Supplementary Materials of 'Genome-wide Analyses of Sparse Mediation Effects Under Composite Null Hypotheses' by YT Huang

1 Proof of Lemma 3.2

We let $\sigma_2^2 > \sigma_1^2$ and $\sigma^2 = \frac{w_1\sigma_1^2 + w_2\sigma_2^2}{w_1+w_2}$, and first show the result for $k = 2$:

$$w_1 F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) + w_2 F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) \approx (w_1+w_2) F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right).$$

We express the left hand side as follows:

$$\begin{aligned}
&w_1 F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) + w_2 F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) \\
=&(w_1+w_2) F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) + w_2\left\{F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) - F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right)\right\} \\
=&-(w_1+w_2)\left\{F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right) - F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right)\right\} + w_2\left\{F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) - F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right)\right\} \\
&+(w_1+w_2) F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right).
\end{aligned}$$

We need to find σ^2 such that

$$F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right) - F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) = \frac{w_2}{w_1+w_2}\left\{F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) - F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right)\right\}. \tag{1}$$

There exist c in the interval $-dF\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) \leq c \leq -dF\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right)$ such that the left hand side of (1) can be expressed as

$$c\left(\frac{ab}{\sqrt{1+\sigma_1^2}} - \frac{ab}{\sqrt{1+\sigma^2}}\right) = cab\left(1 - \frac{\sigma_1^2}{2} - \left(1 - \frac{\sigma^2}{2}\right) + \epsilon_1\right),$$

where $\epsilon_1 = \sum_{k=2}^{\infty}(-1)^k \prod_{h=1}^{k}\left(1-\frac{1}{2h}\right)(\sigma_1^{2k} - \sigma^{2k})$. Similarly, we express the right hand side of (1) as

$$\frac{c' w_2}{w_1+w_2}\left(\frac{ab}{\sqrt{1+\sigma_1^2}} - \frac{ab}{\sqrt{1+\sigma_2^2}}\right) = \frac{w_1 cab}{w_1+w_2}\left(1-\frac{\sigma_1^2}{2} - \left(1-\frac{\sigma_2^2}{2}\right) + \epsilon_2\right),$$

where $-dF\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) \leq c' \leq -dF\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right)$ and $\epsilon_2 = \sum_{k=2}^{\infty}(-1)^k \prod_{h=1}^{k}\left(1-\frac{1}{2h}\right)(\sigma_1^{2k} - \sigma_2^{2k})$. By equating the two expressions: $cab(\sigma^2 - \sigma_1^2 + 2\epsilon_1) = \frac{w_2 cab}{w_1+w_2}(\sigma_2^2 - \sigma_1^2 + 2\epsilon_2)$, we obtain

$$\begin{aligned}\sigma^{*2} &= \sigma_1^2 + \frac{c' w_2}{c(w_1+w_2)}(\sigma_2^2 - \sigma_1^2 + 2\epsilon_2) - 2\epsilon_1 \\ &= \frac{w_1\sigma_1^2 + w_2\sigma_2^2}{w_1+w_2} + \epsilon.\end{aligned}$$

$\epsilon = \frac{w_2}{w_1+w_2}(\sigma_2^2 - \sigma_1^2)\left(\frac{c'}{c} - 1\right) + \frac{2w_2 c' \epsilon_2}{(w_1+w_2)c} - 2\epsilon_1 \to 0$ if both σ_1^2 and σ_2^2 are small or close. And,

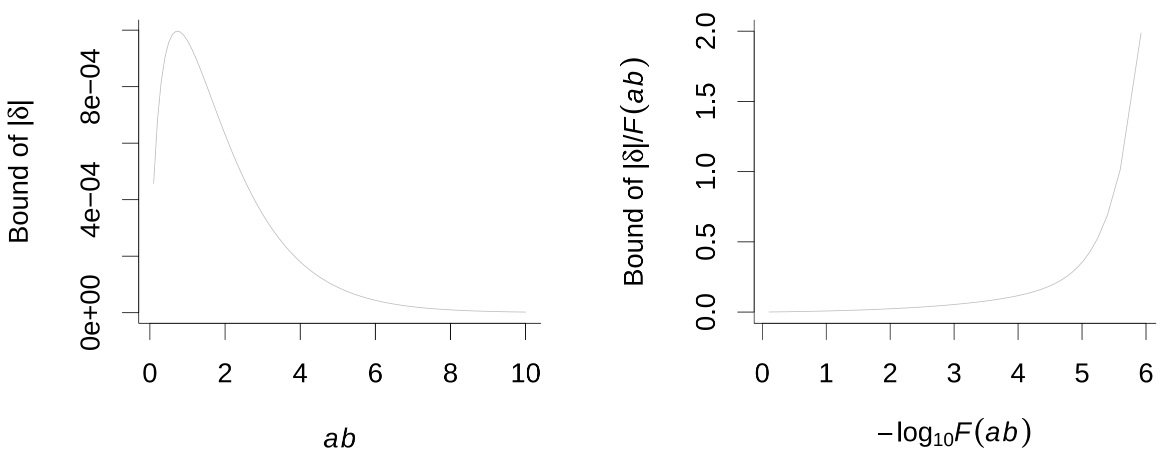
$$\begin{aligned} w_1 F\left(\frac{ab}{\sqrt{1+\sigma_1^2}}\right) + w_2 F\left(\frac{ab}{\sqrt{1+\sigma_2^2}}\right) &= (w_1+w_2)F\left(\frac{ab}{\sqrt{1+\sigma^{*2}}}\right) \\ &= (w_1+w_2)F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right) + \delta,\end{aligned}$$

