**Supplemental Figure S1.** Plots of negative log base 10 of mediation p-values versus the percentage of reduction in trans-effects. The mediation p-values are calculated after accounting for cis-mediation, based on mediation tests for all 44 tissue types adjusting for known covariates including age, gender and genotype derived PCs and (A) with no adjustment of hidden confounders, (B) adjusting for all PEER factors, (C) adjusting for adaptively selected PEER factors, and (D) adjusting for selected expression-derived PCs (i.e., our final analysis). P-values are truncated at 10^{-16}.

**Adipose_Subcutaneous**

A. Adjust Known Covariates Only
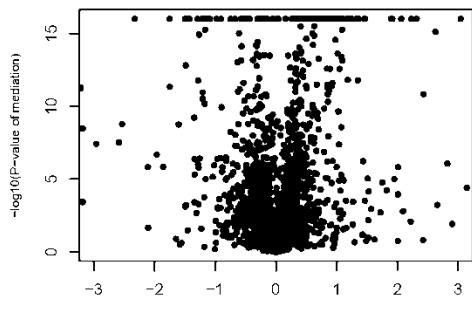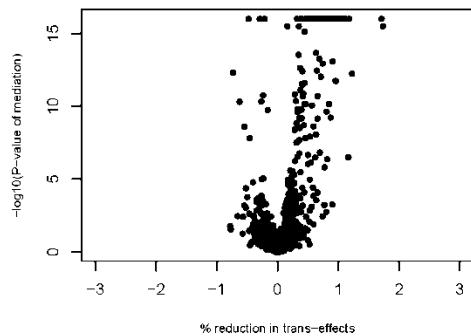
B. Adjust Known + All PEER


C. Adjust Known + Adaptively Selected PEER
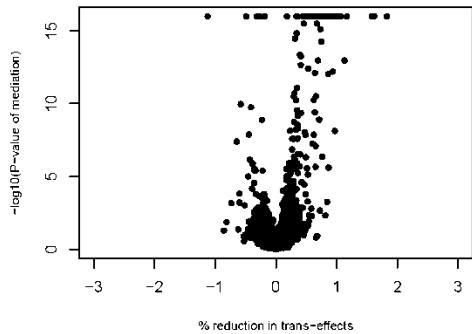
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
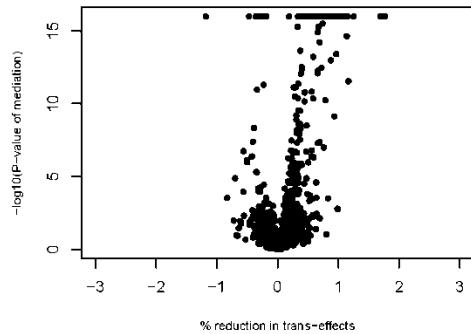
Adipose_Visceral_Omentum

A. Adjust Known Covariates Only
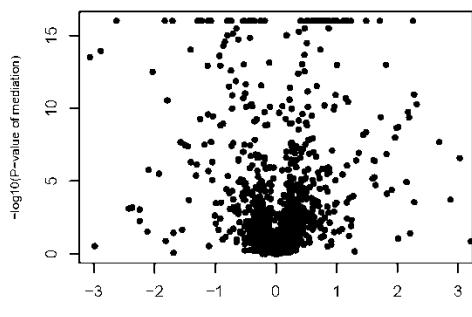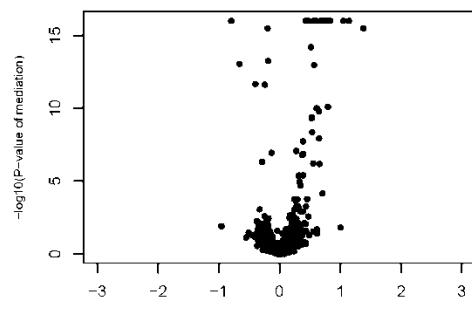
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C. Adjust Known + Adaptively Selected PEER
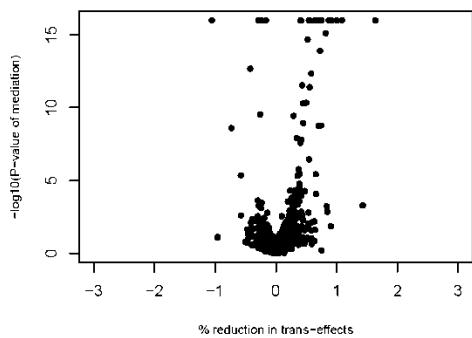
**D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)**
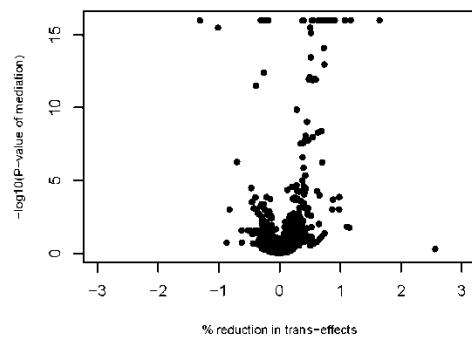
# Adrenal_Gland

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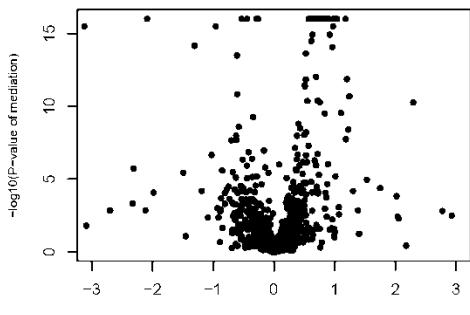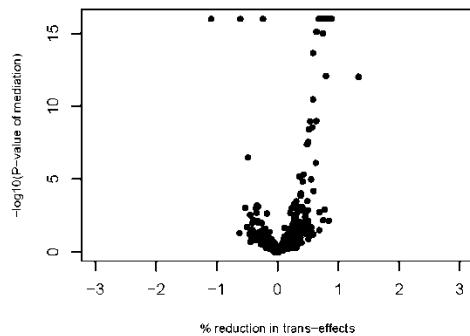
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C. Adjust Known + Adaptively Selected PEER
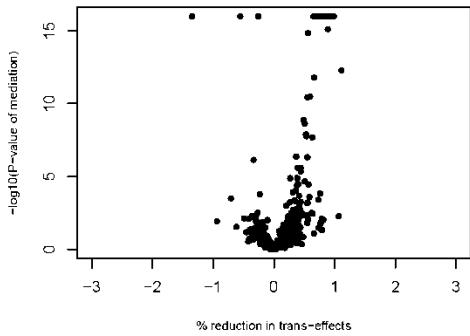
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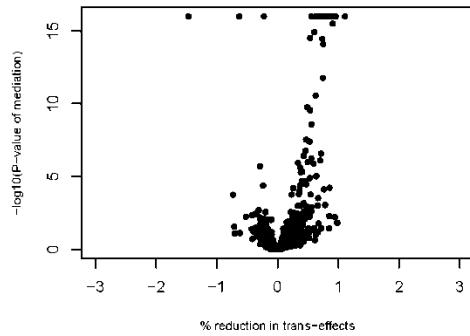
Artery_Aorta

A. Adjust Known Covariates Only
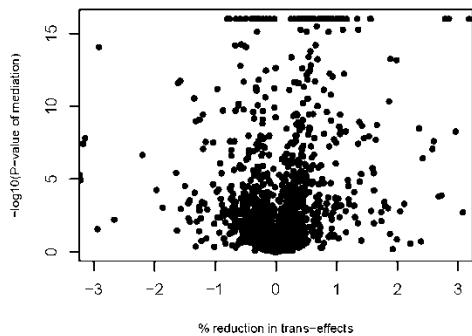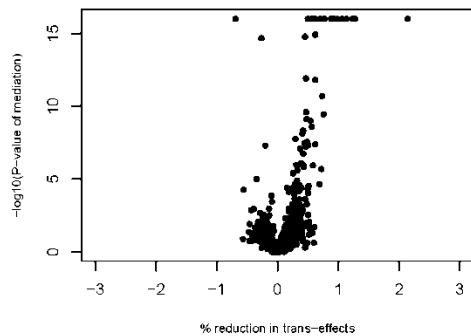
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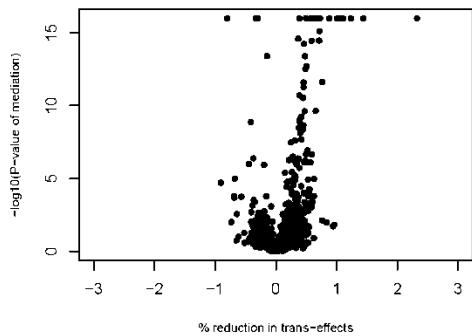
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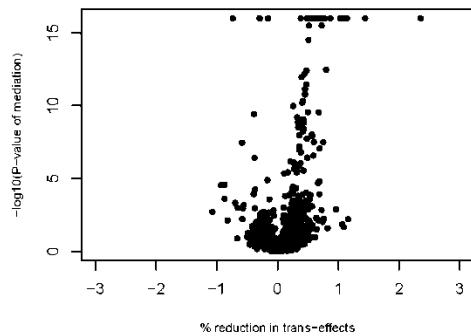
Artery_Coronary

A. Adjust Known Covariates Only
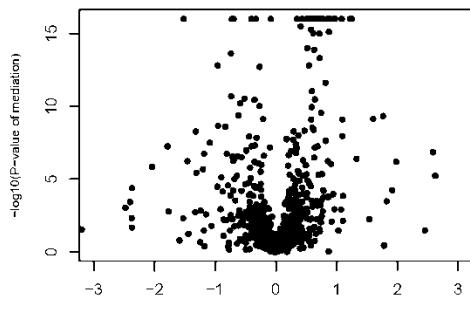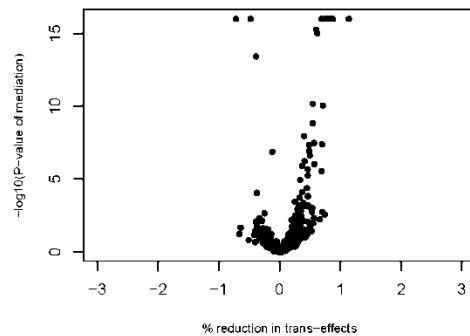
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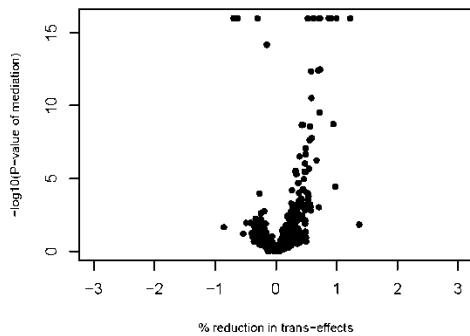
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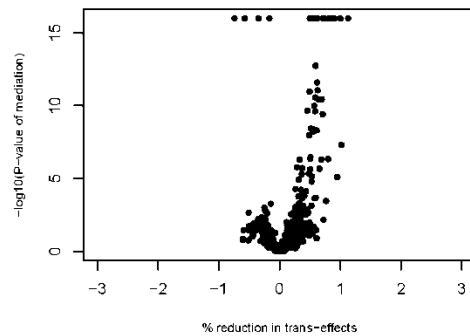
Artery_Tibial

A. Adjust Known Covariates Only
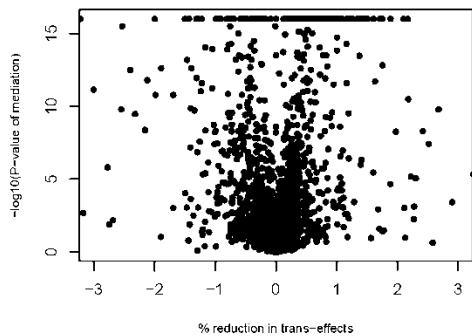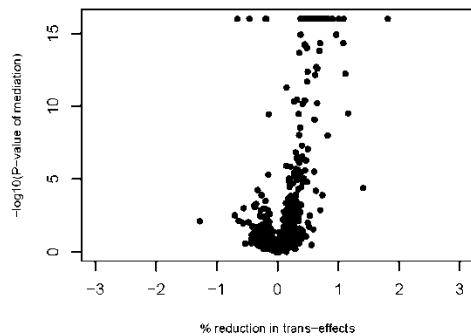
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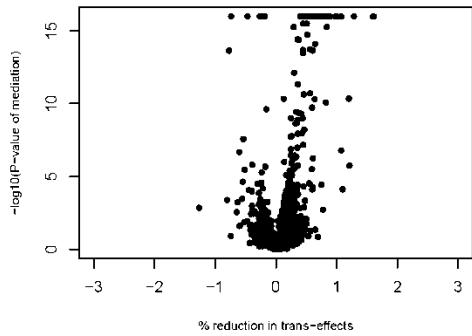
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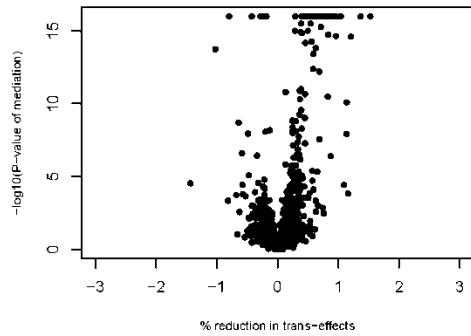
# Brain_Anterior_cingulate_cortex_BA24

