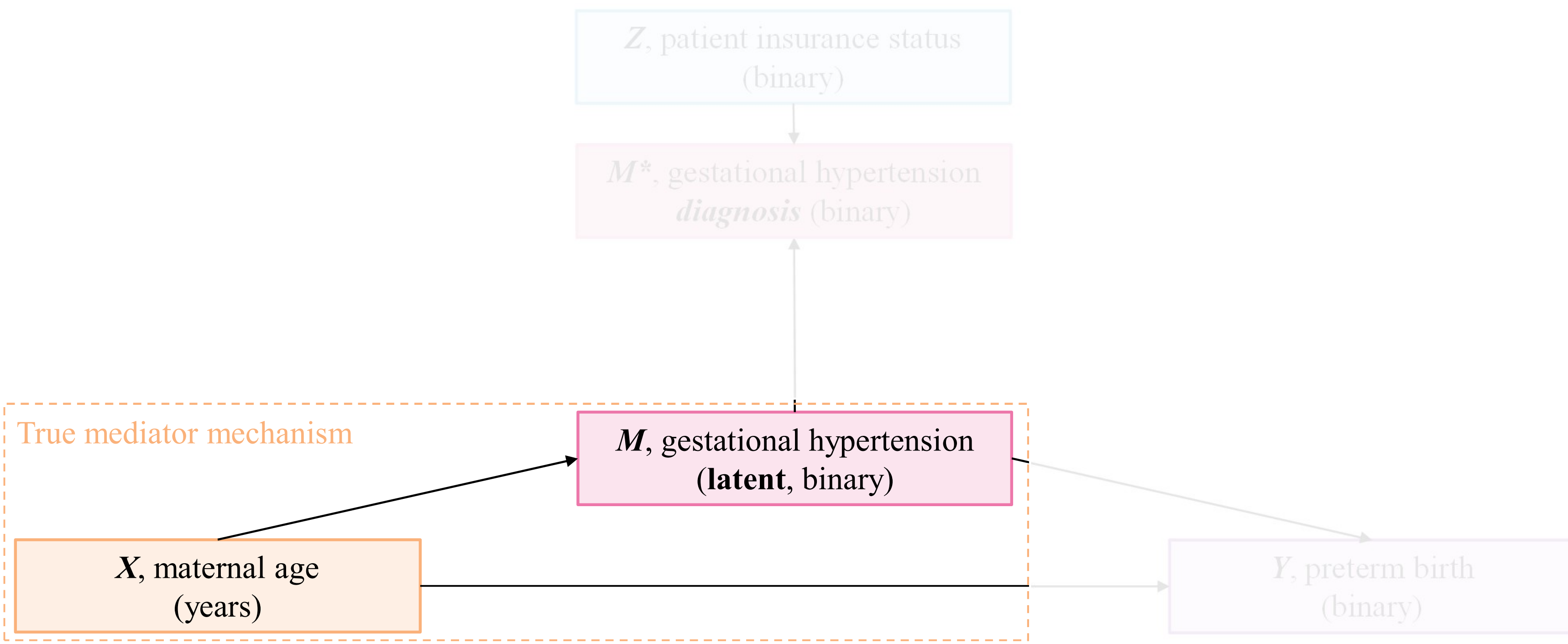

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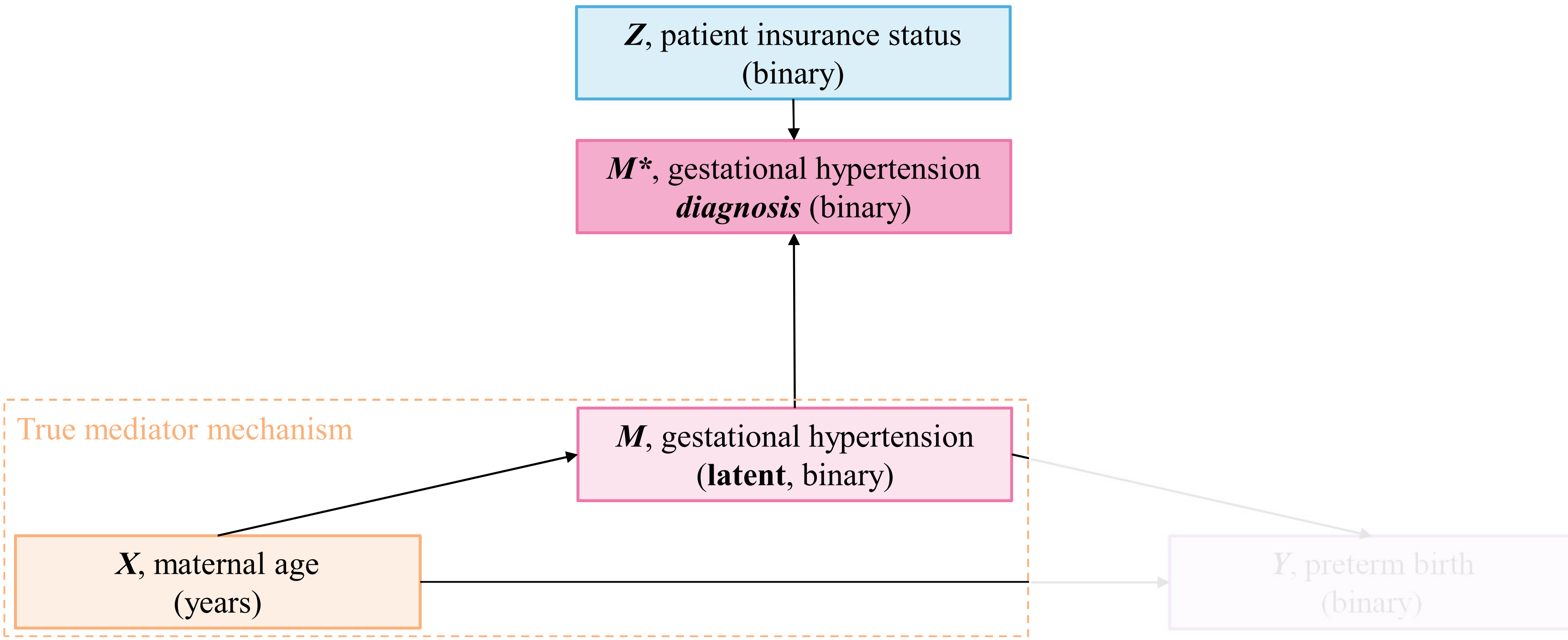