where assuming $\sigma^{*2} > \sigma^2$,

$$\begin{aligned}\frac{|\delta|}{2} &= (w_1+w_2)\int_{\frac{|ab|}{\sqrt{1+\sigma^{*2}}}}^{\frac{|ab|}{\sqrt{1+\sigma^2}}} \pi^{-1} K_0(|u|)du \\ &< \frac{w_1+w_2}{\pi}\left(\frac{|ab|}{\sqrt{1+\sigma^2}} - \frac{|ab|}{\sqrt{1+\sigma^{*2}}}\right) K_0\left(\frac{|ab|}{\sqrt{1+\sigma^{*2}}}\right).\end{aligned}$$

By induction, the general results can be shown: $\sum_{j=1}^{J} w_j F\left(\frac{ab}{\sqrt{1+\sigma_j^2}}\right) = \left(\sum_{j=1}^{J} w_j\right) F\left(\frac{ab}{\sqrt{1+\sigma^2}}\right) + \delta$, where $\sigma^2 = \frac{\sum_{j=1}^{J} w_j \sigma_j^2}{\sum_{j=1}^{J} w_j}$, $|\delta| < \frac{2\sum_j w_j}{\pi}\left(\frac{|ab|}{\sqrt{1+\sigma^2}} - \frac{|ab|}{\sqrt{1+\sigma^{*2}}}\right) K_0\left(\frac{|ab|}{\sqrt{1+\sigma^{*2}}}\right)$ and σ^{*2} satisfies $\sum_{j=1}^{J} w_j F\left(\frac{ab}{\sqrt{1+\sigma_j^2}}\right) = \left(\sum_{j=1}^{J} w_j\right) F\left(\frac{ab}{\sqrt{1+\sigma^{*2}}}\right)$.

Figure S1: The bound of $|\delta|$. (a) bound for $|\delta|$ as a function of ab, (b) ratio of bound for $|\delta|$ to $F(ab)$ as a function of $-\log_{10} F(ab)$, where $F(ab)$ can be viewed as a lower bound of p_{comp}.



(a) (b)

$\tilde{p}_{comp}$ is from the test implementing the idea from a conference abstract (Lin, 2017). However, we note that our $\tilde{p}_{comp}$ might not be entirely identical to their proposed method since the detail is not available to us. We conducted a simulation study by plugging in the true proportions of $H_0^{(1)}$, $H_0^{(2)}$ and $H_0^{(3)}$. Specifically, the simulation was conducted under the condition that μ_a and μ_b follow a mixture of normal distributions and we investigated the performance by varying sample size. The results suggest that its performance varies with sample size (Figure S2) and how to better estimate the proportion of different types of null under sparse effects may require additional research.

References

Lin, X. Testing of mediation effects in genome-wide studies: testing a large number of composite null hypotheses. In *Joint Statistical Meeting, Baltimore*, 2017. [conference abstract].

Table S1: Proportion (with Monte Carlo standard deviation) of p-values at various cut-offs using different tests under the null where $m_0 = 9.9 \times 10^6$, $m_1 = 5 \times 10^4$, $m_2 = 5 \times 10^4$ and $m_3 = 0$.

