Appendix and Supplementary Material for Testing multiple biological mediators simultaneously: Controlling FWER and FDR

Joshua N. Sampson[1], Simina M. Boca[2], Steven C. Moore[3], and Ruth Heller[4]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, US, joshua.sampson@nih.gov

[2]Innovation Center for Biomedical Informatics, Georgetown University, Washington, DC, US, smb310@georgetown.edu

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, US, steven.moore@nih.gov

[4]Department of Statistics and Operations Research, Tel Aviv University, Tel Aviv, Il, ruheller@post.tau.ac.il

In the appendix, we present the proofs for theorems in our paper. In section I of the "supplementary material", we report the results from our simulations exploring power and FWER when, conditioned on the exposure, the biomarkers are correlated. In these simulations, Σ_0 is block diagonal, with blocks of size 5 (m=110) or 20 (m=1010), and let the off-diagonal elements be either 0.5 or 0.9. In section II of the "supplementary material", we report the results from our simulations exploring FDR.

Appendix

Logistic vs Probit Regression

In the main paper, when dealing with a binary outcome, we purposely chose to use the probit link instead of the logit link for one key reason. For the probit link, the following two models (equations 1 and 2) are consistent:

$$Y_i^\dagger = \gamma_0 + \gamma_E E_i + \gamma_j M_{ij} + \epsilon_{Yij} \tag{1}$$

$$Y_i^\dagger = \gamma_0 + \gamma_E E_i + \sum_j \gamma_j^* M_{ij} + \epsilon_{Yij}^* \tag{2}$$

with $Y_i = 1(Y_i^\dagger > 0)$. In contrast, for the logistic link, the following two models (equations 3 and equations 4) are unlikely to be consistent:

$$Logit(E[Y_i]) = \gamma_0 + \gamma_E E_i + \gamma_j M_{ij} + \epsilon_{Yij} \tag{3}$$

$$Logit(E[Y_i]) = \gamma_0 + \gamma_E E_i + \sum_j \gamma_j^* M_{ij} + \epsilon_{Yij}^* \tag{4}$$

If we truly believed equation 4 was true, then we could not necessary defend using equation 3, nor could we necessarily defend that $\gamma_j = 0$ is equivalent to $Y_i \perp\!\!\!\perp M_{ij}|E_i$. However, in practice, we expect our MCP's to work when using logistic regression. First, we note that if the biomarker effects (i.e. γ_j^*) are small, then equation 3 is approximately true and all is well. Second, we could define $\gamma_j^\dagger$ to be the value that maximizes the log-likelihood when equation 3 is assumed to be true.

Then, we could just redefine H_{02}^{j} to be $H_{02}^{j\dagger}: \gamma_j^\dagger = 0$. We admittedly did not explore the conditions for when $H_{02}^{j\dagger} = 0$ is equivalent to $Y_i \perp\!\!\!\perp M_{ij}|E_i$, but note, in some sense, this equivalence is an implied assumption when interpreting logistic parameters in practice.

Proofs of Family-Wise Error Rate and False Discovery Rate

Let $\Theta_E = \{\beta_1, ..., \beta_m\}$ corresponding to equation 4 from the main paper, $\Theta_Y = \{\gamma_1, ..., \gamma_m\}$ corresponding to equation 5 or equation 8 from the main paper, and let $\Theta = \{\Theta_E, \Theta_Y\}$. Let $\hat{\Theta}_E$, $\hat{\Theta}_M$, and $\hat{\Theta}$ be the corresponding MLE. Let $\hat{\sigma}^2_{\beta j}$ be a consistent estimate of the variance $var(\sqrt{n}(\hat{\beta}_j - \beta_j))$, $Z_{1j} = \sqrt{n}\hat{\beta}_j/\hat{\sigma}_{\beta_j}$, and $P_{1j} = \Phi(-|Z_{1j}|)$. Similarly, let $\hat{\sigma}^2_{\gamma j}$ be a consistent estimate of the variance $var(\sqrt{n}(\hat{\gamma}_j - \gamma_j))$, $Z_{2j} = \sqrt{n}\hat{\gamma}_j/\hat{\sigma}_{\gamma_j}$, and $P_{2j} = \Phi(-|Z_{2j}|)$. We define four sets of biomarkers, ω_{00}, ω_{01}, ω_{10}, ω_{11} where $\omega_{xy} = \{j : sign(|\beta_j|) = x, sign(|\gamma_j|) = y\}$. We let $\omega_{\cdot 0} = \omega_{00} \cup \omega_{10}$, $\omega_{0\cdot} = \omega_{00} \cup \omega_{01}$, $\omega_{\varnothing} = \omega_{00} \cup \omega_{01} \cup \omega_{10}$, and $S_{xy} = C(\omega_{xy})$. Furthermore, we define a new variable and let W=1 if $P_{1j} < t_1 \ \forall \ j \in \omega_{1\cdot}$ and $P_{2j} < t_2 \ \forall \ j \in \omega_{\cdot 1}$, 0 otherwise.

