Using genetic instruments to estimate interactions in Mendelian Randomization studies

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Supplemental Material

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1 BACKGROUND LITERATURE ON INTERACTIONS WITH INSTRUMENTAL VARIABLES

Methods have been developed for the examination of gene-environment interactions (1). External to the MR literature, instrumental variable approaches for interaction terms have been considered, and our proposed approach draws on the models used in these non-genetic IV analyses (2, 3). A recent study by Rees et al. also considers the Factorial MR approach and, like this study, concludes it has very low statistical power (4). Like the analyses presented here, Rees et al. consider a 2SLS approach using the genetic risk scores for each exposure and their product as the IV, and show that this has far greater power than the factorial MR approach (4). In contrast to this paper, Rees et al. do not consider scenarios where mediation is present (i.e. where one exposure has a causal effect on the other), which we show has implications for the choice of IV. In addition to using genetic risk scores as IVs, Rees et al. consider as IVs each separate genetic variant for each exposure, and all cross-products, as well as a reduced set of IVs where cross-products are only included for non-shared variants. The authors conclude this approach is preferable to the use of continuous genetic risk scores, owing to increased efficiency. However, there is potential for weak instrument bias with this approach, which led us to focus here on the use of genetic risk scores.

2 SIMULATION STUDY: DATA GENERATING PROCESS

We explore an extension to MVMR that enables the estimation of an additive interaction between two exposures, by using the genetic risk scores for each exposure (Z_1 and Z_2) and the product of the two genetic risk scores, i.e. $Z=(Z_1,Z_2,Z_1Z_2)$ as the instrumental variables (Z). When the first exposure has a causal effect on the second exposure, i.e. exposure 2 mediates the effect of exposure 1 on the outcome, the instrument is $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$; further details on the justification of this are in Section 4. We use simulations to evaluate the performance of the 2SLS MVMR estimator for assessing additive interactions, with and without a causal effect of exposure 1 on exposure 2 (mediation), and compare these estimators with a factorial MR design.

Figure *1* provides a schematic diagram of the system excluding confounders and error terms.

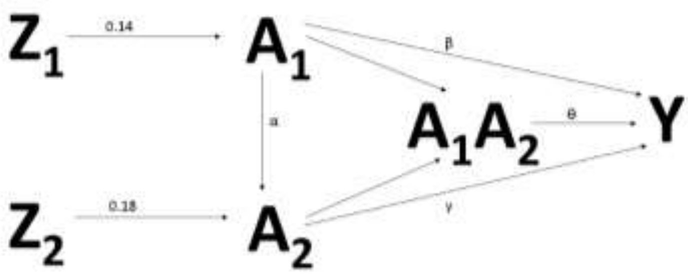

Figure 1: Schematic diagram of simulated data system, excluding confounder and error terms

Standard random normal variables were generated to represent error terms (U, V and E), confounders (C) and genetic instruments (Z_1 and Z_2) (1 - 3). Z_1 is the genetic risk score for exposure 1 (A_1) and Z_2 is the (independent) genetic risk score for exposure 2 (A_2).

$$\mathrm{U, V, E} \sim \mathrm{N}(0,1) \quad (1)$$

$$\mathrm{C} \sim \mathrm{N}(0,1) \quad (2)$$

$$\mathrm{Z1, Z2} \sim \mathrm{N}(0,1) \quad (3)$$

The random variables were used to generate values for each exposure (A_1 and A_2) and the outcome (Y), as shown in Equation 4.

$$A_1 = C + V + 0.14Z_1$$

$$A_2 = C + E + 0.18Z_2 + \alpha A_1$$

$$Y = C + U + \beta A_1 + \gamma A_2 + \theta A_1 A_2 + \lambda C A_1 + \tau C A_2$$

Equation 4: Description of system

Interactions between the confounder variable (C) and A_1 and A_2 separately were included in the Y equation (5, 6). A_1 was allowed to affect A_2, implying the effect of A_1 on Y is partially mediated by A_2. We tested 25 alternative scenarios, which represented permutations of 5 coefficients for A_1 in the A_2 equation (α in Equation 4, took values -0.333, 0, 0.333, 0.5 and 1), 5 coefficients for A_1 and A_2 in the Y equation (β and γ in equation 4, took values -0.333, 0, 0.333, 0.5 and 1) and 5 coefficients for A_1A_2, CA_1 and CA_2 in the Y equation (θ, λ and τ in equation 4, took values -0.111, 0, 0.111, 0.167 and 0.333).

25 combinations of these parameters were tested, which were representative of the parameter space, including scenarios with and without an interaction between A_1 and A_2, and with and without a causal effect of A_1 on A_2. A table of parameter permutations is provided in Section 3. The interaction parameters in the Y equation (θ, λ and τ) were set to be one third of the main effect's parameters (β and γ) to impose a limit on the variance explained by interaction terms.

The coefficients of 0.14 and 0.18 for the effect of the instrument on the exposures (A_1 and A_2) in Equation 4 were chosen to impose an approximate proportion of variance explained by the genetic risk scores of 1-2%. This aims to emulate the R^2 from a typical genetic risk score in the literature.

We simulated twelve sample sizes: N=10,000 to N=100,000 (in steps of 10,000), N=500,000 and N=1,000,000. Models were run 1,000 times for each sample size and results pooled across repeats. All regression analyses and subsequent testing were performed using functions in the R systemfit package (7) version 1.1-22, the AER package (8) version 1.2-5, or using R's lm function.

3 PARAMETER PERMUTATIONS

α	β	γ	θ	λ	τ
-0.333	-0.333	-0.333	-0.111	-0.111	-0.111
0	-0.333	-0.333	-0.111	-0.111	-0.111
0.333	-0.333	-0.333	-0.111	-0.111	-0.111
0.5	-0.333	-0.333	-0.111	-0.111	-0.111
1	-0.333	-0.333	-0.111	-0.111	-0.111
-0.333	0	0	0.000	0.000	0.000
0	0	0	0.000	0.000	0.000
0.333	0	0	0.000	0.000	0.000
0.5	0	0	0.000	0.000	0.000
1	0	0	0.000	0.000	0.000
-0.333	0.333	0.333	0.111	0.111	0.111
0	0.333	0.333	0.111	0.111	0.111
0.333	0.333	0.333	0.111	0.111	0.111
0.5	0.333	0.333	0.111	0.111	0.111
1	0.333	0.333	0.111	0.111	0.111
-0.333	0.5	0.5	0.167	0.167	0.167
0	0.5	0.5	0.167	0.167	0.167

0.333	0.5	0.5	0.167	0.167	0.167
0.5	0.5	0.5	0.167	0.167	0.167
1	0.5	0.5	0.167	0.167	0.167
-0.333	1	1	0.333	0.333	0.333
0	1	1	0.333	0.333	0.333
0.333	1	1	0.333	0.333	0.333
0.5	1	1	0.333	0.333	0.333
1	1	1	0.333	0.333	0.333

4 STATISTICAL METHODS

4.1 Inclusion of Z_1Z_1 term in the instrument

If we substitute the A1 equation into the A2 equation and multiply we get

$$A_1A_2=C^2 + CE + 0.18CZ_2 + \alpha C^2 + \alpha CV + 0.14C\alpha Z_1 +$$
$$VC + VE + 0.18VZ_2 + \alpha VC + \alpha V^2 + 0.14V\alpha Z_1+$$
$$0.14CZ_1 + 0.14EZ_1 + 0.14*0.18\mathbf{Z_1Z_2} + 0.14\alpha CZ_1 +$$
$$0.14\alpha VZ_1 + 0.14*0.14\alpha\mathbf{Z_1Z_1}$$

We see that when mediation is assumed (α is assumed to be non-zero), there are Z_1Z_2 and Z_1Z_1 terms. When mediation is not assumed, the Z_1Z_1 term vanishes.

4.2 Two-stage least squares estimation

Instrumental variable regression in AER (8) (using the *ivreg* command) or systemfit (7) was implemented. This uses the instruments Z to generate predicted values for A_1, A_2 and A_1A_2 (interaction coefficient), and regresses these predicted values against Y. The standard errors in the second stage are adjusted to account for the fact that the A_1, A_2 and A_1A_2 are predictions based on the instruments Z. For all simulations, we evaluated two IV: i) the genetic risk score for each exposure (Z_1 and Z_2) and the product of the two genetic risk scores, i.e. $Z=(Z_1,Z_2,Z_1Z_2)$, and ii) an IV that allows for when the first exposure has a causal effect on the second exposure, $Z= (Z_1,Z_2,Z_1Z_2,Z_1Z_1)$. The instruments are described as vectors here because all of the instruments are included in the first stage regression models in 2SLS to predict the values of each of the exposures.

4.3 Factorial MR estimation

We modelled the factorial MR approach, by splitting the two genetic instruments Z_1 and Z_2 at the median to generate four subgroups representing low A_1-low A_2, low A_1-high A_2, high A_1-low A_2 and high A_1-high A_2. An ordinary least squares regression of the outcome against these four categories was performed (low-low was treated as the reference category) and a linear combination of the regression coefficients tested using an F statistic and Wald test (using the -linearHypothesis- R function from the car package (9)) to conclude presence or absence of an interaction between A_1 and A_2 on Y. The linear hypothesis we tested was that the sum of the regression coefficients for the low A_1-high A_2 and the high A_1-low A_2 categories equalled the high A_1-high A_2 coefficient. Rejection of this hypothesis at p=0.05 was regarded as suggestive of an interaction between the two exposures. This formal interaction test was not included in the original application of factorial MR (10) but we have adopted it to enable comparisons with the 2SLS approaches.

4.4 Evaluation of approaches to estimate interaction

Coefficients and standard errors were collapsed across the 1,000 simulation runs; the regression coefficients were averaged to give $\bar{\hat{\theta}} = \frac{\sum_{i=1}^{1000} \hat{\theta}}{1000}$. This provides a measure of the bias. The 95% Monte Carlo confidence interval (MC CI) (11) for these coefficients was calculated using the formula $\bar{\hat{\theta}} \pm 1.96 \frac{sd(\hat{\theta})}{\sqrt{1000}}$, where sd is the sample standard deviation. If the 95% MC CI includes the true value we conclude that the regression coefficient from this estimating procedure is unbiased (11). We also examined the mean estimated standard error of $\hat{\theta}$ across simulation repeats and calculated the standard deviation of the regression coefficients ($sd(\hat{\theta})$) across repeats to evaluate precision (12). As the number of simulation repeats tends to infinity, $sd(\hat{\theta})$ estimates the true precision of the estimator and deviation from the mean estimated standard error of $\hat{\theta}$ is indicative of bias in the estimate of precision. We also considered power, type I error and coverage. Power was defined as detecting an interaction at the 5% level (two-sided test) when an interaction ($\theta \neq 0$) was present. A power of 68% therefore represents 680 of the 1,000 repeats detecting an interaction at $p \leq 0.05$ when the true interaction parameter was non-zero. Type I error was similarly calculated by counting the number of repeats where an interaction was detected at $p \leq 0.05$ when the true parameter value was zero. 'Interaction detection' was defined as the 95% confidence interval not including 0 for the 2SLS and observational linear regression approaches. Coverage was calculated as the percentage of repeats where the 95% confidence interval contained the true parameter value. Due to the nature of the factorial design, coverage could not be calculated because a confidence interval for the interaction parameter is not available. However, power and type I error were calculated by testing for an interaction using the linear contrast described previously.

4.5 Sensitivity analyses

4.5.1 Pleiotropy

Pleiotropy refers to deviation from the assumption that an IV only affects the outcome through the exposure (13). A sensitivity analysis allowing for a pleiotropic effect of A_2's instrument on A_1 was run with N=500,000. We compared the performance of the 2SLS approach using the instrument $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ under a model of no pleiotropy versus pleiotropy using data from 1,000 random variable simulations generated by ten new seeds. We also considered the power and type I error of the factorial MR approach. The updated A_1 equation for the pleiotropic scenario is given by equation 5.

$$A_1 = C + V + 0.1Z_1 + 0.1Z_2 \quad (5)$$

4.5.2 Instrumental variable strength

With N=50,000, we changed the coefficients of Z_1 and Z_2 in the A_1 and A_2 equations respectively (Equation 6) to increase the percentage variance explained by the instruments (achieving 2.4-8.9% for A_2).

$$A_1 = C + V + 0.32Z_1$$

$$A_2 = C + E + 0.39Z_2 + \alpha A_1$$

Equation 6: Updated equations with increased percentage variance explained by the instruments

4.5.3 Robust standard errors

To explore whether the use of robust standard errors (e.g. to account for deviations from assumptions of normality or other potential violations of assumptions) affected our findings, the observational and 2SLS regressions (using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$) in the main analysis were repeated with heteroskedastic robust standard errors using the *coeftest* R function or the *robust.se* R function (the former from the lmtest (14) R package and the latter from the ivpack (15) R package) with the results examined at N=50,000 and N=500,000.

4.5.4 Weak instrument bias

The Sanderson-Windmeijer F statistics (16) were examined after the 2SLS regressions in the main analysis to test for weak-instrument bias and the correlation with sample size.

4.6 Statistical analysis code

All code used for statistical analyses is shown below, and is also available at

https://github.com/sean-harrison-bristol/MR_interactions

4.6.1 Code for creating simulated data

```
#script_name: factorial_mr_v4_h_vi.r
#project: 4-way decomp
#script author: Teri North
#script purpose: simulation to examine performance of Ference (2015)
factorial MR approach - same as v2 script but with coeffs to impose 1%
variance for z1 and z2
#date created: 12/04/2017
#last edited: 11/1/2019
#notes:
#https://cran.r-project.org/web/packages/systemfit/systemfit.pdf
#https://stat.ethz.ch/R-manual/R-devel/library/utils/html/write.table.html
#https://stat.ethz.ch/R-manual/R-devel/library/base/html/Random.html

#read in seed
seedval=commandArgs(6)
print(seedval)
seedval=as.numeric(seedval)

library("AER")
library("ivpack")

sessionInfo()

#define headers
headers=c("x_coeff_m","x_coeff_y","m_coeff_y","xm_coeff_y",
          "x_obs", "x_obs_se",
          "m_obs", "m_obs_se",
          "xm_obs", "xm_obs_se",
          "f1", "f1_se",
          "f2", "f2_se",
          "f3","f3_se",
          "fmr_interac_p",
          "x_2sls", "x_2sls_se",
          "m_2sls", "m_2sls_se",
          "xm_2sls", "xm_2sls_se",
          "x_z1_2sls", "x_z1_2sls_se",
          "m_z1_2sls", "m_z1_2sls_se",
          "xm_z1_2sls", "xm_z1_2sls_se")


rob_headers=c("x_coeff_m","x_coeff_y","m_coeff_y","xm_coeff_y",
              "x_obs", "x_obs_se",
              "m_obs", "m_obs_se",
              "xm_obs", "xm_obs_se",
              "f1", "f1_se",
              "f2", "f2_se",
              "f3","f3_se",
              "fmr_interac_p",
              "x_2sls", "x_2sls_se",
              "m_2sls", "m_2sls_se",
```

```
             "xm_2sls", "xm_2sls_se",
             "x_z1_2sls", "x_z1_2sls_se",
             "m_z1_2sls", "m_z1_2sls_se",
             "xm_z1_2sls", "xm_z1_2sls_se")

F_headers=c("x_coeff_m","x_coeff_y","m_coeff_y","xm_coeff_y",
            "F_2SLS", "F_Z1_2SLS")



set.seed(seedval)

for (nval in
c(10000,20000,30000,40000,50000,60000,70000,80000,90000,100000,500000,10000
00)){
  for (rep in c(1:100)){
    #log session for each seed, sample size and sim repeat
    sink(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRlog.txt",sep=""))

    #write file headers
    #begin with append=FALSE to overwrite current file
    write.table(headers,
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=FAL
SE, quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")
    write.table(rob_headers,
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res.txt",sep=""),ap
pend=FALSE, quote=FALSE, row.names=FALSE, col.names=FALSE, sep =
"\t",eol="\t")
    write.table(F_headers,
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_F_res.txt",sep=""),append=
FALSE, quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")

    #generate data for system
    samp_size=nval
    #error terms
    u=rnorm(samp_size)
    v=rnorm(samp_size)
    e=rnorm(samp_size)
    #confounders
    c=rnorm(samp_size)
    #instruments
    z1=rnorm(samp_size)
    z2=rnorm(samp_size)


    #begin looping over coefficient combinations

    for (i in c(0,0.333,0.5,1,-0.333)) {

      for (othcomb in c(1,2,3,4,5)){

        if (othcomb==1){
          j=0
          k=0
          l=0/3
          m=0/3
          n=0/3

        } else if (othcomb==2){
          j=0.333
          k=0.333
```

```
  l=0.333/3
  m=0.333/3
  n=0.333/3

} else if (othcomb==3){
  j=0.5
  k=0.5
  l=0.5/3
  m=0.5/3
  n=0.5/3

} else if (othcomb==4){
  j=1
  k=1
  l=1/3
  m=1/3
  n=1/3

} else if (othcomb==5){
  j=-0.333
  k=-0.333
  l=-0.333/3
  m=-0.333/3
  n=-0.333/3

}



print(i)
print(j)
print(k)
print(l)
coeff_list<- c(i,j,k,l)

#define models
#Exposure
a1=c+v+0.14*z1
#Mediator
a2=i*a1+e+0.18*z2+c
#Outcome
y=j*a1+k*a2+u+c+l*a1*a2+m*c*a1+n*c*a2

a1a2=a1*a2
z1z2=z1*z2
z1z1=z1*z1
z2z2=z2*z2

#observational
fitols <- lm(y ~ a1 + a2 + a1a2)
sum_ols=coef(summary(fitols))
rob_fitols <- coeftest(fitols,vcov=vcovHC(fitols,type="HC0"))

obs_vec=c(sum_ols[2,1],sum_ols[2,2],
          sum_ols[3,1],sum_ols[3,2],
          sum_ols[4,1],sum_ols[4,2])

rob_obs_vec=c(rob_fitols[2,1],rob_fitols[2,2],
              rob_fitols[3,1],rob_fitols[3,2],
              rob_fitols[4,1],rob_fitols[4,2])
```

```
        #split the observations into 4 groups based on median splits of
Instruments
        med_z1=median(z1)
        med_z2=median(z2)

        fact_group=c(1:nval)
        f0=c(1:nval)
        f1=c(1:nval)
        f2=c(1:nval)
        f3=c(1:nval)

        for (z in c(1:nval)){
          fact_group[z]=NA
          f0[z]=NA
          f1[z]=NA
          f2[z]=NA
          f3[z]=NA
        }

        for (z in c(1:nval)){
          if ((z1[z]<=med_z1) & (z2[z]<=med_z2)){
            fact_group[z]=0
            f0[z]=1
            f1[z]=0
            f2[z]=0
            f3[z]=0
          } else if ((z1[z]<=med_z1) & (z2[z]>med_z2)){
            fact_group[z]=1
            f0[z]=0
            f1[z]=1
            f2[z]=0
            f3[z]=0
          } else if ((z1[z]>med_z1) & (z2[z]<=med_z2)){
            fact_group[z]=2
            f0[z]=0
            f1[z]=0
            f2[z]=1
            f3[z]=0
          } else if ((z1[z]>med_z1) & (z2[z]>med_z2)){
            fact_group[z]=3
            f0[z]=0
            f1[z]=0
            f2[z]=0
            f3[z]=1
          }
        }



        #FACTORIAL MR (median split)
        fitfmr <- lm(y ~ f1 + f2 + f3)
        sum_fmr=coef(summary(fitfmr))
        rob_fitfmr <- coeftest(fitfmr,vcov=vcovHC(fitfmr,type="HC0"))

        #f0 as the baseline - see fig 2 reference paper

        #reality check on regression coefficients
        mean(y[f1==1]) - fitfmr$coefficients[2]
        mean(y[f2==1]) - fitfmr$coefficients[3]
```

```
        mean(y[f3==1]) - fitfmr$coefficients[4]

        mean(y[f0==1]) - fitfmr$coefficients[1] #intercept is mean outcome
for baseline group

        #formal test for interaction using linear contrast of coeffs - use
Wald test comparable to stata's 'test'
        lhyp='1*f1 + 1*f2 - 1*f3 = 0'
        lincon=linearHypothesis(fitfmr,lhyp,test='F')
        int_p=lincon$`Pr(>F)`[2]

        fmr_vec=c(sum_fmr[2,1],sum_fmr[2,2], #f1 vs f0
                  sum_fmr[3,1],sum_fmr[3,2], #f2 vs f0
                  sum_fmr[4,1],sum_fmr[4,2], #f3 vs f0
                  int_p)

        rob_fmr_vec=c(rob_fitfmr[2,1],rob_fitfmr[2,2], #f1 vs f0
                      rob_fitfmr[3,1],rob_fitfmr[3,2], #f2 vs f0
                      rob_fitfmr[4,1],rob_fitfmr[4,2], #f3 vs f0
                      "NA")


        #instrumental variable 2sls: inst=z1+z2+z1z2 [when no mediation
expected]
        eqy<- y ~ a1 + a2 + a1a2 | z1 + z2 + z1z2
        fit2sls <- ivreg(eqy)
        sum_2sls=coef(summary(fit2sls))

        #hetroskedastic robust SEs
        rob_fit2sls<-robust.se(fit2sls)

        tsls_vec=c(sum_2sls[2,1],sum_2sls[2,2],
                   sum_2sls[3,1],sum_2sls[3,2],
                   sum_2sls[4,1],sum_2sls[4,2])

        rob_tsls_vec=c(rob_fit2sls[2,1],rob_fit2sls[2,2],
                       rob_fit2sls[3,1],rob_fit2sls[3,2],
                       rob_fit2sls[4,1],rob_fit2sls[4,2])

        freg = ivreg(a1a2 ~ a1 + a2 | z1 + z2 + z1z2)
        fregres = freg$residuals
        F_a1a2 = summary(lm(fregres ~ z1 + z2 + z1z2))$fstatistic[1]
        F_adj_a1a2=F_a1a2*(3/(3-3+1))


        #instrumental variable 2sls: inst=z1+z2+z1z2+z1z1 [when mediation
expected]
        eq2y<- y ~ a1 + a2 + a1a2 | z1 + z2 + z1z2 + z1z1
        fitz12sls <- ivreg(eq2y)
        sum_z12sls=coef(summary(fitz12sls))

        #hetroskedastic robust SEs
        rob_fitz12sls<-robust.se(fitz12sls)

        tslsz1_vec=c(sum_z12sls[2,1],sum_z12sls[2,2],
                     sum_z12sls[3,1],sum_z12sls[3,2],
                     sum_z12sls[4,1],sum_z12sls[4,2])

        rob_tslsz1_vec=c(rob_fitz12sls[2,1],rob_fitz12sls[2,2],
                         rob_fitz12sls[3,1],rob_fitz12sls[3,2],
                         rob_fitz12sls[4,1],rob_fitz12sls[4,2])
```

```
        z1freg = ivreg(a1a2 ~ a1 + a2 | z1 + z2 + z1z2 + z1z1)
        z1fregres = z1freg$residuals
        Fz1_a1a2 = summary(lm(z1fregres ~ z1 + z2 + z1z2 + 
z1z1))$fstatistic[1]
        Fz1_adj_a1a2=Fz1_a1a2*(4/(4-3+1))



        #all results
        res_vec=c(coeff_list,obs_vec,fmr_vec,tsls_vec,tslsz1_vec)
        
rob_res_vec=c(coeff_list,rob_obs_vec,rob_fmr_vec,rob_tsls_vec,rob_tslsz1_ve
c)
        f_res_vec=c(coeff_list,F_adj_a1a2,Fz1_adj_a1a2)

        write("", 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=TRU
E, sep = "\n")
        write.table(res_vec, 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=TRU
E, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")

        write("", 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res.txt",sep=""),ap
pend=TRUE, sep = "\n")
        write.table(rob_res_vec, 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res.txt",sep=""),ap
pend=TRUE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")

        write("", 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_F_res.txt",sep=""),append=
TRUE, sep = "\n")
        write.table(f_res_vec, 
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_F_res.txt",sep=""),append=
TRUE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")




      }

    }

    sink()
  }
}
```