A. Adjust Known Covariates Only
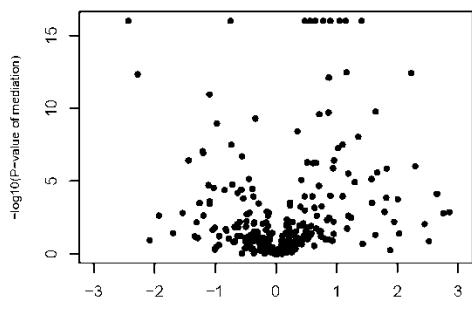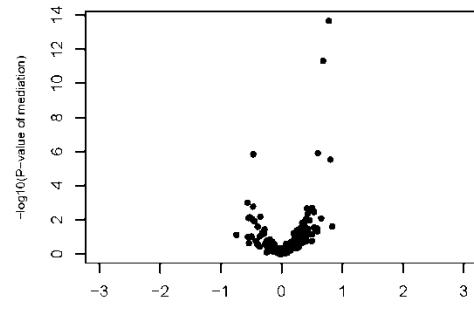
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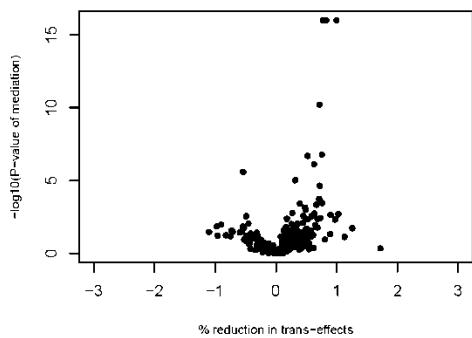
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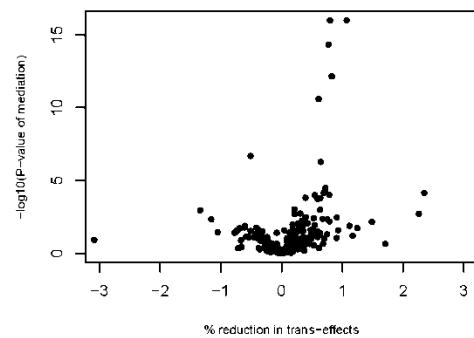
Brain_Caudate_basal_ganglia

A. Adjust Known Covariates Only
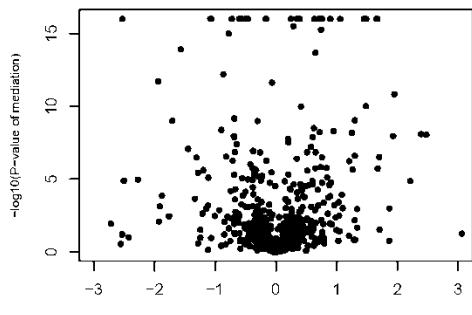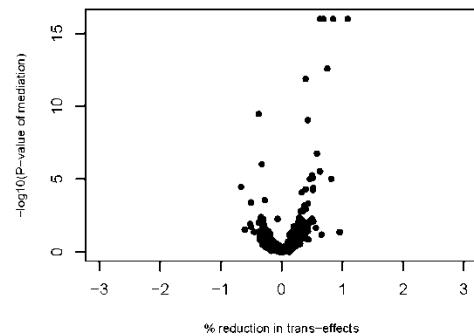
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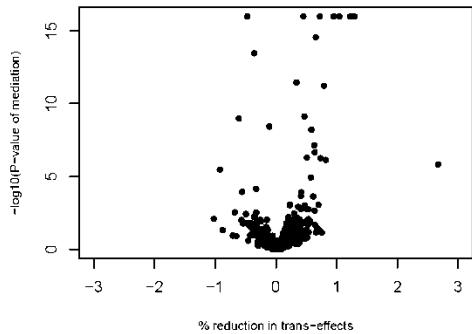
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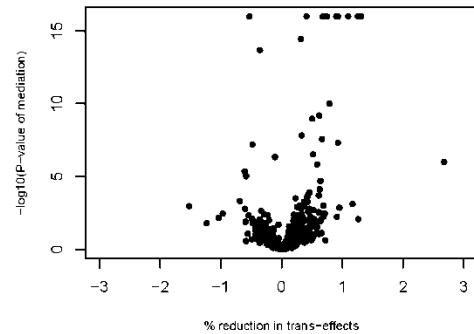
Brain_Cerebellar_Hemisphere

A. Adjust Known Covariates Only
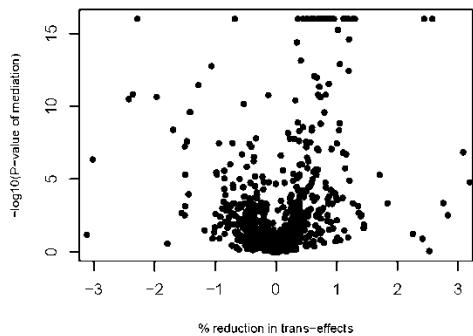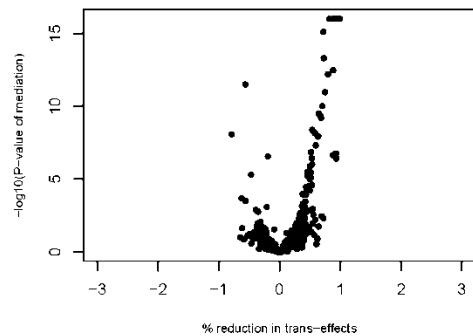
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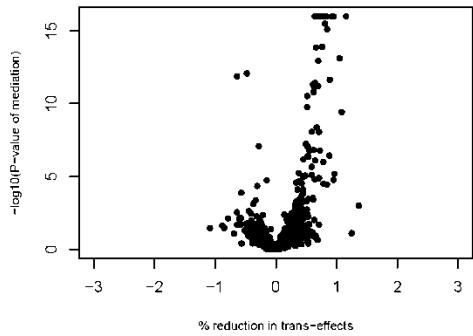
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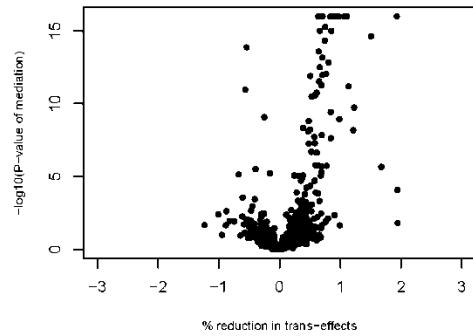
Brain_Cerebellum

A. Adjust Known Covariates Only
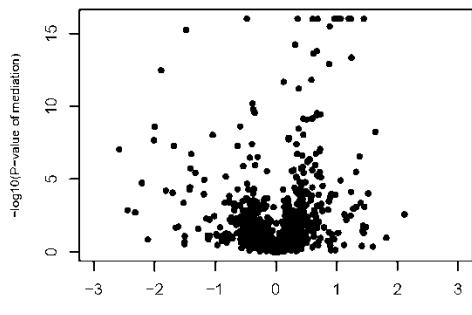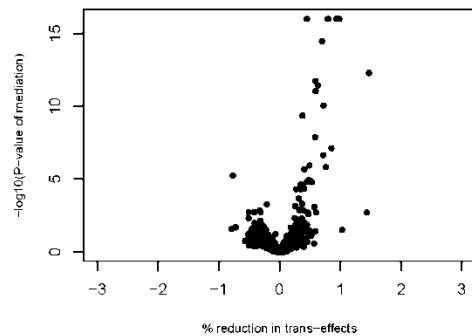
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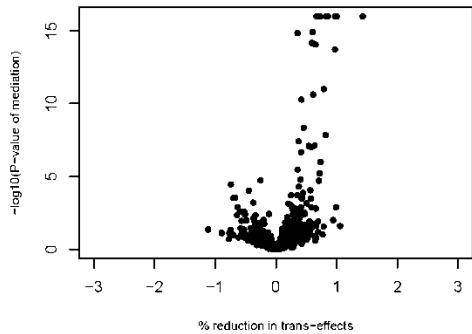
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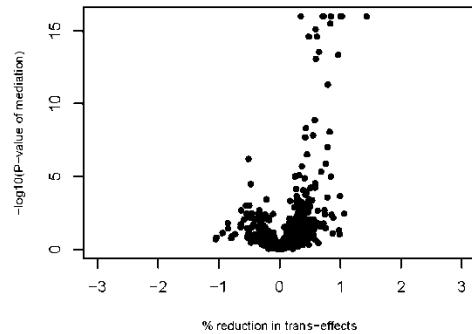
Brain_Cortex

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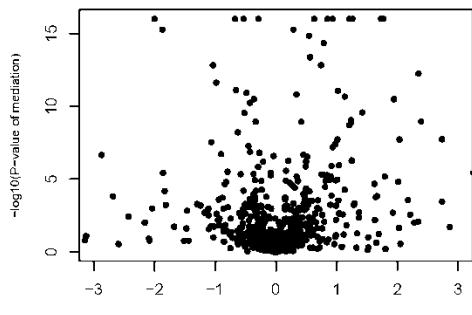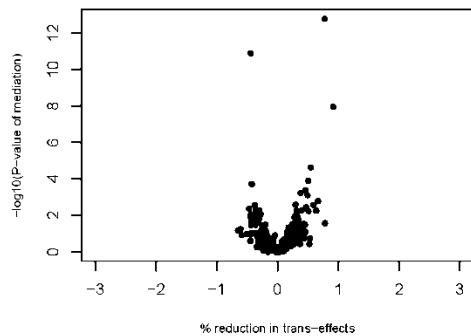
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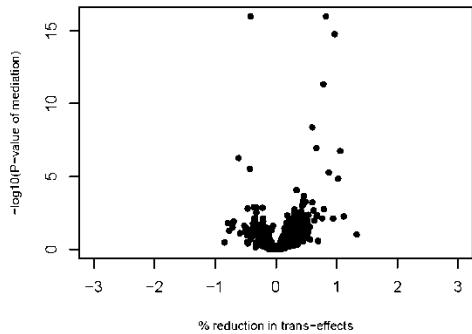
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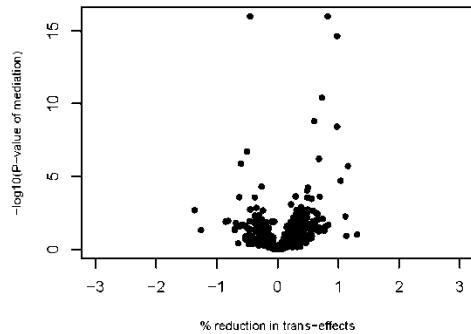
Brain_Frontal_Cortex_BA9

A. Adjust Known Covariates Only
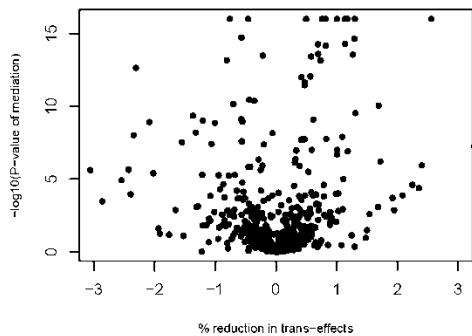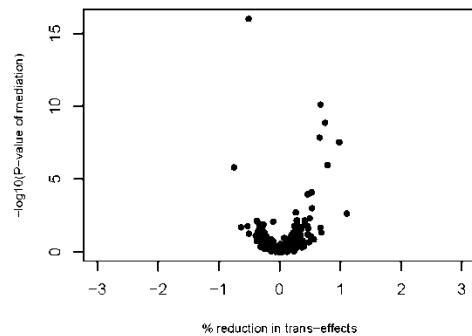
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
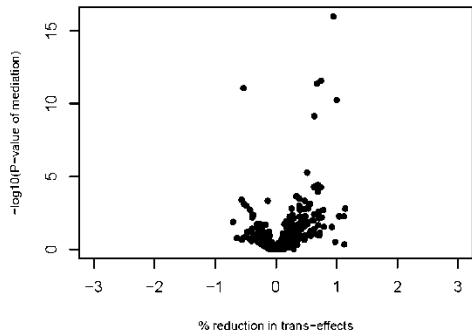
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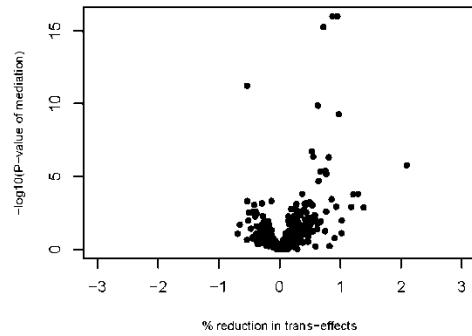
Brain_Hippocampus

