

Analysis of FHS Offspring CVD Incidence EWAS Results

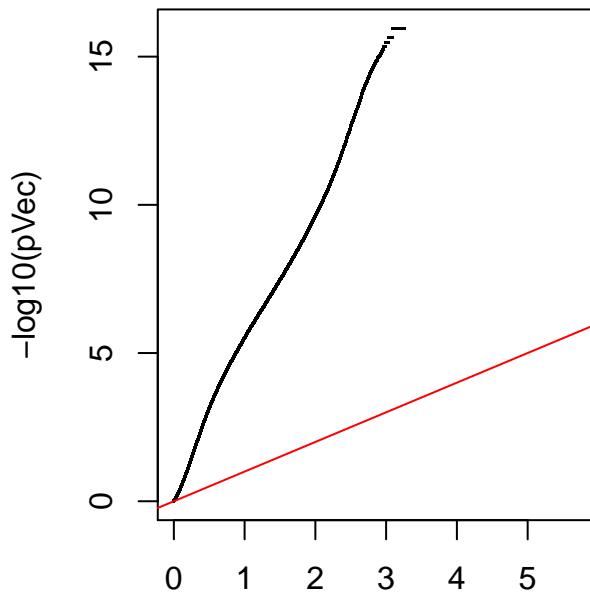
Kenny Westerman

These methylation data come from Framingham Offspring Study, Exam 8. Results are from Cox proportional hazards regression of incidence of cardiovascular events on baseline methylation levels.

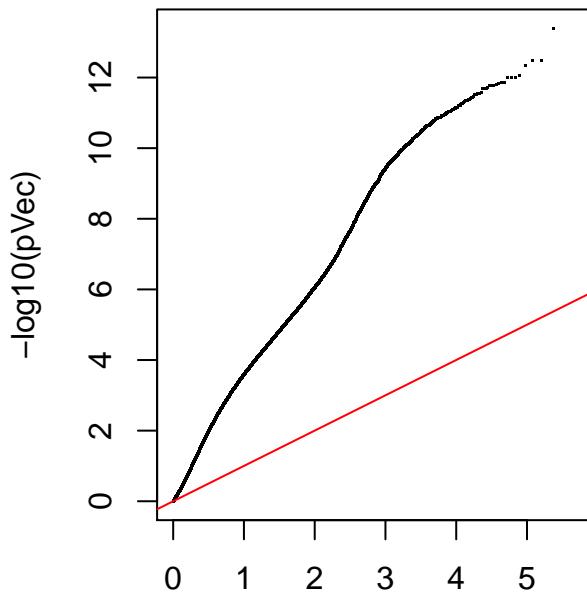
QQ plots

Increasing adjustment for potential confounders from left to right.

