MR Data Challenge 2024 results

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Analysis methods: MR IVW, Egger, Weighted median, Weighted mode, and Radial-MR.
Results: Tables and Figures are listed below.
Software: R packages TwoSampleMR, MendelianRandomization, and RadialMR

Part I. AUD and MDD from 196 genetic variants in African ancestry.

```
load("AUD_MDD_AFR_TwoSampleMR.RData")
dat1 <- dat[dat$pval.exposure < 5e-8, ]   ### GWAS significant variants, n=2


### run MR IVW and get first-stage F statistic

library(MendelianRandomization)

mr_ivw(mr_input(bx = dat$beta.exposure, bxse = dat$se.exposure, by =
dat$beta.outcome, byse = dat$se.outcome))

###  results
inverse-variance weighted method
(variants uncorrelated, random-effect model)

Number of Variants : 196

------------------------------------------------------------------
 Method Estimate Std Error 95% CI       p-value
    IVW    0.259     0.038 0.186  0.333   0.000
------------------------------------------------------------------
Residual standard error =  1.051
Heterogeneity test statistic (Cochrans' '  Q) = 215.5464 on 195 degrees of freedom,
(p-value = 0.1493). I^2 = 9.5%.
F statistic = 16.2.
```

F statistic > 10, indicating strong instruments.

Table 1. Causal relationship between AUD and MDD by various MR methods.

Exposure	Outcome	Method	nsnp	b	se	pval
AUD	MDD	Maximum likelihood	195	0.27682481	0.04289403	0.0000000001091586377
AUD	MDD	MR Egger	195	0.15781230	0.05994815	0.0091625125242689349
AUD	MDD	MR Egger (bootstrap)s	195	0.09406661	0.05585027	0.0529999999999999985
AUD	MDD	Simple median	195	0.44650997	0.07560212	0.0000000035040614715
AUD	MDD	Weighted median	195	0.10363145	0.06706749	0.1223023549583271141
AUD	MDD	Penalised weighted median	195	0.10316874	0.06397250	0.1068087156232399443
AUD	MDD	Inverse variance weighted (fixed effects)	195	0.26042419	0.03587902	0.0000000000003917016
AUD	MDD	Inverse variance weighted (multiplicative random effects)	195	0.26042419	0.03780122	0.0000000000056065038
AUD	MDD	Simple mode	195	0.46476918	2.01072644	0.8174458269328955806
AUD	MDD	Weighted mode	195	0.08182490	2.08564549	0.9687454355889602020
AUD	MDD	WeigsOME)	195	0.08182490	0.11230089	0.4671115118171373926
AUD	MDD	Simple mode (NOME)	195	0.46476918	0.17006722	0.0068590087229004910

In the fixed effects IVW analysis, higher genetically predicted AUD are associated with increased risk of MDD in African ancestry. However, the majority of pleiotropy robust methods are non-significant, suggesting that the causal effects may be biased.

Table 2. Pleiotropy by MR Egger intercept

MR Egger intercept	se	pval
0.005	0.002	0.034

There is significant horizontal pleiotropy.

Table 3. Heterogeneity by Cochran's Q Test.

method	Q	Q-df	Q_pval
MR IVW	210.12	193	0.189
MR Egger	215.34	194	0.140

There is no significant heterogeneity.

Table 4. Causal relationship between AUD and MDD by Radial-MR.

	b	se	statistic	p
IVW				
Effect (Mod.2nd)	0.27	0.04	7.03	2.1×10^{-12}
Iterative	0.27	0.04	7.03	1.9×10^{-12}
Exact (FE)	0.31	0.04	8.27	1.3×10^{-16}
Exact (RE)	0.31	0.06	5.13	7.1×10^{-7}
Q-Statistic	NA	NA	209.53	0.21
Egger				
(Intercept)	0.45	0.12	3.92	1.2×10^{-4}
Wj	0.85	0.06	1.46	0.15
Q-Statistic	NA	NA	198.85	0.39

 # No significant outliers.

 # As with our core MR methods, we observed that the Radial-MR causal estimates indicated that AUD is causaly associated with MDD, however, there is significant horizontal pleiotropy.

Figure 1. Scatter plot illustrating the relationship between SNP effects on AUD and their effects on the outcome.