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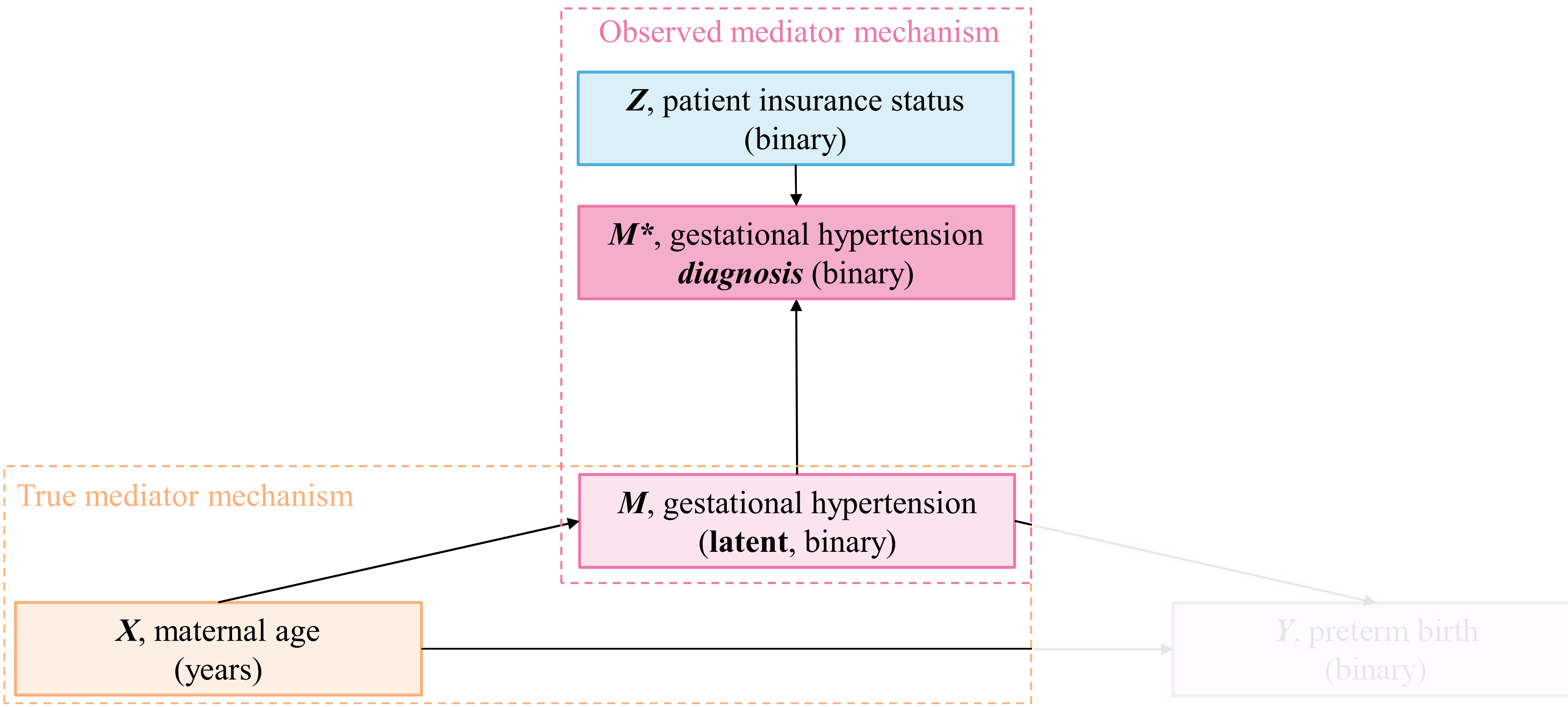