The key to the proof of FWER is that, asymptotically, $P_{1j'} \perp\!\!\!\perp P_{2j^\dagger}$ for $j' \in \omega_{0\cdot}$ and $j^\dagger \in \omega_{\cdot 0}$ by assumption A1. To see this independence, note that $P_{1j'} \perp\!\!\!\perp P_{2j^\dagger}$ if $Z_{1j'} \perp\!\!\!\perp Z_{2j^\dagger}$. Furthermore, $Z_{1j'}$ and $Z_{2j^\dagger}$ are, asymptotically, normal random variables so $Z_{1j'} \perp\!\!\!\perp Z_{2j^\dagger}$ if cov($Z_{1j'}$,$Z_{2j^\dagger}$)=E[$Z_{1j'} \times Z_{2j^\dagger}$]=0. Finally, we know that $E[E[Z_{1j'} \times Z_{2j^\dagger}|M_{\cdot j'}, E_\cdot]] = E[Z_{1j'} \times 0|M_{\cdot j'}, E_\cdot]$ by assumption 1.

Theorem 1. *For $MCP_S(\cdot|t_1, t_2, \alpha)$, if A1 holds and $\{M_{i1}, ..., M_{im}, Y_i\}$ follow equations 4 and either 5 or 8, then $lim_{n\to\infty} FWER \leq \alpha$*

Proof. Clearly, $Pr(W = 1) \to 1$. Let $\alpha^* = \alpha/2$.

$$FWER \leq$$

$$E[\sum_{j\in\omega_\varnothing} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))] =$$

$$E[\sum_{j\in\omega_\varnothing} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1]P_W +$$

$$E[\sum_{j\in\omega_\varnothing} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W \neq 1]Q_W$$

with $P_W \equiv 1 - Q_W \equiv Pr(W = 1)$. Therefore, for n large enough

$$FWER <$$

$$E[\sum_{j \in \omega_\emptyset} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1] + \epsilon$$

Next, we split $FWER_1 \equiv E[\sum_{j\in\omega_\emptyset} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1]$ into three components

$$FWER_1 =$$

$$E[\sum_{j \in \omega_{01}} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1]+$$

$$E[\sum_{j \in \omega_{10}} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1]+$$

$$E[\sum_{j \in \omega_{00}} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1]$$

For set ω_{01} (and similarly for ω_{10}),

$$E[\sum_{j \in \omega_{01}} 1(P_{1j} < min(t_1, \alpha^*/S_2), P_{2j} < min(t_2, \alpha^*/S_1))|W = 1] \leq$$

$$E[\sum_{j \in \omega_{01}} 1(P_{1j} < \alpha^*/S_2)|W = 1] \rightarrow E[S_{01}\alpha^*/S_2|W = 1]$$

For set ω_{00},

$$E[\sum_{j \in \omega_{00}} 1(P_{1j} < min(t_1, \alpha^*/S_2)1(P_{2j} < min(t_2, \alpha^*/S_1))|W = 1] \leq$$

$$E[\sum_{j \in \omega_{00}, P_{2j} < t_2} 1(P_{1j} < \alpha^*/S_2)|W = 1] \rightarrow$$

$$E[(S_2 - S_{01})\alpha^*/S_2|W = 1]$$

The final convergence in each step relies on $P_{1j'} \perp\!\!\!\perp P_{2j^\dagger}$ for $j' \in \omega_{0\cdot}$ and $j^\dagger \in \omega_{\cdot 0}$ and n being large enough so that the p-values for all non-null hypotheses are below the stated threshold. Combined, we see that FWER $\leq E[S_{01}\alpha^*/S_2+S_{10}\alpha^*/S_1+(S_2-S_{01})\alpha^*/S_2|W=1] \leq 2\alpha^* = \alpha$ so $FWER < \alpha+\epsilon$.