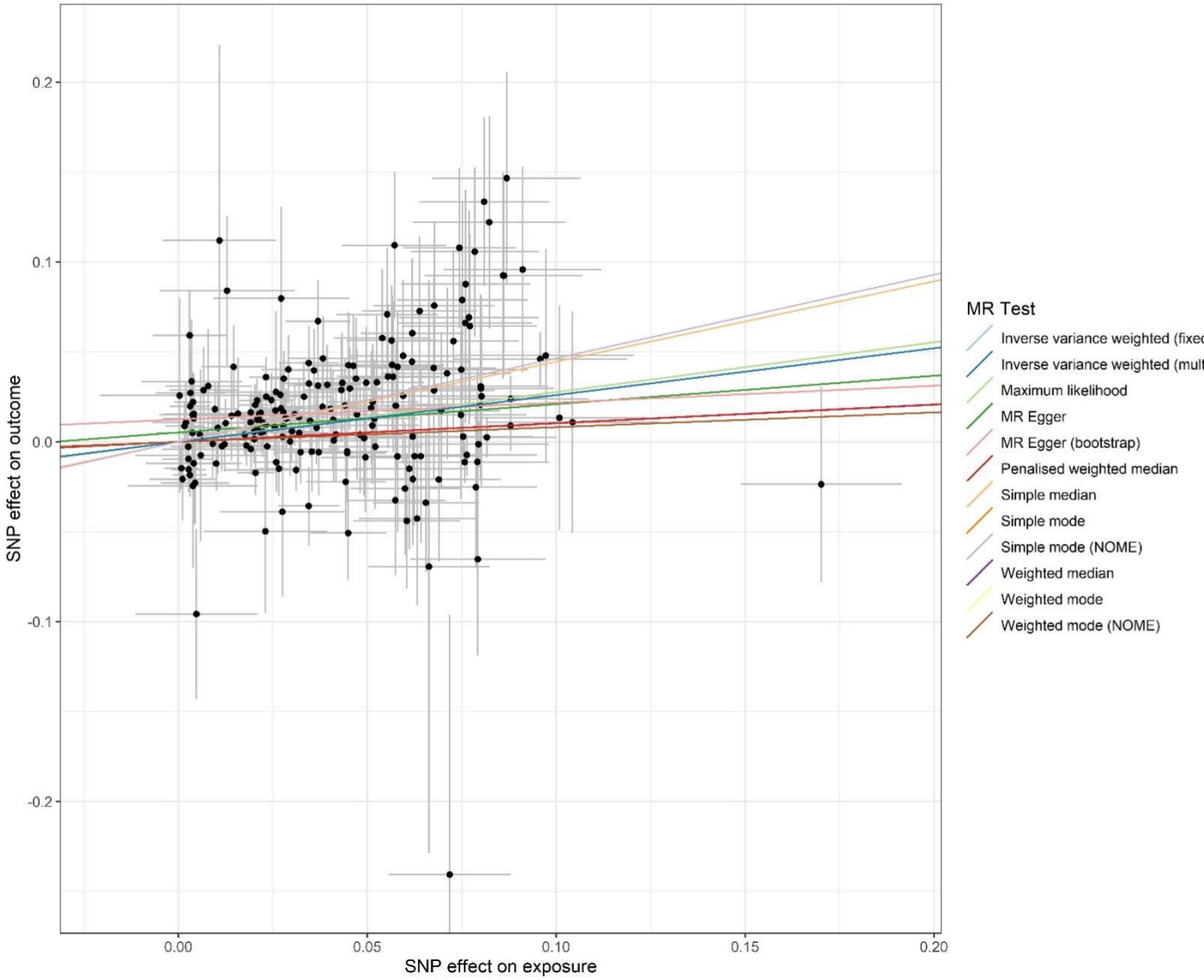


Figure 2. Forest plots presenting the Wald ratio for individual SNPs and their combined effects.

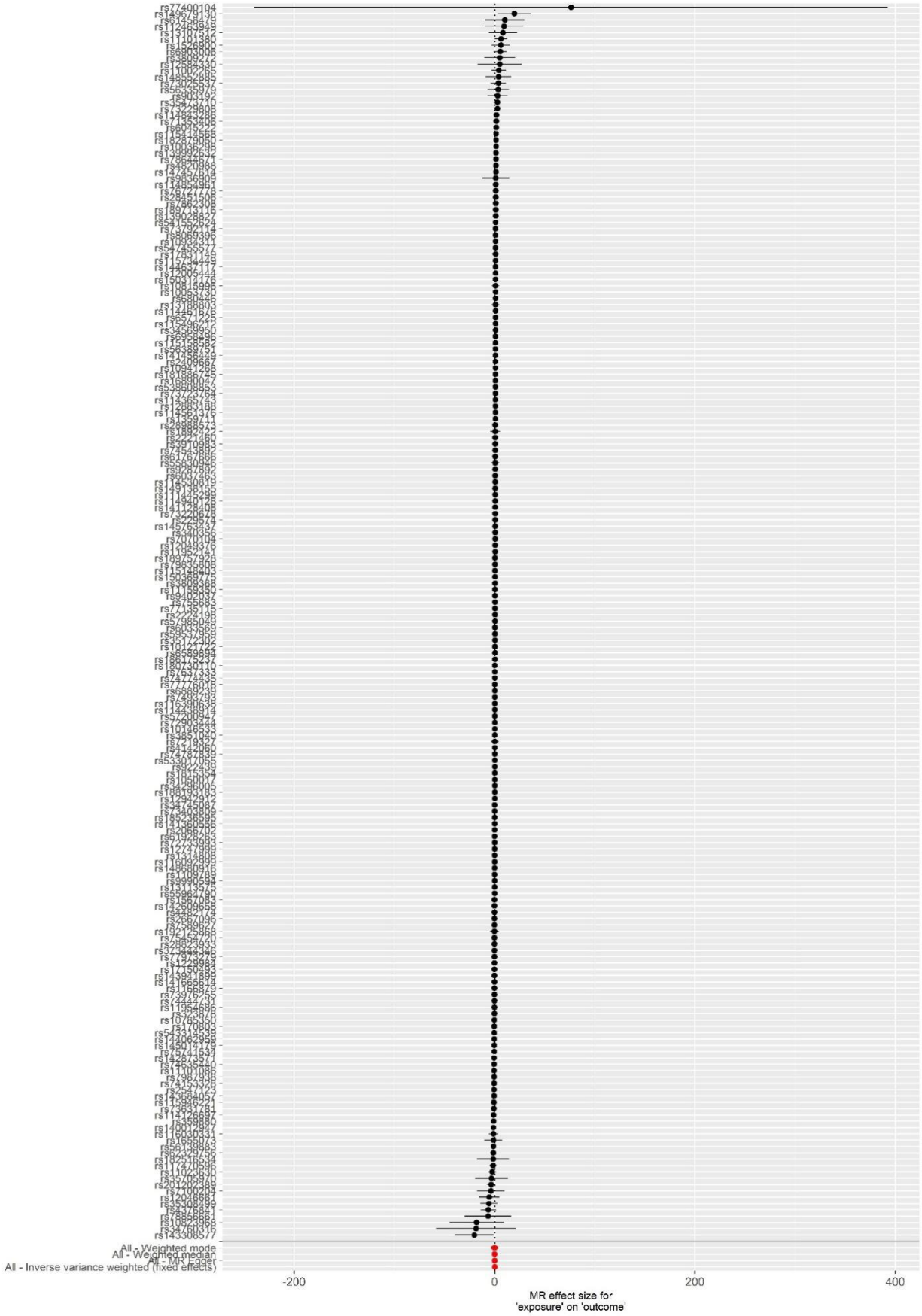


Figure 3. Funnel plots inspecting for horizontal pleitropy.