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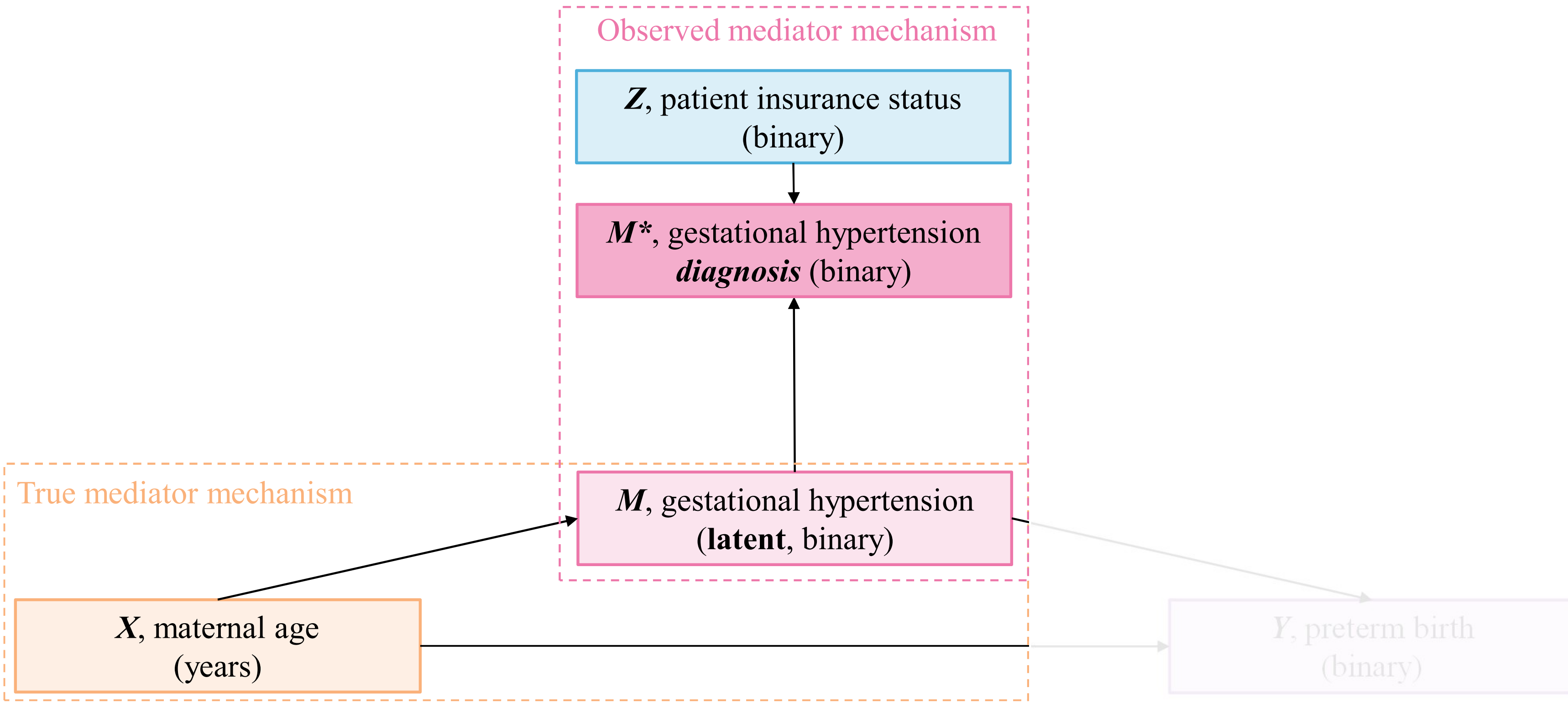

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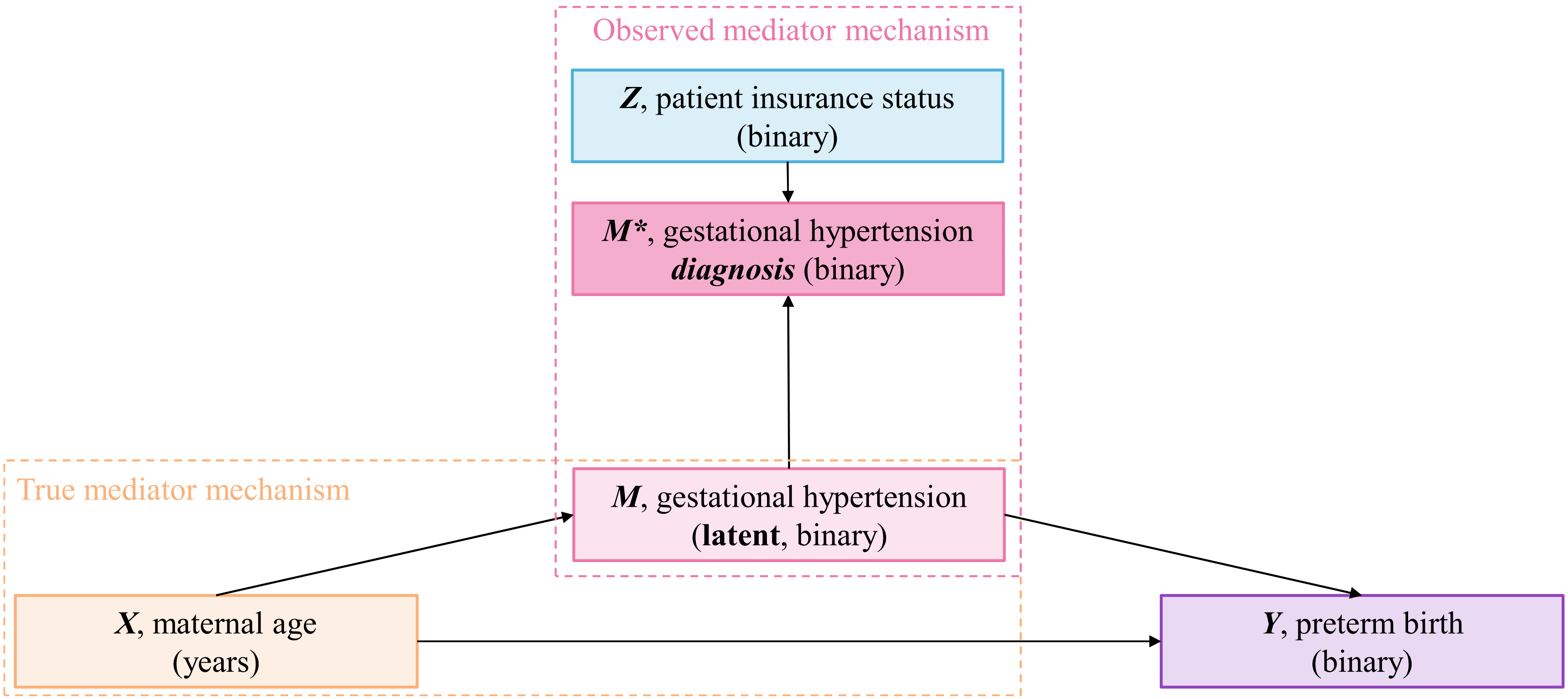