$\square$

For discussing FDR, we require an assumption of conditional independence, which results in, asymptotically, $P_{1j'} \perp\!\!\!\perp P_{2j^\dagger}$ for $j' \in \omega_{0\cdot}$ and $j^\dagger \in \omega_{\cdot 0}$. In practice, we have found that this procedure is robust to deviations from this assumption.

Assumption A2: $M_{ij'} \perp\!\!\!\perp M_{j^\dagger}|E_i \;\forall\; j', j^\dagger \in \{1, ..., m\}$

It is straight forward to show that assumption A2 implies that, aymptotically,
$P_{1j} \perp\!\!\!\perp \{P_{11}, ..., P_{1(j-1)}, P_{1(j+1)}, ..., P_{1m}\}|E, S_2$ and $P_{2j} \perp\!\!\!\perp \{P_{21}, ..., P_{2(j-1)}, P_{2(j+1)}, ..., P_{2m}\}|E, S_1$.

Theorem 2. *For $MCP_D(\cdot|t_1, t_2, \alpha)$, if assumption A2 holds, $lim_{n\to\infty} FDR \leq \alpha$.*

Proof. The MCP_D procedure is equivalent to the following two-step procedure, with $MCP_D(\cdot|\alpha) = \{j : R_j = 1\}$.

Step 1: Compute $\mathscr{R} = max\{r : \sum_{j\in\omega_{S1}\cap\omega_{S_2}} 1[(P_{1j}, P_{2j}) \leq (\frac{r\alpha/2}{S_2}, \frac{r\alpha/2}{S_1})] = r\}$
Step 2: Define $R_j = I[(P_{1j}, P_{2j}) \leq (\frac{\mathscr{R}\alpha/2}{S_2}, \frac{\mathscr{R}\alpha/2}{S_1}), j \in \omega_{S1} \cap \omega_{S_2}]$

We need only show that $\sum_{j\in\omega_\varnothing} E[R_j/max(\mathscr{R}, 1)] \leq \alpha$.

Let us start by defining T_i^j and $C_r^{(j)}$.

$$T_i^j = max\{\frac{(\sum_{k\neq j} 1[P_{2k} < t_2] + 1)P_{1i}}{\alpha/2}, \frac{(\sum_{k\neq j} 1[P_{1k} < t_1] + 1)P_{2i}}{\alpha/2}\} \tag{5}$$

if $(P_{1i}, P_{2i}) < (t_1, t_2)$, ∞ & otherwise. Order and relabel the T_i^js so $T_2^j \leq ... \leq T_m^j$ and define

$$C_r^{(j)} = \{[T_1^j, \ldots, T_{j-1}^j, T_{j+1}^j, \ldots, T_m^j] : T_r^j \leq r \text{ and } T_k^j > k \text{ for } k > r\}$$

Assume that $\beta_j = 0$.Then

$$E[\frac{R_j}{max(\mathscr{R},1)}|S_2,E,P_{2j}] =$$
$$\sum_{r=1}^{m}\frac{1}{r}P[P_{1j} < min(\frac{r\alpha/2}{S_2},t_1), P_{2j} < min(\frac{r\alpha/2}{S_1},t_2), C_r^{(j)}|S_2,E,P_{2j}]$$
$$\leq \sum_{r=1}^{m}\frac{1}{r}P[P_{1j} < min(\frac{r\alpha/2}{S_2},t_1), C_r^{(j)}|S_2,E,P_{2j}]1[P_{2j} \leq t_2]$$
$$\approx \sum_{r=1}^{m}\frac{1}{r}\frac{r\alpha/2}{S_2}P[C_r^{(j)}|S_2,E,P_{2j}]1[P_{2j} \leq t_2]$$
$$= \frac{\alpha/2}{S_2}(\sum_{r=1}^{m}P[C_r^{(j)}|S_2,E,P_{2j}])1[P_{2j} \leq t_2]$$
$$= \frac{\alpha/2}{S_2}1[P_{2j} \leq t_2]$$

where the approximation uses the independence of P_{1j} and $\{C_r^{(j)}, S_2, E, P_{2j}\}$ which holds by assumption A2 and can be made precise by the Berry-Esseen theorem. Similarly, we can show that for $\gamma_j = 0$

$$E[\frac{R_j}{max(\mathscr{R},1)}|S_1,E,P_{1j}] \approx \frac{\alpha/2}{S_1}1[P_{1j} \leq t_1]$$