Cut-offs	p_{comp}	$\hat{p}_{comp}$	$\tilde{p}_{comp}$	p_{JT}
$(\mu_a, \mu_b) \sim$ normal distribution				
$p < 10^{-1}$	0.99 (0.0009) $\times 10^{-1}$	0.99 (0.0006) $\times 10^{-1}$	1.00 (0.0009) $\times 10^{-1}$	0.10 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.004) $\times 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.01 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.99 (0.009) $\times 10^{-3}$	0.98 (0.009) $\times 10^{-3}$	0.001 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.94 (0.04) $\times 10^{-4}$	0.0001 (0.0003) $\times 10^{-4}$
$p < 10^{-5}$	0.98 (0.10) $\times 10^{-5}$	0.99 (0.10) $\times 10^{-5}$	0.79 (0.08) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.91 (0.36) $\times 10^{-6}$	0.93 (0.37) $\times 10^{-6}$	0.50 (0.26) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.85 (1.18) $\times 10^{-7}$	0.90 (1.17) $\times 10^{-7}$	0.20 (0.41) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim$ mixture of normal distribution				
$p < 10^{-1}$	0.99 (0.0009) $\times 10^{-1}$	0.99 (0.0006) $\times 10^{-1}$	1.00 (0.0009) $\times 10^{-1}$	0.10 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.004) $\times 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.01 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.99 (0.009) $\times 10^{-3}$	0.001 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.94 (0.04) $\times 10^{-4}$	0.0001 (0.0003) $\times 10^{-4}$
$p < 10^{-5}$	0.99 (0.11) $\times 10^{-5}$	1.00 (0.10) $\times 10^{-5}$	0.80 (0.08) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.97 (0.37) $\times 10^{-6}$	0.99 (0.37) $\times 10^{-6}$	0.54 (0.23) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.95 (1.15) $\times 10^{-7}$	1.00 (1.17) $\times 10^{-7}$	0.20 (0.41) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim t$ distribution				
$p < 10^{-1}$	0.99 (0.0008) $\times 10^{-1}$	0.99 (0.0005) $\times 10^{-1}$	1.00 (0.0008) $\times 10^{-1}$	0.10 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	0.01 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	1.00 (0.01) $\times 10^{-3}$	1.00 (0.01) $\times 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.001 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	1.00 (0.04) $\times 10^{-4}$	1.01 (0.04) $\times 10^{-4}$	0.96 (0.04) $\times 10^{-4}$	0.0001 (0.0003) $\times 10^{-4}$
$p < 10^{-5}$	1.00 (0.07) $\times 10^{-5}$	1.00 (0.07) $\times 10^{-5}$	0.82 (0.08) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	1.14 (0.39) $\times 10^{-6}$	1.17 (0.39) $\times 10^{-6}$	0.58 (0.23) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	1.25 (1.02) $\times 10^{-7}$	1.30 (0.98) $\times 10^{-7}$	0.25 (0.44) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim$ uniform distribution				
$p < 10^{-1}$	0.99 (0.0009) $\times 10^{-1}$	0.99 (0.0006) $\times 10^{-1}$	1.00 (0.0009) $\times 10^{-1}$	0.10 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.004) $\times 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.01 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.99 (0.01) $\times 10^{-3}$	0.98 (0.01) $\times 10^{-3}$	0.001 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.99 (0.04) $\times 10^{-4}$	0.94 (0.04) $\times 10^{-4}$	0.0001 (0.0003) $\times 10^{-4}$
$p < 10^{-5}$	0.98 (0.10) $\times 10^{-5}$	0.99 (0.10) $\times 10^{-5}$	0.79 (0.08) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.91 (0.36) $\times 10^{-6}$	0.93 (0.37) $\times 10^{-6}$	0.47 (0.25) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.90 (1.17) $\times 10^{-7}$	0.95 (1.15) $\times 10^{-7}$	0.20 (0.41) $\times 10^{-7}$	0.0 (0.0)

Table S2: Proportion (with Monte Carlo standard deviation) of p-values at various cut-offs using different tests under the null where $m_0 = 5 \times 10^6$, $m_1 = 5 \times 10^6$, and $m_2 = m_3 = 0$.