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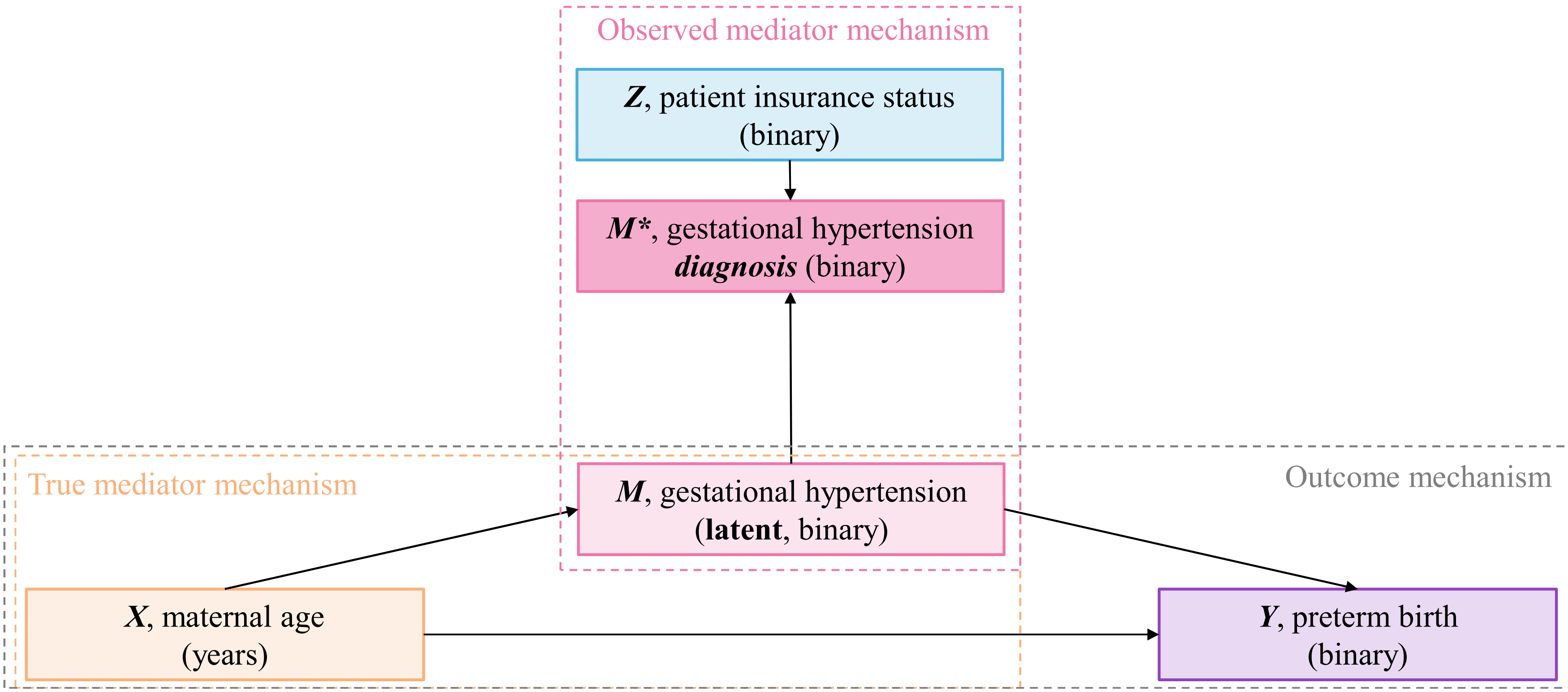

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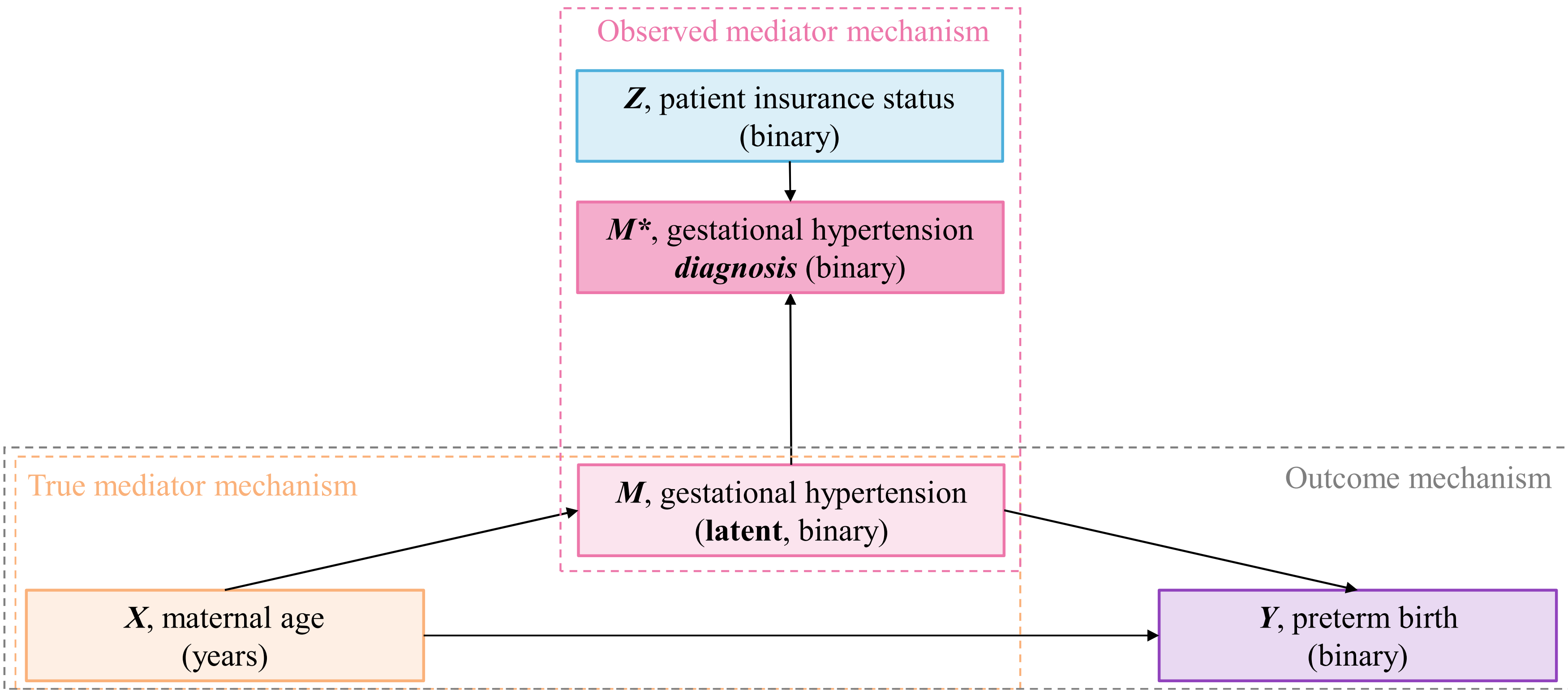