Therefore

$$\sum_{j\in\omega_{\emptyset}} E[\frac{R_j}{max(\mathscr{R},1)}] = \sum_{j\in\omega_{0\cdot}} E[\frac{R_j}{max(\mathscr{R},1)}] + \sum_{j\in\omega_{10}} E[\frac{R_j}{max(\mathscr{R},1)}] \leq$$
$$\frac{\alpha}{2}E[\frac{\sum_{j\in\omega_{0\cdot}}1[P_{2j} \leq t_2]}{S_2}] + \frac{\alpha}{2}E[\frac{\sum_{j\in\omega_{10}}1[P_{1j} \leq t_1]}{S_1}] \leq \alpha$$

□

1 Supplementary Material: FWER and Power

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
110	0	0	0	0.00	0.03	0.01	0.02	0.01
95	15	0	0	0.00	0.04	0.02	0.02	0.02
70	40	0	0	0.01	0.08	0.02	0.02	0.02
95	0	15	0	0.01	0.06	0.02	0.02	0.03
80	15	15	0	0.01	0.04	0.02	0.02	0.03
55	40	15	0	0.01	0.04	0.02	0.03	0.04
1010	0	0	0	0.00	0.02	0.00	0.00	0.00
995	15	0	0	0.00	0.04	0.01	0.01	0.01
700	310	0	0	0.01	0.05	0.02	0.02	0.03
995	0	15	0	0.00	0.05	0.00	0.01	0.02
980	15	15	0	0.00	0.02	0.01	0.01	0.02
685	310	15	0	0.00	0.05	0.01	0.02	0.05

Table 1: FWER for continuous outcomes with correlation = 0.5. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FWER, defined to be the mean proportion of simulations with at least one biomarker identified as a mediatior, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
100	0	0	10	0.69	0.78	0.82	0.82	0.85
85	15	0	10	0.69	0.76	0.81	0.82	0.85
60	40	0	10	0.68	0.73	0.80	0.80	0.84
85	0	15	10	0.68	0.72	0.72	0.72	0.78
70	15	15	10	0.68	0.71	0.72	0.72	0.79
45	40	15	10	0.68	0.69	0.70	0.70	0.78
1000	0	0	10	0.28	0.69	0.61	0.61	0.78
985	15	0	10	0.28	0.60	0.58	0.58	0.76
690	310	0	10	0.27	0.35	0.45	0.46	0.68
985	0	15	10	0.27	0.56	0.49	0.49	0.77
970	15	15	10	0.27	0.53	0.45	0.46	0.75
675	310	15	10	0.27	0.34	0.36	0.37	0.75

Table 2: Power for continuous outcomes with correlation = 0.5. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the power, defined to be the mean proportion of true mediators identified, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
110	0	0	0	0.00	0.02	0.00	0.11	0.01
95	15	0	0	0.00	0.04	0.01	0.02	0.01
70	40	0	0	0.01	0.08	0.01	0.03	0.01
95	0	15	0	0.01	0.06	0.02	0.03	0.03
80	15	15	0	0.01	0.04	0.01	0.02	0.03
55	40	15	0	0.02	0.04	0.03	0.04	0.03
1010	0	0	0	0.00	0.02	0.00	0.00	0.00
995	15	0	0	0.00	0.04	0.01	0.01	0.01
700	310	0	0	0.00	0.04	0.01	0.03	0.01
995	0	15	0	0.00	0.06	0.00	0.02	0.02
980	15	15	0	0.00	0.05	0.00	0.02	0.03
685	310	15	0	0.01	0.06	0.02	0.04	0.03

Table 3: FWER for continuous outcomes with correlation = 0.9. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FWER, defined to be the mean proportion of simulations with at least one biomarker identified as a mediatior, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
100	0	0	10	0.72	0.84	0.84	0.84	0.85
85	15	0	10	0.72	0.84	0.84	0.84	0.85
60	40	0	10	0.71	0.83	0.83	0.84	0.85
85	0	15	10	0.71	0.84	0.84	0.84	0.85
70	15	15	10	0.71	0.84	0.84	0.84	0.85
45	40	15	10	0.71	0.83	0.83	0.83	0.84
1000	0	0	10	0.28	0.69	0.62	0.68	0.81
985	15	0	10	0.28	0.60	0.58	0.63	0.78
690	310	0	10	0.27	0.43	0.45	0.54	0.69
985	0	15	10	0.27	0.49	0.45	0.56	0.76
970	15	15	10	0.28	0.49	0.42	0.52	0.76
675	310	15	10	0.26	0.39	0.32	0.45	0.76