4.6.2 Pooling of main results

```
#script_name: pool_sim_pap1_obs_and_other_est_SC_1krep_v7.r
#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: pool estimates across simulation repeats by
```

```
#                  -taking the mean betahat & SE of betahats (to generate MC
95% CI for betahat)
#                  -take the mean SE and the SD of betahats
#                  -calculate power, type i error and coverage where
applicable
#date created: 03/01/2019
#last edited: 03/01/2019
#notes:

setwd('') #Folder 1

#number of repeats in each sim
repeats=100

#tracker for erroneous calls
n_problem=c(1:12)
for (j in c(1:12)){n_problem[j]=0}
n_prob_track=1

n_z1problem=c(1:12)
for (j in c(1:12)){n_z1problem[j]=0}
n_z1prob_track=1

for (nval in
c(10000,20000,30000,40000,50000,60000,70000,80000,90000,100000,500000,10000
00)){

  xm_2sls_detec=c(1:25) # counter for # times interaction is detected (null
is rejected) at 5% level
  for (i in c(1:25)){
    xm_2sls_detec[i]=0
  }
  xm_z1_2sls_detec=c(1:25)
  for (i in c(1:25)){
    xm_z1_2sls_detec[i]=0
  }
  xm_obs_detec=c(1:25) # counter for # times interaction is detected (null
is rejected) at 5% level
  for (i in c(1:25)){
    xm_obs_detec[i]=0
  }


  coverage=c(1:25) # counter for # times 95% CI contains true value
  for (i in c(1:25)){
    coverage[i]=0
  }
  z1_coverage=c(1:25)
  for (i in c(1:25)){
    z1_coverage[i]=0
  }
  obscoverage=c(1:25)
  for (i in c(1:25)){
    obscoverage[i]=0
  }

  #reality check
  #how many times is the interaction detected (p<0.05), but the estimate is
in the opposite direction to true effect?
  problem=c(1:25)
  for (i in c(1:25)){
```

```
    problem[i]=0
  }
  z1problem=c(1:25)
  for (i in c(1:25)){
    z1problem[i]=0
  }



  fmr_y_int=c(1:25)  # counter for # times interaction detected factorial
approach (Wald test 5%)
  for (i in c(1:25)){
    fmr_y_int[i]=0
  }


  #calculating the mean betas
  first=1


  for (seedval in
c(7821897,8376154,649384402,238140535,170379645,312006101,713795870,1693789
34,456561608,28335714)){

    for (rep in c(1:repeats)){

      if (first==1){


data=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",se
p=''),sep='\t',header=TRUE)
        true_vals=data.frame(data$x_coeff_m,data$x_coeff_y,data$m_coeff_y,
data$xm_coeff_y)
        first=0

        ll=data.frame(
          xm_2sls_ll=data$xm_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_2sls_se,
          xm_z1_2sls_ll=data$xm_z1_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_z1_2sls_se,
          xm_obs_ll=data$xm_obs-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_obs_se
        )

        ul=data.frame(
          xm_2sls_ul=data$xm_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_2sls_se,
          xm_z1_2sls_ul=data$xm_z1_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_z1_2sls_se,
          xm_obs_ul=data$xm_obs+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_obs_se
        )


        for (i in c(1:25)){
          if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
            xm_2sls_detec[i]=NA
          } else if (ll$xm_2sls_ll[i]>0 |
ul$xm_2sls_ul[i]<0){xm_2sls_detec[i]=1}
        }
```

```
        for (i in c(1:25)){
          if (ll$xm_z1_2sls_ll[i]>0 |
ul$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=1}
        }


        for (i in c(1:25)){
          if (ll$xm_obs_ll[i]>0 | ul$xm_obs_ul[i]<0){xm_obs_detec[i]=1}
        }


        for (i in c(1:25)){
          if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
            coverage[i]=NA
          } else if ((ll$xm_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_2sls_ul[i]>data$xm_coeff_y[i])){coverage[i]=1}
        }

        for (i in c(1:25)){
          if ((ll$xm_z1_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_z1_2sls_ul[i]>data$xm_coeff_y[i])){z1_coverage[i]=1}
        }


        for (i in c(1:25)){
          if ((ll$xm_obs_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_obs_ul[i]>data$xm_coeff_y[i])){obscoverage[i]=1}
        }


        for (i in c(1:25)){
          if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
            problem[i]=NA
          } else if (((ll$xm_2sls_ll[i]>0) &
(data$xm_coeff_y[i]<0))|((ul$xm_2sls_ul[i]<0) & (data$xm_coeff_y[i]>0)))
{problem[i]=1}#if interac detec, but coeff wrong direc
        }

        for (i in c(1:25)){
          if (((ll$xm_z1_2sls_ll[i]>0) &
(data$xm_coeff_y[i]<0))|((ul$xm_z1_2sls_ul[i]<0) & (data$xm_coeff_y[i]>0)))
{z1problem[i]=1}#if interac detec, but coeff wrong direc
        }


        for (i in c(1:25)){
          if (data$fmr_interac_p[i]<0.05){fmr_y_int[i]=1}
        }



      } else if (first==0){


new=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep
=''),sep='\t',header=TRUE)
        data=data+new

        ll_new=data.frame(
          xm_2sls_ll=new$xm_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_2sls_se,
```

```
          xm_z1_2sls_ll=new$xm_z1_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_z1_2sls_se,
          xm_obs_ll=new$xm_obs-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_obs_se
        )

        ul_new=data.frame(
          xm_2sls_ul=new$xm_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_2sls_se,
          xm_z1_2sls_ul=new$xm_z1_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_z1_2sls_se,
          xm_obs_ul=new$xm_obs+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_obs_se
        )


        for (i in c(1:25)){
          if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){
            xm_2sls_detec[i]=NA
          } else if (ll_new$xm_2sls_ll[i]>0 |
ul_new$xm_2sls_ul[i]<0){xm_2sls_detec[i]=xm_2sls_detec[i]+1}
        }

        for (i in c(1:25)){
          if (ll_new$xm_z1_2sls_ll[i]>0 |
ul_new$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=xm_z1_2sls_detec[i]+1}
        }


        for (i in c(1:25)){
          if (ll_new$xm_obs_ll[i]>0 |
ul_new$xm_obs_ul[i]<0){xm_obs_detec[i]=xm_obs_detec[i]+1}
        }



        for (i in c(1:25)){
          if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){
            coverage[i]=NA
          } else if ((ll_new$xm_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_2sls_ul[i]>new$xm_coeff_y[i])){coverage[i]=coverage[i]+1}
        }

        for (i in c(1:25)){
          if ((ll_new$xm_z1_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_z1_2sls_ul[i]>new$xm_coeff_y[i])){z1_coverage[i]=z1_coverage[i]+
1}
        }


        for (i in c(1:25)){
          if ((ll_new$xm_obs_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_obs_ul[i]>new$xm_coeff_y[i])){obscoverage[i]=obscoverage[i]+1}
        }




        for (i in c(1:25)){
          if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){
            problem[i]=NA
```

```
          } else if (((ll_new$xm_2sls_ll[i]>0) &
(new$xm_coeff_y[i]<0))|((ul_new$xm_2sls_ul[i]<0) & (new$xm_coeff_y[i]>0)))
{problem[i]=problem[i]+1}#if interac detec, but coeff wrong direc
        }

        for (i in c(1:25)){
          if (((ll_new$xm_z1_2sls_ll[i]>0) &
(new$xm_coeff_y[i]<0))|((ul_new$xm_z1_2sls_ul[i]<0) &
(new$xm_coeff_y[i]>0))) {z1problem[i]=z1problem[i]+1}#if interac detec, but
coeff wrong direc
        }


        for (i in c(1:25)){
          if (new$fmr_interac_p[i]<0.05){fmr_y_int[i]=fmr_y_int[i]+1}
        }



      }



    }

  }



  #remove true values
  data_est=data.frame(data$x_obs,data$x_obs_se,
                      data$m_obs,data$m_obs_se,
                      data$xm_obs,data$xm_obs_se,
                      data$x_2sls,data$x_2sls_se,
                      data$x_z1_2sls,data$x_z1_2sls_se,
                      data$m_2sls,data$m_2sls_se,
                      data$m_z1_2sls,data$m_z1_2sls_se,
                      data$xm_2sls,data$xm_2sls_se,
                      data$xm_z1_2sls,data$xm_z1_2sls_se
  )



  #mean betas
  mean_denom=repeats*10 #no. rep within seeds * no. seeds
  data_mean=data_est/mean_denom #gives mean beta and mean se
  #add in the true params
  mean_betas=cbind(true_vals,data_mean)



############################################################################
############################################################################
#######################

  #now for the standard error
  checker=1

  for (seeds in
c(7821897,8376154,649384402,238140535,170379645,312006101,713795870,1693789
34,456561608,28335714)){
```

```
    for (rep in c(1:repeats)){

      if (checker==1){


newdata=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMRres.txt",s
ep=''),sep='\t',header=TRUE)
        newdata=(newdata-(data/mean_denom))^2
        checker=0

      } else if (checker==0){



newer=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMRres.txt",sep
=''),sep='\t',header=TRUE)
        newdata=newdata+(newer-(data/mean_denom))^2
        newdata=data.frame(newdata)


      }

    }
  }


  newdata_est=data.frame(newdata$x_obs,
                         newdata$m_obs,
                         newdata$xm_obs,
                         newdata$x_2sls,
                         newdata$x_z1_2sls,
                         newdata$m_2sls,
                         newdata$m_z1_2sls,
                         newdata$xm_2sls,
                         newdata$xm_z1_2sls
  )



  #divide by n-1 to get s^2
  s2=newdata_est/(repeats*10-1)
  se=sqrt(s2/(repeats*10))



###########################################################################
###########################################################################
############

  xm_2sls_detec=data.frame(xm_2sls_detec)
  xm_z1_2sls_detec=data.frame(xm_z1_2sls_detec)
  xm_obs_detec=data.frame(xm_obs_detec)
  coverage=data.frame(coverage)
  z1_coverage=data.frame(z1_coverage)
  obscoverage=data.frame(obscoverage)
  fmr_y_int=data.frame(fmr_y_int)

  #results table
  res=data.frame(mean_betas$data.x_coeff_m,
                 mean_betas$data.x_coeff_y,
```

```
                 mean_betas$data.m_coeff_y,
                 mean_betas$data.xm_coeff_y,
                 mean_betas$data.x_obs,
                 se$newdata.x_obs,
                 mean_betas$data.m_obs,
                 se$newdata.m_obs,
                 mean_betas$data.xm_obs,
                 se$newdata.xm_obs,
                 mean_betas$data.x_2sls,
                 se$newdata.x_2sls,
                 mean_betas$data.x_z1_2sls,
                 se$newdata.x_z1_2sls,
                 mean_betas$data.m_2sls,
                 se$newdata.m_2sls,
                 mean_betas$data.m_z1_2sls,
                 se$newdata.m_z1_2sls,
                 mean_betas$data.xm_2sls,
                 se$newdata.xm_2sls,
                 mean_betas$data.xm_z1_2sls,
                 se$newdata.xm_z1_2sls,
                 mean_betas$data.xm_obs_se,
                 mean_betas$data.xm_2sls_se,
                 mean_betas$data.xm_z1_2sls_se,
                 xm_obs_detec$xm_obs_detec,
                 xm_2sls_detec$xm_2sls_detec,
                 xm_z1_2sls_detec$xm_z1_2sls_detec,
                 coverage$coverage,
                 z1_coverage$z1_coverage,
                 obscoverage$obscoverage,
                 s2$newdata.xm_obs,
                 s2$newdata.xm_2sls,
                 s2$newdata.xm_z1_2sls,
                 fmr_y_int$fmr_y_int
  )




write.table(res,file=paste(nval,'_EXTRA_final_res.txt',sep=''),sep='\t',row
.names=FALSE)


  #how many times across all models and repeat sims is an interaction
detected in the incorrect direction?
  n_problem[n_prob_track]=sum(problem)
  n_prob_track=n_prob_track+1

  n_z1problem[n_z1prob_track]=sum(z1problem)
  n_z1prob_track=n_z1prob_track+1



}

write(n_problem, file='problem.txt',append=FALSE, sep = "\n")
write(n_z1problem, file='z1problem.txt',append=FALSE, sep = "\n")
```

```
#Now read back in so that we have all the data across all sample sizes

n_t1=c(1:25)
for (i in c(1:25)){
  n_t1[i]=10000
}
n_t2=c(1:25)
for (i in c(1:25)){
  n_t2[i]=20000
}
n_t3=c(1:25)
for (i in c(1:25)){
  n_t3[i]=30000
}
n_t4=c(1:25)
for (i in c(1:25)){
  n_t4[i]=40000
}
n_t5=c(1:25)
for (i in c(1:25)){
  n_t5[i]=50000
}
n_t6=c(1:25)
for (i in c(1:25)){
  n_t6[i]=60000
}
n_t7=c(1:25)
for (i in c(1:25)){
  n_t7[i]=70000
}
n_t8=c(1:25)
for (i in c(1:25)){
  n_t8[i]=80000
}
n_t9=c(1:25)
for (i in c(1:25)){
  n_t9[i]=90000
}
n_t10=c(1:25)
for (i in c(1:25)){
  n_t10[i]=100000
}
n_t50=c(1:25)
for (i in c(1:25)){
  n_t50[i]=500000
}
n_t100=c(1:25)
for (i in c(1:25)){
  n_t100[i]=1000000
}


sampsize=n_t1
t1=data.frame(sampsize,read.table(file=paste(10000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t2
t2=data.frame(sampsize,read.table(file=paste(20000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t3
t3=data.frame(sampsize,read.table(file=paste(30000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
```

```
sampsize=n_t4
t4=data.frame(sampsize,read.table(file=paste(40000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t5
t5=data.frame(sampsize,read.table(file=paste(50000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t6
t6=data.frame(sampsize,read.table(file=paste(60000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t7
t7=data.frame(sampsize,read.table(file=paste(70000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t8
t8=data.frame(sampsize,read.table(file=paste(80000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t9
t9=data.frame(sampsize,read.table(file=paste(90000,'_EXTRA_final_res.txt',s
ep=''),header=TRUE))
sampsize=n_t10
t10=data.frame(sampsize,read.table(file=paste(100000,'_EXTRA_final_res.txt'
,sep=''),header=TRUE))
sampsize=n_t50
t50=data.frame(sampsize,read.table(file=paste(500000,'_EXTRA_final_res.txt'
,sep=''),header=TRUE))
sampsize=n_t100
t100=data.frame(sampsize,read.table(file=paste(1000000,'_EXTRA_final_res.tx
t',sep=''),header=TRUE))

all=rbind(t1,t2,t3,t4,t5,t6,t7,t8,t9,t10,t50,t100)

headers=c('mediator_coeff','\t','interac_coeff', '\t',
'sample_size','\t','mean_est','\t',
          'sd(est)','\t','mean(se(est))','\t','se(est)','\t',
          'power','\t','type_i','\t','coverage')

res_l_0=all[round(all$mean_betas.data.xm_coeff_y,3)==0.000,]
res_l_m3=all[round(all$mean_betas.data.xm_coeff_y,3)==-0.111,]
res_l_3=all[round(all$mean_betas.data.xm_coeff_y,3)==0.111,]
res_l_5=all[round(all$mean_betas.data.xm_coeff_y,3)==0.167,]
res_l_1=all[round(all$mean_betas.data.xm_coeff_y,3)==0.333,]

res_l_0=res_l_0[order(res_l_0$mean_betas.data.x_coeff_m,res_l_0$sampsize),]
res_l_m3=res_l_m3[order(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$sampsiz
e),]
res_l_3=res_l_3[order(res_l_3$mean_betas.data.x_coeff_m,res_l_3$sampsize),]
res_l_5=res_l_5[order(res_l_5$mean_betas.data.x_coeff_m,res_l_5$sampsize),]
res_l_1=res_l_1[order(res_l_1$mean_betas.data.x_coeff_m,res_l_1$sampsize),]

blank=c(1:60)
for (i in c(1:60)){blank[i]='NA'}

##################################INTERACTION
COEFFICIENT#################################################################
#####################################################

#REMEMBER THAT THE VARIANCE NEEDS TO BE SQRT'D TO CONVERT TO SD
#POWER, TYPE I AND COVERAGE NEED TO BE DIVIDED BY 10 TO CONVERT TO %
##############
#Z=Z1+Z2+Z1Z2#
##############
```

```
edit_res_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_beta
s.data.xm_coeff_y,res_l_0$sampsize,res_l_0$mean_betas.data.xm_2sls,

sqrt(res_l_0$s2.newdata.xm_2sls),res_l_0$mean_betas.data.xm_2sls_se,res_l_0
$se.newdata.xm_2sls,blank,

(res_l_0$xm_2sls_detec.xm_2sls_detec)/10,(res_l_0$coverage.coverage)/10)
edit_res_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mean_b
etas.data.xm_coeff_y,res_l_m3$sampsize,res_l_m3$mean_betas.data.xm_2sls,

sqrt(res_l_m3$s2.newdata.xm_2sls),res_l_m3$mean_betas.data.xm_2sls_se,
res_l_m3$se.newdata.xm_2sls,(res_l_m3$xm_2sls_detec.xm_2sls_detec)/10,
                         blank, (res_l_m3$coverage.coverage)/10)
edit_res_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_beta
s.data.xm_coeff_y,res_l_3$sampsize,res_l_3$mean_betas.data.xm_2sls,

sqrt(res_l_3$s2.newdata.xm_2sls),res_l_3$mean_betas.data.xm_2sls_se,res_l_3
$se.newdata.xm_2sls,(res_l_3$xm_2sls_detec.xm_2sls_detec)/10,
                        blank, (res_l_3$coverage.coverage)/10)
edit_res_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_beta
s.data.xm_coeff_y,res_l_5$sampsize,res_l_5$mean_betas.data.xm_2sls,

sqrt(res_l_5$s2.newdata.xm_2sls),res_l_5$mean_betas.data.xm_2sls_se,res_l_5
$se.newdata.xm_2sls,(res_l_5$xm_2sls_detec.xm_2sls_detec)/10,
                        blank, (res_l_5$coverage.coverage)/10)
edit_res_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_beta
s.data.xm_coeff_y,res_l_1$sampsize,res_l_1$mean_betas.data.xm_2sls,

sqrt(res_l_1$s2.newdata.xm_2sls),res_l_1$mean_betas.data.xm_2sls_se,res_l_1
$se.newdata.xm_2sls,(res_l_1$xm_2sls_detec.xm_2sls_detec)/10,
                        blank, (res_l_1$coverage.coverage)/10)


#interaction coefficient=0
write.table(headers, file='TSLS_NOMED_L0.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED_L0.txt',append=TRUE, sep = "\n")
write.table(edit_res_l_0, file='TSLS_NOMED_L0.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers, file='TSLS_NOMED_LM3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED_LM3.txt',append=TRUE, sep = "\n")
write.table(edit_res_l_m3, file='TSLS_NOMED_LM3.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers, file='TSLS_NOMED_L3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED_L3.txt',append=TRUE, sep = "\n")
write.table(edit_res_l_3, file='TSLS_NOMED_L3.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=5
write.table(headers, file='TSLS_NOMED_L5.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED_L5.txt',append=TRUE, sep = "\n")
write.table(edit_res_l_5, file='TSLS_NOMED_L5.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
write.table(headers, file='TSLS_NOMED_L1.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED_L1.txt',append=TRUE, sep = "\n")
```

```
write.table(edit_res_l_1, file='TSLS_NOMED_L1.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)

###################
#Z=Z1+Z2+Z1Z2+Z1Z1#
###################

editZ1_res_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_be
tas.data.xm_coeff_y,res_l_0$sampsize,res_l_0$mean_betas.data.xm_z1_2sls,

sqrt(res_l_0$s2.newdata.xm_z1_2sls),res_l_0$mean_betas.data.xm_z1_2sls_se,r
es_l_0$se.newdata.xm_z1_2sls, blank,

(res_l_0$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,(res_l_0$z1_coverage.z1_cove
rage)/10)
editZ1_res_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mean
_betas.data.xm_coeff_y,res_l_m3$sampsize,res_l_m3$mean_betas.data.xm_z1_2sl
s,

sqrt(res_l_m3$s2.newdata.xm_z1_2sls),res_l_m3$mean_betas.data.xm_z1_2sls_se
,res_l_m3$se.newdata.xm_z1_2sls,(res_l_m3$xm_z1_2sls_detec.xm_z1_2sls_detec
)/10,
                           blank, (res_l_m3$z1_coverage.z1_coverage)/10)
editZ1_res_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_be
tas.data.xm_coeff_y,res_l_3$sampsize,res_l_3$mean_betas.data.xm_z1_2sls,

sqrt(res_l_3$s2.newdata.xm_z1_2sls),res_l_3$mean_betas.data.xm_z1_2sls_se,r
es_l_3$se.newdata.xm_z1_2sls,(res_l_3$xm_z1_2sls_detec.xm_z1_2sls_detec)/10
,
                          blank, (res_l_3$z1_coverage.z1_coverage)/10)
editZ1_res_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_be
tas.data.xm_coeff_y,res_l_5$sampsize,res_l_5$mean_betas.data.xm_z1_2sls,

sqrt(res_l_5$s2.newdata.xm_z1_2sls),res_l_5$mean_betas.data.xm_z1_2sls_se,r
es_l_5$se.newdata.xm_z1_2sls,(res_l_5$xm_z1_2sls_detec.xm_z1_2sls_detec)/10
,
                          blank, (res_l_5$z1_coverage.z1_coverage)/10)
editZ1_res_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_be
tas.data.xm_coeff_y,res_l_1$sampsize,res_l_1$mean_betas.data.xm_z1_2sls,

sqrt(res_l_1$s2.newdata.xm_z1_2sls),res_l_1$mean_betas.data.xm_z1_2sls_se,r
es_l_1$se.newdata.xm_z1_2sls,(res_l_1$xm_z1_2sls_detec.xm_z1_2sls_detec)/10
,
                          blank, (res_l_1$z1_coverage.z1_coverage)/10)


#interaction coefficient=0
write.table(headers, file='TSLS_MED_L0.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_L0.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_l_0, file='TSLS_MED_L0.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers, file='TSLS_MED_LM3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_LM3.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_l_m3, file='TSLS_MED_LM3.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers, file='TSLS_MED_L3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
```

```
write("", file='TSLS_MED_L3.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_l_3, file='TSLS_MED_L3.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=5
write.table(headers, file='TSLS_MED_L5.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_L5.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_l_5, file='TSLS_MED_L5.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
write.table(headers, file='TSLS_MED_L1.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_L1.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_l_1, file='TSLS_MED_L1.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)



#####
#FMR#
#####

headers2=c('mediator_coeff','\t','interac_coeff', '\t',
'sample_size','\t','power','\t','type_i')


editfmr_res_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_b
etas.data.xm_coeff_y,res_l_0$sampsize,blank,(res_l_0$fmr_y_int.fmr_y_int)/1
0)
editfmr_res_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mea
n_betas.data.xm_coeff_y,res_l_m3$sampsize,(res_l_m3$fmr_y_int.fmr_y_int)/10
,blank)
editfmr_res_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_b
etas.data.xm_coeff_y,res_l_3$sampsize,(res_l_3$fmr_y_int.fmr_y_int)/10,blan
k)
editfmr_res_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_b
etas.data.xm_coeff_y,res_l_5$sampsize,(res_l_5$fmr_y_int.fmr_y_int)/10,blan
k)
editfmr_res_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_b
etas.data.xm_coeff_y,res_l_1$sampsize,(res_l_1$fmr_y_int.fmr_y_int)/10,blan
k)


#interaction coefficient=0
write.table(headers2, file='fmr_L0.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='fmr_L0.txt',append=TRUE, sep = "\n")
write.table(editfmr_res_l_0, file='fmr_L0.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers2, file='fmr_LM3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='fmr_LM3.txt',append=TRUE, sep = "\n")
write.table(editfmr_res_l_m3, file='fmr_LM3.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers2, file='fmr_L3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='fmr_L3.txt',append=TRUE, sep = "\n")
write.table(editfmr_res_l_3, file='fmr_L3.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
```

```
#interaction coefficient=5
write.table(headers2, file='fmr_L5.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='fmr_L5.txt',append=TRUE, sep = "\n")
write.table(editfmr_res_l_5, file='fmr_L5.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
write.table(headers2, file='fmr_L1.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='fmr_L1.txt',append=TRUE, sep = "\n")
write.table(editfmr_res_l_1, file='fmr_L1.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)



###############
#OBSERVATIONAL#
###############

edit_obsres_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_b
etas.data.xm_coeff_y,res_l_0$sampsize,res_l_0$mean_betas.data.xm_obs,

sqrt(res_l_0$s2.newdata.xm_obs),res_l_0$mean_betas.data.xm_obs_se,res_l_0$s
e.newdata.xm_obs,blank,

(res_l_0$xm_obs_detec.xm_obs_detec)/10,(res_l_0$obscoverage.obscoverage)/10
)

edit_obsres_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mea
n_betas.data.xm_coeff_y,res_l_m3$sampsize,res_l_m3$mean_betas.data.xm_obs,

sqrt(res_l_m3$s2.newdata.xm_obs),res_l_m3$mean_betas.data.xm_obs_se,res_l_m
3$se.newdata.xm_obs,(res_l_m3$xm_obs_detec.xm_obs_detec)/10,
                            blank, (res_l_m3$obscoverage.obscoverage)/10)

edit_obsres_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_b
etas.data.xm_coeff_y,res_l_3$sampsize,res_l_3$mean_betas.data.xm_obs,

sqrt(res_l_3$s2.newdata.xm_obs),res_l_3$mean_betas.data.xm_obs_se,res_l_3$s
e.newdata.xm_obs,(res_l_3$xm_obs_detec.xm_obs_detec)/10,
                           blank, (res_l_3$obscoverage.obscoverage)/10)

edit_obsres_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_b
etas.data.xm_coeff_y,res_l_5$sampsize,res_l_5$mean_betas.data.xm_obs,

sqrt(res_l_5$s2.newdata.xm_obs),res_l_5$mean_betas.data.xm_obs_se,res_l_5$s
e.newdata.xm_obs,(res_l_5$xm_obs_detec.xm_obs_detec)/10,
                           blank, (res_l_5$obscoverage.obscoverage)/10)

edit_obsres_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_b
etas.data.xm_coeff_y,res_l_1$sampsize,res_l_1$mean_betas.data.xm_obs,

sqrt(res_l_1$s2.newdata.xm_obs),res_l_1$mean_betas.data.xm_obs_se,res_l_1$s
e.newdata.xm_obs,(res_l_1$xm_obs_detec.xm_obs_detec)/10,
                           blank, (res_l_1$obscoverage.obscoverage)/10)



#interaction coefficient=0
write.table(headers, file='OBS_L0.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
```

```
write("", file='OBS_L0.txt',append=TRUE, sep = "\n")
write.table(edit_obsres_l_0, file='OBS_L0.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers, file='OBS_LM3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_LM3.txt',append=TRUE, sep = "\n")
write.table(edit_obsres_l_m3, file='OBS_LM3.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers, file='OBS_L3.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_L3.txt',append=TRUE, sep = "\n")
write.table(edit_obsres_l_3, file='OBS_L3.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=5
write.table(headers, file='OBS_L5.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_L5.txt',append=TRUE, sep = "\n")
write.table(edit_obsres_l_5, file='OBS_L5.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
write.table(headers, file='OBS_L1.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_L1.txt',append=TRUE, sep = "\n")
write.table(edit_obsres_l_1, file='OBS_L1.txt',append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
```