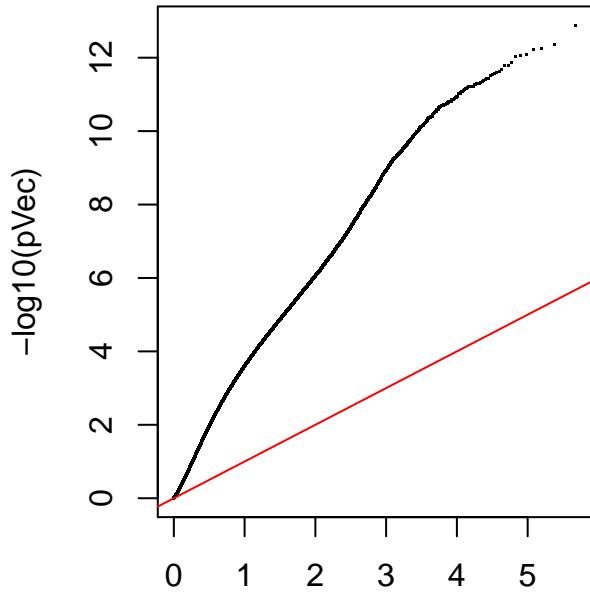
model_unadj



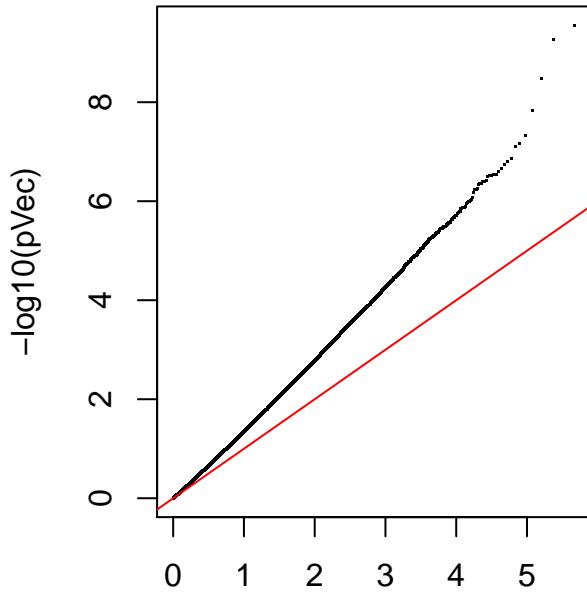
model_basic

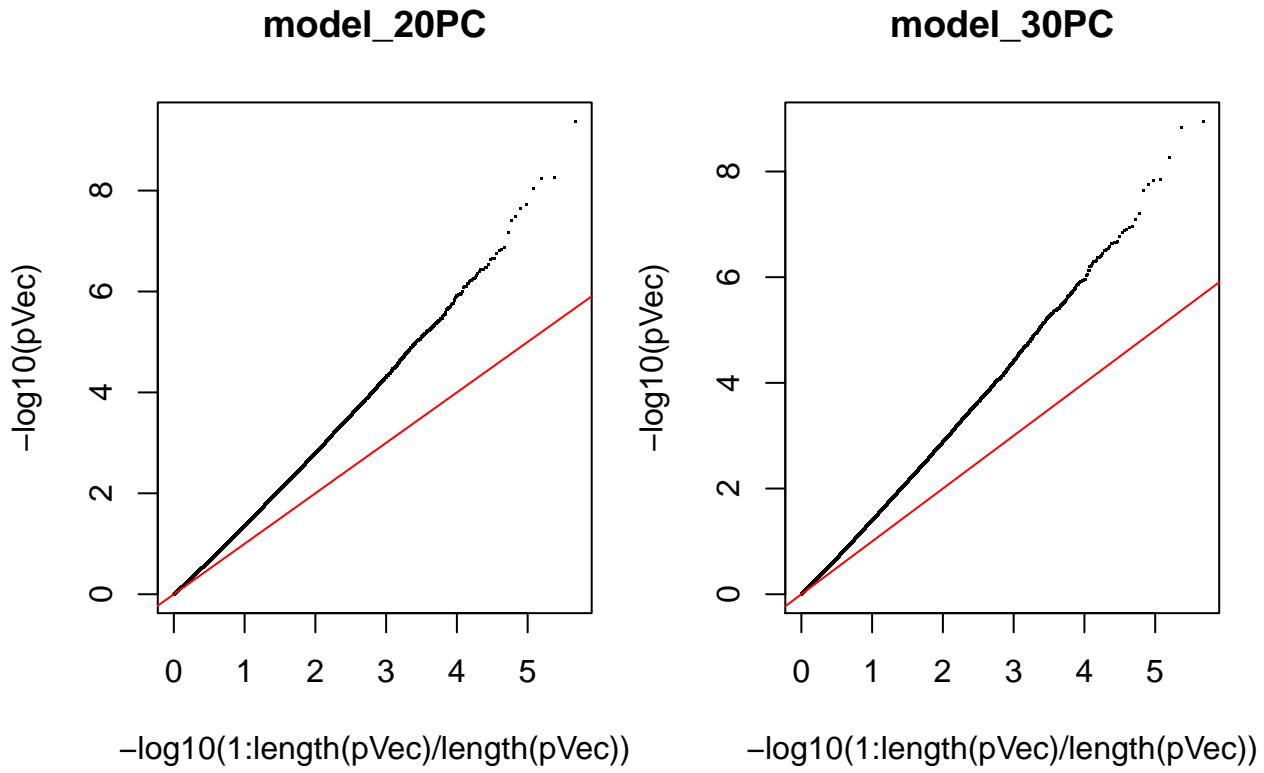


$-\log_{10}(1:\text{length}(p\text{Vec})/\text{length}(p\text{Vec}))$
model_wbc



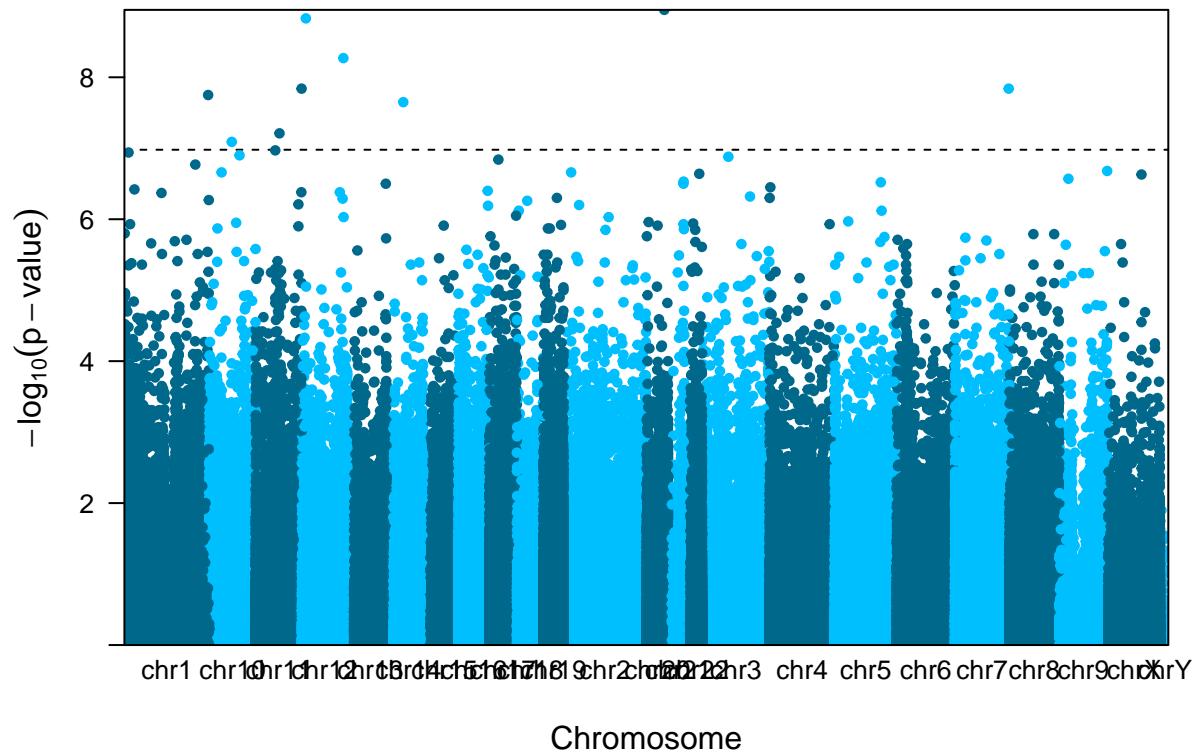
$-\log_{10}(1:\text{length}(p\text{Vec})/\text{length}(p\text{Vec}))$
model_10PC