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Mediation parameters:
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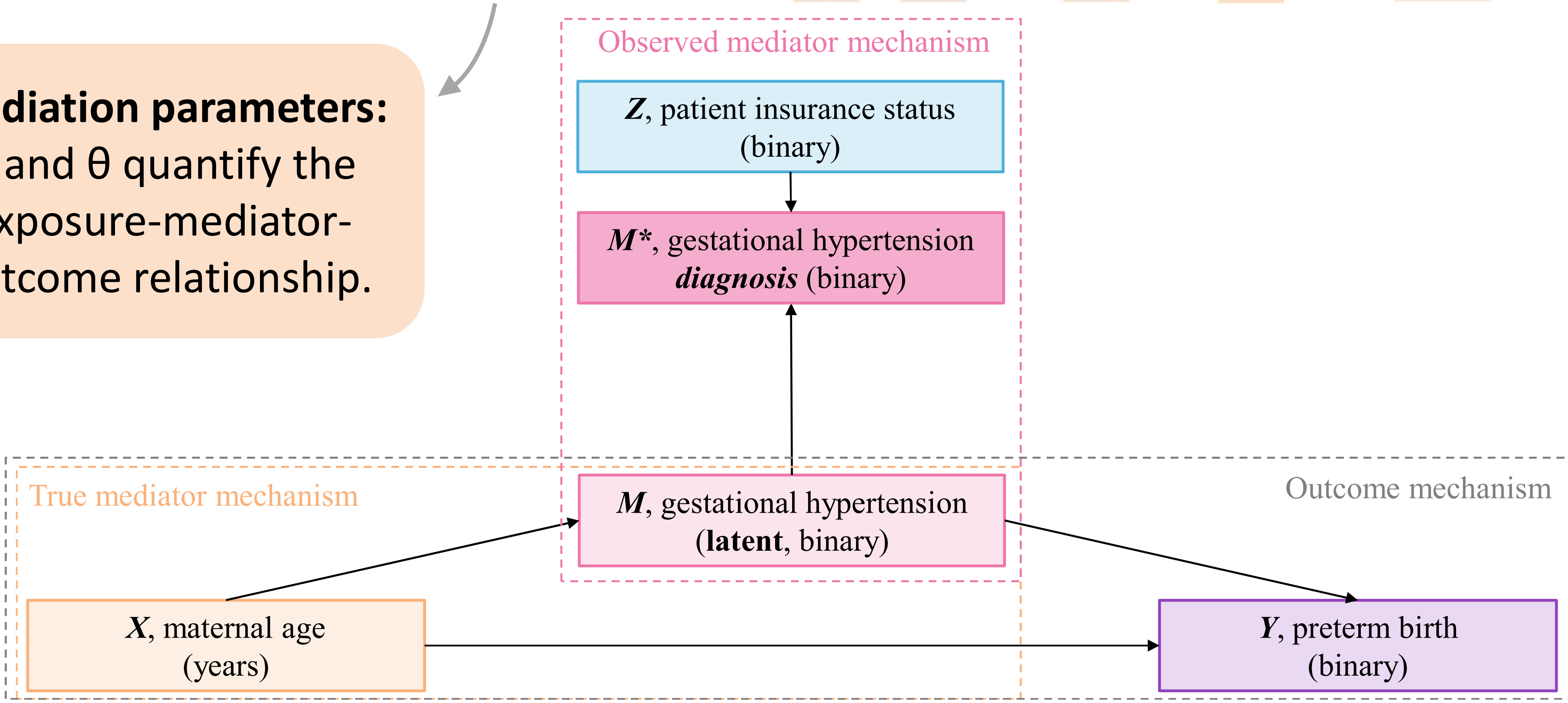