4.6.3 Pooling of results with robust SEs

```
#script_name: pool_sim_pap1_obs_and_other_est_SC_1krep_v7_b.r
#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: pool estimates across simulation repeats by
#                 -taking the mean betahat & SE of betahats (to generate MC
95% CI for betahat)
#                 -take the mean SE and the SD of betahats
#                 -calculate power, type i error and coverage where
applicable
#date created: 03/01/2019
#last edited: 17/01/2019
#notes:

setwd('') #Folder 1

#number of repeats in each sim
repeats=100

n_z1problem=c(1:2)
for (j in c(1:2)){n_z1problem[j]=0}
n_z1prob_track=1

for (nval in c(50000,500000)){
```

```
  xm_z1_2sls_detec=c(1:25)
  for (i in c(1:25)){
    xm_z1_2sls_detec[i]=0
  }
  xm_obs_detec=c(1:25) # counter for # times interaction is detected (null
is rejected) at 5% level
  for (i in c(1:25)){
    xm_obs_detec[i]=0
  }


  z1_coverage=c(1:25)
  for (i in c(1:25)){
    z1_coverage[i]=0
  }
  obscoverage=c(1:25)
  for (i in c(1:25)){
    obscoverage[i]=0
  }

  #reality check
  #how many times is the interaction detected (p<0.05), but the estimate is
in the opposite direction to true effect?
  z1problem=c(1:25)
  for (i in c(1:25)){
    z1problem[i]=0
  }


  #calculating the mean betas
  first=1


  for (seedval in
c(7821897,8376154,649384402,238140535,170379645,312006101,713795870,1693789
34,456561608,28335714)){

    for (rep in c(1:repeats)){

      if (first==1){


data=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res
.txt",sep=''),sep='\t',header=TRUE)
        true_vals=data.frame(data$x_coeff_m,data$x_coeff_y,data$m_coeff_y,
data$xm_coeff_y)
        first=0

        ll=data.frame(
          xm_z1_2sls_ll=data$xm_z1_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_z1_2sls_se,
          xm_obs_ll=data$xm_obs-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_obs_se
        )

        ul=data.frame(
          xm_z1_2sls_ul=data$xm_z1_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_z1_2sls_se,
          xm_obs_ul=data$xm_obs+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_obs_se
        )
```

```
        for (i in c(1:25)){
          if (ll$xm_z1_2sls_ll[i]>0 |
ul$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=1}
        }


        for (i in c(1:25)){
          if (ll$xm_obs_ll[i]>0 | ul$xm_obs_ul[i]<0){xm_obs_detec[i]=1}
        }


        for (i in c(1:25)){
          if ((ll$xm_z1_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_z1_2sls_ul[i]>data$xm_coeff_y[i])){z1_coverage[i]=1}
        }


        for (i in c(1:25)){
          if ((ll$xm_obs_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_obs_ul[i]>data$xm_coeff_y[i])){obscoverage[i]=1}
        }


        for (i in c(1:25)){
          if (((ll$xm_z1_2sls_ll[i]>0) &
(data$xm_coeff_y[i]<0))|((ul$xm_z1_2sls_ul[i]<0) & (data$xm_coeff_y[i]>0)))
{z1problem[i]=1}#if interac detec, but coeff wrong direc
        }




      } else if (first==0){


new=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res.
txt",sep=''),sep='\t',header=TRUE)
        data=data+new

        ll_new=data.frame(
          xm_z1_2sls_ll=new$xm_z1_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_z1_2sls_se,
          xm_obs_ll=new$xm_obs-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_obs_se
        )

        ul_new=data.frame(
          xm_z1_2sls_ul=new$xm_z1_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_z1_2sls_se,
          xm_obs_ul=new$xm_obs+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_obs_se
        )



        for (i in c(1:25)){
          if (ll_new$xm_z1_2sls_ll[i]>0 |
ul_new$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=xm_z1_2sls_detec[i]+1}
        }
```

```
        for (i in c(1:25)){
          if (ll_new$xm_obs_ll[i]>0 |
ul_new$xm_obs_ul[i]<0){xm_obs_detec[i]=xm_obs_detec[i]+1}
        }



        for (i in c(1:25)){
          if ((ll_new$xm_z1_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_z1_2sls_ul[i]>new$xm_coeff_y[i])){z1_coverage[i]=z1_coverage[i]+
1}
        }


        for (i in c(1:25)){
          if ((ll_new$xm_obs_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_obs_ul[i]>new$xm_coeff_y[i])){obscoverage[i]=obscoverage[i]+1}
        }




        for (i in c(1:25)){
          if (((ll_new$xm_z1_2sls_ll[i]>0) &
(new$xm_coeff_y[i]<0))|((ul_new$xm_z1_2sls_ul[i]<0) &
(new$xm_coeff_y[i]>0))) {z1problem[i]=z1problem[i]+1}#if interac detec, but
coeff wrong direc
        }




      }




    }

  }



  #remove true values
  data_est=data.frame(data$x_obs,data$x_obs_se,
                      data$m_obs,data$m_obs_se,
                      data$xm_obs,data$xm_obs_se,
                      data$x_2sls,data$x_2sls_se,
                      data$x_z1_2sls,data$x_z1_2sls_se,
                      data$m_2sls,data$m_2sls_se,
                      data$m_z1_2sls,data$m_z1_2sls_se,
                      data$xm_2sls,data$xm_2sls_se,
                      data$xm_z1_2sls,data$xm_z1_2sls_se
  )



  #mean betas
  mean_denom=repeats*10 #no. rep within seeds * no. seeds
  data_mean=data_est/mean_denom #gives mean beta and mean se
```

```
  #add in the true params
  mean_betas=cbind(true_vals,data_mean)



##########################################################################
##########################################################################
#######################

  #now for the standard error
  checker=1

  for (seeds in
c(7821897,8376154,649384402,238140535,170379645,312006101,713795870,1693789
34,456561608,28335714)){

    for (rep in c(1:repeats)){

      if (checker==1){


newdata=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMR_ROBUST_re
s.txt",sep=''),sep='\t',header=TRUE)
        newdata=(newdata-(data/mean_denom))^2
        checker=0

      } else if (checker==0){



newer=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMR_ROBUST_res.
txt",sep=''),sep='\t',header=TRUE)
        newdata=newdata+(newer-(data/mean_denom))^2
        newdata=data.frame(newdata)


      }

    }
  }


  newdata_est=data.frame(newdata$x_obs,
                         newdata$m_obs,
                         newdata$xm_obs,
                         newdata$x_2sls,
                         newdata$x_z1_2sls,
                         newdata$m_2sls,
                         newdata$m_z1_2sls,
                         newdata$xm_2sls,
                         newdata$xm_z1_2sls
  )



  #divide by n-1 to get s^2
  s2=newdata_est/(repeats*10-1)
  se=sqrt(s2/(repeats*10))
```

```
##########################################################################
##########################################################################
############

  xm_z1_2sls_detec=data.frame(xm_z1_2sls_detec)
  xm_obs_detec=data.frame(xm_obs_detec)
  z1_coverage=data.frame(z1_coverage)
  obscoverage=data.frame(obscoverage)

  #results table
  res=data.frame(mean_betas$data.x_coeff_m,
                 mean_betas$data.x_coeff_y,
                 mean_betas$data.m_coeff_y,
                 mean_betas$data.xm_coeff_y,
                 mean_betas$data.xm_obs,
                 se$newdata.xm_obs,
                 mean_betas$data.xm_z1_2sls,
                 se$newdata.xm_z1_2sls,
                 mean_betas$data.xm_obs_se,
                 mean_betas$data.xm_z1_2sls_se,
                 xm_obs_detec$xm_obs_detec,
                 xm_z1_2sls_detec$xm_z1_2sls_detec,
                 z1_coverage$z1_coverage,
                 obscoverage$obscoverage,
                 s2$newdata.xm_obs,
                 s2$newdata.xm_z1_2sls)





write.table(res,file=paste(nval,'_EXTRA_final_ROBUST_res.txt',sep=''),sep='
\t',row.names=FALSE)


  #how many times across all models and repeat sims is an interaction
detected in the incorrect direction?
  n_z1problem[n_z1prob_track]=sum(z1problem)
  n_z1prob_track=n_z1prob_track+1



}

write(n_z1problem, file='z1_ROBUST_problem.txt',append=FALSE, sep = "\n")


#Now read back in so that we have all the data across all sample sizes


n_t5=c(1:25)
for (i in c(1:25)){
  n_t5[i]=50000
}
n_t50=c(1:25)
for (i in c(1:25)){
  n_t50[i]=500000
}
```

```
sampsize=n_t5
t5=data.frame(sampsize,read.table(file=paste(50000,'_EXTRA_final_ROBUST_res
.txt',sep=''),header=TRUE))
sampsize=n_t50
t50=data.frame(sampsize,read.table(file=paste(500000,'_EXTRA_final_ROBUST_r
es.txt',sep=''),header=TRUE))

all=rbind(t5,t50)

headers=c('mediator_coeff','\t','interac_coeff', '\t',
'sample_size','\t','mean_est','\t',
          'sd(est)','\t','mean(se(est))','\t','se(est)','\t',
          'power/type_i','\t','coverage')

res_N_50=all[all$sampsize==50000,]
res_N_500=all[all$sampsize==500000,]

res_N_50=res_N_50[order(res_N_50$mean_betas.data.x_coeff_m,res_N_50$mean_be
tas.data.xm_coeff_y),]
res_N_500=res_N_500[order(res_N_500$mean_betas.data.x_coeff_m,res_N_500$mea
n_betas.data.xm_coeff_y),]

##################################INTERACTION
COEFFICIENT#########################################################
####################################################

#REMEMBER THAT THE VARIANCE NEEDS TO BE SQRT'D TO CONVERT TO SD
#POWER, TYPE I AND COVERAGE NEED TO BE DIVIDED BY 10 TO CONVERT TO %

###################
#Z=Z1+Z2+Z1Z2+Z1Z1#
###################

editZ1_res_N_50=data.frame(res_N_50$mean_betas.data.x_coeff_m,res_N_50$mean
_betas.data.xm_coeff_y,res_N_50$sampsize,res_N_50$mean_betas.data.xm_z1_2sl
s,

sqrt(res_N_50$s2.newdata.xm_z1_2sls),res_N_50$mean_betas.data.xm_z1_2sls_se
,res_N_50$se.newdata.xm_z1_2sls,

(res_N_50$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,(res_N_50$z1_coverage.z1_co
verage)/10)
editZ1_res_N_500=data.frame(res_N_500$mean_betas.data.x_coeff_m,res_N_500$m
ean_betas.data.xm_coeff_y,res_N_500$sampsize,res_N_500$mean_betas.data.xm_z
1_2sls,

sqrt(res_N_500$s2.newdata.xm_z1_2sls),res_N_500$mean_betas.data.xm_z1_2sls_
se,res_N_500$se.newdata.xm_z1_2sls,(res_N_500$xm_z1_2sls_detec.xm_z1_2sls_d
etec)/10,
                           (res_N_500$z1_coverage.z1_coverage)/10)



#sample size=50k
write.table(headers, file='TSLS_MED_SS50K_ROBSE.txt',append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_SS50K_ROBSE.txt',append=TRUE, sep = "\n")
```

```
write.table(editZ1_res_N_50, file='TSLS_MED_SS50K_ROBSE.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#sample size=500k
write.table(headers, file='TSLS_MED_SS500K_ROBSE.txt',append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='TSLS_MED_SS500K_ROBSE.txt',append=TRUE, sep = "\n")
write.table(editZ1_res_N_500, file='TSLS_MED_SS500K_ROBSE.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)



###############
#OBSERVATIONAL#
###############

edit_obs_res_N_50=data.frame(res_N_50$mean_betas.data.x_coeff_m,res_N_50$me
an_betas.data.xm_coeff_y,res_N_50$sampsize,res_N_50$mean_betas.data.xm_obs,

sqrt(res_N_50$s2.newdata.xm_obs),res_N_50$mean_betas.data.xm_obs_se,res_N_5
0$se.newdata.xm_obs,

(res_N_50$xm_obs_detec.xm_obs_detec)/10,(res_N_50$obscoverage.obscoverage)/
10)

edit_obs_res_N_500=data.frame(res_N_500$mean_betas.data.x_coeff_m,res_N_500
$mean_betas.data.xm_coeff_y,res_N_500$sampsize,res_N_500$mean_betas.data.xm
_obs,

sqrt(res_N_500$s2.newdata.xm_obs),res_N_500$mean_betas.data.xm_obs_se,res_N
_500$se.newdata.xm_obs,(res_N_500$xm_obs_detec.xm_obs_detec)/10,
                            (res_N_500$obscoverage.obscoverage)/10)

#sample size=50k
write.table(headers, file='OBS_SS50K_ROBSE.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_SS50K_ROBSE.txt',append=TRUE, sep = "\n")
write.table(edit_obs_res_N_50, file='OBS_SS50K_ROBSE.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
#sample size=500k
write.table(headers, file='OBS_SS500K_ROBSE.txt',append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file='OBS_SS500K_ROBSE.txt',append=TRUE, sep = "\n")
write.table(edit_obs_res_N_500, file='OBS_SS500K_ROBSE.txt',append=TRUE,
quote=FALSE, row.names=FALSE, col.names=FALSE)
```