Cut-offs	p_{comp}	$\hat{p}_{comp}$	$\tilde{p}_{comp}$	p_{JT}
		$(\mu_a, \mu_b) \sim$ normal distribution		
$p < 10^{-1}$	0.99 (0.001) $\times 10^{-1}$	0.99 (0.0007) $\times 10^{-1}$	1.06 (0.0009) $\times 10^{-1}$	0.12 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.003) $\times 10^{-2}$	1.00 (0.002) $\times 10^{-2}$	0.99 (0.002) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	1.00 (0.01) $\times 10^{-3}$	1.03 (0.01) $\times 10^{-3}$	0.75 (0.007) $\times 10^{-3}$	0.002 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	1.01 (0.03) $\times 10^{-4}$	1.08 (0.03) $\times 10^{-4}$	0.49 (0.02) $\times 10^{-4}$	0.0004 (0.0007) $\times 10^{-4}$
$p < 10^{-5}$	1.00 (0.10) $\times 10^{-5}$	1.12 (0.12) $\times 10^{-5}$	0.29 (0.05) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.89 (0.28) $\times 10^{-6}$	1.14 (0.35) $\times 10^{-6}$	0.18 (0.11) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	1.05 (1.23) $\times 10^{-7}$	1.40 (1.43) $\times 10^{-7}$	0.10 (0.31) $\times 10^{-7}$	0.0 (0.0)
		$(\mu_a, \mu_b) \sim$ mixture of normal distribution		
$p < 10^{-1}$	0.99 (0.001) $\times 10^{-1}$	0.99 (0.0009) $\times 10^{-1}$	1.06 (0.0008) $\times 10^{-1}$	0.12 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.01 (0.003) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	1.01 (0.01) $\times 10^{-3}$	1.04 (0.01) $\times 10^{-3}$	0.76 (0.01) $\times 10^{-3}$	0.002 (0.0006) $\times 10^{-3}$
$p < 10^{-4}$	1.03 (0.04) $\times 10^{-4}$	1.10 (0.04) $\times 10^{-4}$	0.49 (0.03) $\times 10^{-4}$	0.0003 (0.0006) $\times 10^{-4}$
$p < 10^{-5}$	1.06 (0.12) $\times 10^{-5}$	1.18 (0.13) $\times 10^{-5}$	0.28 (0.06) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	1.10 (0.36) $\times 10^{-6}$	1.28 (0.40) $\times 10^{-6}$	0.20 (0.17) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	1.45 (1.39) $\times 10^{-7}$	1.70 (1.42) $\times 10^{-7}$	0.10 (0.31) $\times 10^{-7}$	0.0 (0.0)
		$(\mu_a, \mu_b) \sim t$ distribution		
$p < 10^{-1}$	0.99 (0.0008) $\times 10^{-1}$	0.99 (0.0007) $\times 10^{-1}$	1.06 (0.0007) $\times 10^{-1}$	0.12 (0.0003) $\times 10^{-1}$
$p < 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.01 (0.003) $\times 10^{-2}$	1.01 (0.003) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	1.06 (0.01) $\times 10^{-3}$	1.09 (0.01) $\times 10^{-3}$	0.78 (0.01) $\times 10^{-3}$	0.003 (0.0005) $\times 10^{-3}$
$p < 10^{-4}$	1.23 (0.03) $\times 10^{-4}$	1.30 (0.03) $\times 10^{-4}$	0.51 (0.03) $\times 10^{-4}$	0.0004 (0.0007) $\times 10^{-4}$
$p < 10^{-5}$	1.72 (0.16) $\times 10^{-5}$	1.87 (0.16) $\times 10^{-5}$	0.31 (0.05) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	3.37 (0.69) $\times 10^{-6}$	3.79 (0.76) $\times 10^{-6}$	0.18 (0.15) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	10.6 (2.65) $\times 10^{-7}$	11.9 (3.09) $\times 10^{-7}$	0.10 (0.31) $\times 10^{-7}$	0.0 (0.0)
		$(\mu_a, \mu_b) \sim$ uniform distribution		
$p < 10^{-1}$	1.00 (0.001) $\times 10^{-1}$	0.99 (0.0008) $\times 10^{-1}$	1.06 (0.0009) $\times 10^{-1}$	0.12 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.004) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.98 (0.004) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	0.97 (0.008) $\times 10^{-3}$	1.00 (0.008) $\times 10^{-3}$	0.73 (0.008) $\times 10^{-3}$	0.002 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.94 (0.03) $\times 10^{-4}$	1.01 (0.03) $\times 10^{-4}$	0.46 (0.02) $\times 10^{-4}$	0.0002 (0.0004) $\times 10^{-4}$
$p < 10^{-5}$	0.87 (0.09) $\times 10^{-5}$	0.97 (0.09) $\times 10^{-5}$	0.28 (0.05) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.75 (0.30) $\times 10^{-6}$	0.95 (0.29) $\times 10^{-6}$	0.08 (0.12) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.80 (1.15) $\times 10^{-7}$	0.95 (1.19) $\times 10^{-7}$	0.15 (0.37) $\times 10^{-7}$	0.0 (0.0)

Table S3: Proportion (with Monte Carlo standard deviation) of p-values at various cut-offs using different tests under the null where $\sigma_a = 0.2$, $\sigma_b = 0.8$, $m_0 = 5 \times 10^6$, $m_1 = 3 \times 10^6$, and $m_2 = 2 \times 10^6$, $m_3 = 0$.