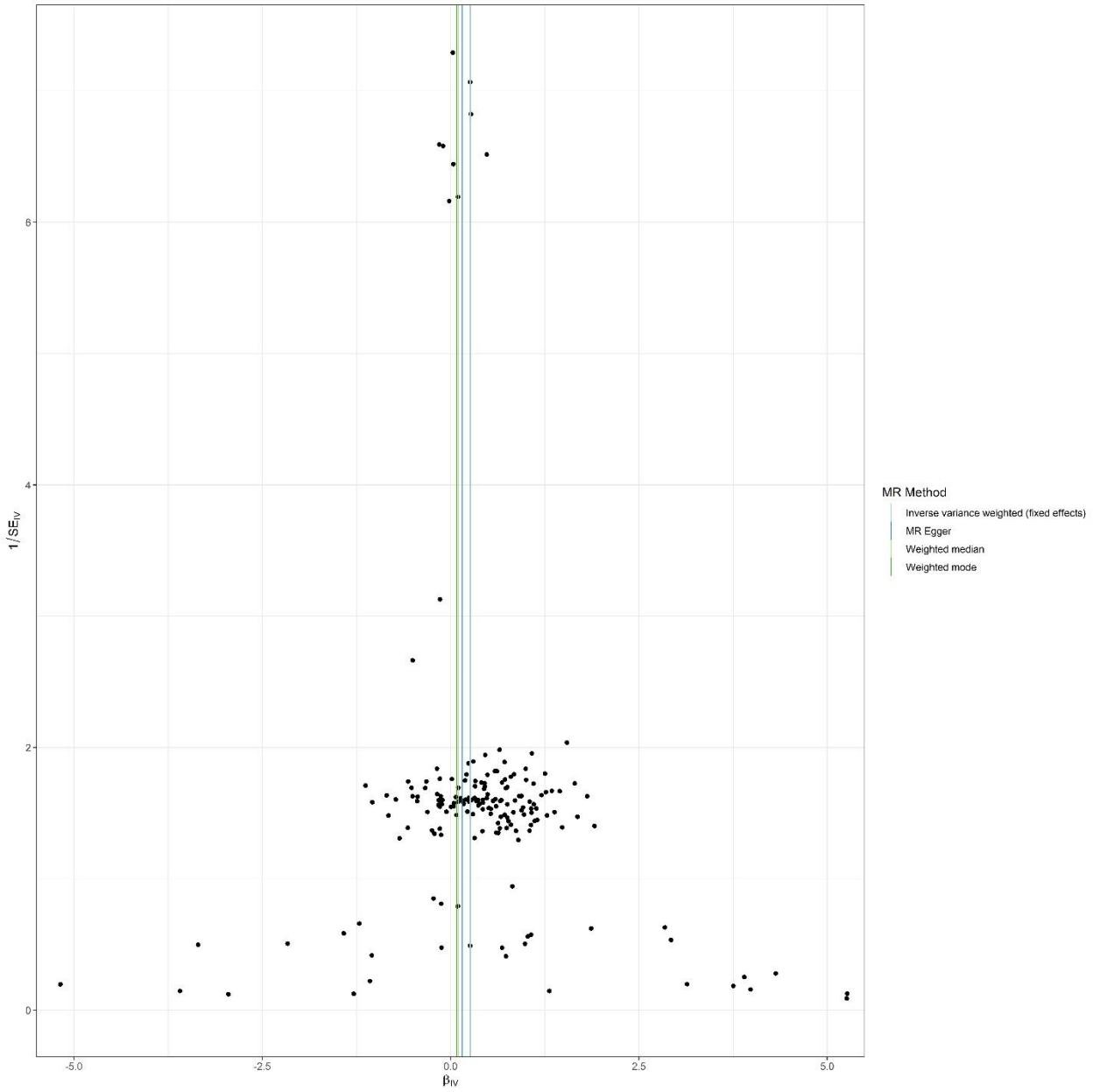
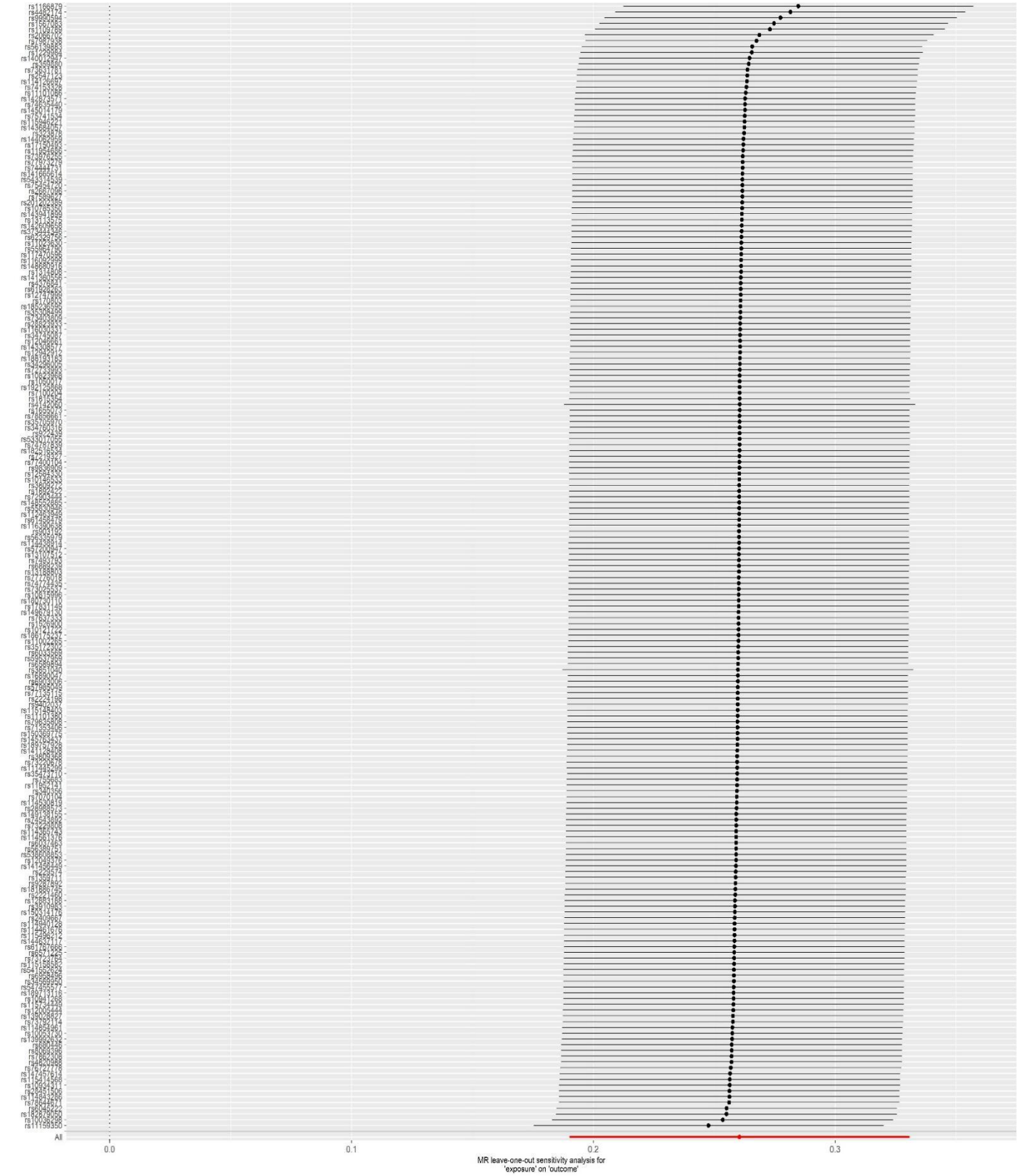


Figure 4. Leave-one-out plot of potential horizontal pleiotropic effect.



###**The pleiotropic effect may be balanced.**

Part II. AUD and MDD from 182 genetic variants in East Asian ancestry.

```
load("AUD_MDD_EAS_TwoSampleMR.RData")
dat1 <- dat[dat$pval.exposure < 5e-8, ]   ### GWAS significant variants, n=2


### run MR IVW and get first-stage F statistic
library(MendelianRandomization)

mr_ivw(mr_input(bx = dat$beta.exposure, bxse = dat$se.exposure, by =
dat$beta.outcome, byse = dat$se.outcome))
###  results
Inverse-variance weighted method
(variants uncorrelated, random-effect model)

Number of Variants : 182

------------------------------------------------------------------
 Method Estimate Std Error  95% CI        p-value
    IVW   -0.079     0.034 -0.147, -0.012   0.021
------------------------------------------------------------------
Residual standard error =  1.019
Heterogeneity test statistic (Cochrans' '  Q) = 188.0082 on 181 degrees of freedom,
(p-value = 0.3451). I^2 = 3.7%.
F statistic = 6.5.

### F statistic < 10, indicating weak instruments.
```

Table 1. Causal relationship between AUD and MDD by various MR methods.