4.6.4 F statistics

```
#script_name: pool_sim_pap1_obs_and_other_est_SC_1krep_v7_c.r
#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: pool estimates across simulation repeats by
#                 -taking the mean betahat & SE of betahats (to generate MC
95% CI for betahat)
#                 -take the mean SE and the SD of betahats
```

```
#                  -calculate power, type i error and coverage where
applicable
#date created: 15/01/2019
#last edited: 18/01/2019
#notes:

setwd('') #Folder 1

install.packages('car')
library('car')

#number of repeats in each sim
repeats=100

#headers
headers=c('mediator_coeff','interac_coeff',
'F_statistic_2sls_assuming_no_mediation','F_statistic_2sls_assuming_mediati
on')

for (nval in
c(10000,20000,30000,40000,50000,60000,70000,80000,90000,100000,500000,10000
00)){

  meanF=c(1:25)
  for (i in c(1:25)){
    meanF[i]=NA
  }

  meanz1F=c(1:25)
  for (i in c(1:25)){
    meanz1F[i]=NA
  }


  #calculating the mean F statistics
  first=1


  for (seedval in
c(7821897,8376154,649384402,238140535,170379645,312006101,713795870,1693789
34,456561608,28335714)){

    for (rep in c(1:repeats)){

      if (first==1){


data=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_F_res.txt"
,sep=''),sep='\t',header=TRUE)
        true_vals=data.frame(data$x_coeff_m,data$xm_coeff_y)
        first=0

      } else if (first==0){


new=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMR_F_res.txt",
sep=''),sep='\t',header=TRUE)
        data=data+new


      }
```

```
    }

  }

  #remove true values
  data_est=data.frame(data$F_2SLS,data$F_Z1_2SLS)

  #mean betas
  mean_denom=repeats*10 #no. rep within seeds * no. seeds

  mean_F_stats=data_est/mean_denom

  #add in the true params
  mean_F_stats=cbind(true_vals,mean_F_stats)
  mean_F_stats=rbind(headers,mean_F_stats)


write.table(mean_F_stats,file=paste(nval,'_mean_F_stats.txt',sep=''),sep='\
t',row.names=FALSE,quote=FALSE,col.names=FALSE)

}



#now read back in, de-duplicate and analyse across sample sizes
F_10K=read.table(file="10000_mean_F_stats.txt",sep='\t',header=TRUE)
F_20K=read.table(file="20000_mean_F_stats.txt",sep='\t',header=TRUE)
F_30K=read.table(file="30000_mean_F_stats.txt",sep='\t',header=TRUE)
F_40K=read.table(file="40000_mean_F_stats.txt",sep='\t',header=TRUE)
F_50K=read.table(file="50000_mean_F_stats.txt",sep='\t',header=TRUE)
F_60K=read.table(file="60000_mean_F_stats.txt",sep='\t',header=TRUE)
F_70K=read.table(file="70000_mean_F_stats.txt",sep='\t',header=TRUE)
F_80K=read.table(file="80000_mean_F_stats.txt",sep='\t',header=TRUE)
F_90K=read.table(file="90000_mean_F_stats.txt",sep='\t',header=TRUE)
F_100K=read.table(file="1e+05_mean_F_stats.txt",sep='\t',header=TRUE)
F_500K=read.table(file="5e+05_mean_F_stats.txt",sep='\t',header=TRUE)
F_1000K=read.table(file="1e+06_mean_F_stats.txt",sep='\t',header=TRUE)

F_10K=data.frame(F_10K$mediator_coeff,F_10K$F_statistic_2sls_assuming_no_me
diation,F_10K$F_statistic_2sls_assuming_mediation)
F_20K=data.frame(F_20K$mediator_coeff,F_20K$F_statistic_2sls_assuming_no_me
diation,F_20K$F_statistic_2sls_assuming_mediation)
F_30K=data.frame(F_30K$mediator_coeff,F_30K$F_statistic_2sls_assuming_no_me
diation,F_30K$F_statistic_2sls_assuming_mediation)
F_40K=data.frame(F_40K$mediator_coeff,F_40K$F_statistic_2sls_assuming_no_me
diation,F_40K$F_statistic_2sls_assuming_mediation)
F_50K=data.frame(F_50K$mediator_coeff,F_50K$F_statistic_2sls_assuming_no_me
diation,F_50K$F_statistic_2sls_assuming_mediation)
F_60K=data.frame(F_60K$mediator_coeff,F_60K$F_statistic_2sls_assuming_no_me
diation,F_60K$F_statistic_2sls_assuming_mediation)
F_70K=data.frame(F_70K$mediator_coeff,F_70K$F_statistic_2sls_assuming_no_me
diation,F_70K$F_statistic_2sls_assuming_mediation)
F_80K=data.frame(F_80K$mediator_coeff,F_80K$F_statistic_2sls_assuming_no_me
diation,F_80K$F_statistic_2sls_assuming_mediation)
F_90K=data.frame(F_90K$mediator_coeff,F_90K$F_statistic_2sls_assuming_no_me
diation,F_90K$F_statistic_2sls_assuming_mediation)
F_100K=data.frame(F_100K$mediator_coeff,F_100K$F_statistic_2sls_assuming_no
_mediation,F_100K$F_statistic_2sls_assuming_mediation)
```

```
F_500K=data.frame(F_500K$mediator_coeff,F_500K$F_statistic_2sls_assuming_no
_mediation,F_500K$F_statistic_2sls_assuming_mediation)
F_1000K=data.frame(F_1000K$mediator_coeff,F_1000K$F_statistic_2sls_assuming
_no_mediation,F_1000K$F_statistic_2sls_assuming_mediation)

F_10K=unique(F_10K)
F_20K=unique(F_20K)
F_30K=unique(F_30K)
F_40K=unique(F_40K)
F_50K=unique(F_50K)
F_60K=unique(F_60K)
F_70K=unique(F_70K)
F_80K=unique(F_80K)
F_90K=unique(F_90K)
F_100K=unique(F_100K)
F_500K=unique(F_500K)
F_1000K=unique(F_1000K)

n_10k=c(10000,10000,10000,10000,10000)
n_20k=c(20000,20000,20000,20000,20000)
n_30k=c(30000,30000,30000,30000,30000)
n_40k=c(40000,40000,40000,40000,40000)
n_50k=c(50000,50000,50000,50000,50000)
n_60k=c(60000,60000,60000,60000,60000)
n_70k=c(70000,70000,70000,70000,70000)
n_80k=c(80000,80000,80000,80000,80000)
n_90k=c(90000,90000,90000,90000,90000)
n_100k=c(100000,100000,100000,100000,100000)
n_500k=c(500000,500000,500000,500000,500000)
n_1000k=c(1000000,1000000,1000000,1000000,1000000)

F_10K=cbind(F_10K,n_10k)
F_20K=cbind(F_20K,n_20k)
F_30K=cbind(F_30K,n_30k)
F_40K=cbind(F_40K,n_40k)
F_50K=cbind(F_50K,n_50k)
F_60K=cbind(F_60K,n_60k)
F_70K=cbind(F_70K,n_70k)
F_80K=cbind(F_80K,n_80k)
F_90K=cbind(F_90K,n_90k)
F_100K=cbind(F_100K,n_100k)
F_500K=cbind(F_500K,n_500k)
F_1000K=cbind(F_1000K,n_1000k)


colnames(F_10K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_20K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_30K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_40K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_50K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_60K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_70K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_80K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
```

```
colnames(F_90K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation'
,'F_statistic_2sls_assuming_mediation','N')
colnames(F_100K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation
','F_statistic_2sls_assuming_mediation','N')
colnames(F_500K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediation
','F_statistic_2sls_assuming_mediation','N')
colnames(F_1000K)=c('mediator_coeff','F_statistic_2sls_assuming_no_mediatio
n','F_statistic_2sls_assuming_mediation','N')

ALLDAT=rbind(F_10K,F_20K,F_30K,F_40K,F_50K,F_60K,F_70K,F_80K,F_90K,F_100K,F
_500K,F_1000K)

ALLDAT=ALLDAT[order(ALLDAT$mediator_coeff,ALLDAT$N),]
#write table to file
write.table(ALLDAT,file="F_stats_final_table.txt",sep='\t',row.names=FALSE,
quote=FALSE,col.names=TRUE)

#plots
setwd('plots/')

tiff('SWF_nomed.tif',width=7,height=3.5,units='in',res=400)
scatterplot(ALLDAT$N,ALLDAT$F_statistic_2sls_assuming_no_mediation,groups=A
LLDAT$mediator_coeff,xlab='sample size',
            ylab='S-W F Statistic,
Z=(Z1,Z2,Z1Z2)',legend=list(title='alpha',cex=0.5),cex.lab=0.5,cex.axis=0.5
)
abline(h=10)
dev.off()

tiff('SWF_med.tif',width=7,height=3.5,units='in',res=400)
scatterplot(ALLDAT$N,ALLDAT$F_statistic_2sls_assuming_mediation,groups=ALLD
AT$mediator_coeff,xlab='sample size',
            ylab='S-W F Statistic,
Z=(Z1,Z2,Z1Z2,Z1Z1)',legend=list(title='alpha',cex=0.5),cex.lab=0.5,cex.axi
s=0.5)
abline(h=10)
dev.off()

smallsamp=ALLDAT[ALLDAT$N<=100000,]

tiff('SWF_nomed_smallsamp.tif',width=7,height=3.5,units='in',res=400)
scatterplot(smallsamp$N,smallsamp$F_statistic_2sls_assuming_no_mediation,gr
oups=smallsamp$mediator_coeff,xlab='sample size',
            ylab='S-W F Statistic,
Z=(Z1,Z2,Z1Z2)',legend=list(title='alpha',cex=0.5),cex.lab=0.5,cex.axis=0.5
)
abline(h=10)
dev.off()

tiff('SWF_med_smallsamp.tif',width=7,height=3.5,units='in',res=400)
scatterplot(smallsamp$N,smallsamp$F_statistic_2sls_assuming_mediation,group
s=smallsamp$mediator_coeff,xlab='sample size',
            ylab='S-W F Statistic,
Z=(Z1,Z2,Z1Z2,Z1Z1)',legend=list(title='alpha',cex=0.5),cex.lab=0.5,cex.axi
s=0.5)
abline(h=10)
dev.off()
```