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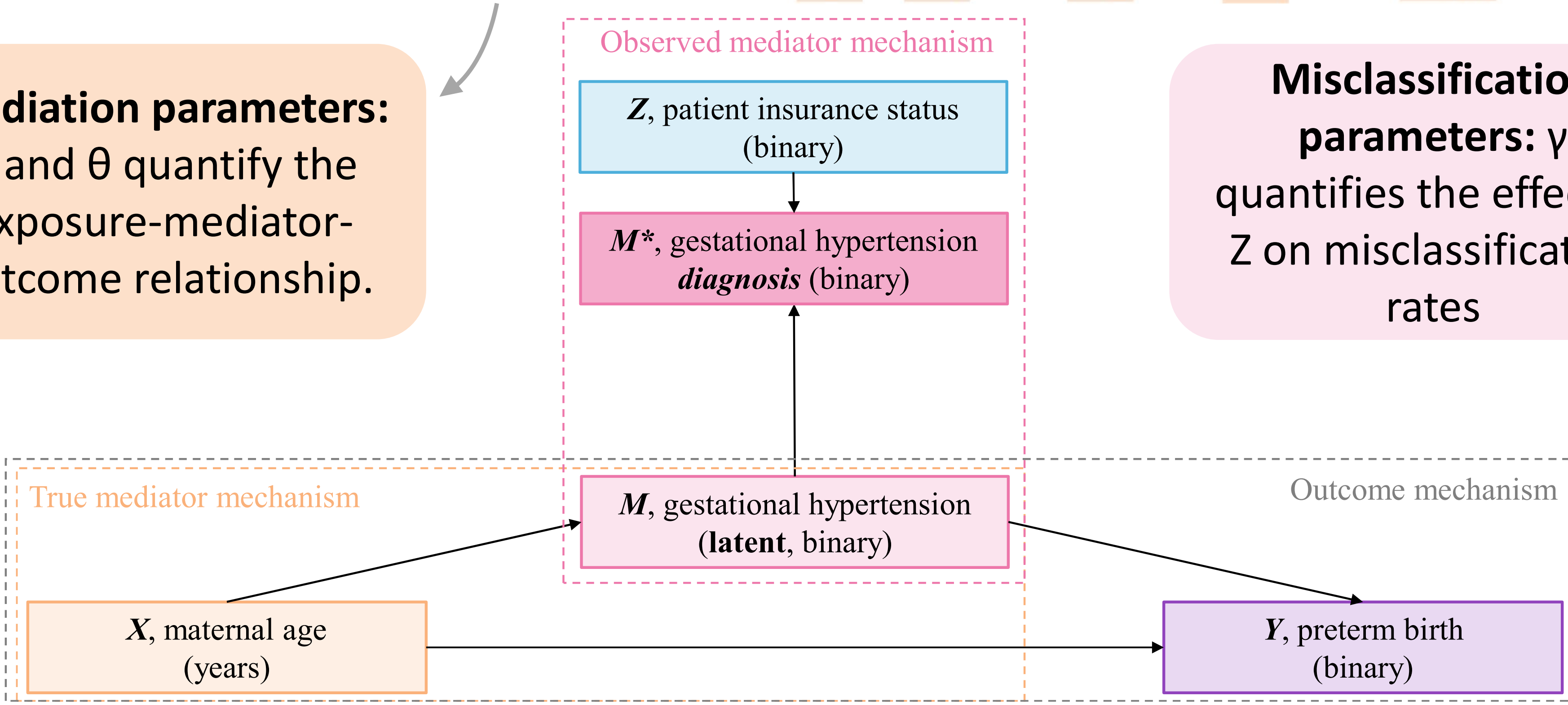
Mediation parameters: β and θ quantify the exposure-mediator-outcome relationship.

Misclassification parameters: γ quantifies the effect of Z on misclassification rates



2

We developed 3 estimation methods

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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".

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Complete data log-likelihood:

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

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

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

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

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Expectation Step

Apply label switching correction from Webb and Wells (2023)

Maximization Step

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

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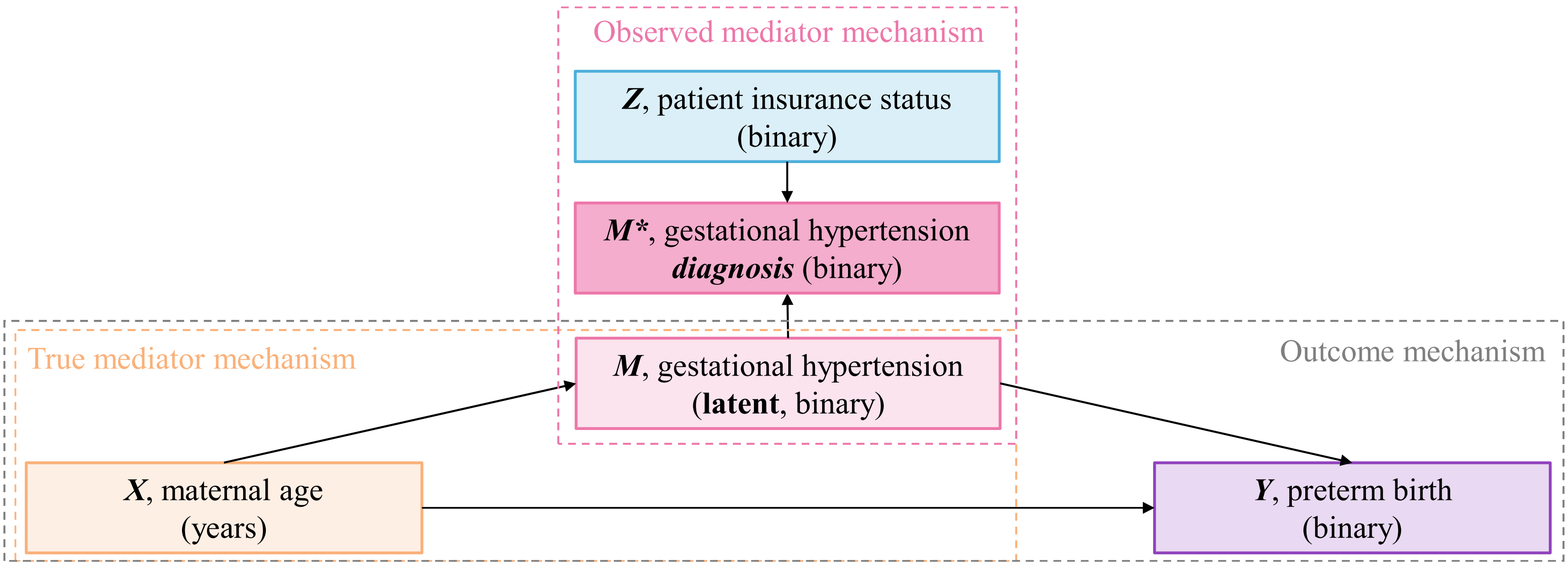
- Use the resulting bias-corrected parameter estimates to compute **(in)direct effects** for a change from **x̃ to x:**