Exposure	Outcome	Method	nsnp	b	se	pval
AUD	MDD	Maximum likelihood	174	-0.10296354	0.03866327	0.007742806
AUD	MDD	MR Egger	174	-0.12480481	0.04385727	0.004970072
AUD	MDD	MR Egger (bootstrap)s	174	-0.09150573	0.05273017	0.037000000
AUD	MDD	Simple median	174	0.01993959	0.08297861	0.810099329
AUD	MDD	Weighted median	174	-0.05593929	0.05440168	0.303825622
AUD	MDD	Penalised weighted median	174	-0.05338284	0.05749863	0.353190105
AUD	MDD	Inverse variance weighted (fixed effects)	174	-0.09514207	0.03475890	0.006196462
AUD	MDD	Inverse variance weighted (multiplicative random effects)	174	-0.09514207	0.03471610	0.006133180
AUD	MDD	Simple mode	174	0.12164907	30.20365717	0.996791068
AUD	MDD	Weighted mode	174	0.12164907	31.07080166	0.996880624
AUD	MDD	WeigsOME)	174	0.12164907	0.48687686	0.802995206
AUD	MDD	Simple mode (NOME)	174	0.12164907	0.51553176	0.813736520

In the fixed effects IVW analysis, higher genetically predicted AUD are associated with decreased risk of MDD in East Asian ancestry. However, the majority of pleiotropy robust methods are non-significant, suggesting that the causal effects may be biased.

Table 2. Pleiotropy by MR Egger intercept

MR Egger intercept	se	pval
0.004	0.003	0.210

There is no significant horizontal pleiotropy.

Table 3. Heterogeneity by Cochran's Q Test.

method	Q	Q-df	Q_pval
MR IVW	172.57	173	0.495
MR Egger	171.34	172	0.500

There is no significant heterogeneity.

Table 4. Causal relationship between AUD and MDD by Radial-MR.

	b	se	statistic	p
IVW				
Effect (Mod.2nd)	-0.10	0.03	-2.74	0.006
Iterative	-0.10	0.03	-2.74	0.006
Exact (FE)	-0.12	0.04	-3.29	9.9×10^{-4}
Exact (RE)	-0.12	0.04	-2.69	0.008
Q-Statistic	NA	NA	171.26	0.52
Egger				
(Intercept)	0.11	0.10	1.18	0.241
Wj	-0.13	0.04	-2.88	0.004
Q-Statistic	NA	NA	171.26	0.523

No significant outliers.

As with our core MR methods, we observed that the Radial-MR causal estimates indicated that AUD is causally associated with MDD, and there is no significant horizontal pleiotropy.

Figure 1. Scatter plot illustrating the relationship between SNP effects on AUD and their effects on the outcome.

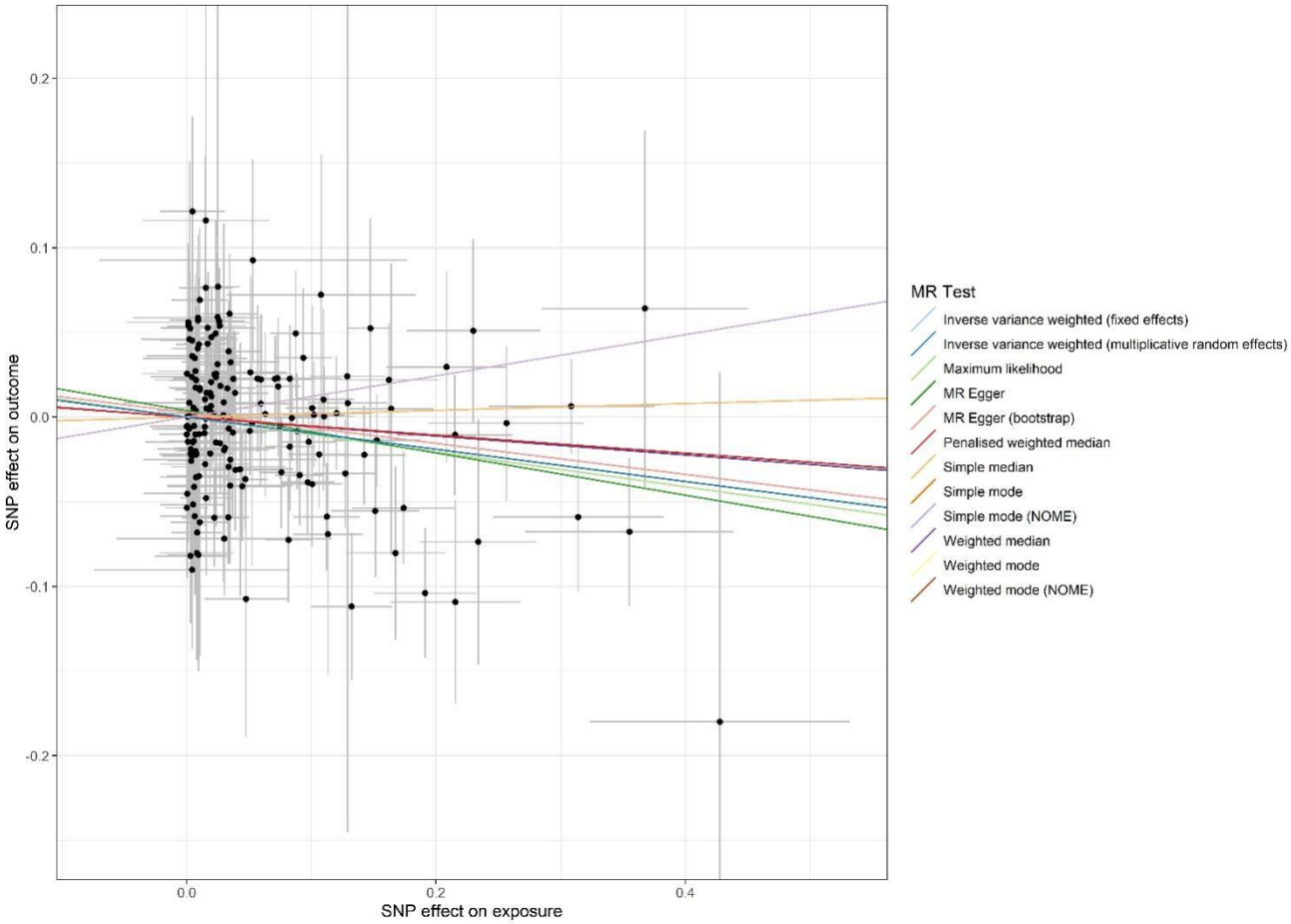


Figure 2. Forest plots presenting the Wald ratio for individual SNPs and their combined effects.