Cut-offs	p_{comp}	$\hat{p}_{comp}$	$\tilde{p}_{comp}$	p_{JT}
$(\mu_a, \mu_b) \sim$ normal distribution				
$p < 10^{-1}$	1.00 (0.001) $\times 10^{-1}$	0.98 (0.0008) $\times 10^{-1}$	1.06 (0.001) $\times 10^{-1}$	0.12 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.99 (0.003) $\times 10^{-2}$	1.02 (0.003) $\times 10^{-2}$	1.03 (0.004) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	0.99 (0.009) $\times 10^{-3}$	1.11 (0.01) $\times 10^{-3}$	0.75 (0.01) $\times 10^{-3}$	0.003 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.99 (0.03) $\times 10^{-4}$	1.30 (0.03) $\times 10^{-4}$	0.37 (0.02) $\times 10^{-4}$	0.0008 (0.001) $\times 10^{-4}$
$p < 10^{-5}$	1.00 (0.09) $\times 10^{-5}$	1.62 (0.10) $\times 10^{-5}$	0.11 (0.03) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	1.04 (0.30) $\times 10^{-6}$	2.15 (0.41) $\times 10^{-6}$	0.03 (0.04) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.85 (0.88) $\times 10^{-7}$	3.05 (1.73) $\times 10^{-7}$	0.0 (0.0) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim$ mixture of normal distribution				
$p < 10^{-1}$	0.99 (0.0008) $\times 10^{-1}$	0.98 (0.0006) $\times 10^{-1}$	1.06 (0.0006) $\times 10^{-1}$	0.12 (0.0003) $\times 10^{-1}$
$p < 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.02 (0.003) $\times 10^{-2}$	1.05 (0.003) $\times 10^{-2}$	0.02 (0.0003) $\times 10^{-2}$
$p < 10^{-3}$	1.05 (0.01) $\times 10^{-3}$	1.17 (0.01) $\times 10^{-3}$	0.79 (0.01) $\times 10^{-3}$	0.003 (0.0007) $\times 10^{-3}$
$p < 10^{-4}$	1.16 (0.03) $\times 10^{-4}$	1.50 (0.03) $\times 10^{-4}$	0.41 (0.03) $\times 10^{-4}$	0.0007 (0.0007) $\times 10^{-4}$
$p < 10^{-5}$	1.33 (0.11) $\times 10^{-5}$	2.11 (0.14) $\times 10^{-5}$	0.12 (0.04) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	1.70 (0.54) $\times 10^{-6}$	3.17 (0.82) $\times 10^{-6}$	0.04 (0.05) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	2.10 (1.65) $\times 10^{-7}$	5.45 (3.24) $\times 10^{-7}$	0.0 (0.0) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim t$ distribution				
$p < 10^{-1}$	0.99 (0.001) $\times 10^{-1}$	0.98 (0.0009) $\times 10^{-1}$	1.06 (0.001) $\times 10^{-1}$	0.12 (0.0003) $\times 10^{-1}$
$p < 10^{-2}$	1.00 (0.003) $\times 10^{-2}$	1.02 (0.003) $\times 10^{-2}$	1.05 (0.003) $\times 10^{-2}$	0.02 (0.0004) $\times 10^{-2}$
$p < 10^{-3}$	1.09 (0.01) $\times 10^{-3}$	1.21 (0.01) $\times 10^{-3}$	0.80 (0.01) $\times 10^{-3}$	0.003 (0.0005) $\times 10^{-3}$
$p < 10^{-4}$	1.41 (0.05) $\times 10^{-4}$	1.77 (0.06) $\times 10^{-4}$	0.42 (0.02) $\times 10^{-4}$	0.001 (0.002) $\times 10^{-4}$
$p < 10^{-5}$	2.52 (0.16) $\times 10^{-5}$	3.51 (0.20) $\times 10^{-5}$	0.13 (0.04) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	6.85 (0.91) $\times 10^{-6}$	9.93 (0.83) $\times 10^{-6}$	0.03 (0.09) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	24.1 (4.57) $\times 10^{-7}$	36.9 (5.30) $\times 10^{-7}$	0.0 (0.0) $\times 10^{-7}$	0.0 (0.0)
$(\mu_a, \mu_b) \sim$ uniform distribution				
$p < 10^{-1}$	0.90 (0.001) $\times 10^{-1}$	0.99 (0.0009) $\times 10^{-1}$	1.01 (0.001) $\times 10^{-1}$	0.10 (0.0004) $\times 10^{-1}$
$p < 10^{-2}$	0.77 (0.003) $\times 10^{-2}$	1.00 (0.004) $\times 10^{-2}$	0.99 (0.004) $\times 10^{-2}$	0.01 (0.0003) $\times 10^{-2}$
$p < 10^{-3}$	0.62 (0.006) $\times 10^{-3}$	1.00 (0.008) $\times 10^{-3}$	0.90 (0.008) $\times 10^{-3}$	0.001 (0.0004) $\times 10^{-3}$
$p < 10^{-4}$	0.46 (0.02) $\times 10^{-4}$	0.99 (0.03) $\times 10^{-4}$	0.63 (0.03) $\times 10^{-4}$	0.0001 (0.0002) $\times 10^{-4}$
$p < 10^{-5}$	0.31 (0.06) $\times 10^{-5}$	0.97 (0.11) $\times 10^{-5}$	0.26 (0.06) $\times 10^{-5}$	0.0 (0.0)
$p < 10^{-6}$	0.19 (0.18) $\times 10^{-6}$	0.95 (0.37) $\times 10^{-6}$	0.06 (0.07) $\times 10^{-6}$	0.0 (0.0)
$p < 10^{-7}$	0.10 (0.31) $\times 10^{-7}$	1.00 (1.08) $\times 10^{-7}$	0.0 (0.0) $\times 10^{-7}$	0.0 (0.0)