$$OR^{NDE}\cong\frac{\exp\left(\theta_X x\right)\left\{1+\exp\left(\theta_M+\theta_{XM}x+\beta_0+\beta_X\tilde{x}+\beta_C c\right)\right\}}{\exp\left(\theta_X\tilde{x}\right)\left\{1+\exp\left(\theta_M+\theta_{XM}\tilde{x}+\beta_0+\beta_X\tilde{x}+\beta_C c\right)\right\}}$$

$$OR^{NIE}\cong\frac{\left\{1+\exp\left(\beta_0+\beta_X\tilde{x}+\beta_C c\right)\right\}1+\exp\left(\theta_X+\theta_{XM}x+\beta_0+\beta_X x+\beta_C c\right)\right\}}{\left\{1+\exp\left(\beta_0+\beta_X x+\beta_C c\right)\right\}\left\{1+\exp\left(\theta_M+\theta_{XM}x+\beta_0+\beta_X\tilde{x}+\beta_C c\right)\right\}}$$

We applied our methods to a preterm birth study

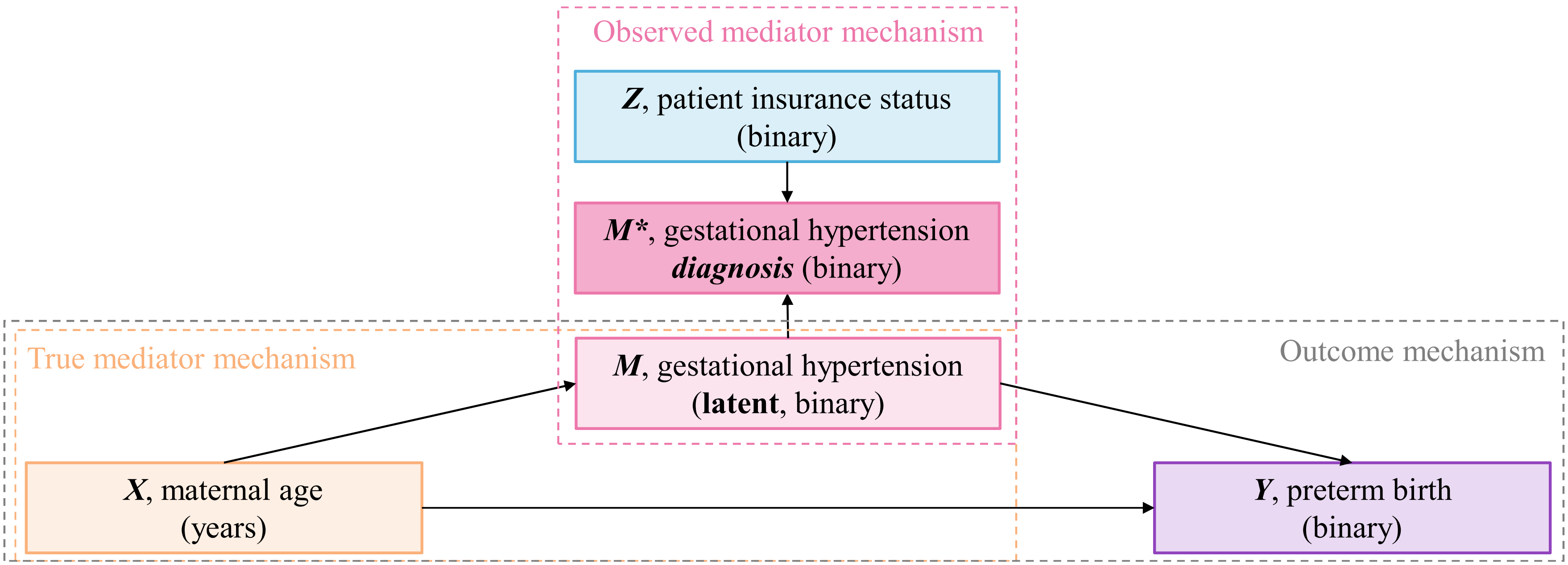
Does gestational hypertension mediate the association between maternal age and preterm birth, after accounting for potential misdiagnosis of gestational hypertension based on patient insurance status?



We applied our methods to a preterm birth study

Data: National Vital Statistics System

- Provides demographic and health data for all births in a year in the US.
- Random subsample from calendar year 2021, **N = 20,000**.