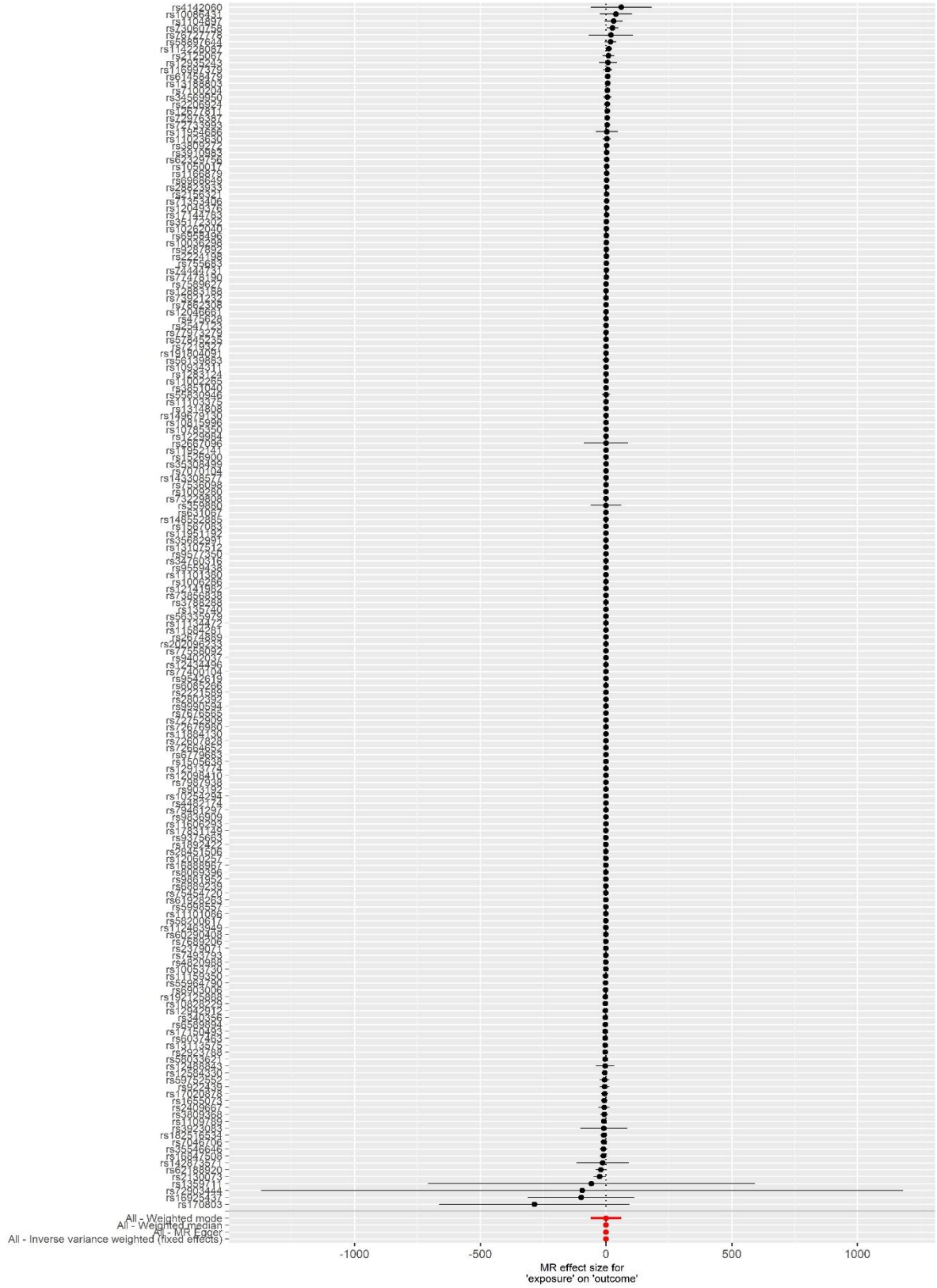


Figure 3. Funnel plots inspecting for horizontal pleitropy.