Figure S2: Quantile-quantile plots of $\tilde{p}_{comp}$ with true π_0, π_a, and π_b by different sample sizes. (a) the noncentrality parameters for α_S and β_M $(\mu_a, \mu_b) \sim$ normal distribution; (b) $(\mu_a, \mu_b) \sim$ mixture of normal distribution; (c) $(\mu_a, \mu_b) \sim t$ distribution; and (d) $(\mu_a, \mu_b) \sim$ uniform distribution.

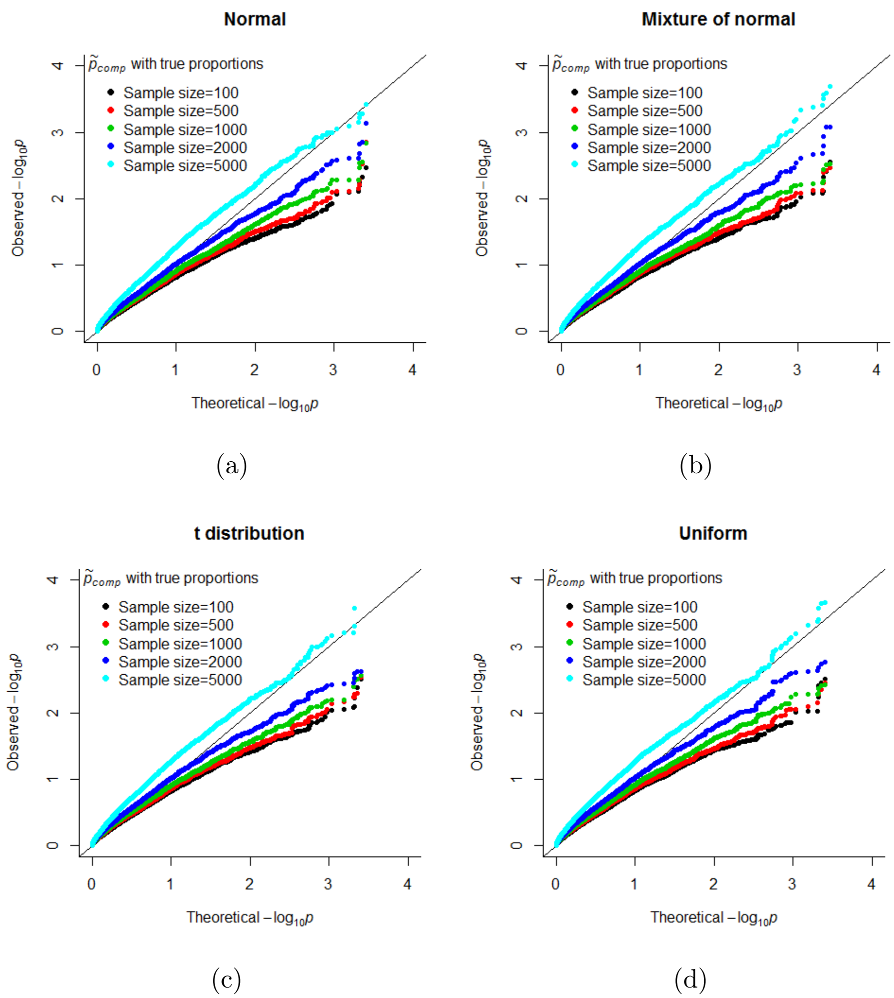
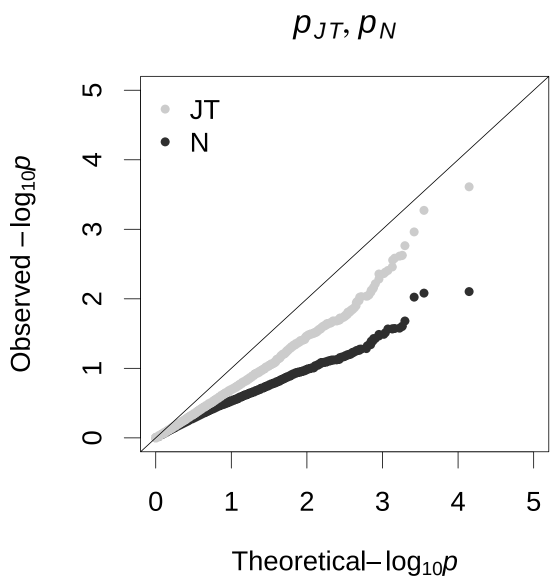