Table 4: Power for continuous outcomes with correlation = 0.9. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the power, defined to be the mean proportion of true mediators identified, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
110	0	0	0	0.00	0.03	0.02	0.04	0.02
95	15	0	0	0.00	0.03	0.03	0.03	0.03
70	40	0	0	0.01	0.06	0.02	0.02	0.02
95	0	15	0	0.01	0.06	0.01	0.02	0.03
80	15	15	0	0.01	0.05	0.03	0.03	0.05
55	40	15	0	0.01	0.05	0.02	0.03	0.04
1010	0	0	0	0.00	0.02	0.00	0.00	0.00
995	15	0	0	0.00	0.05	0.00	0.01	0.01
700	310	0	0	0.01	0.04	0.02	0.02	0.02
995	0	15	0	0.00	0.05	0.00	0.00	0.01
980	15	15	0	0.00	0.05	0.01	0.01	0.01
685	310	15	0	0.01	0.07	0.02	0.02	0.04

Table 5: FWER for binary outcomes with correlation = 0.5. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FWER, defined to be the mean proportion of simulations with at least one biomarker identified as a mediatior, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
100	0	0	10	0.49	0.65	0.69	0.70	0.80
85	15	0	10	0.50	0.57	0.64	0.65	0.79
60	40	0	10	0.51	0.51	0.59	0.60	0.77
85	0	15	10	0.49	0.60	0.62	0.62	0.78
70	15	15	10	0.49	0.54	0.57	0.57	0.77
45	40	15	10	0.49	0.49	0.53	0.54	0.77
1000	0	0	10	0.10	0.48	0.35	0.36	0.45
985	15	0	10	0.10	0.37	0.31	0.32	0.41
690	310	0	10	0.10	0.14	0.18	0.19	0.23
985	0	15	10	0.10	0.42	0.30	0.31	0.60
970	15	15	10	0.10	0.34	0.27	0.28	0.59
675	310	15	10	0.10	0.15	0.16	0.17	0.39

Table 6: Power for binary outcomes with correlation = 0.5. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the power, defined to be the mean proportion of true mediators identified, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
110	0	0	0	0.00	0.02	0.00	0.11	0.01
95	15	0	0	0.00	0.05	0.01	0.01	0.01
70	40	0	0	0.01	0.07	0.02	0.03	0.02
95	0	15	0	0.01	0.06	0.02	0.03	0.03
80	15	15	0	0.01	0.04	0.03	0.04	0.02
55	40	15	0	0.01	0.03	0.01	0.02	0.03
1010	0	0	0	0.00	0.02	0.00	0.00	0.00
995	15	0	0	0.00	0.05	0.01	0.02	0.00
700	310	0	0	0.01	0.03	0.01	0.01	0.01
995	0	15	0	0.00	0.04	0.00	0.01	0.01
980	15	15	0	0.00	0.04	0.01	0.02	0.02
685	310	15	0	0.00	0.06	0.01	0.01	0.01

Table 7: FWER for binary outcomes with correlation = 0.9. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FWER, defined to be the mean proportion of simulations with at least one biomarker identified as a mediatior, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_B	MCP_P	MCP_S	MCP_S^{WY}	MCP_S^{MV}
100	0	0	10	0.69	0.79	0.82	0.83	0.85
85	15	0	10	0.69	0.77	0.82	0.83	0.85
60	40	0	10	0.68	0.74	0.80	0.81	0.85
85	0	15	10	0.68	0.78	0.83	0.83	0.85
70	15	15	10	0.68	0.76	0.82	0.82	0.85
45	40	15	10	0.68	0.75	0.80	0.81	0.84
1000	0	0	10	0.11	0.48	0.36	0.43	0.48
985	15	0	10	0.10	0.37	0.32	0.37	0.43
690	310	0	10	0.10	0.20	0.18	0.25	0.23
985	0	15	10	0.10	0.36	0.27	0.36	0.62
970	15	15	10	0.11	0.33	0.24	0.31	0.60
675	310	15	10	0.11	0.21	0.14	0.22	0.42

Table 8: Power for binary outcomes with correlation = 0.9. We compared the performance of five multiple comparison procedures: MCP_B, MCP_P, MCP_S, MCP_S^{WY}, and MCP_S^{MV} using simulations when the outcome is continuous. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure nor outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the power, defined to be the mean proportion of true mediators identified, when $\alpha = 0.05$. Details of the simulation can be found in the methods section.