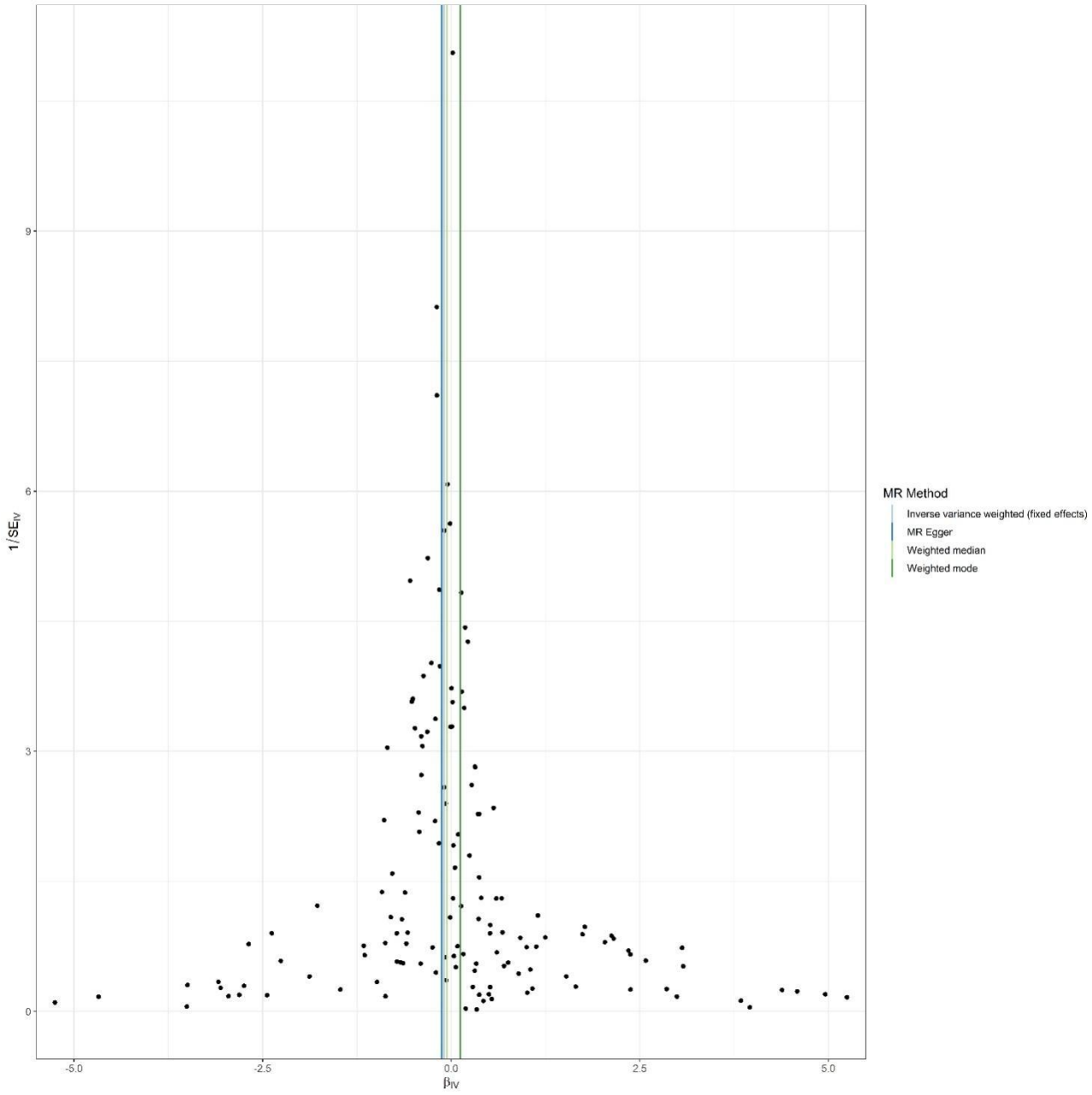
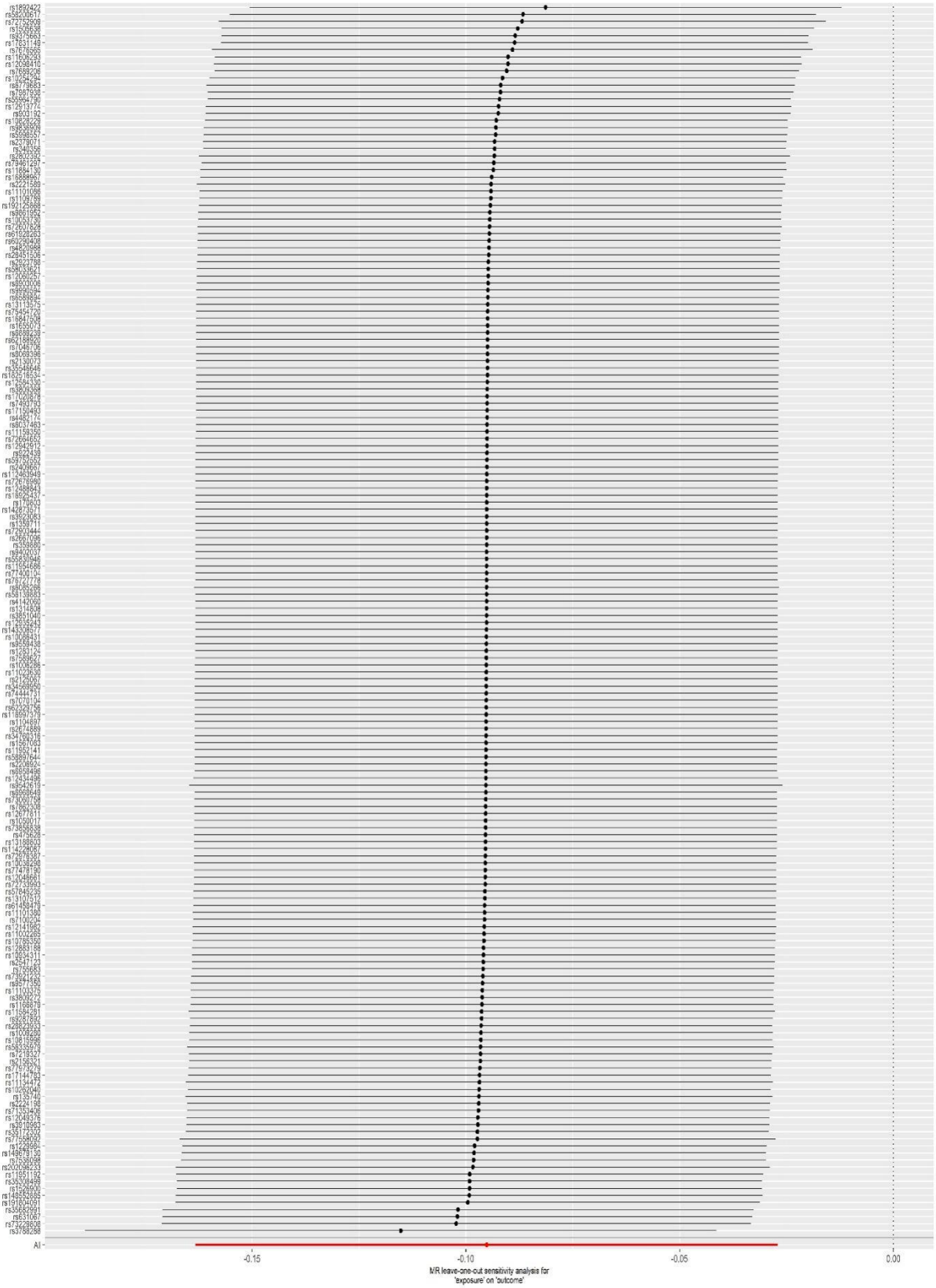


Figure 4. Leave-one-out plot of potential horizontal pleiotropic effect.



Part III. problematic alcohol use (PAU, a proxy to AUD) and MDD from 160 genetic variants in South Asian ancestry.

```
load("AUD_MDD_SAS_TwoSampleMR.RData")
dat1 <- dat[dat$pval.exposure < 5e-8, ]  ### GWAS significant variants, n=1

### run MR IVW and get first-stage F statistic
library(MendelianRandomization)

mr_ivw(mr_input(bx = dat$beta.exposure, bxse = dat$se.exposure, by =
dat$beta.outcome, byse = dat$se.outcome))
###  results
Inverse-variance weighted method
(variants uncorrelated, random-effect model)

Number of Variants : 160

------------------------------------------------------------------
 Method Estimate Std Error  95% CI       p-value
    IVW   -0.010     0.016 -0.041, 0.021    0.520
------------------------------------------------------------------
Residual standard error =  0.889
Residual standard error is set to 1 in calculation of confidence interval when its
estimate is less than 1.
Heterogeneity test statistic (Cochrans' Q) = 125.6711 on 159 degrees of freedom, (p-
value = 0.9762). I^2 = 0.0%.
F statistic = 10.6.
### F statistic > 10, indicating strong instruments.
```

Table 1. Causal relationship between AUD and MDD by various MR methods.

Exposure	Outcome	Method	nsnp	b	se	pval
AUD	MDD	Maximum likelihood	158	-0.010862992	0.01640922	0.5079677
AUD	MDD	MR Egger	158	0.016036028	0.02287426	0.4843155
AUD	MDD	MR Egger (bootstrap)s	158	0.009233244	0.03336552	0.3870000
AUD	MDD	Simple median	158	0.005577012	0.02842572	0.8444568
AUD	MDD	Weighted median	158	0.020011905	0.02415018	0.4073059
AUD	MDD	Penalised weighted median	158	0.020452121	0.02319928	0.3780017
AUD	MDD	Inverse variance weighted (fixed effects)	158	-0.010736727	0.01580829	0.4970217
AUD	MDD	Inverse variance weighted (multiplicative random effects)	158	-0.010736727	0.01412982	0.4473365
AUD	MDD	Simple mode	158	0.131864686	3.66094215	0.9713127
AUD	MDD	Weighted mode	158	0.131864686	3.63802605	0.9711321
AUD	MDD	WeigsOME)	158	0.131864686	0.10147716	0.1956938
AUD	MDD	Simple mode (NOME)	158	0.131864686	0.10741069	0.2214091

AUD was not causally associated with MDD in South Asian ancestry.