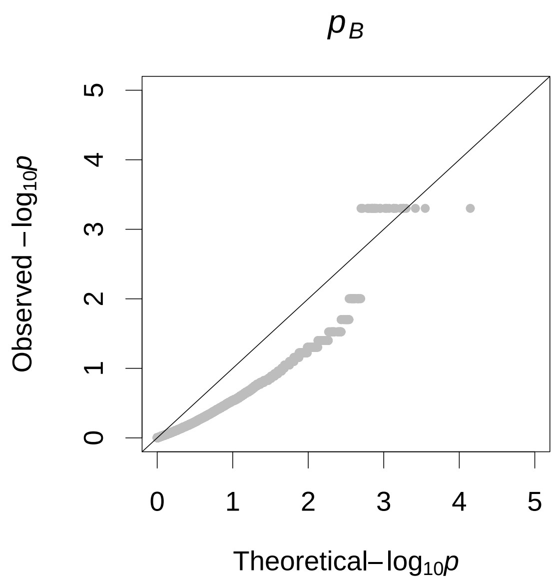
Table S4: Proportion of p-values at various cut-offs by different numbers of hypothesis tests (mediators) within a study under the null where $m_0 = 5 \times 10^6$, $m_1 = 5 \times 10^6$, and $m_2 = m_3 = 0$.

	No. of hypothesis tests within a study			
	10^5	10^4	10^3	10^2
$(\mu_a, \mu_b) \sim$ normal distribution				
$p < 10^{-1}$	0.099	0.099	0.10	0.10
$p < 10^{-2}$	0.010	0.010	0.010	0.010
$p < 10^{-3}$	0.0013	0.0013	0.0012	0.0012
$p < 10^{-4}$	0.00009	0.00009	0.00008	0.00009
$(\mu_a, \mu_b) \sim$ mixture of normal distribution				
$p < 10^{-1}$	0.099	0.099	0.099	0.10
$p < 10^{-2}$	0.0099	0.0099	0.010	0.010
$p < 10^{-3}$	0.0011	0.0011	0.0011	0.00097
$p < 10^{-4}$	0.00011	0.00011	0.00011	0.00011
$(\mu_a, \mu_b) \sim$ t distribution				
$p < 10^{-1}$	0.10	0.10	0.10	0.10
$p < 10^{-2}$	0.010	0.010	0.010	0.010
$p < 10^{-3}$	0.0012	0.0012	0.0011	0.0010
$p < 10^{-4}$	0.00011	0.00011	0.00011	0.00013
$(\mu_a, \mu_b) \sim$ uniform distribution				
$p < 10^{-1}$	0.10	0.10	0.10	0.10
$p < 10^{-2}$	0.010	0.010	0.010	0.0098
$p < 10^{-3}$	0.00094	0.00094	0.00093	0.00096
$p < 10^{-4}$	0.00006	0.00006	0.00007	0.00005

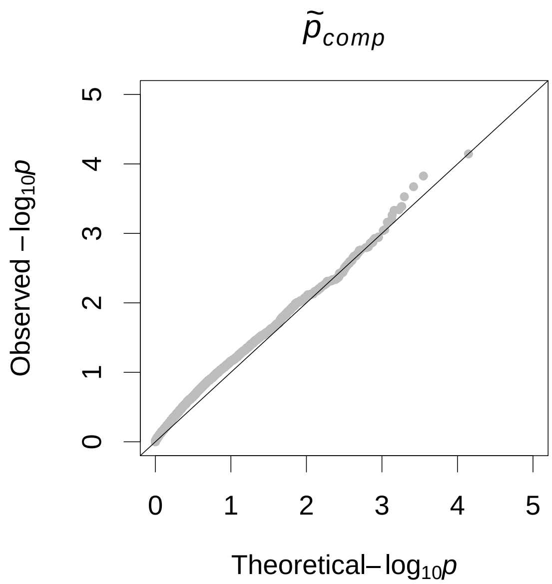
Figure S3: Quantile-quantile plots of p-values for mediation effects of 16,394 CpG loci on chromosome 17 for the socioeconomic index-BMI association. (a) p_{JT}, p-value of joint significance tests (JT) and p_N, p-value of normality-based tests (N); (b) p_B, p-value of bootstrap tests; (c) $\tilde{p}_{comp}$ defined in Section 4; and (d) $\hat{p}_{comp}$ defined in (8).