4.6.5 Create plots

```
#script_name: forest_plot_PAP1_V4.r
#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: plot results for mr interactions paper
#date created: 22/01/2019
#last edited:02/02/2019
#notes:

writeplot='' #Folder 2
dataloc='' #Folder 1
setwd(dataloc)

#COEFFICIENT PLOTS
#PREP THE N=50K DATA
N_50=data.frame(read.table(file=paste(50000,"_EXTRA_final_res.txt",sep=''),
sep='\t',header=TRUE))
N_50=N_50[order(N_50$mean_betas.data.xm_coeff_y,N_50$mean_betas.data.x_coef
f_m),]
tsls_xm_lower_N_50=N_50$mean_betas.data.xm_2sls-
1.96*N_50$se.newdata.xm_2sls
tsls_xm_upper_N_50=N_50$mean_betas.data.xm_2sls+1.96*N_50$se.newdata.xm_2sl
s
tsls_z1_xm_lower_N_50=N_50$mean_betas.data.xm_z1_2sls-
1.96*N_50$se.newdata.xm_z1_2sls
tsls_z1_xm_upper_N_50=N_50$mean_betas.data.xm_z1_2sls+1.96*N_50$se.newdata.
xm_z1_2sls
obs_xm_lower_N_50=N_50$mean_betas.data.xm_obs-1.96*N_50$se.newdata.xm_obs
obs_xm_upper_N_50=N_50$mean_betas.data.xm_obs+1.96*N_50$se.newdata.xm_obs
N_50=data.frame(N_50,tsls_xm_lower_N_50,tsls_xm_upper_N_50,tsls_z1_xm_lower
_N_50,tsls_z1_xm_upper_N_50,
                obs_xm_lower_N_50,obs_xm_upper_N_50)
N_50_interac_m3=N_50[round(N_50$mean_betas.data.xm_coeff_y,3)==-0.111,]
N_50_interac_0=N_50[round(N_50$mean_betas.data.xm_coeff_y,3)==0,]
N_50_interac_3=N_50[round(N_50$mean_betas.data.xm_coeff_y,3)==0.111,]
N_50_interac_5=N_50[round(N_50$mean_betas.data.xm_coeff_y,3)==0.167,]
N_50_interac_1=N_50[round(N_50$mean_betas.data.xm_coeff_y,3)==0.333,]

#2SLS Z=(Z1,Z2,Z1Z2) N=50K
setwd(writeplot)
tiff('coef_plot_z1z2_50k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_50_interac_m3$mean_betas.data.xm_2sls,N_50_interac_m3$mean_betas.dat
a.x_coeff_m,xlim=c(-2,2),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2)',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_50_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-2,-1.5,-1,-0.5,-0.111,0,0.5,1,1.5,2),labels=c('-2','-
1.5','-1','-0.5','-0.111','0','0.5','1','1.5','2'),cex.axis=0.25)
lines(c(N_50_interac_m3$tsls_xm_lower_N_50[1],N_50_interac_m3$tsls_xm_upper
_N_50[1]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[1],N_50_interac_m3$me
an_betas.data.x_coeff_m[1]))
```

```
lines(c(N_50_interac_m3$tsls_xm_lower_N_50[2],N_50_interac_m3$tsls_xm_upper
_N_50[2]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[2],N_50_interac_m3$me
an_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_m3$tsls_xm_lower_N_50[3],N_50_interac_m3$tsls_xm_upper
_N_50[3]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[3],N_50_interac_m3$me
an_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_m3$tsls_xm_lower_N_50[4],N_50_interac_m3$tsls_xm_upper
_N_50[4]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[4],N_50_interac_m3$me
an_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_m3$tsls_xm_lower_N_50[5],N_50_interac_m3$tsls_xm_upper
_N_50[5]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[5],N_50_interac_m3$me
an_betas.data.x_coeff_m[5]))
plot(N_50_interac_0$mean_betas.data.xm_2sls,N_50_interac_0$mean_betas.data.
x_coeff_m,xlim=c(-2,2),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_50_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-2,-1.5,-1,-0.5,0,0.5,1,1.5,2),labels=c('-2','-1.5','-
1','-0.5','0','0.5','1','1.5','2'),cex.axis=0.25)
lines(c(N_50_interac_0$tsls_xm_lower_N_50[1],N_50_interac_0$tsls_xm_upper_N
_50[1]),c(N_50_interac_0$mean_betas.data.x_coeff_m[1],N_50_interac_0$mean_b
etas.data.x_coeff_m[1]))
lines(c(N_50_interac_0$tsls_xm_lower_N_50[2],N_50_interac_0$tsls_xm_upper_N
_50[2]),c(N_50_interac_0$mean_betas.data.x_coeff_m[2],N_50_interac_0$mean_b
etas.data.x_coeff_m[2]))
lines(c(N_50_interac_0$tsls_xm_lower_N_50[3],N_50_interac_0$tsls_xm_upper_N
_50[3]),c(N_50_interac_0$mean_betas.data.x_coeff_m[3],N_50_interac_0$mean_b
etas.data.x_coeff_m[3]))
lines(c(N_50_interac_0$tsls_xm_lower_N_50[4],N_50_interac_0$tsls_xm_upper_N
_50[4]),c(N_50_interac_0$mean_betas.data.x_coeff_m[4],N_50_interac_0$mean_b
etas.data.x_coeff_m[4]))
lines(c(N_50_interac_0$tsls_xm_lower_N_50[5],N_50_interac_0$tsls_xm_upper_N
_50[5]),c(N_50_interac_0$mean_betas.data.x_coeff_m[5],N_50_interac_0$mean_b
etas.data.x_coeff_m[5]))
plot(N_50_interac_3$mean_betas.data.xm_2sls,N_50_interac_3$mean_betas.data.
x_coeff_m,xlim=c(-2,2),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_50_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-2,-1.5,-1,-0.5,0,0.111,0.5,1,1.5,2),labels=c('-2','-
1.5','-1','-0.5','0','0.111','0.5','1','1.5','2'),cex.axis=0.25)
lines(c(N_50_interac_3$tsls_xm_lower_N_50[1],N_50_interac_3$tsls_xm_upper_N
_50[1]),c(N_50_interac_3$mean_betas.data.x_coeff_m[1],N_50_interac_3$mean_b
etas.data.x_coeff_m[1]))
lines(c(N_50_interac_3$tsls_xm_lower_N_50[2],N_50_interac_3$tsls_xm_upper_N
_50[2]),c(N_50_interac_3$mean_betas.data.x_coeff_m[2],N_50_interac_3$mean_b
etas.data.x_coeff_m[2]))
lines(c(N_50_interac_3$tsls_xm_lower_N_50[3],N_50_interac_3$tsls_xm_upper_N
_50[3]),c(N_50_interac_3$mean_betas.data.x_coeff_m[3],N_50_interac_3$mean_b
etas.data.x_coeff_m[3]))
lines(c(N_50_interac_3$tsls_xm_lower_N_50[4],N_50_interac_3$tsls_xm_upper_N
_50[4]),c(N_50_interac_3$mean_betas.data.x_coeff_m[4],N_50_interac_3$mean_b
etas.data.x_coeff_m[4]))
lines(c(N_50_interac_3$tsls_xm_lower_N_50[5],N_50_interac_3$tsls_xm_upper_N
_50[5]),c(N_50_interac_3$mean_betas.data.x_coeff_m[5],N_50_interac_3$mean_b
etas.data.x_coeff_m[5]))
plot(N_50_interac_5$mean_betas.data.xm_2sls,N_50_interac_5$mean_betas.data.
x_coeff_m,xlim=c(-2,2),cex=0.5,
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     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_50_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-2,-1.5,-1,-0.5,0,0.167,0.5,1,1.5,2),labels=c('-2','-
1.5','-1','-0.5','0','0.167','0.5','1','1.5','2'),cex.axis=0.25)
lines(c(N_50_interac_5$tsls_xm_lower_N_50[1],N_50_interac_5$tsls_xm_upper_N
_50[1]),c(N_50_interac_5$mean_betas.data.x_coeff_m[1],N_50_interac_5$mean_b
etas.data.x_coeff_m[1]))
lines(c(N_50_interac_5$tsls_xm_lower_N_50[2],N_50_interac_5$tsls_xm_upper_N
_50[2]),c(N_50_interac_5$mean_betas.data.x_coeff_m[2],N_50_interac_5$mean_b
etas.data.x_coeff_m[2]))
lines(c(N_50_interac_5$tsls_xm_lower_N_50[3],N_50_interac_5$tsls_xm_upper_N
_50[3]),c(N_50_interac_5$mean_betas.data.x_coeff_m[3],N_50_interac_5$mean_b
etas.data.x_coeff_m[3]))
lines(c(N_50_interac_5$tsls_xm_lower_N_50[4],N_50_interac_5$tsls_xm_upper_N
_50[4]),c(N_50_interac_5$mean_betas.data.x_coeff_m[4],N_50_interac_5$mean_b
etas.data.x_coeff_m[4]))
lines(c(N_50_interac_5$tsls_xm_lower_N_50[5],N_50_interac_5$tsls_xm_upper_N
_50[5]),c(N_50_interac_5$mean_betas.data.x_coeff_m[5],N_50_interac_5$mean_b
etas.data.x_coeff_m[5]))
plot(N_50_interac_1$mean_betas.data.xm_2sls,N_50_interac_1$mean_betas.data.
x_coeff_m,xlim=c(-2,2),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_50_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-2,-1.5,-1,-0.5,0,0.333,0.5,1,1.5,2),labels=c('-2','-
1.5','-1','-0.5','0','0.333','0.5','1','1.5','2'),cex.axis=0.25)
lines(c(N_50_interac_1$tsls_xm_lower_N_50[1],N_50_interac_1$tsls_xm_upper_N
_50[1]),c(N_50_interac_1$mean_betas.data.x_coeff_m[1],N_50_interac_1$mean_b
etas.data.x_coeff_m[1]))
lines(c(N_50_interac_1$tsls_xm_lower_N_50[2],N_50_interac_1$tsls_xm_upper_N
_50[2]),c(N_50_interac_1$mean_betas.data.x_coeff_m[2],N_50_interac_1$mean_b
etas.data.x_coeff_m[2]))
lines(c(N_50_interac_1$tsls_xm_lower_N_50[3],N_50_interac_1$tsls_xm_upper_N
_50[3]),c(N_50_interac_1$mean_betas.data.x_coeff_m[3],N_50_interac_1$mean_b
etas.data.x_coeff_m[3]))
lines(c(N_50_interac_1$tsls_xm_lower_N_50[4],N_50_interac_1$tsls_xm_upper_N
_50[4]),c(N_50_interac_1$mean_betas.data.x_coeff_m[4],N_50_interac_1$mean_b
etas.data.x_coeff_m[4]))
lines(c(N_50_interac_1$tsls_xm_lower_N_50[5],N_50_interac_1$tsls_xm_upper_N
_50[5]),c(N_50_interac_1$mean_betas.data.x_coeff_m[5],N_50_interac_1$mean_b
etas.data.x_coeff_m[5]))
dev.off()

#2SLS Z=(Z1,Z2,Z1Z2,Z1Z1) N=50K
tiff('coef_plot_z1z1_50k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_50_interac_m3$mean_betas.data.xm_z1_2sls,N_50_interac_m3$mean_betas.
data.x_coeff_m,xlim=c(-0.25,0.45),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2,Z1Z1)',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_50_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
```

```
axis(side=1,at=c(-0.25,-0.2,-0.15,-0.111,-0.1,-
0.05,0,0.05,0.1,0.15,0.2,0.25,0.3,0.35,0.4,0.45),labels=c('-0.25','-0.2','-
0.15','-0.111','-0.1','-
0.05','0','0.05','0.1','0.15','0.2','0.25','0.3','0.35','0.4','0.45'),cex.a
xis=0.25)
lines(c(N_50_interac_m3$tsls_z1_xm_lower_N_50[1],N_50_interac_m3$tsls_z1_xm
_upper_N_50[1]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[1],N_50_interac
_m3$mean_betas.data.x_coeff_m[1]))
lines(c(N_50_interac_m3$tsls_z1_xm_lower_N_50[2],N_50_interac_m3$tsls_z1_xm
_upper_N_50[2]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[2],N_50_interac
_m3$mean_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_m3$tsls_z1_xm_lower_N_50[3],N_50_interac_m3$tsls_z1_xm
_upper_N_50[3]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[3],N_50_interac
_m3$mean_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_m3$tsls_z1_xm_lower_N_50[4],N_50_interac_m3$tsls_z1_xm
_upper_N_50[4]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[4],N_50_interac
_m3$mean_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_m3$tsls_z1_xm_lower_N_50[5],N_50_interac_m3$tsls_z1_xm
_upper_N_50[5]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[5],N_50_interac
_m3$mean_betas.data.x_coeff_m[5]))
plot(N_50_interac_0$mean_betas.data.xm_z1_2sls,N_50_interac_0$mean_betas.da
ta.x_coeff_m,xlim=c(-0.25,0.45),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_50_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.25,-0.2,-0.15,-0.1,-
0.05,0,0.05,0.1,0.15,0.2,0.25,0.3,0.35,0.4,0.45),labels=c('-0.25','-0.2','-
0.15','-0.1','-
0.05','0','0.05','0.1','0.15','0.2','0.25','0.3','0.35','0.4','0.45'),cex.a
xis=0.25)
lines(c(N_50_interac_0$tsls_z1_xm_lower_N_50[1],N_50_interac_0$tsls_z1_xm_u
pper_N_50[1]),c(N_50_interac_0$mean_betas.data.x_coeff_m[1],N_50_interac_0$
mean_betas.data.x_coeff_m[1]))
lines(c(N_50_interac_0$tsls_z1_xm_lower_N_50[2],N_50_interac_0$tsls_z1_xm_u
pper_N_50[2]),c(N_50_interac_0$mean_betas.data.x_coeff_m[2],N_50_interac_0$
mean_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_0$tsls_z1_xm_lower_N_50[3],N_50_interac_0$tsls_z1_xm_u
pper_N_50[3]),c(N_50_interac_0$mean_betas.data.x_coeff_m[3],N_50_interac_0$
mean_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_0$tsls_z1_xm_lower_N_50[4],N_50_interac_0$tsls_z1_xm_u
pper_N_50[4]),c(N_50_interac_0$mean_betas.data.x_coeff_m[4],N_50_interac_0$
mean_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_0$tsls_z1_xm_lower_N_50[5],N_50_interac_0$tsls_z1_xm_u
pper_N_50[5]),c(N_50_interac_0$mean_betas.data.x_coeff_m[5],N_50_interac_0$
mean_betas.data.x_coeff_m[5]))
plot(N_50_interac_3$mean_betas.data.xm_z1_2sls,N_50_interac_3$mean_betas.da
ta.x_coeff_m,xlim=c(-0.25,0.45),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_50_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.25,-0.2,-0.15,-0.1,-
0.05,0,0.05,0.1,0.111,0.15,0.2,0.25,0.3,0.35,0.4,0.45),labels=c('-0.25','-
0.2','-0.15','-0.1','-
0.05','0','0.05','0.1','0.111','0.15','0.2','0.25','0.3','0.35','0.4','0.45
'),cex.axis=0.25)
lines(c(N_50_interac_3$tsls_z1_xm_lower_N_50[1],N_50_interac_3$tsls_z1_xm_u
pper_N_50[1]),c(N_50_interac_3$mean_betas.data.x_coeff_m[1],N_50_interac_3$
mean_betas.data.x_coeff_m[1]))
```

```
lines(c(N_50_interac_3$tsls_z1_xm_lower_N_50[2],N_50_interac_3$tsls_z1_xm_u
pper_N_50[2]),c(N_50_interac_3$mean_betas.data.x_coeff_m[2],N_50_interac_3$
mean_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_3$tsls_z1_xm_lower_N_50[3],N_50_interac_3$tsls_z1_xm_u
pper_N_50[3]),c(N_50_interac_3$mean_betas.data.x_coeff_m[3],N_50_interac_3$
mean_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_3$tsls_z1_xm_lower_N_50[4],N_50_interac_3$tsls_z1_xm_u
pper_N_50[4]),c(N_50_interac_3$mean_betas.data.x_coeff_m[4],N_50_interac_3$
mean_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_3$tsls_z1_xm_lower_N_50[5],N_50_interac_3$tsls_z1_xm_u
pper_N_50[5]),c(N_50_interac_3$mean_betas.data.x_coeff_m[5],N_50_interac_3$
mean_betas.data.x_coeff_m[5]))
plot(N_50_interac_5$mean_betas.data.xm_z1_2sls,N_50_interac_5$mean_betas.da
ta.x_coeff_m,xlim=c(-0.25,0.45),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_50_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.25,-0.2,-0.15,-0.1,-
0.05,0,0.05,0.1,0.15,0.167,0.2,0.25,0.3,0.35,0.4,0.45),labels=c('-0.25','-
0.2','-0.15','-0.1','-
0.05','0','0.05','0.1','0.15','0.167','0.2','0.25','0.3','0.35','0.4','0.45
'),cex.axis=0.25)
lines(c(N_50_interac_5$tsls_z1_xm_lower_N_50[1],N_50_interac_5$tsls_z1_xm_u
pper_N_50[1]),c(N_50_interac_5$mean_betas.data.x_coeff_m[1],N_50_interac_5$
mean_betas.data.x_coeff_m[1]))
lines(c(N_50_interac_5$tsls_z1_xm_lower_N_50[2],N_50_interac_5$tsls_z1_xm_u
pper_N_50[2]),c(N_50_interac_5$mean_betas.data.x_coeff_m[2],N_50_interac_5$
mean_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_5$tsls_z1_xm_lower_N_50[3],N_50_interac_5$tsls_z1_xm_u
pper_N_50[3]),c(N_50_interac_5$mean_betas.data.x_coeff_m[3],N_50_interac_5$
mean_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_5$tsls_z1_xm_lower_N_50[4],N_50_interac_5$tsls_z1_xm_u
pper_N_50[4]),c(N_50_interac_5$mean_betas.data.x_coeff_m[4],N_50_interac_5$
mean_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_5$tsls_z1_xm_lower_N_50[5],N_50_interac_5$tsls_z1_xm_u
pper_N_50[5]),c(N_50_interac_5$mean_betas.data.x_coeff_m[5],N_50_interac_5$
mean_betas.data.x_coeff_m[5]))
plot(N_50_interac_1$mean_betas.data.xm_z1_2sls,N_50_interac_1$mean_betas.da
ta.x_coeff_m,xlim=c(-0.25,0.45),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_50_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.25,-0.2,-0.15,-0.1,-
0.05,0,0.05,0.1,0.15,0.2,0.25,0.3,0.333,0.35,0.4,0.45),labels=c('-0.25','-
0.2','-0.15','-0.1','-
0.05','0','0.05','0.1','0.15','0.2','0.25','0.3','0.333','0.35','0.4','0.45
'),cex.axis=0.25)
lines(c(N_50_interac_1$tsls_z1_xm_lower_N_50[1],N_50_interac_1$tsls_z1_xm_u
pper_N_50[1]),c(N_50_interac_1$mean_betas.data.x_coeff_m[1],N_50_interac_1$
mean_betas.data.x_coeff_m[1]))
lines(c(N_50_interac_1$tsls_z1_xm_lower_N_50[2],N_50_interac_1$tsls_z1_xm_u
pper_N_50[2]),c(N_50_interac_1$mean_betas.data.x_coeff_m[2],N_50_interac_1$
mean_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_1$tsls_z1_xm_lower_N_50[3],N_50_interac_1$tsls_z1_xm_u
pper_N_50[3]),c(N_50_interac_1$mean_betas.data.x_coeff_m[3],N_50_interac_1$
mean_betas.data.x_coeff_m[3]))
```

```
lines(c(N_50_interac_1$tsls_z1_xm_lower_N_50[4],N_50_interac_1$tsls_z1_xm_u
pper_N_50[4]),c(N_50_interac_1$mean_betas.data.x_coeff_m[4],N_50_interac_1$
mean_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_1$tsls_z1_xm_lower_N_50[5],N_50_interac_1$tsls_z1_xm_u
pper_N_50[5]),c(N_50_interac_1$mean_betas.data.x_coeff_m[5],N_50_interac_1$
mean_betas.data.x_coeff_m[5]))
dev.off()

#OBSERVATIONAL N=50K
tiff('coef_plot_obs_50k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_50_interac_m3$mean_betas.data.xm_obs,N_50_interac_m3$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='Ordinary least sqaures estimate of theta
coefficient',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_50_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-0.111,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-0.111','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_50_interac_m3$obs_xm_lower_N_50[1],N_50_interac_m3$obs_xm_upper_N
_50[1]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[1],N_50_interac_m3$mean
_betas.data.x_coeff_m[1]))
lines(c(N_50_interac_m3$obs_xm_lower_N_50[2],N_50_interac_m3$obs_xm_upper_N
_50[2]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[2],N_50_interac_m3$mean
_betas.data.x_coeff_m[2]))
lines(c(N_50_interac_m3$obs_xm_lower_N_50[3],N_50_interac_m3$obs_xm_upper_N
_50[3]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[3],N_50_interac_m3$mean
_betas.data.x_coeff_m[3]))
lines(c(N_50_interac_m3$obs_xm_lower_N_50[4],N_50_interac_m3$obs_xm_upper_N
_50[4]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[4],N_50_interac_m3$mean
_betas.data.x_coeff_m[4]))
lines(c(N_50_interac_m3$obs_xm_lower_N_50[5],N_50_interac_m3$obs_xm_upper_N
_50[5]),c(N_50_interac_m3$mean_betas.data.x_coeff_m[5],N_50_interac_m3$mean
_betas.data.x_coeff_m[5]))
plot(N_50_interac_0$mean_betas.data.xm_obs,N_50_interac_0$mean_betas.data.x
_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_50_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_50_interac_0$obs_xm_lower_N_50[1],N_50_interac_0$obs_xm_upper_N_5
0[1]),c(N_50_interac_0$mean_betas.data.x_coeff_m[1],N_50_interac_0$mean_bet
as.data.x_coeff_m[1]))
lines(c(N_50_interac_0$obs_xm_lower_N_50[2],N_50_interac_0$obs_xm_upper_N_5
0[2]),c(N_50_interac_0$mean_betas.data.x_coeff_m[2],N_50_interac_0$mean_bet
as.data.x_coeff_m[2]))