A. Adjust Known Covariates Only
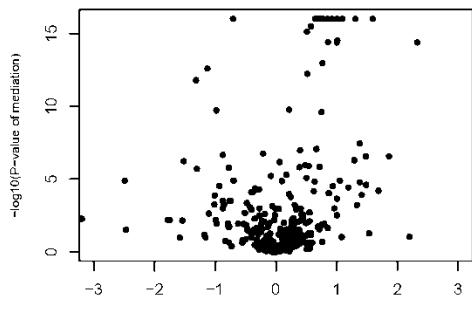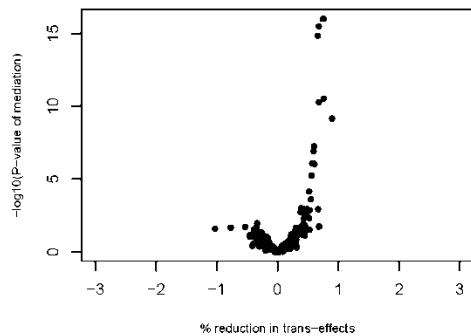
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
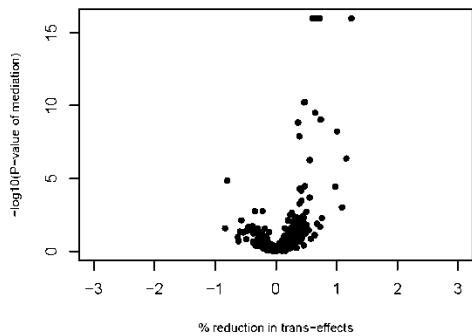
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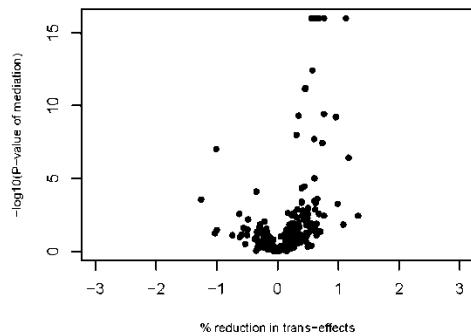
Brain_Hypothalamus

A. Adjust Known Covariates Only
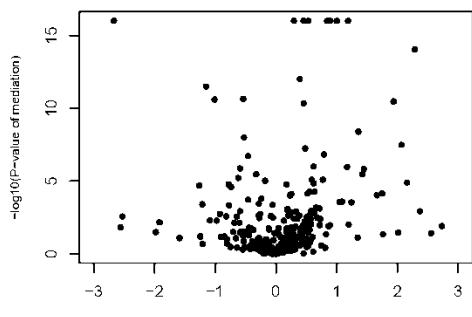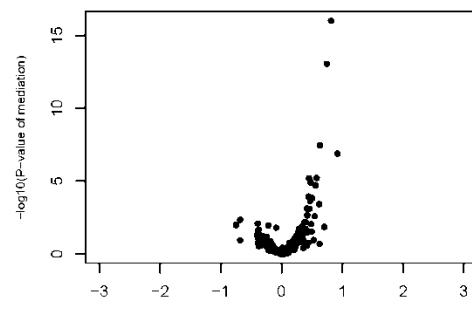
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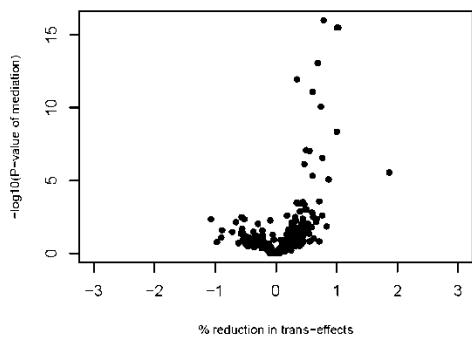
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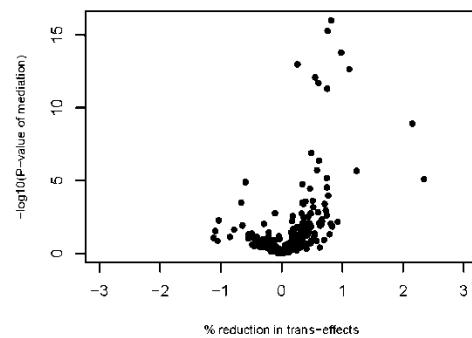
Brain_Nucleus_accumbens_basal_ganglia

A. Adjust Known Covariates Only
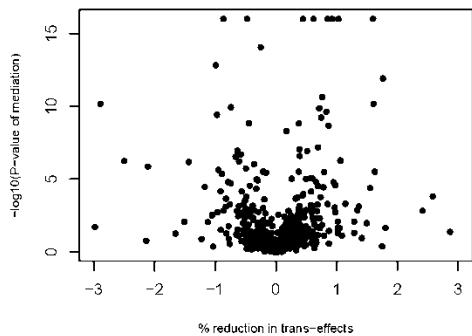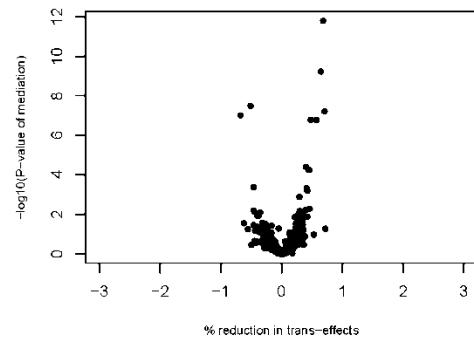
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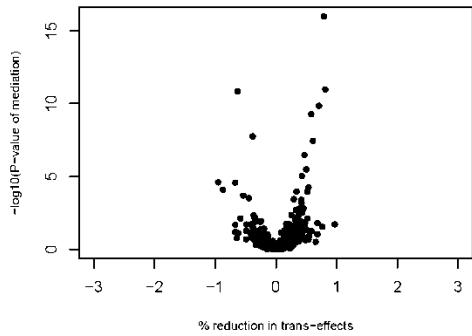
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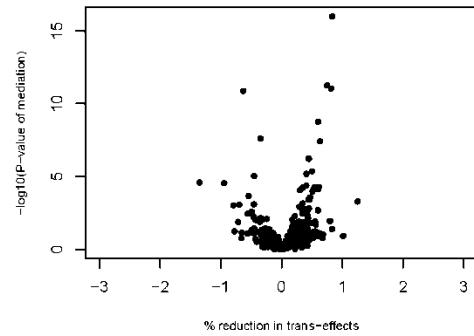
Brain_Putamen_basal_ganglia

A. Adjust Known Covariates Only
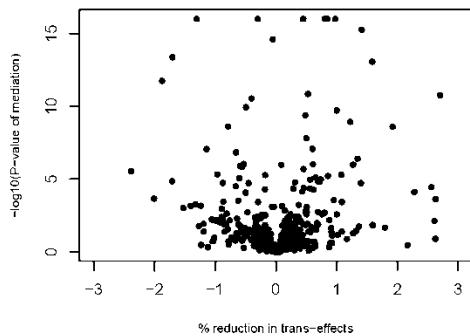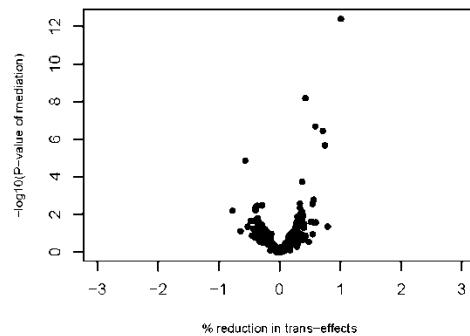
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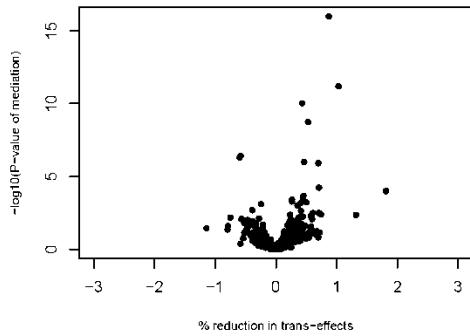
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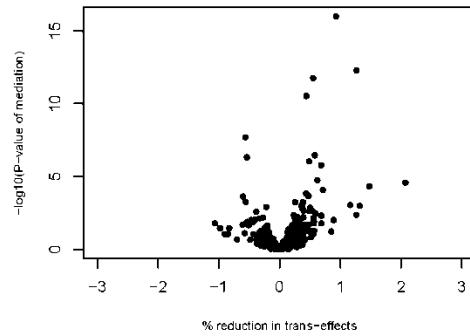
Breast_Mammary_Tissue

**A. Adjust Known Covariates Only**
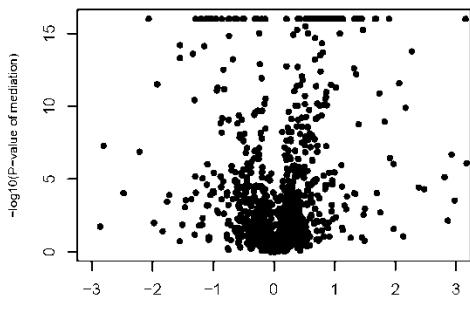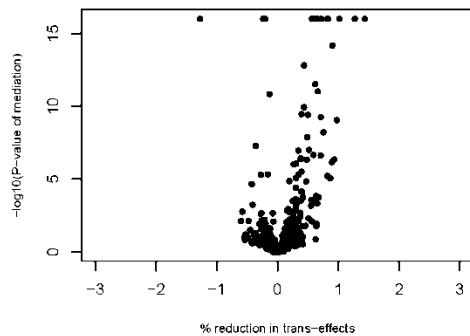
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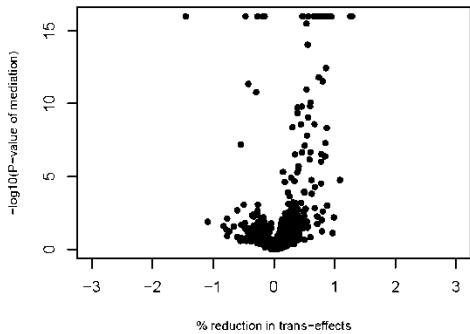
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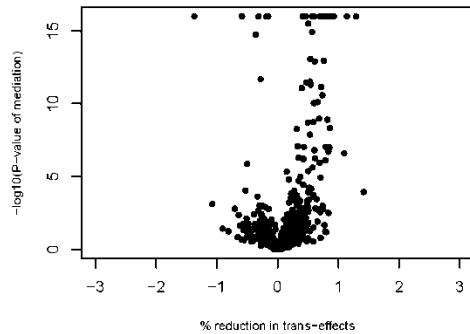
Cells_EBV-transformed_lymphocytes