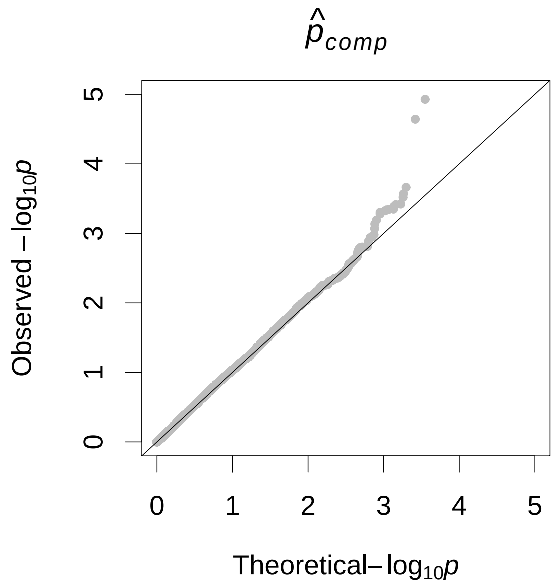
(a)



(b)



(c)



(d)

Figure S4: Histograms of 16,394 p-values in epigenome-wide mediation analyses of CpG loci on chromosome 17 using the normality-based test (p_N), the joint significance test (p_{JT}), the bootstrap test (p_B) as well as $\tilde{p}_{comp}$ defined in Section 4 and $\hat{p}_{comp}$ defined in (8).

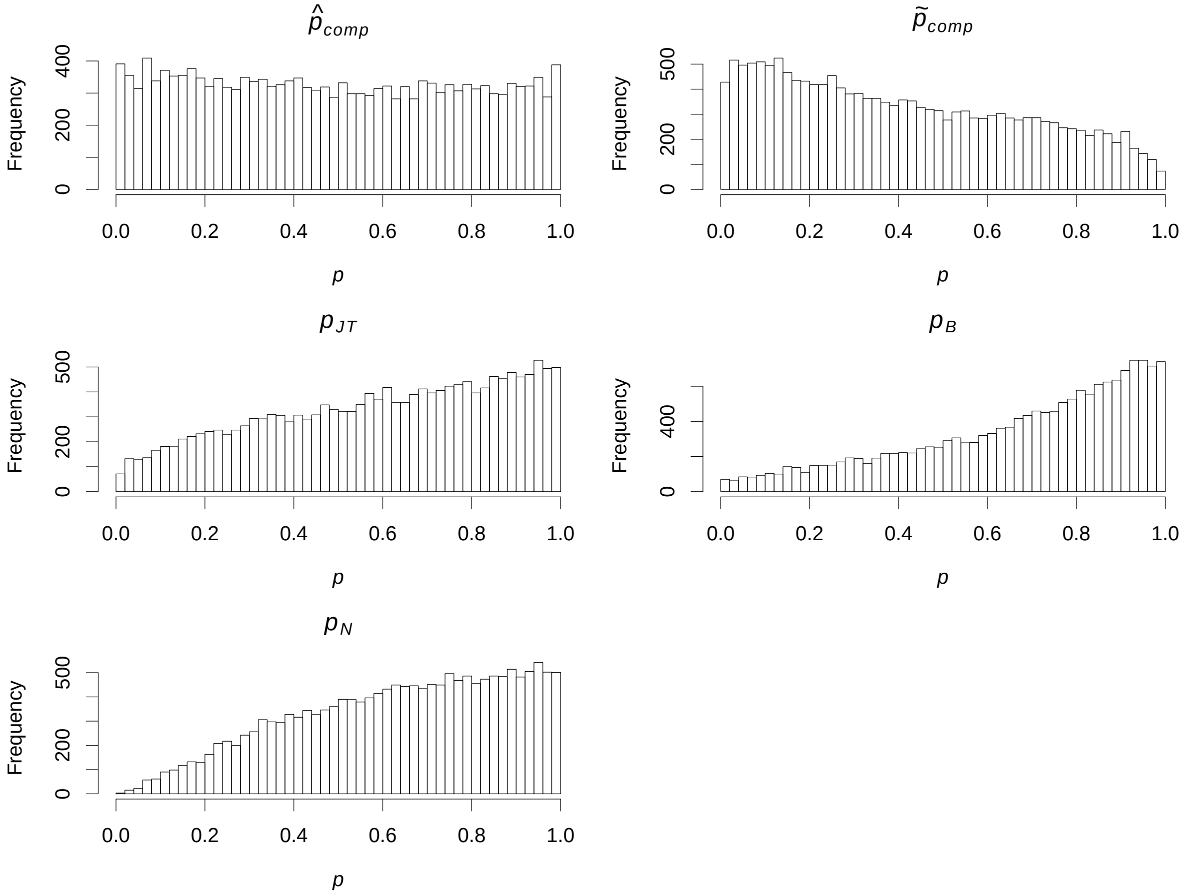


Figure S5: p-values of epigenome-wide mediation analyses of 16,394 CpG loci on chromosome 17 against their genomic location. $\hat{p}_{comp}$ defined in (8); $\tilde{p}_{comp}$ defined in Section 4; p_{JT}, p-value of joint significance tests; p_B, p-value of bootstrap tests; and p_N, p-value of normality-based tests. Red dots: $p < 0.005$.