lines(c(N_50_interac_0$obs_xm_lower_N_50[3],N_50_interac_0$obs_xm_upper_N_5
0[3]),c(N_50_interac_0$mean_betas.data.x_coeff_m[3],N_50_interac_0$mean_bet
as.data.x_coeff_m[3]))
lines(c(N_50_interac_0$obs_xm_lower_N_50[4],N_50_interac_0$obs_xm_upper_N_5
0[4]),c(N_50_interac_0$mean_betas.data.x_coeff_m[4],N_50_interac_0$mean_bet
as.data.x_coeff_m[4]))
```

```
lines(c(N_50_interac_0$obs_xm_lower_N_50[5],N_50_interac_0$obs_xm_upper_N_5
0[5]),c(N_50_interac_0$mean_betas.data.x_coeff_m[5],N_50_interac_0$mean_bet
as.data.x_coeff_m[5]))
plot(N_50_interac_3$mean_betas.data.xm_obs,N_50_interac_3$mean_betas.data.x
_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_50_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.111,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.111','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_50_interac_3$obs_xm_lower_N_50[1],N_50_interac_3$obs_xm_upper_N_5
0[1]),c(N_50_interac_3$mean_betas.data.x_coeff_m[1],N_50_interac_3$mean_bet
as.data.x_coeff_m[1]))
lines(c(N_50_interac_3$obs_xm_lower_N_50[2],N_50_interac_3$obs_xm_upper_N_5
0[2]),c(N_50_interac_3$mean_betas.data.x_coeff_m[2],N_50_interac_3$mean_bet
as.data.x_coeff_m[2]))
lines(c(N_50_interac_3$obs_xm_lower_N_50[3],N_50_interac_3$obs_xm_upper_N_5
0[3]),c(N_50_interac_3$mean_betas.data.x_coeff_m[3],N_50_interac_3$mean_bet
as.data.x_coeff_m[3]))
lines(c(N_50_interac_3$obs_xm_lower_N_50[4],N_50_interac_3$obs_xm_upper_N_5
0[4]),c(N_50_interac_3$mean_betas.data.x_coeff_m[4],N_50_interac_3$mean_bet
as.data.x_coeff_m[4]))
lines(c(N_50_interac_3$obs_xm_lower_N_50[5],N_50_interac_3$obs_xm_upper_N_5
0[5]),c(N_50_interac_3$mean_betas.data.x_coeff_m[5],N_50_interac_3$mean_bet
as.data.x_coeff_m[5]))
plot(N_50_interac_5$mean_betas.data.xm_obs,N_50_interac_5$mean_betas.data.x
_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_50_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.167,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.167','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_50_interac_5$obs_xm_lower_N_50[1],N_50_interac_5$obs_xm_upper_N_5
0[1]),c(N_50_interac_5$mean_betas.data.x_coeff_m[1],N_50_interac_5$mean_bet
as.data.x_coeff_m[1]))
lines(c(N_50_interac_5$obs_xm_lower_N_50[2],N_50_interac_5$obs_xm_upper_N_5
0[2]),c(N_50_interac_5$mean_betas.data.x_coeff_m[2],N_50_interac_5$mean_bet
as.data.x_coeff_m[2]))
lines(c(N_50_interac_5$obs_xm_lower_N_50[3],N_50_interac_5$obs_xm_upper_N_5
0[3]),c(N_50_interac_5$mean_betas.data.x_coeff_m[3],N_50_interac_5$mean_bet
as.data.x_coeff_m[3]))
lines(c(N_50_interac_5$obs_xm_lower_N_50[4],N_50_interac_5$obs_xm_upper_N_5
0[4]),c(N_50_interac_5$mean_betas.data.x_coeff_m[4],N_50_interac_5$mean_bet
as.data.x_coeff_m[4]))
lines(c(N_50_interac_5$obs_xm_lower_N_50[5],N_50_interac_5$obs_xm_upper_N_5
0[5]),c(N_50_interac_5$mean_betas.data.x_coeff_m[5],N_50_interac_5$mean_bet
as.data.x_coeff_m[5]))
plot(N_50_interac_1$mean_betas.data.xm_obs,N_50_interac_1$mean_betas.data.x
_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
```

```
axis(side=2,at=N_50_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.333,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.333','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_50_interac_1$obs_xm_lower_N_50[1],N_50_interac_1$obs_xm_upper_N_5
0[1]),c(N_50_interac_1$mean_betas.data.x_coeff_m[1],N_50_interac_1$mean_bet
as.data.x_coeff_m[1]))
lines(c(N_50_interac_1$obs_xm_lower_N_50[2],N_50_interac_1$obs_xm_upper_N_5
0[2]),c(N_50_interac_1$mean_betas.data.x_coeff_m[2],N_50_interac_1$mean_bet
as.data.x_coeff_m[2]))
lines(c(N_50_interac_1$obs_xm_lower_N_50[3],N_50_interac_1$obs_xm_upper_N_5
0[3]),c(N_50_interac_1$mean_betas.data.x_coeff_m[3],N_50_interac_1$mean_bet
as.data.x_coeff_m[3]))
lines(c(N_50_interac_1$obs_xm_lower_N_50[4],N_50_interac_1$obs_xm_upper_N_5
0[4]),c(N_50_interac_1$mean_betas.data.x_coeff_m[4],N_50_interac_1$mean_bet
as.data.x_coeff_m[4]))
lines(c(N_50_interac_1$obs_xm_lower_N_50[5],N_50_interac_1$obs_xm_upper_N_5
0[5]),c(N_50_interac_1$mean_betas.data.x_coeff_m[5],N_50_interac_1$mean_bet
as.data.x_coeff_m[5]))
dev.off()

#PREP THE N=100K DATA
setwd(dataloc)
N_100=data.frame(read.table(file=paste(100000,"_EXTRA_final_res.txt",sep=''
),sep='\t',header=TRUE))
N_100=N_100[order(N_100$mean_betas.data.xm_coeff_y,N_100$mean_betas.data.x_
coeff_m),]
tsls_xm_lower_N_100=N_100$mean_betas.data.xm_2sls-
1.96*N_100$se.newdata.xm_2sls
tsls_xm_upper_N_100=N_100$mean_betas.data.xm_2sls+1.96*N_100$se.newdata.xm_
2sls
tsls_z1_xm_lower_N_100=N_100$mean_betas.data.xm_z1_2sls-
1.96*N_100$se.newdata.xm_z1_2sls
tsls_z1_xm_upper_N_100=N_100$mean_betas.data.xm_z1_2sls+1.96*N_100$se.newda
ta.xm_z1_2sls
obs_xm_lower_N_100=N_100$mean_betas.data.xm_obs-
1.96*N_100$se.newdata.xm_obs
obs_xm_upper_N_100=N_100$mean_betas.data.xm_obs+1.96*N_100$se.newdata.xm_ob
s
N_100=data.frame(N_100,tsls_xm_lower_N_100,tsls_xm_upper_N_100,tsls_z1_xm_l
ower_N_100,tsls_z1_xm_upper_N_100,
                 obs_xm_lower_N_100,obs_xm_upper_N_100)
N_100_interac_m3=N_100[round(N_100$mean_betas.data.xm_coeff_y,3)==-0.111,]
N_100_interac_0=N_100[round(N_100$mean_betas.data.xm_coeff_y,3)==0,]
N_100_interac_3=N_100[round(N_100$mean_betas.data.xm_coeff_y,3)==0.111,]
N_100_interac_5=N_100[round(N_100$mean_betas.data.xm_coeff_y,3)==0.167,]
N_100_interac_1=N_100[round(N_100$mean_betas.data.xm_coeff_y,3)==0.333,]

#2SLS Z=(Z1,Z2,Z1Z2) N=100K
setwd(writeplot)
tiff('coef_plot_z1z2_100k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_100_interac_m3$mean_betas.data.xm_2sls,N_100_interac_m3$mean_betas.d
ata.x_coeff_m,xlim=c(-0.6,0.5),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2)',cex.main=0.7)
abline(v=-0.111)
```

```
axis(side=2,at=N_100_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.6,-0.5,-0.4,-0.3,-0.2,-0.111,-
0.1,0,0.1,0.2,0.3,0.4,0.5),labels=c('-0.6','-0.5','-0.4','-0.3','-0.2','-
0.111','-0.1','0','0.1','0.2','0.3','0.4','0.5'),cex.axis=0.25)
lines(c(N_100_interac_m3$tsls_xm_lower_N_100[1],N_100_interac_m3$tsls_xm_up
per_N_100[1]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[1],N_100_interac
_m3$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_m3$tsls_xm_lower_N_100[2],N_100_interac_m3$tsls_xm_up
per_N_100[2]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[2],N_100_interac
_m3$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_m3$tsls_xm_lower_N_100[3],N_100_interac_m3$tsls_xm_up
per_N_100[3]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[3],N_100_interac
_m3$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_m3$tsls_xm_lower_N_100[4],N_100_interac_m3$tsls_xm_up
per_N_100[4]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[4],N_100_interac
_m3$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_m3$tsls_xm_lower_N_100[5],N_100_interac_m3$tsls_xm_up
per_N_100[5]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[5],N_100_interac
_m3$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_0$mean_betas.data.xm_2sls,N_100_interac_0$mean_betas.dat
a.x_coeff_m,xlim=c(-0.6,0.5),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_100_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.6,-0.5,-0.4,-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.4,0.5),labels=c('-0.6','-0.5','-0.4','-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.4','0.5'),cex.axis=0.25)
lines(c(N_100_interac_0$tsls_xm_lower_N_100[1],N_100_interac_0$tsls_xm_uppe
r_N_100[1]),c(N_100_interac_0$mean_betas.data.x_coeff_m[1],N_100_interac_0$
mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_0$tsls_xm_lower_N_100[2],N_100_interac_0$tsls_xm_uppe
r_N_100[2]),c(N_100_interac_0$mean_betas.data.x_coeff_m[2],N_100_interac_0$
mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_0$tsls_xm_lower_N_100[3],N_100_interac_0$tsls_xm_uppe
r_N_100[3]),c(N_100_interac_0$mean_betas.data.x_coeff_m[3],N_100_interac_0$
mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_0$tsls_xm_lower_N_100[4],N_100_interac_0$tsls_xm_uppe
r_N_100[4]),c(N_100_interac_0$mean_betas.data.x_coeff_m[4],N_100_interac_0$
mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_0$tsls_xm_lower_N_100[5],N_100_interac_0$tsls_xm_uppe
r_N_100[5]),c(N_100_interac_0$mean_betas.data.x_coeff_m[5],N_100_interac_0$
mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_3$mean_betas.data.xm_2sls,N_100_interac_3$mean_betas.dat
a.x_coeff_m,xlim=c(-0.6,0.5),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_100_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.6,-0.5,-0.4,-0.3,-0.2,-
0.1,0,0.1,0.111,0.2,0.3,0.4,0.5),labels=c('-0.6','-0.5','-0.4','-0.3','-
0.2','-0.1','0','0.1','0.111','0.2','0.3','0.4','0.5'),cex.axis=0.25)
lines(c(N_100_interac_3$tsls_xm_lower_N_100[1],N_100_interac_3$tsls_xm_uppe
r_N_100[1]),c(N_100_interac_3$mean_betas.data.x_coeff_m[1],N_100_interac_3$
mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_3$tsls_xm_lower_N_100[2],N_100_interac_3$tsls_xm_uppe
r_N_100[2]),c(N_100_interac_3$mean_betas.data.x_coeff_m[2],N_100_interac_3$
mean_betas.data.x_coeff_m[2]))
```

```
lines(c(N_100_interac_3$tsls_xm_lower_N_100[3],N_100_interac_3$tsls_xm_uppe
r_N_100[3]),c(N_100_interac_3$mean_betas.data.x_coeff_m[3],N_100_interac_3$
mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_3$tsls_xm_lower_N_100[4],N_100_interac_3$tsls_xm_uppe
r_N_100[4]),c(N_100_interac_3$mean_betas.data.x_coeff_m[4],N_100_interac_3$
mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_3$tsls_xm_lower_N_100[5],N_100_interac_3$tsls_xm_uppe
r_N_100[5]),c(N_100_interac_3$mean_betas.data.x_coeff_m[5],N_100_interac_3$
mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_5$mean_betas.data.xm_2sls,N_100_interac_5$mean_betas.dat
a.x_coeff_m,xlim=c(-0.6,0.5),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_100_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.6,-0.5,-0.4,-0.3,-0.2,-
0.1,0,0.1,0.167,0.2,0.3,0.4,0.5),labels=c('-0.6','-0.5','-0.4','-0.3','-
0.2','-0.1','0','0.1','0.167','0.2','0.3','0.4','0.5'),cex.axis=0.25)
lines(c(N_100_interac_5$tsls_xm_lower_N_100[1],N_100_interac_5$tsls_xm_uppe
r_N_100[1]),c(N_100_interac_5$mean_betas.data.x_coeff_m[1],N_100_interac_5$
mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_5$tsls_xm_lower_N_100[2],N_100_interac_5$tsls_xm_uppe
r_N_100[2]),c(N_100_interac_5$mean_betas.data.x_coeff_m[2],N_100_interac_5$
mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_5$tsls_xm_lower_N_100[3],N_100_interac_5$tsls_xm_uppe
r_N_100[3]),c(N_100_interac_5$mean_betas.data.x_coeff_m[3],N_100_interac_5$
mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_5$tsls_xm_lower_N_100[4],N_100_interac_5$tsls_xm_uppe
r_N_100[4]),c(N_100_interac_5$mean_betas.data.x_coeff_m[4],N_100_interac_5$
mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_5$tsls_xm_lower_N_100[5],N_100_interac_5$tsls_xm_uppe
r_N_100[5]),c(N_100_interac_5$mean_betas.data.x_coeff_m[5],N_100_interac_5$
mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_1$mean_betas.data.xm_2sls,N_100_interac_1$mean_betas.dat
a.x_coeff_m,xlim=c(-0.6,0.5),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_100_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.6,-0.5,-0.4,-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.333,0.4,0.5),labels=c('-0.6','-0.5','-0.4','-0.3','-
0.2','-0.1','0','0.1','0.2','0.3','0.333','0.4','0.5'),cex.axis=0.25)
lines(c(N_100_interac_1$tsls_xm_lower_N_100[1],N_100_interac_1$tsls_xm_uppe
r_N_100[1]),c(N_100_interac_1$mean_betas.data.x_coeff_m[1],N_100_interac_1$
mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_1$tsls_xm_lower_N_100[2],N_100_interac_1$tsls_xm_uppe
r_N_100[2]),c(N_100_interac_1$mean_betas.data.x_coeff_m[2],N_100_interac_1$
mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_1$tsls_xm_lower_N_100[3],N_100_interac_1$tsls_xm_uppe
r_N_100[3]),c(N_100_interac_1$mean_betas.data.x_coeff_m[3],N_100_interac_1$
mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_1$tsls_xm_lower_N_100[4],N_100_interac_1$tsls_xm_uppe
r_N_100[4]),c(N_100_interac_1$mean_betas.data.x_coeff_m[4],N_100_interac_1$
mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_1$tsls_xm_lower_N_100[5],N_100_interac_1$tsls_xm_uppe
r_N_100[5]),c(N_100_interac_1$mean_betas.data.x_coeff_m[5],N_100_interac_1$
mean_betas.data.x_coeff_m[5]))
dev.off()
```

```
#2SLS Z=(Z1,Z2,Z1Z2,Z1Z1) N=100K
tiff('coef_plot_z1z1_100k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_100_interac_m3$mean_betas.data.xm_z1_2sls,N_100_interac_m3$mean_beta
s.data.x_coeff_m,xlim=c(-0.34,0.36),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2,Z1Z1)',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_100_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.4,-0.3,-0.2,-0.111,-0.1,0,0.1,0.2,0.3,0.4),labels=c('-
0.4','-0.3','-0.2','-0.111','-
0.1','0','0.1','0.2','0.3','0.4'),cex.axis=0.25)
lines(c(N_100_interac_m3$tsls_z1_xm_lower_N_100[1],N_100_interac_m3$tsls_z1
_xm_upper_N_100[1]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[1],N_100_i
nterac_m3$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_m3$tsls_z1_xm_lower_N_100[2],N_100_interac_m3$tsls_z1
_xm_upper_N_100[2]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[2],N_100_i
nterac_m3$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_m3$tsls_z1_xm_lower_N_100[3],N_100_interac_m3$tsls_z1
_xm_upper_N_100[3]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[3],N_100_i
nterac_m3$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_m3$tsls_z1_xm_lower_N_100[4],N_100_interac_m3$tsls_z1
_xm_upper_N_100[4]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[4],N_100_i
nterac_m3$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_m3$tsls_z1_xm_lower_N_100[5],N_100_interac_m3$tsls_z1
_xm_upper_N_100[5]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[5],N_100_i
nterac_m3$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_0$mean_betas.data.xm_z1_2sls,N_100_interac_0$mean_betas.
data.x_coeff_m,xlim=c(-0.34,0.36),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_100_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.4,-0.3,-0.2,-0.1,0,0.1,0.2,0.3,0.4),labels=c('-0.4','-
0.3','-0.2','-0.1','0','0.1','0.2','0.3','0.4'),cex.axis=0.25)
lines(c(N_100_interac_0$tsls_z1_xm_lower_N_100[1],N_100_interac_0$tsls_z1_x
m_upper_N_100[1]),c(N_100_interac_0$mean_betas.data.x_coeff_m[1],N_100_inte
rac_0$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_0$tsls_z1_xm_lower_N_100[2],N_100_interac_0$tsls_z1_x
m_upper_N_100[2]),c(N_100_interac_0$mean_betas.data.x_coeff_m[2],N_100_inte
rac_0$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_0$tsls_z1_xm_lower_N_100[3],N_100_interac_0$tsls_z1_x
m_upper_N_100[3]),c(N_100_interac_0$mean_betas.data.x_coeff_m[3],N_100_inte
rac_0$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_0$tsls_z1_xm_lower_N_100[4],N_100_interac_0$tsls_z1_x
m_upper_N_100[4]),c(N_100_interac_0$mean_betas.data.x_coeff_m[4],N_100_inte
rac_0$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_0$tsls_z1_xm_lower_N_100[5],N_100_interac_0$tsls_z1_x
m_upper_N_100[5]),c(N_100_interac_0$mean_betas.data.x_coeff_m[5],N_100_inte
rac_0$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_3$mean_betas.data.xm_z1_2sls,N_100_interac_3$mean_betas.
data.x_coeff_m,xlim=c(-0.34,0.36),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_100_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
```

```
axis(side=1,at=c(-0.4,-0.3,-0.2,-0.1,0,0.1,0.111,0.2,0.3,0.4),labels=c('-
0.4','-0.3','-0.2','-
0.1','0','0.1','0.111','0.2','0.3','0.4'),cex.axis=0.25)
lines(c(N_100_interac_3$tsls_z1_xm_lower_N_100[1],N_100_interac_3$tsls_z1_x
m_upper_N_100[1]),c(N_100_interac_3$mean_betas.data.x_coeff_m[1],N_100_inte
rac_3$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_3$tsls_z1_xm_lower_N_100[2],N_100_interac_3$tsls_z1_x
m_upper_N_100[2]),c(N_100_interac_3$mean_betas.data.x_coeff_m[2],N_100_inte
rac_3$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_3$tsls_z1_xm_lower_N_100[3],N_100_interac_3$tsls_z1_x
m_upper_N_100[3]),c(N_100_interac_3$mean_betas.data.x_coeff_m[3],N_100_inte
rac_3$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_3$tsls_z1_xm_lower_N_100[4],N_100_interac_3$tsls_z1_x
m_upper_N_100[4]),c(N_100_interac_3$mean_betas.data.x_coeff_m[4],N_100_inte
rac_3$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_3$tsls_z1_xm_lower_N_100[5],N_100_interac_3$tsls_z1_x
m_upper_N_100[5]),c(N_100_interac_3$mean_betas.data.x_coeff_m[5],N_100_inte
rac_3$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_5$mean_betas.data.xm_z1_2sls,N_100_interac_5$mean_betas.
data.x_coeff_m,xlim=c(-0.34,0.36),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_100_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.4,-0.3,-0.2,-0.1,0,0.1,0.167,0.2,0.3,0.4),labels=c('-
0.4','-0.3','-0.2','-
0.1','0','0.1','0.167','0.2','0.3','0.4'),cex.axis=0.25)
lines(c(N_100_interac_5$tsls_z1_xm_lower_N_100[1],N_100_interac_5$tsls_z1_x
m_upper_N_100[1]),c(N_100_interac_5$mean_betas.data.x_coeff_m[1],N_100_inte