Manhattan plot

Using the fully adjusted model.



```
## [1] "262 regressions failed."
```

Genomic control

Estimate genomic inflation factor lambda based on set of p-values.

```
## [1] "lambda = 1.56609297134776"
```

Gene set enrichment analysis

Currently based only on single-CpG annotations rather than differentially methylated regions. Gene sets are taken from the Broad Institute's MSigDB v6 canonical pathways.

```
## [1] "480 relevant genes found."
```

Category	p.value
KEGG_OLFACTOORY_TRANSDUCTION	0.0000011
REACTOME_OLFACTOORY_SIGNALING_PATHWAY	0.0000019
REACTOME_GPCR_DOWNSTREAM_SIGNALING	0.0000034
REACTOME_GPCR_LIGAND_BINDING	0.0000832
REACTOME_SIGNALING_BY_GPCR	0.0001412
REACTOME_METABOLISM_OF_PROTEINS	0.0002073
REACTOME_METABOLISM_OF_RNA	0.0004004
REACTOME_INFLUENZA_LIFE_CYCLE	0.0005656
REACTOME_METABOLISM_OF_AMINO_ACIDS_AND_DERIVATIVES	0.0006462
REACTOME_G_ALPHA_I_SIGNALLING_EVENTS	0.0008065
REACTOME_PEPTIDE_LIGAND_BINDING_RECEPTEORS	0.0010987
REACTOME_TRANSLATION	0.0014747
REACTOME_SR_P_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	0.0016320
REACTOME_CLASS_I_MHC_MEDIATED_ANTIGEN_PROCESSING_PRESENTATION	0.0020350
REACTOME_METABOLISM_OF_MRNA	0.0021843
REACTOME_ANTIGEN_PROCESSING_UBIQUITINATION_PROTEASOME_DEGRADATION	0.0022114
REACTOME_INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION	0.0025265
REACTOME_RNA_POL_I_RNA_POL_III_AND_MTCHONDRIAL_TRANSCRIPTION	0.0026491
REACTOME_CHROMOSOME_MAINTENANCE	0.0026491
REACTOME_IMMUNE_SYSTEM	0.0026811
REACTOME_CLASS_A1_RHODOPSIN_LIKE_RECEPTEORS	0.0033430
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM	0.0035975
REACTOME_INTERFERON_SIGNALING	0.0038994
REACTOME_CELL_CYCLE	0.0041674
REACTOME_G1_S_TRANSITION	0.0043141

Initial MRS calculation and evaluation

45 CpG sites were significant at FDR < 0.01. Multiple regression on methylation M-values at these sites gives coefficient beta values that were then used as weights to construct the MRS. Three regressions were then performed: Framingham risk score alone, methylation risk score alone, and the two together. Note: take these results with a huge grain of salt, since the evaluation is being done in the same dataset as was used to develop the MRS.

```
## [1] "Framingham risk score only (plus covariates)"  
##      coef exp(coef)   se(coef)      z Pr(>|z|)  
## frs 0.3418095 1.407492 0.1240123 2.756253 0.005846767  
## [1] "Methylation risk score only (plus covariates)"
```

```
##           coef  exp(coef)    se(coef)          z  Pr(>|z|)
## mrs  0.8256974  2.283473  0.03806069 21.69423      0
## [1] "FRS and MRS together"
##           coef  exp(coef)    se(coef)          z  Pr(>|z|)
## mrs  0.81891064  2.268028  0.03817415 21.4519662 0.0000000
## frs  0.07624225  1.079224  0.12639204  0.6032204 0.5463621
```