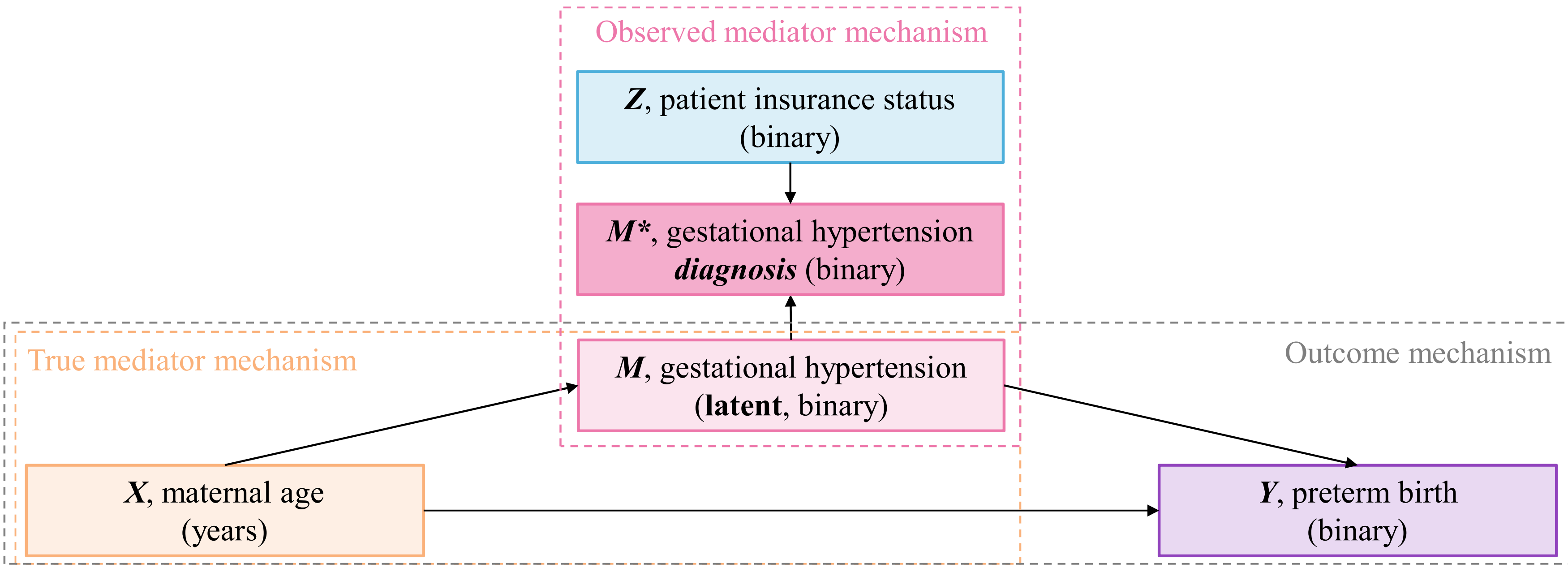


We applied our methods to a preterm birth study

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + **Z**

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M * X**



3

Results change when we account for misdiagnosis

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + **Z**

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M** * **X**

	EM Algorithm		**Naïve Analysis**	
	Est.	SE	Est.	SE
β_X				
$\gamma_{Z, G=1}$				
$\gamma_{Z, G=2}$				
θ_X				
θ_M				
θ_{XM}				

3

Results change when we account for misdiagnosis

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + **Z**

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M * X**

Association between **age** & **gestational hypertension** is unchanged after accounting for misdiagnosis.

	EM Algorithm		Naïve Analysis	
	Est.	SE	Est.	SE
β_X	0.10	0.04	0.08	0.03
$\gamma_{Z, G=1}$				
$\gamma_{Z, G=2}$				
θ_X				
θ_M				
θ_{XM}				

3

Results change when we account for misdiagnosis

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + **Z**

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M * X**

Association between **age** & **gestational hypertension** is unchanged after accounting for misdiagnosis.

Association between **gestational hypertension** & **preterm birth** strengthens.

	EM Algorithm		**Naïve Analysis**	
	Est.	SE	Est.	SE
β_X	0.10	0.04	0.08	0.03
$\gamma_{Z,\, G=1}$				
$\gamma_{Z,\, G=2}$				
θ_X	0.02	0.05	0.10	0.03
θ_M	1.19	0.17	0.88	0.06
θ_{XM}	0.19	0.09	0.06	0.06

3

Results change when we account for misdiagnosis

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + **Z**

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M * X**

Association between **age** & **gestational hypertension** is unchanged after accounting for misdiagnosis.

Association between **gestational hypertension** & **preterm birth** strengthens.

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

Use γ estimates to compute **sensitivity and specificity**.

3

M is measured with perfect specificity and low sensitivity

True mediator mechanism: **M** ~ **X** + Race + Education + Parity + Smoking + BMI

Observed mediator mechanism: **M* | M** ~ Race + Z

Outcome mechanism: **Y** ~ **X** + Race + Education + Parity + Smoking + BMI + **M** + **M** * **X**

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

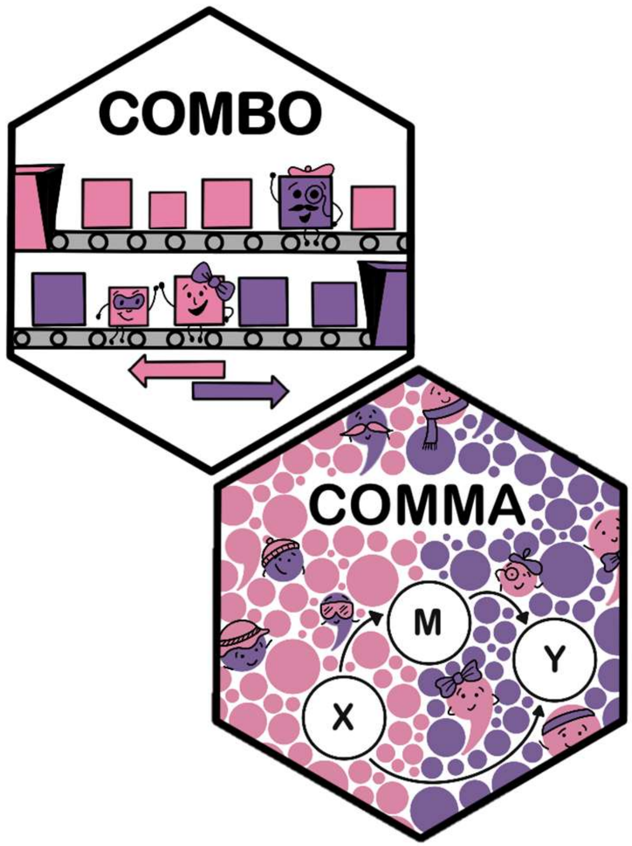
Key takeaways

- Developed new methods for handling misclassified binary mediator variables.
- Computed (in)direct effects using bias-corrected parameter estimates.
- Quantified gestational hypertension misdiagnosis rates based on insurance status.

Software

- Estimation methods for **misclassified outcomes** are available in the *COMBO* R Package on CRAN.
    - **Co**rrecting **M**isclassified **B**inary **O**utcomes

- Estimation methods for **misclassified mediators** are available in the *COMMA* R Package on CRAN.
    - **Co**rrecting **M**isclassified **M**ediation **A**nalysis



Thank you!

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