A. Adjust Known Covariates Only
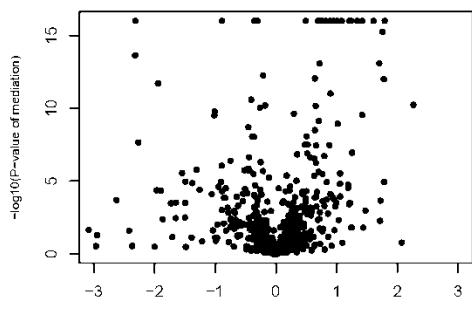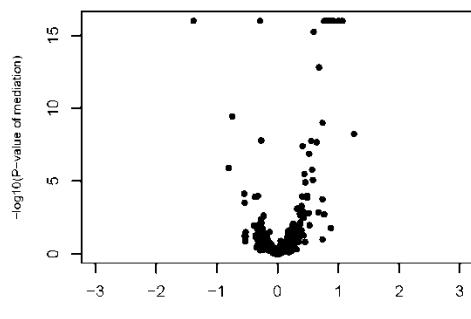
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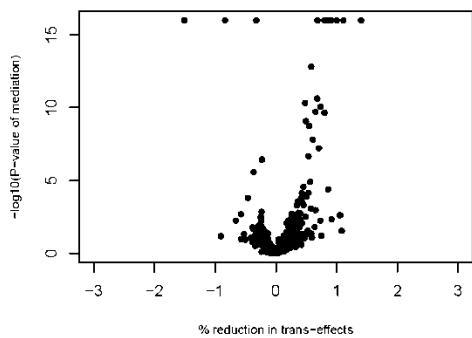
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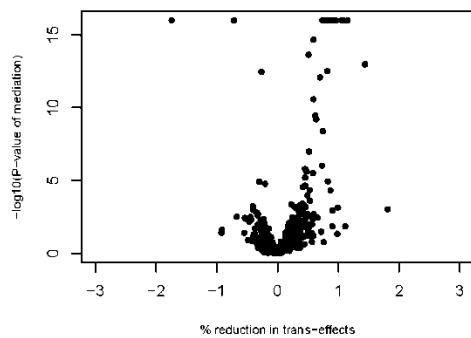
Cells_Transformed_fibroblasts

A. Adjust Known Covariates Only
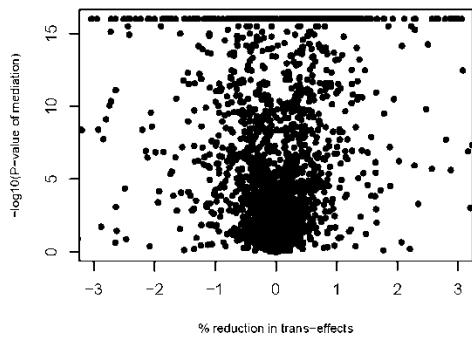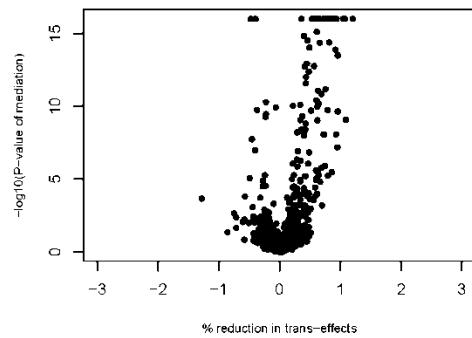
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C. Adjust Known + Adaptively Selected PEER
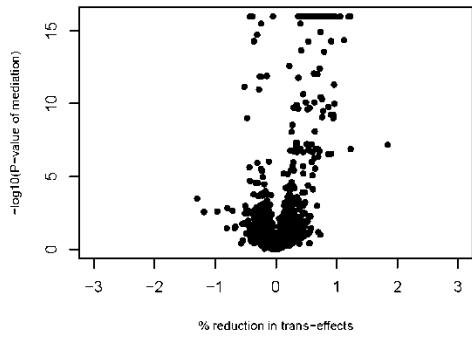
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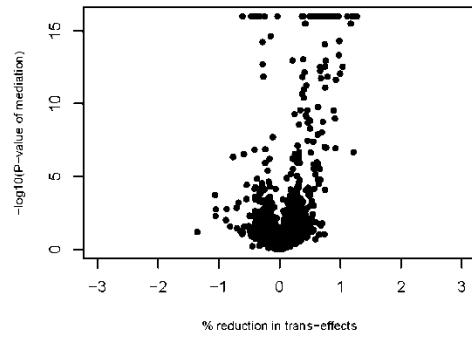
Colon_Sigmoid

A. Adjust Known Covariates Only
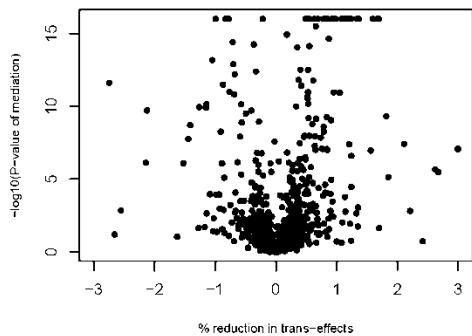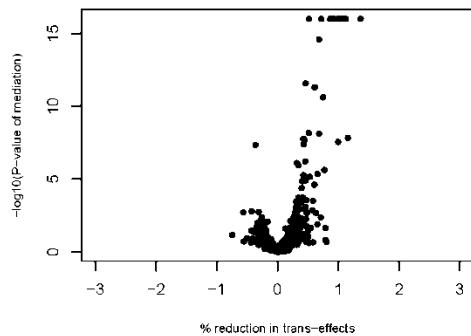
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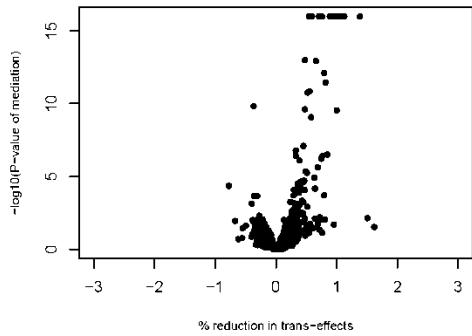
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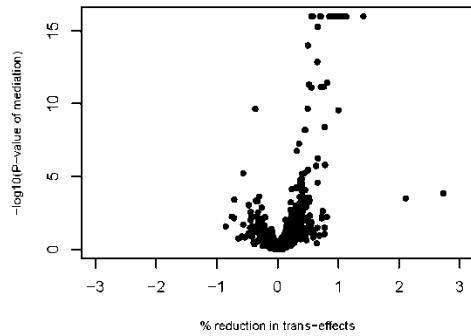
Colon_Transverse

### A. Adjust Known Covariates Only
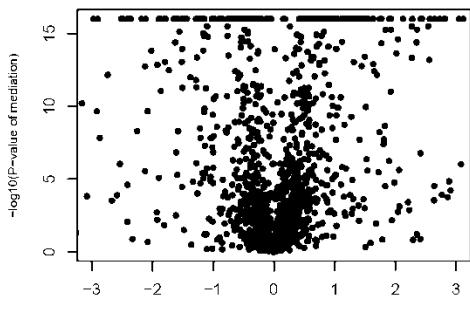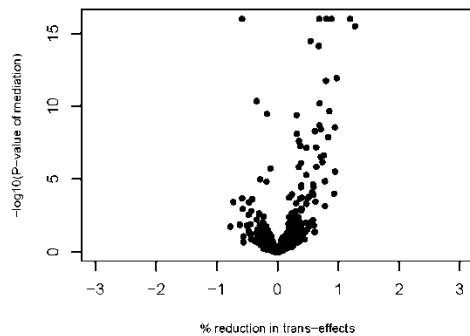
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
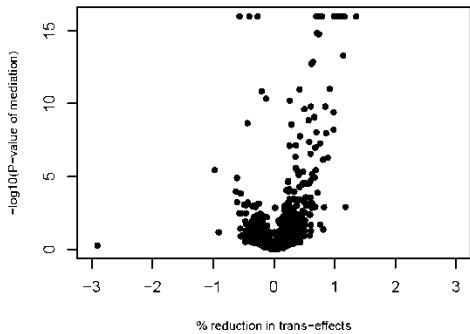
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
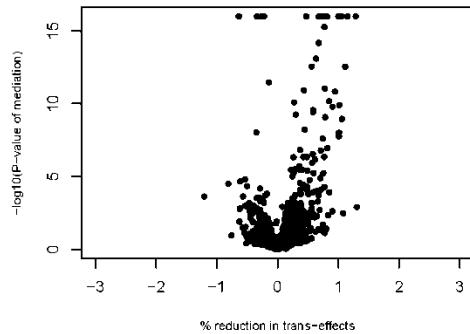
Esophagus_Gastroesophageal_Junction

A. Adjust Known Covariates Only
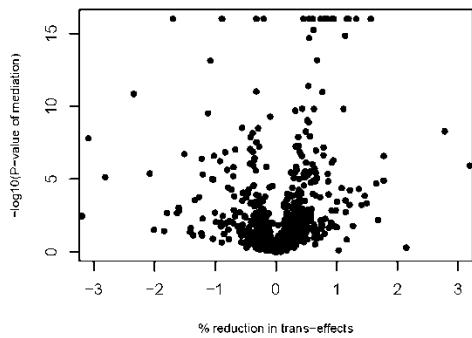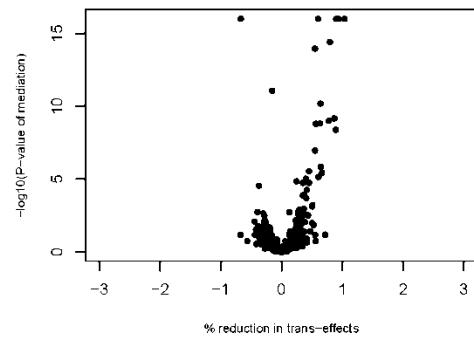
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
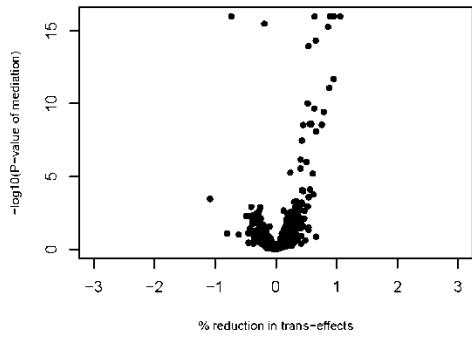
### D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
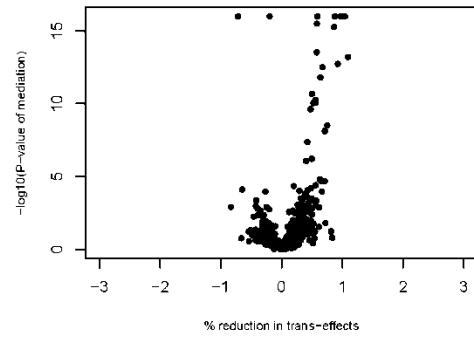
Esophagus_Mucosa

A. Adjust Known Covariates Only
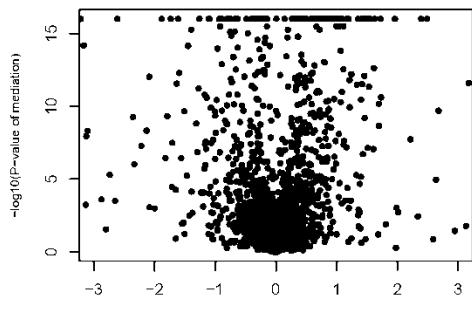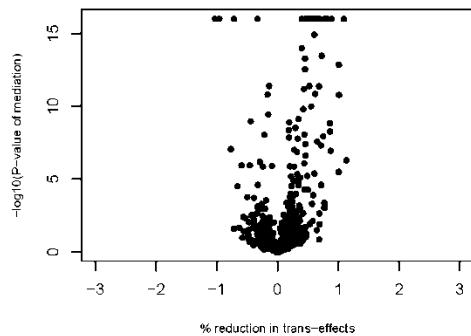
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
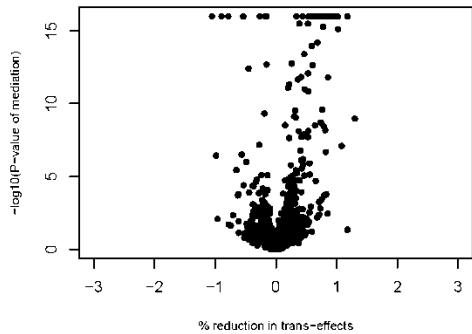
**D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)**
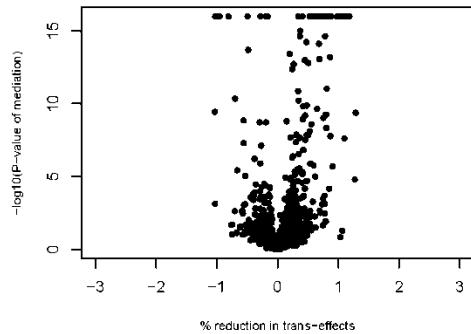
Esophagus_Muscularis