2 Supplementary Material: FDR

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.00
85	15	0	10	0.05	0.02
60	40	0	10	0.08	0.04
85	0	15	10	0.04	0.03
70	15	15	10	0.07	0.03
45	40	15	10	0.11	0.03
1000	0	0	10	0.05	0.02
985	15	0	10	0.07	0.03
690	310	0	10	0.09	0.08
985	0	15	10	0.08	0.03
970	15	15	10	0.10	0.04
675	310	15	10	0.12	0.04

Table 9: FDR for continuous outcomes with correlation = 0. We compared the performance of two multiple comparison procedures: MCP_D, and MCP_D^{MV} using simulations when the outcome is continuous and the conditional correlation between metabolites in the same block is 0. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.01
85	15	0	10	0.05	0.03
60	40	0	10	0.07	0.04
85	0	15	10	0.03	0.03
70	15	15	10	0.07	0.04
45	40	15	10	0.10	0.04
1000	0	0	10	0.06	0.04
985	15	0	10	0.06	0.04
690	310	0	10	0.10	0.11
985	0	15	10	0.08	0.05
970	15	15	10	0.10	0.05
675	310	15	10	0.12	0.09

Table 10: FDR for binary outcomes with correlation = 0. We compared the performance of two multiple comparison procedures: MCP_D and MCP_D^{MV} using simulations when the outcome is binary and the conditional correlation between metabolites in the same block is 0. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.00
85	15	0	10	0.04	0.01
60	40	0	10	0.08	0.02
85	0	15	10	0.07	0.03
70	15	15	10	0.10	0.03
45	40	15	10	0.13	0.03
1000	0	0	10	0.05	0.01
985	15	0	10	0.07	0.02
690	310	0	10	0.09	0.06
985	0	15	10	0.09	0.04
970	15	15	10	0.11	0.04
675	310	15	10	0.12	0.04

Table 11: FDR for continuous outcomes with correlation = 0.5. We compared the performance of two multiple comparison procedures: MCP_D and MCP_D^{MV} using simulations when the outcome is continuous and the conditional correlation between metabolites in the same block is 0.5. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.00
85	15	0	10	0.04	0.01
60	40	0	10	0.08	0.04
85	0	15	10	0.06	0.02
70	15	15	10	0.09	0.03
45	40	15	10	0.12	0.03
1000	0	0	10	0.06	0.02
985	15	0	10	0.07	0.03
690	310	0	10	0.08	0.08
985	0	15	10	0.08	0.04
970	15	15	10	0.10	0.05
675	310	15	10	0.11	0.07

Table 12: FDR for continuous outcomes with correlation = 0.5. We compared the performance of two multiple comparison procedures: MCP_D and MCP_D^{MV} using simulations when the outcome is binary and the conditional correlation between metabolites in the same block is 0.5. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.00
85	15	0	10	0.04	0.00
60	40	0	10	0.07	0.00
85	0	15	10	0.01	0.00
70	15	15	10	0.04	0.00
45	40	15	10	0.07	0.00
1000	0	0	10	0.03	0.01
985	15	0	10	0.06	0.01
690	310	0	10	0.07	0.02
985	0	15	10	0.08	0.04
970	15	15	10	0.10	0.03
675	310	15	10	0.12	0.04

Table 13: FDR for continuous outcomes with correlation = 0.9. We compared the performance of two multiple comparison procedures: MCP_D and MCP_D^{MV} using simulations when the outcome is continuous and the conditional correlation between metabolites in the same block is 0.9. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.

m_{00}	m_{10}	m_{01}	m_{11}	MCP_D	MCP_D^{MV}
100	0	0	10	0.01	0.00
85	15	0	10	0.04	0.00
60	40	0	10	0.07	0.01
85	0	15	10	0.01	0.00
70	15	15	10	0.03	0.00
45	40	15	10	0.08	0.00
1000	0	0	10	0.04	0.01
985	15	0	10	0.06	0.01
690	310	0	10	0.06	0.02
985	0	15	10	0.07	0.04
970	15	15	10	0.09	0.05
675	310	15	10	0.10	0.05

Table 14: FDR for binary outcomes with correlation = 0.9. We compared the performance of two multiple comparison procedures: MCP_D and MCP_D^{MV} using simulations when the outcome is binary and the conditional correlation between metabolites in the same block is 0.9. The first four columns show the number (m_{00}) of biomarkers associated with neither exposure or outcome, the number (m_{10}) associated with only the exposure, the number (m_{01}) associated with only the outcome, and the number (m_{11}) associated with both exposure and outcome. The remaining columns show the FDR when $\alpha = 0.2$. Details of the simulation can be found in the methods section.