Table 2. Pleiotropy by MR Egger intercept

MR Egger intercept	se	pval
-0.006	0.004	0.127

There is no significant horizontal pleiotropy.

Table 3. Heterogeneity by Cochran's Q Test.

method	Q	Q-df	Q_pval
MR IVW	122.81	156	0.977
MR Egger	125.43	157	0.970

There is no significant heterogeneity.

Table 4. Causal relationship between AUD and MDD by Radial-MR.

	b	se	statistic	p
IVW				
Effect (Mod.2nd)	-0.10	0.01	-0.76	0.44
Iterative	-0.10	0.01	-0.76	0.44
Exact (FE)	-0.12	0.02	-0.73	0.46
Exact (RE)	-0.12	0.02	-0.74	0.46
Q-Statistic	NA	NA	125.40	0.97
Egger				
(Intercept)	-0.21	0.12	-1.82	0.07
Wj	0.02	0.02	1.00	0.32
Q-Statistic	NA	NA	122.68	0.98

No significant outliers.

As with our core MR methods, we observed that the Radial-MR causal estimates indicated that AUD is not causally associated with MDD, and there is no significant horizontal pleiotropy.

Figure 1. Scatter plot illustrating the relationship between SNP effects on AUD and their effects on the outcome.

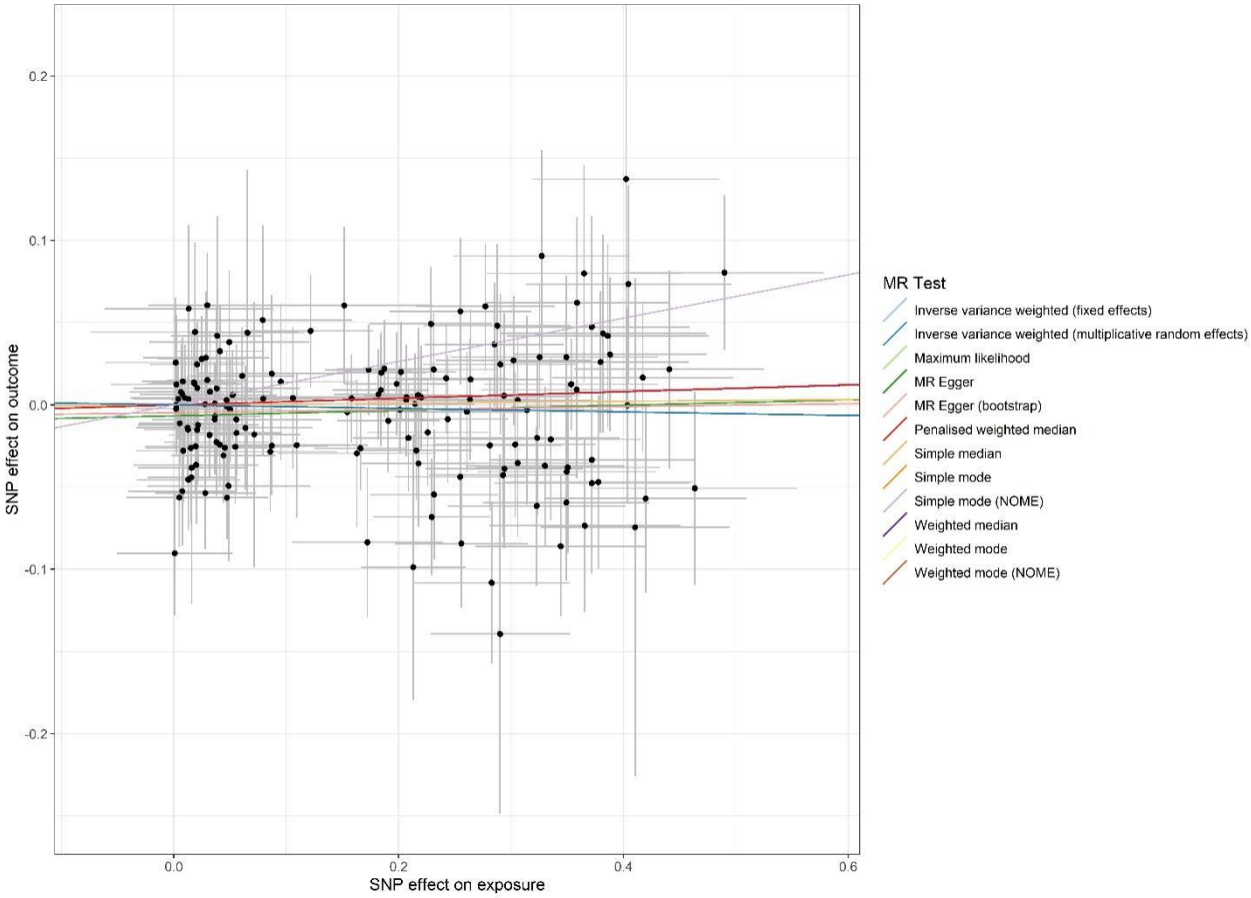
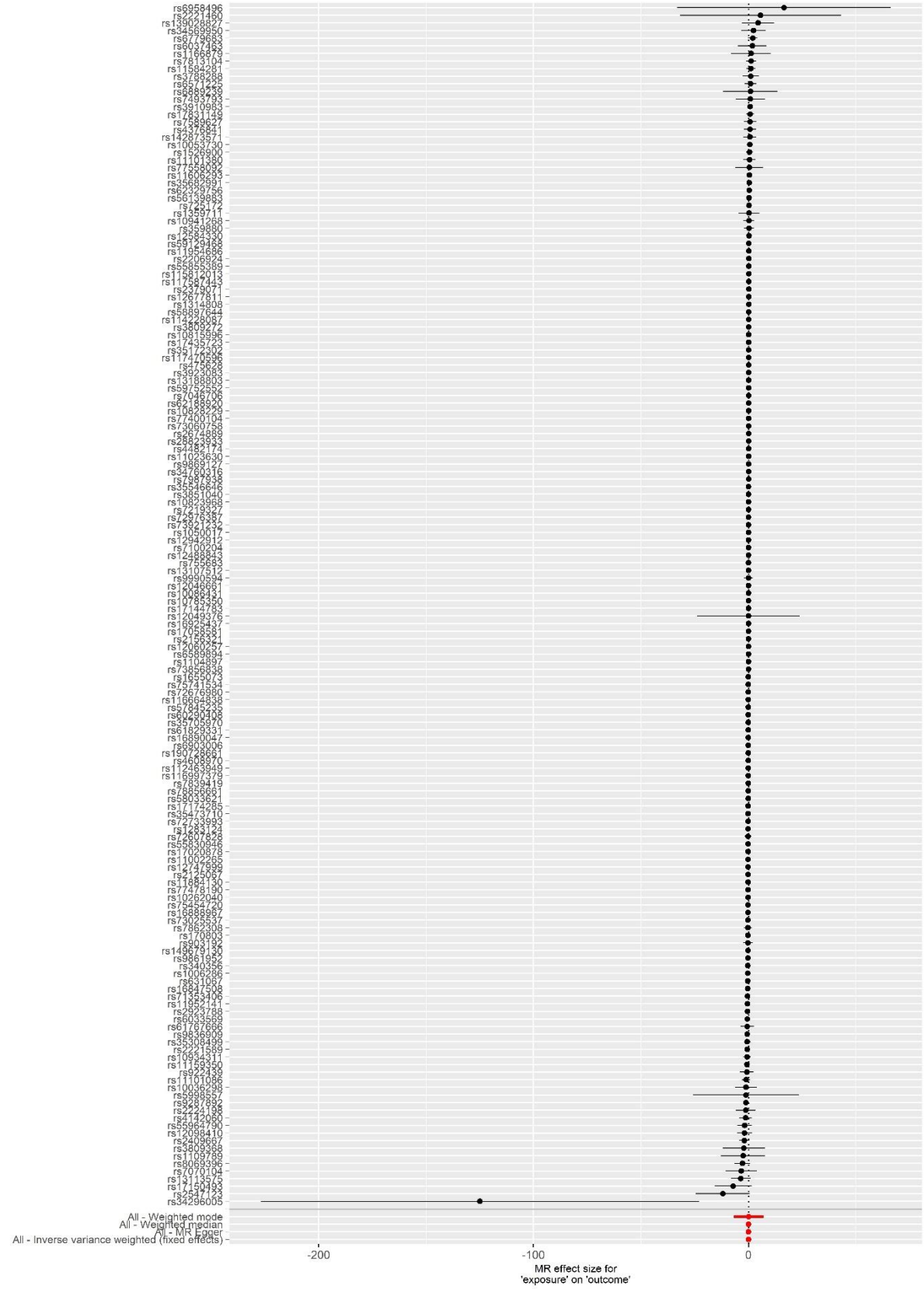