A. Adjust Known Covariates Only
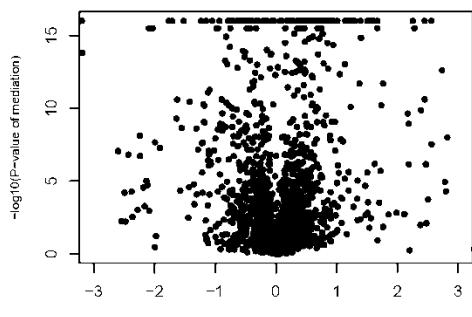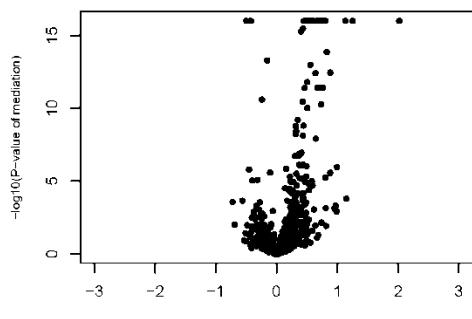
B. Adjust Known + All PEER


C. Adjust Known + Adaptively Selected PEER
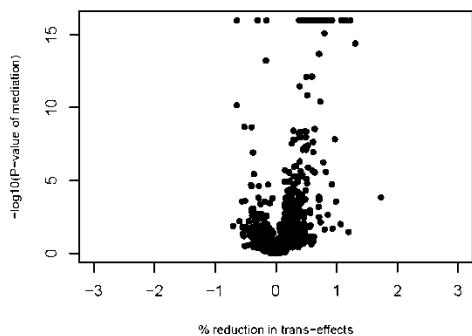
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
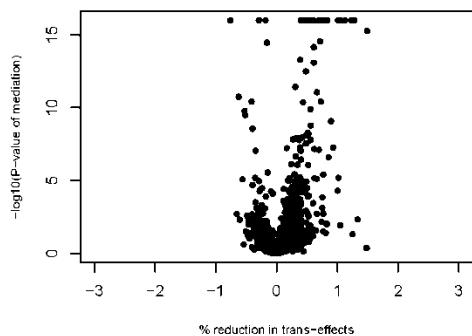
Heart_Atrial_Appendage

A. Adjust Known Covariates Only
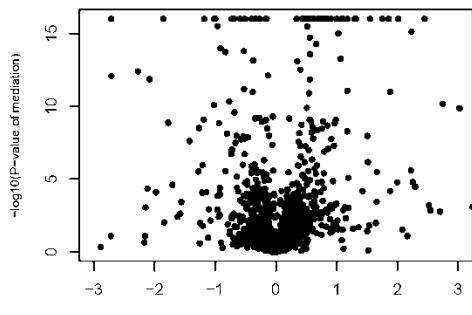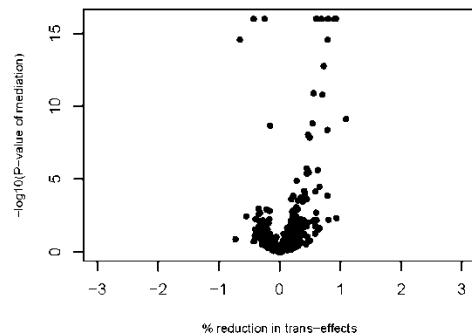
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
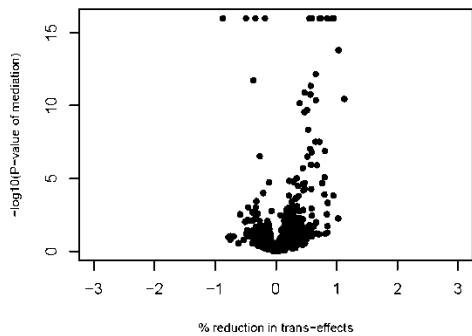
**D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)**
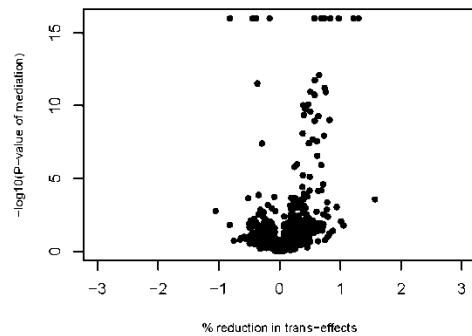
Heart_Left_Ventricle

A. Adjust Known Covariates Only
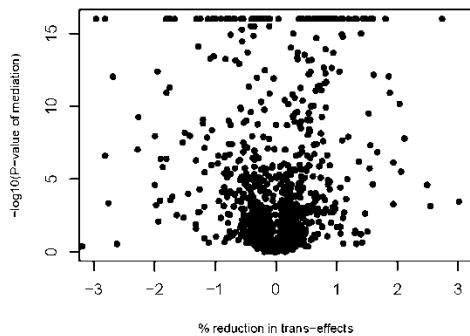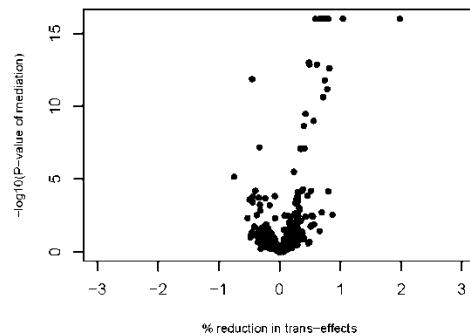
x-axis: % reduction in trans-effects
y-axis: -log10(P-value of mediation)

B. Adjust Known + All PEER

x-axis: % reduction in trans-effects
y-axis: -log10(P-value of mediation)

C. Adjust Known + Adaptively Selected PEER

x-axis: % reduction in trans-effects
y-axis: -log10(P-value of mediation)

D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)

x-axis: % reduction in trans-effects
y-axis: -log10(P-value of mediation)

Liver

A. Adjust Known Covariates Only

B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
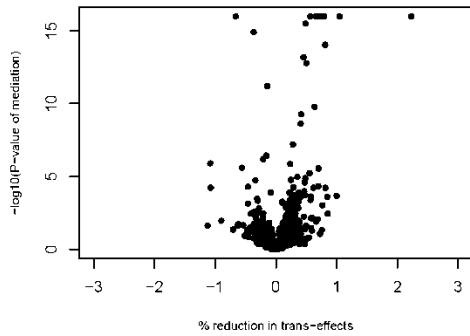
### D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
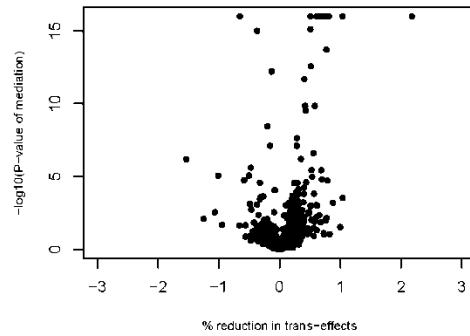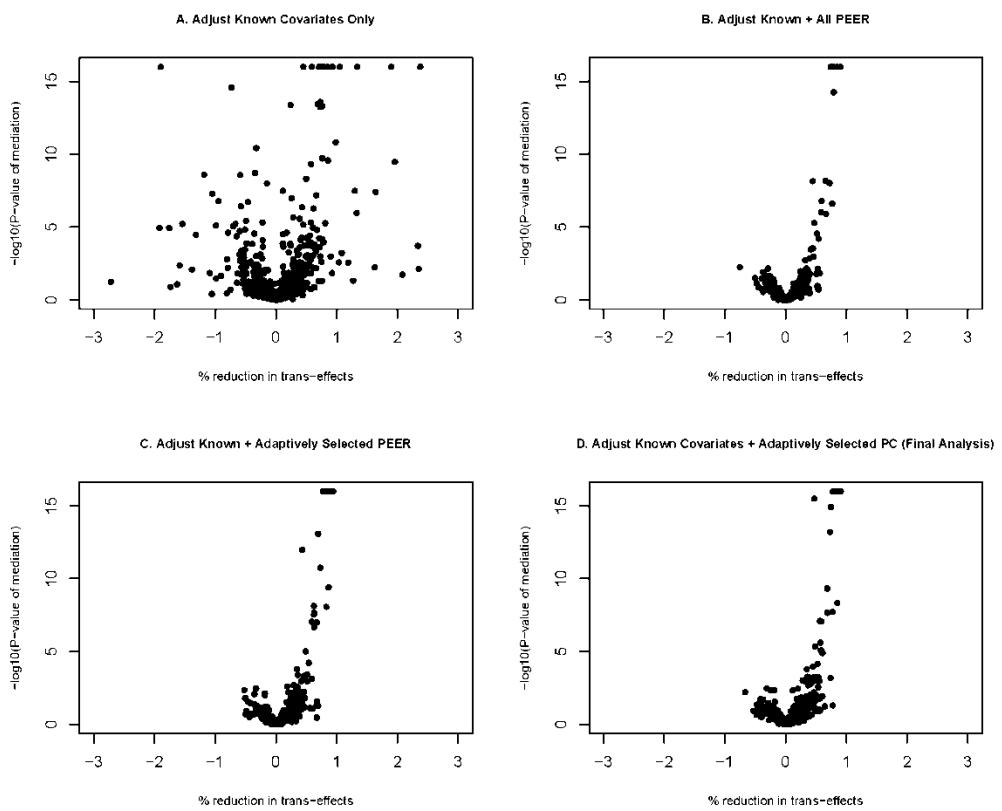
Lung

A. Adjust Known Covariates Only
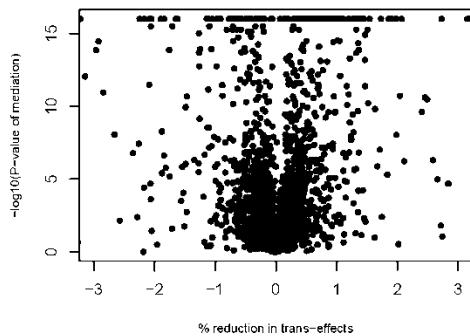
B. Adjust Known + All PEER
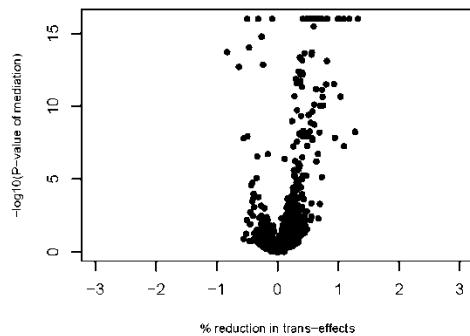
C. Adjust Known + Adaptively Selected PEER
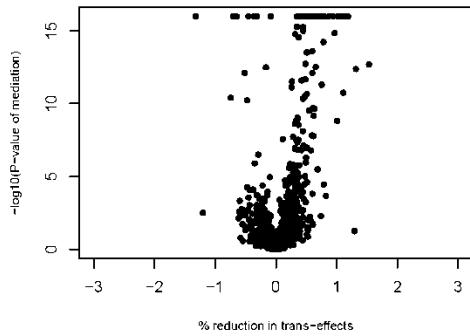
### D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
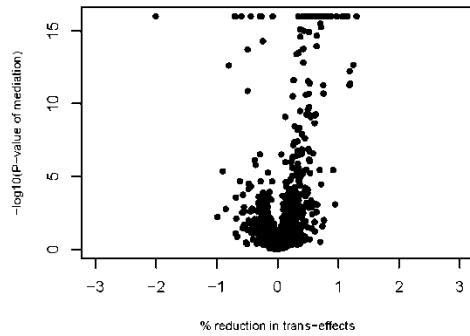
Muscle_Skeletal

A. Adjust Known Covariates Only
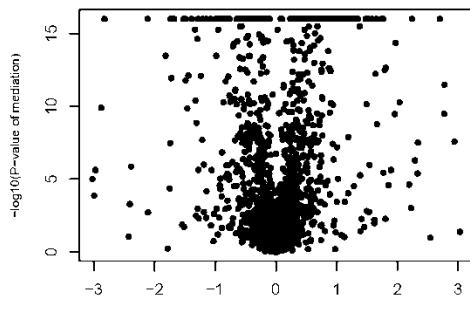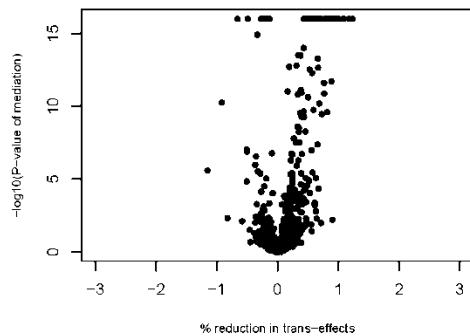
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
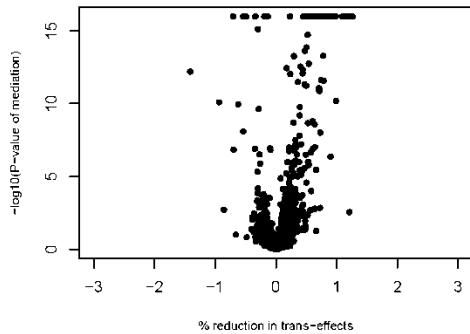
**D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)**
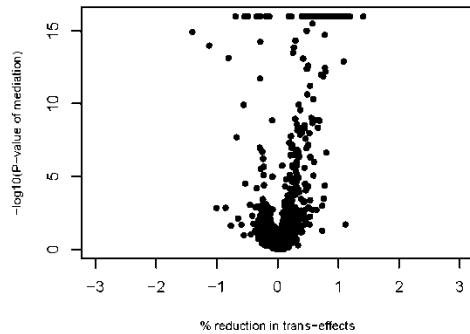
Nerve_Tibial