rac_5$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_5$tsls_z1_xm_lower_N_100[2],N_100_interac_5$tsls_z1_x
m_upper_N_100[2]),c(N_100_interac_5$mean_betas.data.x_coeff_m[2],N_100_inte
rac_5$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_5$tsls_z1_xm_lower_N_100[3],N_100_interac_5$tsls_z1_x
m_upper_N_100[3]),c(N_100_interac_5$mean_betas.data.x_coeff_m[3],N_100_inte
rac_5$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_5$tsls_z1_xm_lower_N_100[4],N_100_interac_5$tsls_z1_x
m_upper_N_100[4]),c(N_100_interac_5$mean_betas.data.x_coeff_m[4],N_100_inte
rac_5$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_5$tsls_z1_xm_lower_N_100[5],N_100_interac_5$tsls_z1_x
m_upper_N_100[5]),c(N_100_interac_5$mean_betas.data.x_coeff_m[5],N_100_inte
rac_5$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_1$mean_betas.data.xm_z1_2sls,N_100_interac_1$mean_betas.
data.x_coeff_m,xlim=c(-0.34,0.36),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_100_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.4,-0.3,-0.2,-0.1,0,0.1,0.2,0.3,0.333,0.4),labels=c('-
0.4','-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.333','0.4'),cex.axis=0.25)
lines(c(N_100_interac_1$tsls_z1_xm_lower_N_100[1],N_100_interac_1$tsls_z1_x
m_upper_N_100[1]),c(N_100_interac_1$mean_betas.data.x_coeff_m[1],N_100_inte
rac_1$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_1$tsls_z1_xm_lower_N_100[2],N_100_interac_1$tsls_z1_x
m_upper_N_100[2]),c(N_100_interac_1$mean_betas.data.x_coeff_m[2],N_100_inte
rac_1$mean_betas.data.x_coeff_m[2]))
```

```
lines(c(N_100_interac_1$tsls_z1_xm_lower_N_100[3],N_100_interac_1$tsls_z1_x
m_upper_N_100[3]),c(N_100_interac_1$mean_betas.data.x_coeff_m[3],N_100_inte
rac_1$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_1$tsls_z1_xm_lower_N_100[4],N_100_interac_1$tsls_z1_x
m_upper_N_100[4]),c(N_100_interac_1$mean_betas.data.x_coeff_m[4],N_100_inte
rac_1$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_1$tsls_z1_xm_lower_N_100[5],N_100_interac_1$tsls_z1_x
m_upper_N_100[5]),c(N_100_interac_1$mean_betas.data.x_coeff_m[5],N_100_inte
rac_1$mean_betas.data.x_coeff_m[5]))
dev.off()

#OBSERVATIONAL N=100K

tiff('coef_plot_obs_100k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_100_interac_m3$mean_betas.data.xm_obs,N_100_interac_m3$mean_betas.da
ta.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='Ordinary least sqaures estimate of theta
coefficient',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_100_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-0.111,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-0.111','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_100_interac_m3$obs_xm_lower_N_100[1],N_100_interac_m3$obs_xm_uppe
r_N_100[1]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[1],N_100_interac_m
3$mean_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_m3$obs_xm_lower_N_100[2],N_100_interac_m3$obs_xm_uppe
r_N_100[2]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[2],N_100_interac_m
3$mean_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_m3$obs_xm_lower_N_100[3],N_100_interac_m3$obs_xm_uppe
r_N_100[3]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[3],N_100_interac_m
3$mean_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_m3$obs_xm_lower_N_100[4],N_100_interac_m3$obs_xm_uppe
r_N_100[4]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[4],N_100_interac_m
3$mean_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_m3$obs_xm_lower_N_100[5],N_100_interac_m3$obs_xm_uppe
r_N_100[5]),c(N_100_interac_m3$mean_betas.data.x_coeff_m[5],N_100_interac_m
3$mean_betas.data.x_coeff_m[5]))
plot(N_100_interac_0$mean_betas.data.xm_obs,N_100_interac_0$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_100_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_100_interac_0$obs_xm_lower_N_100[1],N_100_interac_0$obs_xm_upper_
N_100[1]),c(N_100_interac_0$mean_betas.data.x_coeff_m[1],N_100_interac_0$me
an_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_0$obs_xm_lower_N_100[2],N_100_interac_0$obs_xm_upper_
N_100[2]),c(N_100_interac_0$mean_betas.data.x_coeff_m[2],N_100_interac_0$me
an_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_0$obs_xm_lower_N_100[3],N_100_interac_0$obs_xm_upper_
N_100[3]),c(N_100_interac_0$mean_betas.data.x_coeff_m[3],N_100_interac_0$me
an_betas.data.x_coeff_m[3]))
```

```
lines(c(N_100_interac_0$obs_xm_lower_N_100[4],N_100_interac_0$obs_xm_upper_
N_100[4]),c(N_100_interac_0$mean_betas.data.x_coeff_m[4],N_100_interac_0$me
an_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_0$obs_xm_lower_N_100[5],N_100_interac_0$obs_xm_upper_
N_100[5]),c(N_100_interac_0$mean_betas.data.x_coeff_m[5],N_100_interac_0$me
an_betas.data.x_coeff_m[5]))
plot(N_100_interac_3$mean_betas.data.xm_obs,N_100_interac_3$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_100_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.111,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.111','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_100_interac_3$obs_xm_lower_N_100[1],N_100_interac_3$obs_xm_upper_
N_100[1]),c(N_100_interac_3$mean_betas.data.x_coeff_m[1],N_100_interac_3$me
an_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_3$obs_xm_lower_N_100[2],N_100_interac_3$obs_xm_upper_
N_100[2]),c(N_100_interac_3$mean_betas.data.x_coeff_m[2],N_100_interac_3$me
an_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_3$obs_xm_lower_N_100[3],N_100_interac_3$obs_xm_upper_
N_100[3]),c(N_100_interac_3$mean_betas.data.x_coeff_m[3],N_100_interac_3$me
an_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_3$obs_xm_lower_N_100[4],N_100_interac_3$obs_xm_upper_
N_100[4]),c(N_100_interac_3$mean_betas.data.x_coeff_m[4],N_100_interac_3$me
an_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_3$obs_xm_lower_N_100[5],N_100_interac_3$obs_xm_upper_
N_100[5]),c(N_100_interac_3$mean_betas.data.x_coeff_m[5],N_100_interac_3$me
an_betas.data.x_coeff_m[5]))
plot(N_100_interac_5$mean_betas.data.xm_obs,N_100_interac_5$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_100_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.167,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.167','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_100_interac_5$obs_xm_lower_N_100[1],N_100_interac_5$obs_xm_upper_
N_100[1]),c(N_100_interac_5$mean_betas.data.x_coeff_m[1],N_100_interac_5$me
an_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_5$obs_xm_lower_N_100[2],N_100_interac_5$obs_xm_upper_
N_100[2]),c(N_100_interac_5$mean_betas.data.x_coeff_m[2],N_100_interac_5$me
an_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_5$obs_xm_lower_N_100[3],N_100_interac_5$obs_xm_upper_
N_100[3]),c(N_100_interac_5$mean_betas.data.x_coeff_m[3],N_100_interac_5$me
an_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_5$obs_xm_lower_N_100[4],N_100_interac_5$obs_xm_upper_
N_100[4]),c(N_100_interac_5$mean_betas.data.x_coeff_m[4],N_100_interac_5$me
an_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_5$obs_xm_lower_N_100[5],N_100_interac_5$obs_xm_upper_
N_100[5]),c(N_100_interac_5$mean_betas.data.x_coeff_m[5],N_100_interac_5$me
an_betas.data.x_coeff_m[5]))
plot(N_100_interac_1$mean_betas.data.xm_obs,N_100_interac_1$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
```

```
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_100_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.333,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.333','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_100_interac_1$obs_xm_lower_N_100[1],N_100_interac_1$obs_xm_upper_
N_100[1]),c(N_100_interac_1$mean_betas.data.x_coeff_m[1],N_100_interac_1$me
an_betas.data.x_coeff_m[1]))
lines(c(N_100_interac_1$obs_xm_lower_N_100[2],N_100_interac_1$obs_xm_upper_
N_100[2]),c(N_100_interac_1$mean_betas.data.x_coeff_m[2],N_100_interac_1$me
an_betas.data.x_coeff_m[2]))
lines(c(N_100_interac_1$obs_xm_lower_N_100[3],N_100_interac_1$obs_xm_upper_
N_100[3]),c(N_100_interac_1$mean_betas.data.x_coeff_m[3],N_100_interac_1$me
an_betas.data.x_coeff_m[3]))
lines(c(N_100_interac_1$obs_xm_lower_N_100[4],N_100_interac_1$obs_xm_upper_
N_100[4]),c(N_100_interac_1$mean_betas.data.x_coeff_m[4],N_100_interac_1$me
an_betas.data.x_coeff_m[4]))
lines(c(N_100_interac_1$obs_xm_lower_N_100[5],N_100_interac_1$obs_xm_upper_
N_100[5]),c(N_100_interac_1$mean_betas.data.x_coeff_m[5],N_100_interac_1$me
an_betas.data.x_coeff_m[5]))
dev.off()


#PREP THE N=500K DATA
setwd(dataloc)
N_500=data.frame(read.table(file=paste(500000,"_EXTRA_final_res.txt",sep=''
),sep='\t',header=TRUE))
N_500=N_500[order(N_500$mean_betas.data.xm_coeff_y,N_500$mean_betas.data.x_
coeff_m),]
tsls_xm_lower_N_500=N_500$mean_betas.data.xm_2sls-
1.96*N_500$se.newdata.xm_2sls
tsls_xm_upper_N_500=N_500$mean_betas.data.xm_2sls+1.96*N_500$se.newdata.xm_
2sls
tsls_z1_xm_lower_N_500=N_500$mean_betas.data.xm_z1_2sls-
1.96*N_500$se.newdata.xm_z1_2sls
tsls_z1_xm_upper_N_500=N_500$mean_betas.data.xm_z1_2sls+1.96*N_500$se.newda
ta.xm_z1_2sls
obs_xm_lower_N_500=N_500$mean_betas.data.xm_obs-
1.96*N_500$se.newdata.xm_obs
obs_xm_upper_N_500=N_500$mean_betas.data.xm_obs+1.96*N_500$se.newdata.xm_ob
s
N_500=data.frame(N_500,tsls_xm_lower_N_500,tsls_xm_upper_N_500,tsls_z1_xm_l
ower_N_500,tsls_z1_xm_upper_N_500,
                 obs_xm_lower_N_500,obs_xm_upper_N_500)
N_500_interac_m3=N_500[round(N_500$mean_betas.data.xm_coeff_y,3)==-0.111,]
N_500_interac_0=N_500[round(N_500$mean_betas.data.xm_coeff_y,3)==0,]
N_500_interac_3=N_500[round(N_500$mean_betas.data.xm_coeff_y,3)==0.111,]
N_500_interac_5=N_500[round(N_500$mean_betas.data.xm_coeff_y,3)==0.167,]
N_500_interac_1=N_500[round(N_500$mean_betas.data.xm_coeff_y,3)==0.333,]

#2SLS Z=(Z1,Z2,Z1Z2) N=500K
setwd(writeplot)
tiff('coef_plot_z1z2_500k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_500_interac_m3$mean_betas.data.xm_2sls,N_500_interac_m3$mean_betas.d
ata.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
```

```
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2)',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_500_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.111,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-0.111','-
0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.35'),cex.axis=0.25)
lines(c(N_500_interac_m3$tsls_xm_lower_N_500[1],N_500_interac_m3$tsls_xm_up
per_N_500[1]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[1],N_500_interac
_m3$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_m3$tsls_xm_lower_N_500[2],N_500_interac_m3$tsls_xm_up
per_N_500[2]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[2],N_500_interac
_m3$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_m3$tsls_xm_lower_N_500[3],N_500_interac_m3$tsls_xm_up
per_N_500[3]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[3],N_500_interac
_m3$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_m3$tsls_xm_lower_N_500[4],N_500_interac_m3$tsls_xm_up
per_N_500[4]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[4],N_500_interac
_m3$mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_m3$tsls_xm_lower_N_500[5],N_500_interac_m3$tsls_xm_up
per_N_500[5]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[5],N_500_interac
_m3$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_0$mean_betas.data.xm_2sls,N_500_interac_0$mean_betas.dat
a.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_500_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.35'),cex.axis=0.25)
lines(c(N_500_interac_0$tsls_xm_lower_N_500[1],N_500_interac_0$tsls_xm_uppe
r_N_500[1]),c(N_500_interac_0$mean_betas.data.x_coeff_m[1],N_500_interac_0$
mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_0$tsls_xm_lower_N_500[2],N_500_interac_0$tsls_xm_uppe
r_N_500[2]),c(N_500_interac_0$mean_betas.data.x_coeff_m[2],N_500_interac_0$
mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_0$tsls_xm_lower_N_500[3],N_500_interac_0$tsls_xm_uppe
r_N_500[3]),c(N_500_interac_0$mean_betas.data.x_coeff_m[3],N_500_interac_0$
mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_0$tsls_xm_lower_N_500[4],N_500_interac_0$tsls_xm_uppe
r_N_500[4]),c(N_500_interac_0$mean_betas.data.x_coeff_m[4],N_500_interac_0$
mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_0$tsls_xm_lower_N_500[5],N_500_interac_0$tsls_xm_uppe
r_N_500[5]),c(N_500_interac_0$mean_betas.data.x_coeff_m[5],N_500_interac_0$
mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_3$mean_betas.data.xm_2sls,N_500_interac_3$mean_betas.dat
a.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_500_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.111,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-
0.10','-
```

```
0.05','0','0.05','0.10','0.111','0.15','0.20','0.25','0.30','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_3$tsls_xm_lower_N_500[1],N_500_interac_3$tsls_xm_uppe
r_N_500[1]),c(N_500_interac_3$mean_betas.data.x_coeff_m[1],N_500_interac_3$
mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_3$tsls_xm_lower_N_500[2],N_500_interac_3$tsls_xm_uppe
r_N_500[2]),c(N_500_interac_3$mean_betas.data.x_coeff_m[2],N_500_interac_3$
mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_3$tsls_xm_lower_N_500[3],N_500_interac_3$tsls_xm_uppe
r_N_500[3]),c(N_500_interac_3$mean_betas.data.x_coeff_m[3],N_500_interac_3$
mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_3$tsls_xm_lower_N_500[4],N_500_interac_3$tsls_xm_uppe
r_N_500[4]),c(N_500_interac_3$mean_betas.data.x_coeff_m[4],N_500_interac_3$
mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_3$tsls_xm_lower_N_500[5],N_500_interac_3$tsls_xm_uppe
r_N_500[5]),c(N_500_interac_3$mean_betas.data.x_coeff_m[5],N_500_interac_3$
mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_5$mean_betas.data.xm_2sls,N_500_interac_5$mean_betas.dat
a.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_500_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.167,0.20,0.25,0.30,0.35),labels=c('-0.15','-
0.10','-
0.05','0','0.05','0.10','0.15','0.167','0.20','0.25','0.30','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_5$tsls_xm_lower_N_500[1],N_500_interac_5$tsls_xm_uppe
r_N_500[1]),c(N_500_interac_5$mean_betas.data.x_coeff_m[1],N_500_interac_5$
mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_5$tsls_xm_lower_N_500[2],N_500_interac_5$tsls_xm_uppe
r_N_500[2]),c(N_500_interac_5$mean_betas.data.x_coeff_m[2],N_500_interac_5$
mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_5$tsls_xm_lower_N_500[3],N_500_interac_5$tsls_xm_uppe
r_N_500[3]),c(N_500_interac_5$mean_betas.data.x_coeff_m[3],N_500_interac_5$
mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_5$tsls_xm_lower_N_500[4],N_500_interac_5$tsls_xm_uppe
r_N_500[4]),c(N_500_interac_5$mean_betas.data.x_coeff_m[4],N_500_interac_5$
mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_5$tsls_xm_lower_N_500[5],N_500_interac_5$tsls_xm_uppe
r_N_500[5]),c(N_500_interac_5$mean_betas.data.x_coeff_m[5],N_500_interac_5$
mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_1$mean_betas.data.xm_2sls,N_500_interac_1$mean_betas.dat
a.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_500_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.333,0.35),labels=c('-0.15','-
0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.333','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_1$tsls_xm_lower_N_500[1],N_500_interac_1$tsls_xm_uppe
r_N_500[1]),c(N_500_interac_1$mean_betas.data.x_coeff_m[1],N_500_interac_1$
mean_betas.data.x_coeff_m[1]))
```

```
lines(c(N_500_interac_1$tsls_xm_lower_N_500[2],N_500_interac_1$tsls_xm_uppe
r_N_500[2]),c(N_500_interac_1$mean_betas.data.x_coeff_m[2],N_500_interac_1$
mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_1$tsls_xm_lower_N_500[3],N_500_interac_1$tsls_xm_uppe
r_N_500[3]),c(N_500_interac_1$mean_betas.data.x_coeff_m[3],N_500_interac_1$
mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_1$tsls_xm_lower_N_500[4],N_500_interac_1$tsls_xm_uppe
r_N_500[4]),c(N_500_interac_1$mean_betas.data.x_coeff_m[4],N_500_interac_1$
mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_1$tsls_xm_lower_N_500[5],N_500_interac_1$tsls_xm_uppe
r_N_500[5]),c(N_500_interac_1$mean_betas.data.x_coeff_m[5],N_500_interac_1$
mean_betas.data.x_coeff_m[5]))
dev.off()

#2SLS Z=(Z1,Z2,Z1Z2,Z1Z1) N=500K
tiff('coef_plot_z1z1_500k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_500_interac_m3$mean_betas.data.xm_z1_2sls,N_500_interac_m3$mean_beta
s.data.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='2sls estimate of theta coefficient,
Z=(Z1,Z2,Z1Z2,Z1Z1)',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_500_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.111,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-0.111','-
0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.35'),cex.axis=0.25)
lines(c(N_500_interac_m3$tsls_z1_xm_lower_N_500[1],N_500_interac_m3$tsls_z1
_xm_upper_N_500[1]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[1],N_500_i
nterac_m3$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_m3$tsls_z1_xm_lower_N_500[2],N_500_interac_m3$tsls_z1