Figure 2. Forest plots presenting the Wald ratio for individual SNPs and their combined effects.



 # We observe dramatic changes in the MR causal estimates when SNP – rs34296005 is dropped from the analysis. This suggests that the IVW estimate is particularly sensitive to the inclusion of this variant and that it is the potentially outlier.

Figure 3. Funnel plots inspecting for horizontal pleitropy.

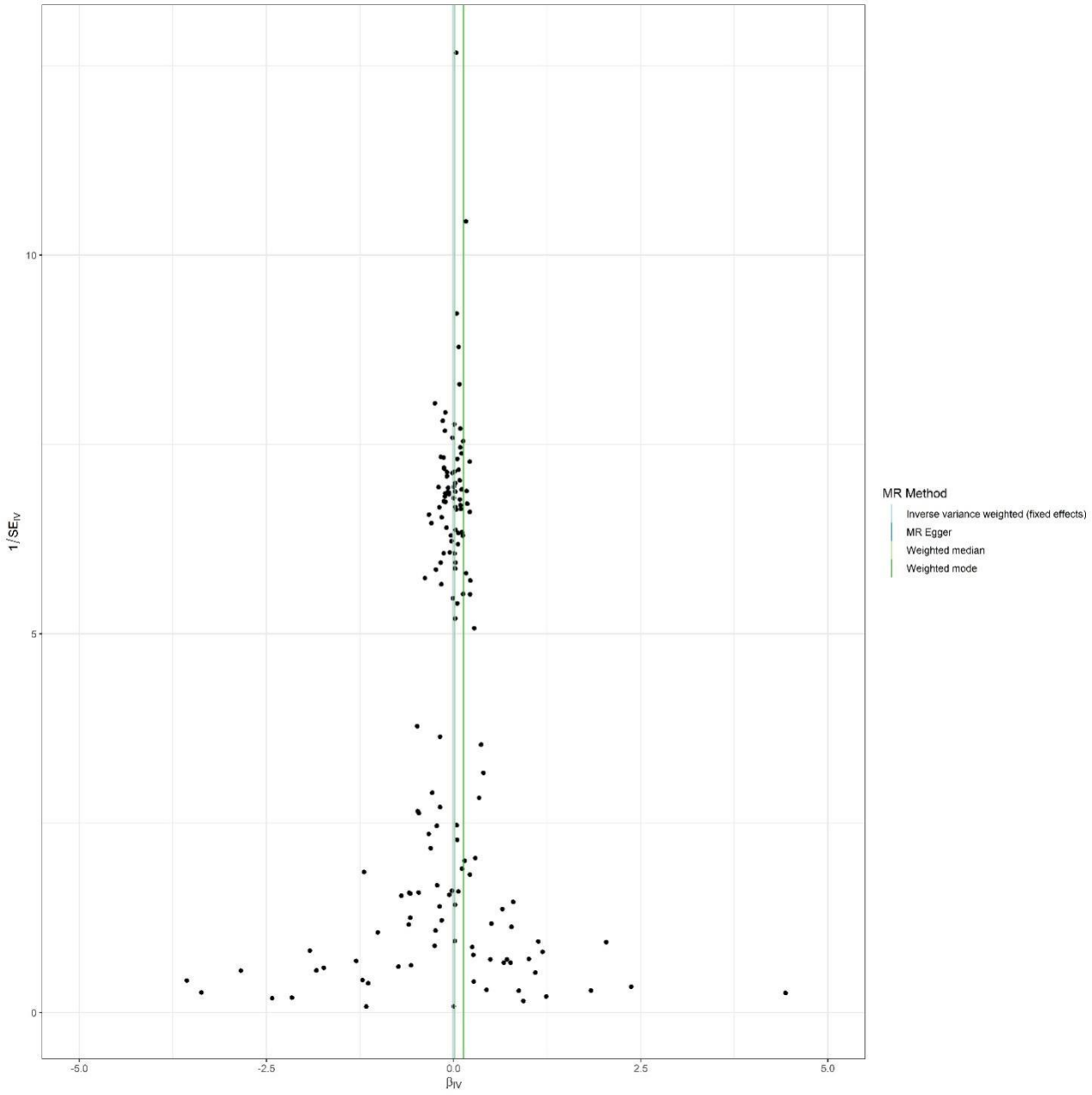


Figure 4. Leave-one-out plot of potential horizontal pleiotropic effect.