A. Adjust Known Covariates Only
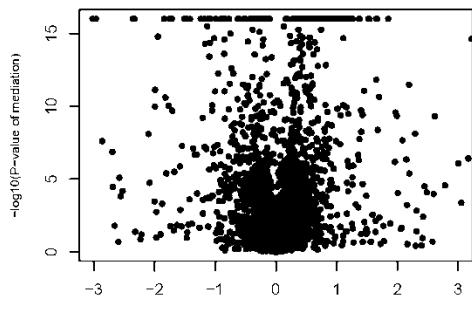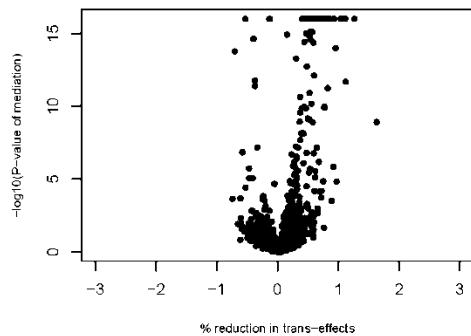
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
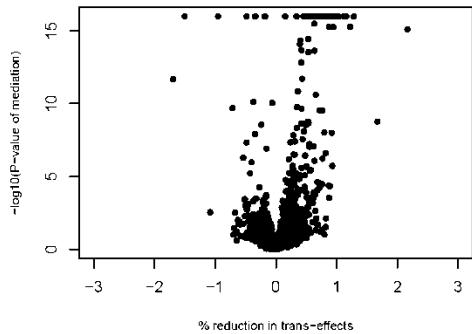
**D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)**
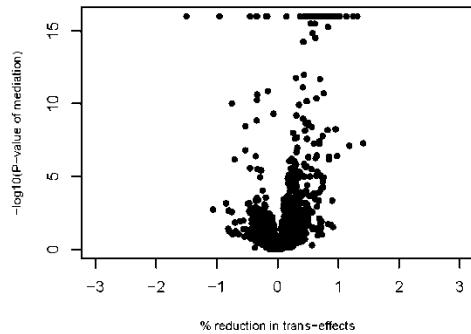
Ovary

A. Adjust Known Covariates Only
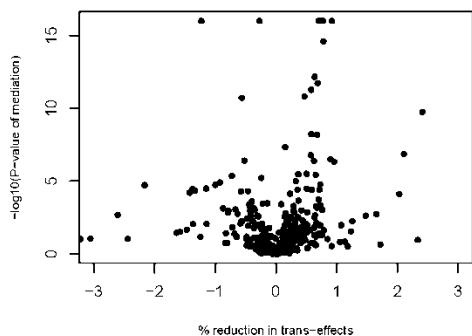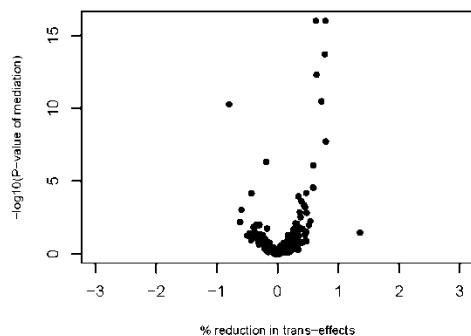
### B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
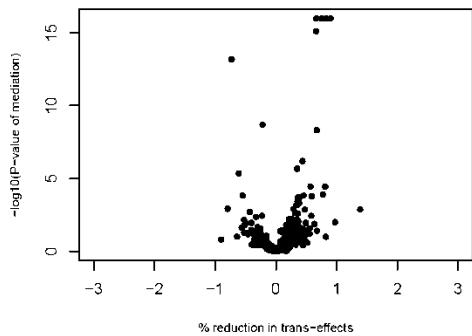
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
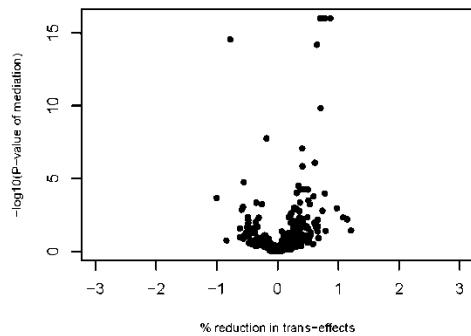
Pancreas

### A. Adjust Known Covariates Only
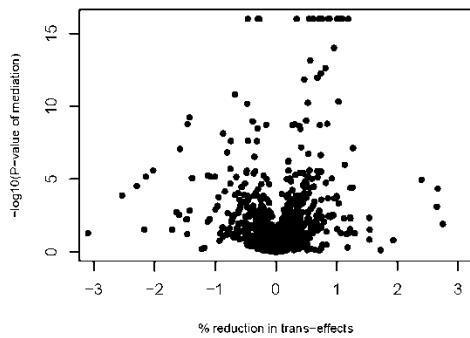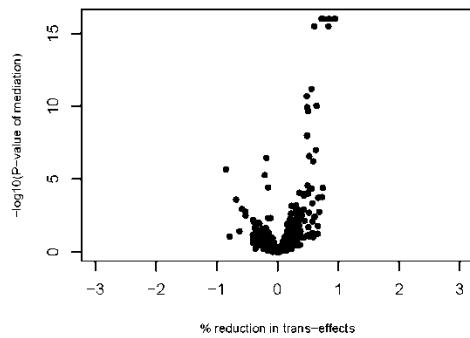
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
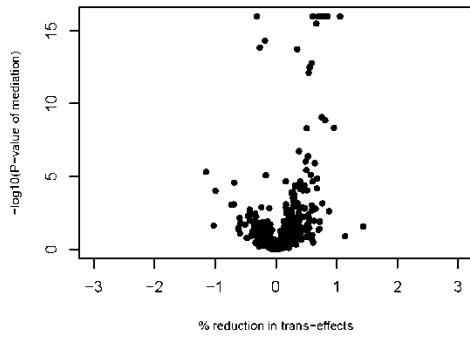
### D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
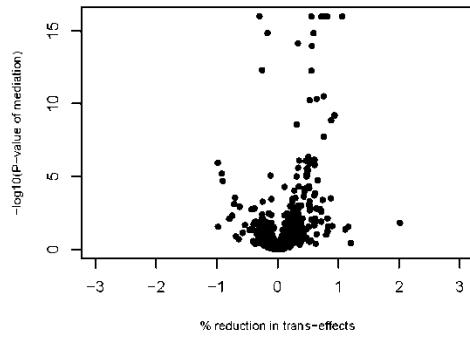
Pituitary

### A. Adjust Known Covariates Only
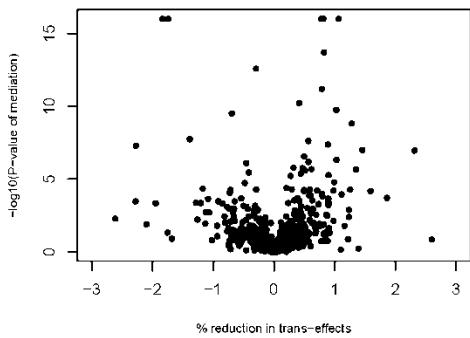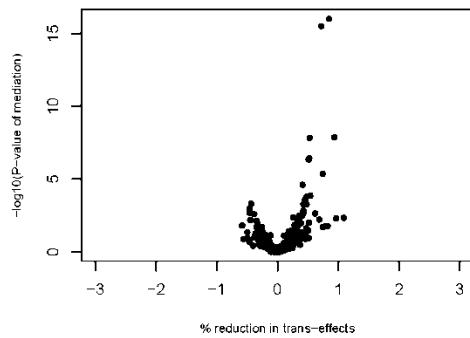
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
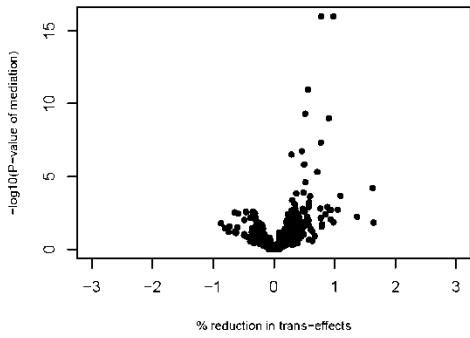
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
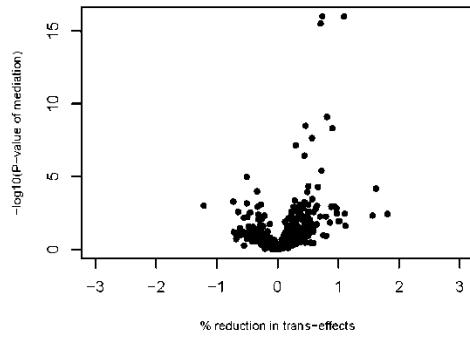
Prostate

### A. Adjust Known Covariates Only
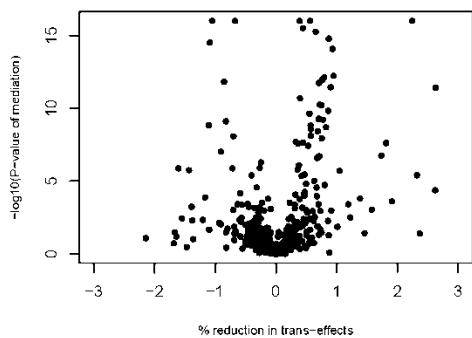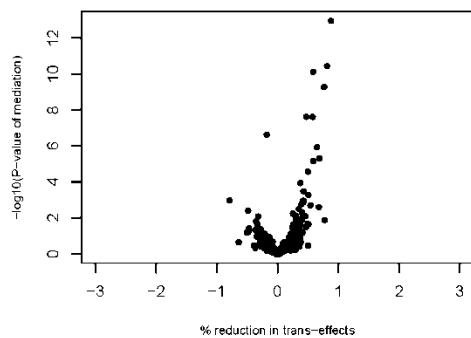
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
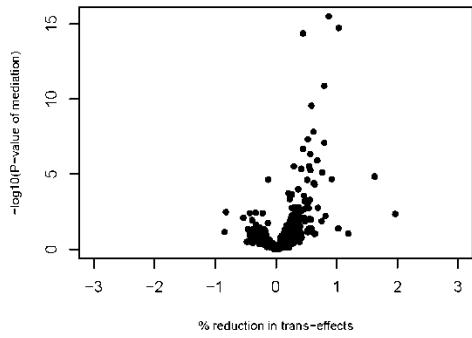
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
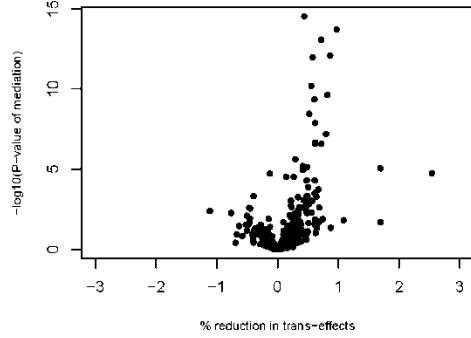
Skin_Not_Sun_Exposed_Suprapubic

A. Adjust Known Covariates Only
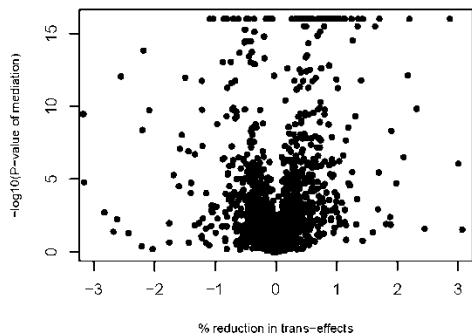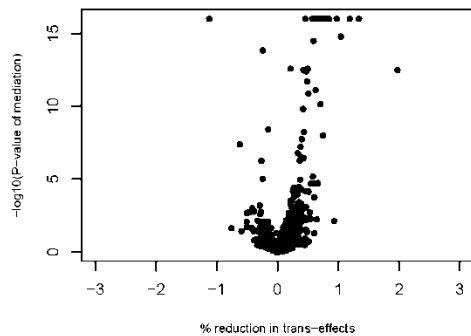
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
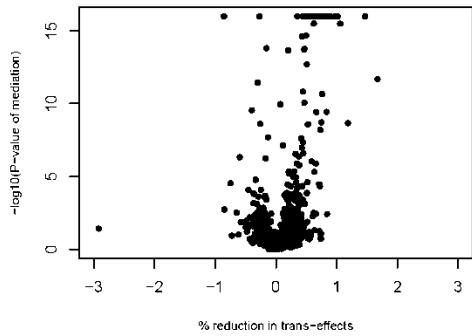
### D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
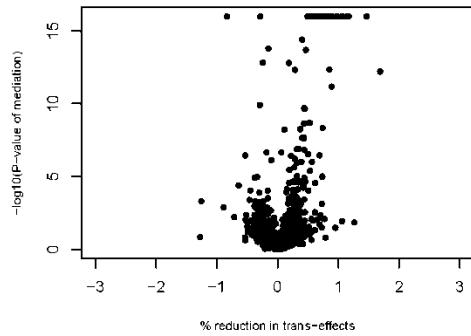
Skin_Sun_Exposed_Lower_leg

A. Adjust Known Covariates Only
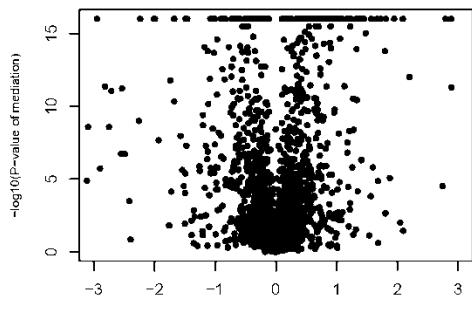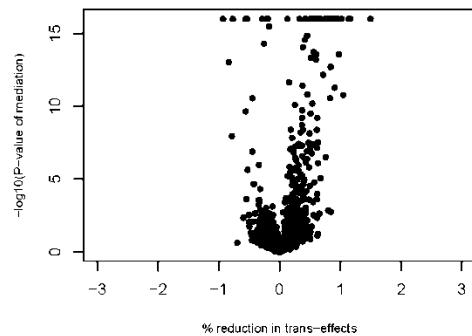
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
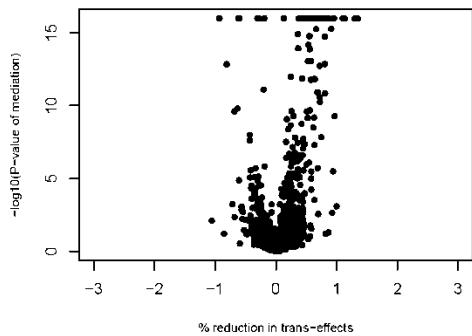
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
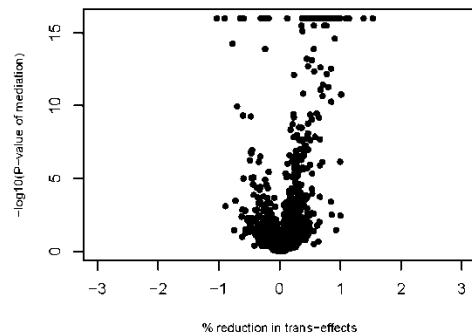
Small_Intestine_Terminal_Ileum

A. Adjust Known Covariates Only
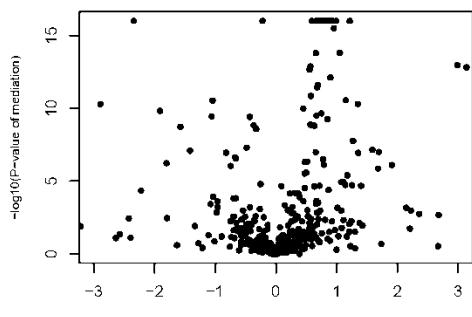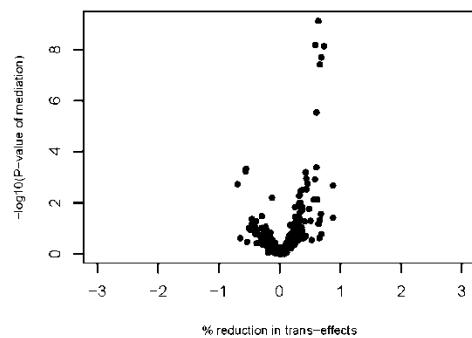
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
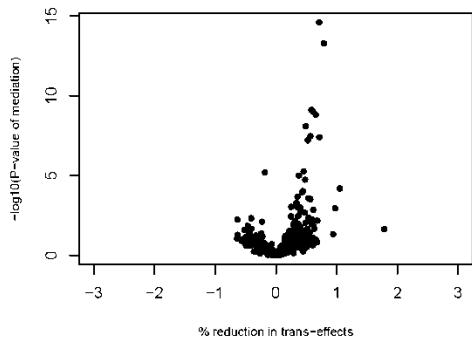
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
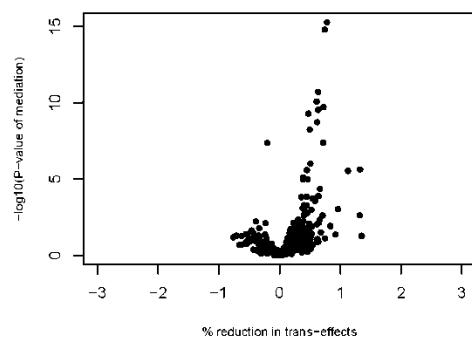
Spleen

A. Adjust Known Covariates Only
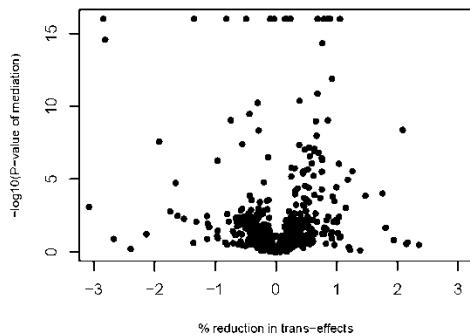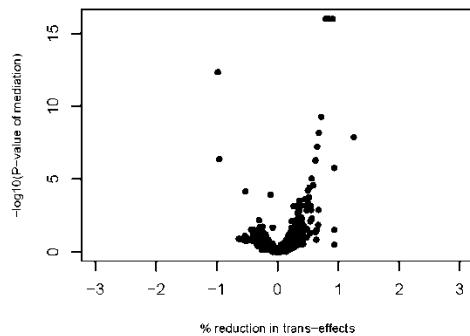
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
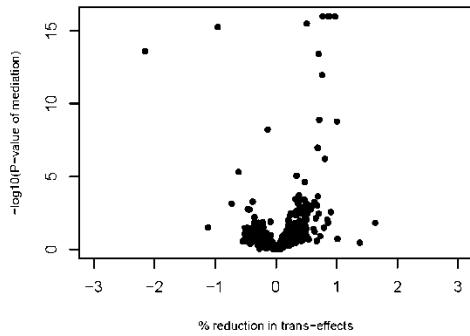
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)

Stomach
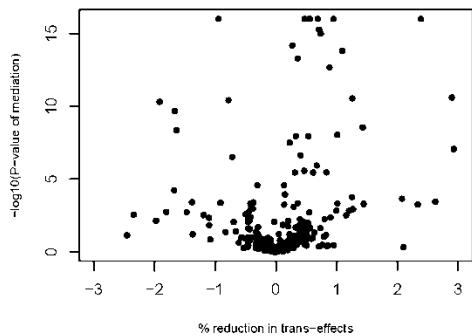
A. Adjust Known Covariates Only

B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER

D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)

Testis

### A. Adjust Known Covariates Only

B. Adjust Known + All PEER



C. Adjust Known + Adaptively Selected PEER

D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)

Thyroid

A. Adjust Known Covariates Only

B. Adjust Known + All PEER


C. Adjust Known + Adaptively Selected PEER

D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)

Uterus

A. Adjust Known Covariates Only

B. Adjust Known + All PEER
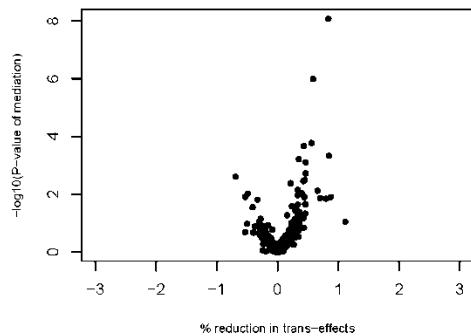
### C. Adjust Known + Adaptively Selected PEER
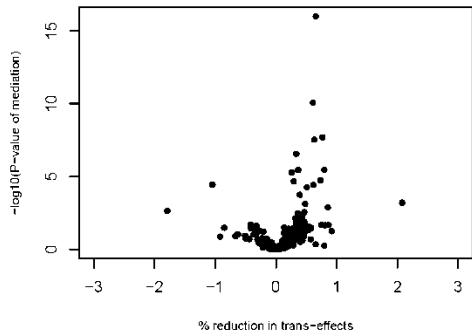
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
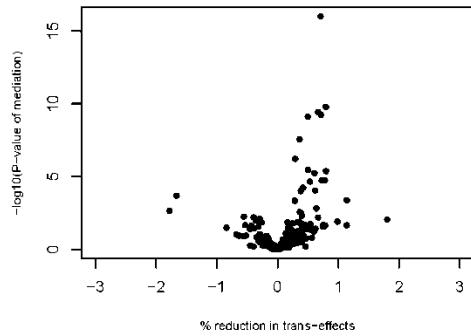
Vagina

### A. Adjust Known Covariates Only
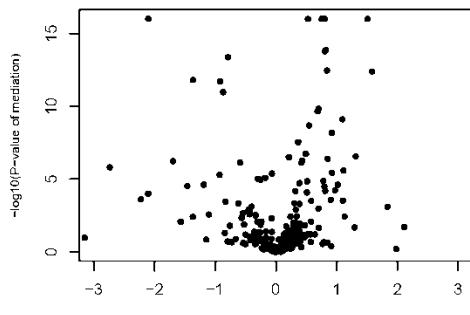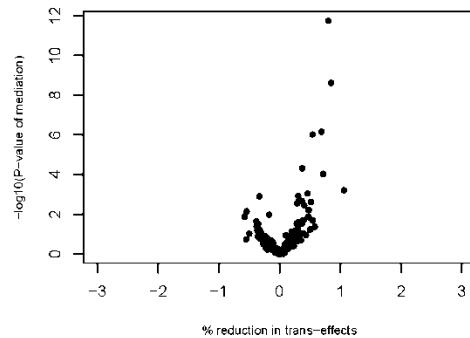
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
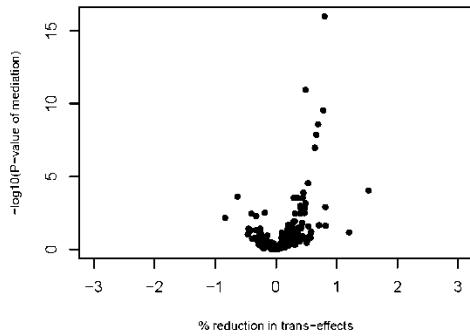
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
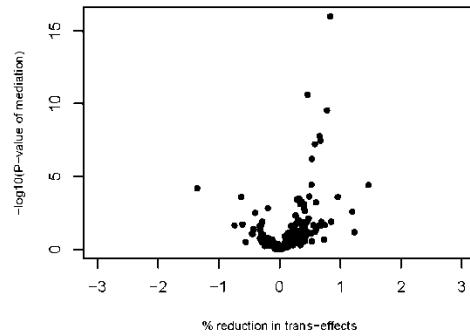
Whole_Blood

A. Adjust Known Covariates Only
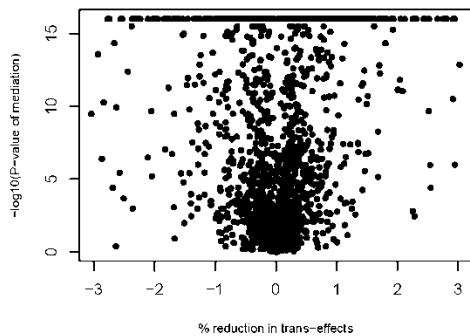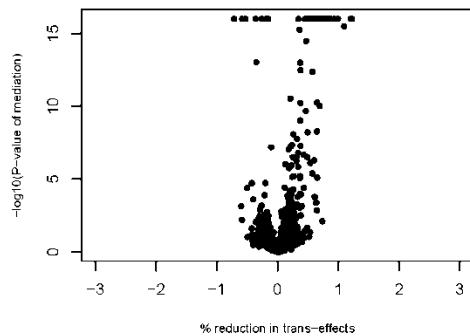
B. Adjust Known + All PEER

C. Adjust Known + Adaptively Selected PEER
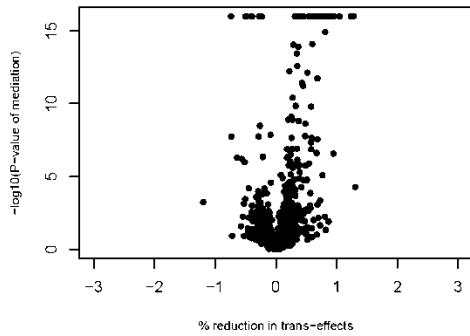
D. Adjust Known Covariates + Adaptively Selected PC (Final Analysis)
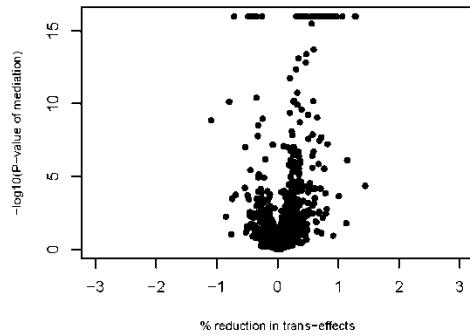
Supplemental Figure S2. Histograms of mappability for cis-genes that appear to mediate a trans-eQTL (mediation P<0.05), stratified by number of trans targets and number of tissues. On the left side, A shows all cis-mediators, B shows those with >2 trans targets, and C shows those >4 trans targets. On the right side, D shows all trans targets of cis-mediators, E contains only the cis-mediators showing evidence of mediation in >2 tissues, and F contains only the cis-mediators showing evidence of mediation in >3 tissues.
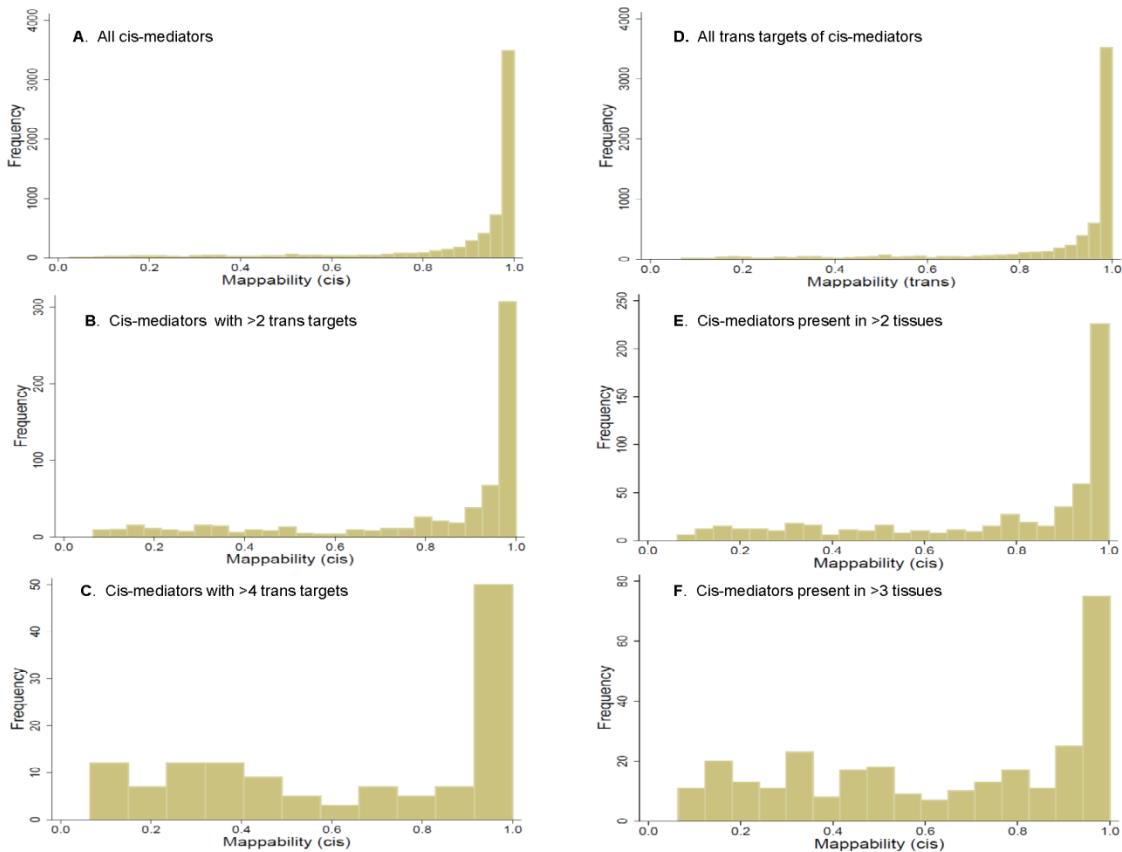
Supplemental Figure S3. Alignment of *IFI44* (query) and *IFI44L* (Sbjct) mRNA sequences shows two regions of similarity. Results obtained from NCBI BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Range 1: 768 to 1521 GenBank Graphics   ▼ Next Match ▲ Previous Match

Score	Expect	Identities	Gaps	Strand
269 bits(298)	5e-70	527/767(69%)	29/767(3%)	Plus/Plus

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Query  659   CCATATGGATCCCTGGTTCAACAAATACGAATTCTGCTGCTGGGTCCAATTGGAGCTGGG  718
             || ||||| |  | ||||| | |||| ||  |||||  || |||||||| ||||   ||||
Sbjct  768   CCCTATGCAGACTTGGTTTCAGAAATTCGTATTCTTTTGGTGGGTCCAGTTGGGTCTGGA  827

Query  719   AAGTCCAGCTTTTTCAACTCAGTGAGGTCTGTTTTCCAAGGGCATGTAACGCATCAGGCT  778
             |||||||| |||||||||||| ||| |||| ||||||| | |||| | |||| || | ||
Sbjct  828   AAGTCCAGTTTTTTCAATTCAGTCAAGTCTATTTTTCATGGCCATGTGACTGGCCAAGCC  887

Query  779   TTGGTGGGCACTAATACAACTGGGATATCTGAGAAGTATAGGACATACTCTATTAGAGAC  838
             | ||||| || |||  ||| | ||| ||||||||| ||| ||| || | ||| || |||
Sbjct  888   GTAGTGGGGTCTGATATCACCAGCATAACCGAGCGGTATAGGATATATTCTGTTAAAGAT  947

Query  839   GGGAAAGATGGCAAATACCTGCCGTTTATTCTGTGTGACTCACTGGGGCTGAGTGAGAAA  898
             || ||| |||| |||| ||||| ||||| ||||||||| |||| |||||| | ||| | |
Sbjct  948   GGAAAAAATGGAAAATCTCTGCCATTTATGTTGTGTGACACTATGGGGCTAGATGGGGCA  1007

Query  899   GAAGGCG---GCCTGTGCAGGGATGACATATTCTATATCTTGAACGGTAACATTCGTGAT  955
             |||||| |  |  |||||||| |||||||  | | ||||| ||||  ||  || ||  ||
Sbjct  1008  GAAGGAGCAGGACTGTGCATGGATGACATTCCCCACATCTTAAAAGGTTGTATGCCAGAC  1067

Query  956   AGATACCAGTTTAAT-CCCATGGAATCAATCAAATTAAATC--ATCATGACTACATTGAT  1012
             ||||| |||||||||  |  | |||  | |||||| | |||  |  ||  || ||||| ||
Sbjct  1068  AGATATCAGTTTAATTCCCGT------AAACCAATTACACCTGAGCATT-CTACTTTTAT  1120

Query  1013  ----TCCCCATCGCTGAAGGACAGAATTCATTGTGTGGCATTTGTATTTGATGCCAGCTC  1068
                 || |||||  | |||||||| |||| || |||||||  | |  | |||| ||  |||
Sbjct  1121  CACCTCTCCATCTCTGAAGGACAGGATTCACTGTGTGGCTTATGTCTTAGACATCAACTC  1180

Query  1069  TATTCAATACTTCTCCTCTCAGATGATAGTAAAGATCAAAAGAATTCGAAGGGAGTTGGT  1128
             ||||  |  |  |  ||| || |||| |||| |||  ||| || |  |  || |  || |
Sbjct  1181  TATTGACAATCTCTACTCTAAAATGTTGGCAAAAGTGAAGCAAGTTCACAAAGAAGTATT  1240

Query  1129  AAACGCTGGTGTGGTACATGTGGCTTTGCTCACTCATGTGGATAGCATGGA-TTTGATTA  1187
             |||| ||||  |  | |||||| |||| ||| |||| ||| |  ||| |  |  | || ||
Sbjct  1241  AAACTGTGGTATAGCATATGTGGCCTTGCTTACTAAAGTGGAT-GATTGCAGTGAGGTTC  1299

Query  1188  CAAAAGGTGACCTTATAGAAATAGAG-AGATGTGAGCCTGTGAGGTCCAAGCTAG---AG  1243
              |||   || || ||  ||  |  ||  |  ||||  ||| | ||  ||  |  |    |
Sbjct  1300  TTCAAGACAACTTTTTAAACAT-GAGTAGATCTATGACT----TCTCAAAGCCGGGTCAT  1354

Query  1244  GAA-GTCCAAAGAAAACTTGGATTTGCTCTTTCTGACATCTCGGTGGTTAGCAATTATTC  1302
             ||| ||| |||| | || | || | | ||  | | | ||  || | |||| |||||||| |
Sbjct  1355  GAATGTCCATAAAATGCTAGGCATTCCTATTTCCAATATTTTGATGGTTGGAAATTATGC  1414

Query  1303  CTCTGAGTGGGAGCTGGACCCTGTAAAGGATGTTCTAATTCTTTCTGCTCTGAGACGAAT  1362
             || || | | ||| |||||| |  || |||| | ||| || | | | |   |||| | ||
Sbjct  1415  TTCAGATTTGGAACTGGACCCCATGAAGGATATTCTCATCCTCTCTGCACTGAGGCAGAT  1474

Query  1363  GCTATGGGCTGCAGATGACTTCTTAGAGGATTTGCCTTTTGAGCAAA  1409
             || |  ||||||||||||  |  ||| | |||||||| || || |||
Sbjct  1475  GCTGCGGGCTGCAGATGATTTTTTTAGAAGATTTGCCTCTTGAGGAAA  1521
```

Range 2: 186 to 388 GenBank Graphics   ▼ Next Match ▲ Previous Match ▲ First Match

Score	Expect	Identities	Gaps	Strand
59.0 bits(64)	2e-06	137/205(67%)	4/205(1%)	Plus/Plus

```
Query  110   AACAGATCAAGAAGTATGGCAGTGACAACTCGTTTGACATGGTTGCACGAAAAGATCCTG  169
             |||||||  ||||  |||| ||||  ||||| | || ||||||| | ||||||  |  |||
Sbjct  186   AACAGATATAGAACAATGGAAGTGACAACAAGATTGACATGGAATGATGAAAATCATCTG  245

Query  170   CAAAATCATTTTGGAGGGAAGCGGCTT--AGCCTTCTCTATAAGGGTAGTGTCCATGGAT  227
             | ||| | |  |||    ||  ||  |  | ||  || ||||||| |||||| ||||||||
Sbjct  246   CGCAAGCTGCTTGGAA--ATGTTTCTTTGAGTCTTCTCTATAAGTCTAGTGTTCATGGAG  303

Query  228   TCCGTAATGGAGTTTTGCTTGACAGATGTTGTAATCAAGGGCCTACTCTAACAGTGATTT  287
             |  | || | | |  | |||||| || | |||  ||| |  || |||| |  || || ||
Sbjct  304   GTAGCATTGAAGATATGGTTGAAAGATGCAGCCGTCAGGGATGTACTATAACAATGGCTT  363

Query  288   ATAGTGAAGATCATATTATTGGAGC  312
             | | | |||| || || | ||||||
Sbjct  364   ACATTGATTACAATATGATTGTAGC  388
```