_xm_upper_N_500[2]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[2],N_500_i
nterac_m3$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_m3$tsls_z1_xm_lower_N_500[3],N_500_interac_m3$tsls_z1
_xm_upper_N_500[3]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[3],N_500_i
nterac_m3$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_m3$tsls_z1_xm_lower_N_500[4],N_500_interac_m3$tsls_z1
_xm_upper_N_500[4]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[4],N_500_i
nterac_m3$mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_m3$tsls_z1_xm_lower_N_500[5],N_500_interac_m3$tsls_z1
_xm_upper_N_500[5]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[5],N_500_i
nterac_m3$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_0$mean_betas.data.xm_z1_2sls,N_500_interac_0$mean_betas.
data.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_500_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.35'),cex.axis=0.25)
lines(c(N_500_interac_0$tsls_z1_xm_lower_N_500[1],N_500_interac_0$tsls_z1_x
m_upper_N_500[1]),c(N_500_interac_0$mean_betas.data.x_coeff_m[1],N_500_inte
rac_0$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_0$tsls_z1_xm_lower_N_500[2],N_500_interac_0$tsls_z1_x
m_upper_N_500[2]),c(N_500_interac_0$mean_betas.data.x_coeff_m[2],N_500_inte
rac_0$mean_betas.data.x_coeff_m[2]))
```

```
lines(c(N_500_interac_0$tsls_z1_xm_lower_N_500[3],N_500_interac_0$tsls_z1_x
m_upper_N_500[3]),c(N_500_interac_0$mean_betas.data.x_coeff_m[3],N_500_inte
rac_0$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_0$tsls_z1_xm_lower_N_500[4],N_500_interac_0$tsls_z1_x
m_upper_N_500[4]),c(N_500_interac_0$mean_betas.data.x_coeff_m[4],N_500_inte
rac_0$mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_0$tsls_z1_xm_lower_N_500[5],N_500_interac_0$tsls_z1_x
m_upper_N_500[5]),c(N_500_interac_0$mean_betas.data.x_coeff_m[5],N_500_inte
rac_0$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_3$mean_betas.data.xm_z1_2sls,N_500_interac_3$mean_betas.
data.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_500_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.111,0.15,0.20,0.25,0.30,0.35),labels=c('-0.15','-
0.10','-
0.05','0','0.05','0.10','0.111','0.15','0.20','0.25','0.30','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_3$tsls_z1_xm_lower_N_500[1],N_500_interac_3$tsls_z1_x
m_upper_N_500[1]),c(N_500_interac_3$mean_betas.data.x_coeff_m[1],N_500_inte
rac_3$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_3$tsls_z1_xm_lower_N_500[2],N_500_interac_3$tsls_z1_x
m_upper_N_500[2]),c(N_500_interac_3$mean_betas.data.x_coeff_m[2],N_500_inte
rac_3$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_3$tsls_z1_xm_lower_N_500[3],N_500_interac_3$tsls_z1_x
m_upper_N_500[3]),c(N_500_interac_3$mean_betas.data.x_coeff_m[3],N_500_inte
rac_3$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_3$tsls_z1_xm_lower_N_500[4],N_500_interac_3$tsls_z1_x
m_upper_N_500[4]),c(N_500_interac_3$mean_betas.data.x_coeff_m[4],N_500_inte
rac_3$mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_3$tsls_z1_xm_lower_N_500[5],N_500_interac_3$tsls_z1_x
m_upper_N_500[5]),c(N_500_interac_3$mean_betas.data.x_coeff_m[5],N_500_inte
rac_3$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_5$mean_betas.data.xm_z1_2sls,N_500_interac_5$mean_betas.
data.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_500_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.167,0.20,0.25,0.30,0.35),labels=c('-0.15','-
0.10','-
0.05','0','0.05','0.10','0.15','0.167','0.20','0.25','0.30','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_5$tsls_z1_xm_lower_N_500[1],N_500_interac_5$tsls_z1_x
m_upper_N_500[1]),c(N_500_interac_5$mean_betas.data.x_coeff_m[1],N_500_inte
rac_5$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_5$tsls_z1_xm_lower_N_500[2],N_500_interac_5$tsls_z1_x
m_upper_N_500[2]),c(N_500_interac_5$mean_betas.data.x_coeff_m[2],N_500_inte
rac_5$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_5$tsls_z1_xm_lower_N_500[3],N_500_interac_5$tsls_z1_x
m_upper_N_500[3]),c(N_500_interac_5$mean_betas.data.x_coeff_m[3],N_500_inte
rac_5$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_5$tsls_z1_xm_lower_N_500[4],N_500_interac_5$tsls_z1_x
m_upper_N_500[4]),c(N_500_interac_5$mean_betas.data.x_coeff_m[4],N_500_inte
rac_5$mean_betas.data.x_coeff_m[4]))
```

```
lines(c(N_500_interac_5$tsls_z1_xm_lower_N_500[5],N_500_interac_5$tsls_z1_x
m_upper_N_500[5]),c(N_500_interac_5$mean_betas.data.x_coeff_m[5],N_500_inte
rac_5$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_1$mean_betas.data.xm_z1_2sls,N_500_interac_1$mean_betas.
data.x_coeff_m,xlim=c(-0.15,0.35),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_500_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.15,-0.10,-
0.05,0,0.05,0.10,0.15,0.20,0.25,0.30,0.333,0.35),labels=c('-0.15','-
0.10','-
0.05','0','0.05','0.10','0.15','0.20','0.25','0.30','0.333','0.35'),cex.axi
s=0.25)
lines(c(N_500_interac_1$tsls_z1_xm_lower_N_500[1],N_500_interac_1$tsls_z1_x
m_upper_N_500[1]),c(N_500_interac_1$mean_betas.data.x_coeff_m[1],N_500_inte
rac_1$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_1$tsls_z1_xm_lower_N_500[2],N_500_interac_1$tsls_z1_x
m_upper_N_500[2]),c(N_500_interac_1$mean_betas.data.x_coeff_m[2],N_500_inte
rac_1$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_1$tsls_z1_xm_lower_N_500[3],N_500_interac_1$tsls_z1_x
m_upper_N_500[3]),c(N_500_interac_1$mean_betas.data.x_coeff_m[3],N_500_inte
rac_1$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_1$tsls_z1_xm_lower_N_500[4],N_500_interac_1$tsls_z1_x
m_upper_N_500[4]),c(N_500_interac_1$mean_betas.data.x_coeff_m[4],N_500_inte
rac_1$mean_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_1$tsls_z1_xm_lower_N_500[5],N_500_interac_1$tsls_z1_x
m_upper_N_500[5]),c(N_500_interac_1$mean_betas.data.x_coeff_m[5],N_500_inte
rac_1$mean_betas.data.x_coeff_m[5]))
dev.off()


#OBSERVATIONAL N=500K
tiff('coef_plot_obs_500k.tif',width=3.5,height=10,units='in',res=400)
par(mfrow=c(5,1),mar=c(4,4.1,2,2.1))
plot(N_500_interac_m3$mean_betas.data.xm_obs,N_500_interac_m3$mean_betas.da
ta.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=-0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n',
     main='Ordinary least sqaures estimate of theta
coefficient',cex.main=0.7)
abline(v=-0.111)
axis(side=2,at=N_500_interac_m3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-0.111,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-0.111','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_500_interac_m3$obs_xm_lower_N_500[1],N_500_interac_m3$obs_xm_uppe
r_N_500[1]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[1],N_500_interac_m
3$mean_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_m3$obs_xm_lower_N_500[2],N_500_interac_m3$obs_xm_uppe
r_N_500[2]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[2],N_500_interac_m
3$mean_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_m3$obs_xm_lower_N_500[3],N_500_interac_m3$obs_xm_uppe
r_N_500[3]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[3],N_500_interac_m
3$mean_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_m3$obs_xm_lower_N_500[4],N_500_interac_m3$obs_xm_uppe
r_N_500[4]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[4],N_500_interac_m
3$mean_betas.data.x_coeff_m[4]))
```

```
lines(c(N_500_interac_m3$obs_xm_lower_N_500[5],N_500_interac_m3$obs_xm_uppe
r_N_500[5]),c(N_500_interac_m3$mean_betas.data.x_coeff_m[5],N_500_interac_m
3$mean_betas.data.x_coeff_m[5]))
plot(N_500_interac_0$mean_betas.data.xm_obs,N_500_interac_0$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0',ylab='alpha coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0)
axis(side=2,at=N_500_interac_0$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=0.25)
lines(c(N_500_interac_0$obs_xm_lower_N_500[1],N_500_interac_0$obs_xm_upper_
N_500[1]),c(N_500_interac_0$mean_betas.data.x_coeff_m[1],N_500_interac_0$me
an_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_0$obs_xm_lower_N_500[2],N_500_interac_0$obs_xm_upper_
N_500[2]),c(N_500_interac_0$mean_betas.data.x_coeff_m[2],N_500_interac_0$me
an_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_0$obs_xm_lower_N_500[3],N_500_interac_0$obs_xm_upper_
N_500[3]),c(N_500_interac_0$mean_betas.data.x_coeff_m[3],N_500_interac_0$me
an_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_0$obs_xm_lower_N_500[4],N_500_interac_0$obs_xm_upper_
N_500[4]),c(N_500_interac_0$mean_betas.data.x_coeff_m[4],N_500_interac_0$me
an_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_0$obs_xm_lower_N_500[5],N_500_interac_0$obs_xm_upper_
N_500[5]),c(N_500_interac_0$mean_betas.data.x_coeff_m[5],N_500_interac_0$me
an_betas.data.x_coeff_m[5]))
plot(N_500_interac_3$mean_betas.data.xm_obs,N_500_interac_3$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.111',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.111)
axis(side=2,at=N_500_interac_3$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.111,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.111','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_500_interac_3$obs_xm_lower_N_500[1],N_500_interac_3$obs_xm_upper_
N_500[1]),c(N_500_interac_3$mean_betas.data.x_coeff_m[1],N_500_interac_3$me
an_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_3$obs_xm_lower_N_500[2],N_500_interac_3$obs_xm_upper_
N_500[2]),c(N_500_interac_3$mean_betas.data.x_coeff_m[2],N_500_interac_3$me
an_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_3$obs_xm_lower_N_500[3],N_500_interac_3$obs_xm_upper_
N_500[3]),c(N_500_interac_3$mean_betas.data.x_coeff_m[3],N_500_interac_3$me
an_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_3$obs_xm_lower_N_500[4],N_500_interac_3$obs_xm_upper_
N_500[4]),c(N_500_interac_3$mean_betas.data.x_coeff_m[4],N_500_interac_3$me
an_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_3$obs_xm_lower_N_500[5],N_500_interac_3$obs_xm_upper_
N_500[5]),c(N_500_interac_3$mean_betas.data.x_coeff_m[5],N_500_interac_3$me
an_betas.data.x_coeff_m[5]))
plot(N_500_interac_5$mean_betas.data.xm_obs,N_500_interac_5$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.167',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.167)
axis(side=2,at=N_500_interac_5$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
```

```
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.167,0.2,0.3,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.167','0.2','0.3','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_500_interac_5$obs_xm_lower_N_500[1],N_500_interac_5$obs_xm_upper_
N_500[1]),c(N_500_interac_5$mean_betas.data.x_coeff_m[1],N_500_interac_5$me
an_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_5$obs_xm_lower_N_500[2],N_500_interac_5$obs_xm_upper_
N_500[2]),c(N_500_interac_5$mean_betas.data.x_coeff_m[2],N_500_interac_5$me
an_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_5$obs_xm_lower_N_500[3],N_500_interac_5$obs_xm_upper_
N_500[3]),c(N_500_interac_5$mean_betas.data.x_coeff_m[3],N_500_interac_5$me
an_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_5$obs_xm_lower_N_500[4],N_500_interac_5$obs_xm_upper_
N_500[4]),c(N_500_interac_5$mean_betas.data.x_coeff_m[4],N_500_interac_5$me
an_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_5$obs_xm_lower_N_500[5],N_500_interac_5$obs_xm_upper_
N_500[5]),c(N_500_interac_5$mean_betas.data.x_coeff_m[5],N_500_interac_5$me
an_betas.data.x_coeff_m[5]))
plot(N_500_interac_1$mean_betas.data.xm_obs,N_500_interac_1$mean_betas.data
.x_coeff_m,xlim=c(-0.3,0.8),cex=0.5,
     xlab='theta=0.333',ylab='alpha
coefficient',cex.lab=0.6,yaxt='n',xaxt='n')
abline(v=0.333)
axis(side=2,at=N_500_interac_1$mean_betas.data.x_coeff_m,labels=c('-
0.333','0','0.333','0.5','1'),cex.axis=0.4)
axis(side=1,at=c(-0.3,-0.2,-
0.1,0,0.1,0.2,0.3,0.333,0.4,0.5,0.6,0.7,0.8),labels=c('-0.3','-0.2','-
0.1','0','0.1','0.2','0.3','0.333','0.4','0.5','0.6','0.7','0.8'),cex.axis=
0.25)
lines(c(N_500_interac_1$obs_xm_lower_N_500[1],N_500_interac_1$obs_xm_upper_
N_500[1]),c(N_500_interac_1$mean_betas.data.x_coeff_m[1],N_500_interac_1$me
an_betas.data.x_coeff_m[1]))
lines(c(N_500_interac_1$obs_xm_lower_N_500[2],N_500_interac_1$obs_xm_upper_
N_500[2]),c(N_500_interac_1$mean_betas.data.x_coeff_m[2],N_500_interac_1$me
an_betas.data.x_coeff_m[2]))
lines(c(N_500_interac_1$obs_xm_lower_N_500[3],N_500_interac_1$obs_xm_upper_
N_500[3]),c(N_500_interac_1$mean_betas.data.x_coeff_m[3],N_500_interac_1$me
an_betas.data.x_coeff_m[3]))
lines(c(N_500_interac_1$obs_xm_lower_N_500[4],N_500_interac_1$obs_xm_upper_
N_500[4]),c(N_500_interac_1$mean_betas.data.x_coeff_m[4],N_500_interac_1$me
an_betas.data.x_coeff_m[4]))
lines(c(N_500_interac_1$obs_xm_lower_N_500[5],N_500_interac_1$obs_xm_upper_
N_500[5]),c(N_500_interac_1$mean_betas.data.x_coeff_m[5],N_500_interac_1$me
an_betas.data.x_coeff_m[5]))
dev.off()

#POWER PLOTS
setwd(writeplot)

tiff('50_forestplot_power.tif',width=12.7,height=9,units='cm',res=400)
#layout(matrix(c(1,2)),widths=c(lcm(4.5),2),heights=c(lcm(12.7),1),byrow=FA
LSE)
layout(matrix(c(1,2),1,2,byrow=FALSE))
#vals=par('usr')
#rem_0interac=N_50[2:26,]
rem_0interac=N_50
rem_0interac=rem_0interac[rem_0interac$mean_betas.data.xm_coeff_y!=0,]
powervals=rbind(rem_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,rem_0interac
$z1_coverage.z1_coverage)
powervals=as.matrix(powervals)
```

```
powervals=powervals/10
acolnames=cbind(round(rem_0interac$mean_betas.data.x_coeff_m,3),round(rem_0
interac$mean_betas.data.xm_coeff_y,3))
colnamesconcat_1=paste('alpha:',acolnames[,1],sep='')
colnamesconcat_2=paste('theta:',acolnames[,2],sep='')
colnamesconcat=paste(colnamesconcat_1,colnamesconcat_2,sep=', ')
par(las=1)
spacevec1=c(1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5)
spacevec2=c(1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5)
colnames(powervals)=colnamesconcat
fmrpowervals=rem_0interac$fmr_y_int.fmr_y_int
fmrpowervals=fmrpowervals/10
#widthspec=c(0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.
1,0.1,0.1,0.1,1)
barplot(powervals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Power and
Coverage of 2sls Estimator of theta (%)',cex.lab=0.4,
        xlim=c(0,100),main="2sls with Z=(Z1,Z2,Z1Z2,Z1Z1)", cex.main="0.5",
        beside=TRUE,col=c('blue','grey'),space=spacevec1)
        #width=widthspec
        #space=spacevec
        #names.arg=colnamesconcat
#text(x=91,y=66,labels="95%",cex=0.3)
mtext("95%",side=1,at=95,cex=0.3)
abline(v=80,lty=2,col='blue')
abline(v=95,lty=2,col='black')
barplot(fmrpowervals,horiz=TRUE,names.arg=colnamesconcat,cex.names=0.3,cex.
axis=0.4,xlab='Power of FMR to detect non-zero theta
(%)',cex.lab=0.4,col='blue',
        space=spacevec2,xlim=c(0,100),main="Factorial MR",cex.main="0.5")
abline(v=80,lty=2,col='blue')
legend(x='bottomleft',inset=c(-0.6,-
0.55),legend=c('power','coverage'),col=c('blue','grey'),pch=19,xpd=TRUE,cex
=0.4)
dev.off()



tiff('100_forestplot_power.tif',width=12.7,height=9,units='cm',res=400)
#layout(matrix(c(1,2)),widths=c(lcm(4.5),2),heights=c(lcm(12.7),1),byrow=FA
LSE)
layout(matrix(c(1,2),1,2,byrow=FALSE))
#vals=par('usr')
#crem_0interac=N_100[2:26,]
crem_0interac=N_100
crem_0interac=crem_0interac[crem_0interac$mean_betas.data.xm_coeff_y!=0,]
cpowervals=rbind(crem_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,crem_0inte
rac$z1_coverage.z1_coverage)
```

```
cpowervals=as.matrix(cpowervals)
cpowervals=cpowervals/10
ccolnames=cbind(round(crem_0interac$mean_betas.data.x_coeff_m,3),round(crem
_0interac$mean_betas.data.xm_coeff_y,3))
ccolnamesconcat_1=paste('alpha:',ccolnames[,1],sep='')
ccolnamesconcat_2=paste('theta:',ccolnames[,2],sep='')
ccolnamesconcat=paste(ccolnamesconcat_1,ccolnamesconcat_2,sep=', ')
par(las=1)
cspacevec1=c(1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5)
cspacevec2=c(1.5,
            0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5)
colnames(cpowervals)=ccolnamesconcat
cfmrpowervals=crem_0interac$fmr_y_int.fmr_y_int
cfmrpowervals=cfmrpowervals/10
#widthspec=c(0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.
1,0.1,0.1,0.1,1)
barplot(cpowervals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Power and
Coverage of 2sls Estimator of theta (%)',cex.lab=0.4,
        xlim=c(0,100),main="2sls with Z=(Z1,Z2,Z1Z2,Z1Z1)", cex.main="0.5",
        beside=TRUE,col=c('blue','grey'),space=cspacevec1)
#width=widthspec
#space=spacevec
#names.arg=colnamesconcat
#text(x=91,y=66,labels="95%",cex=0.3)
mtext("95%",side=1,at=95,cex=0.3)
abline(v=80,lty=2,col='blue')
abline(v=95,lty=2,col='black')
barplot(cfmrpowervals,horiz=TRUE,names.arg=ccolnamesconcat,cex.names=0.3,ce
x.axis=0.4,xlab='Power of FMR to detect non-zero theta
(%)',cex.lab=0.4,col='blue',
        space=cspacevec2,xlim=c(0,100),main="Factorial MR",cex.main="0.5")
abline(v=80,lty=2,col='blue')
legend(x='bottomleft',inset=c(-0.6,-
0.55),legend=c('power','coverage'),col=c('blue','grey'),pch=19,xpd=TRUE,cex
=0.4)
dev.off()




tiff('500_forestplot_power.tif',width=12.7,height=9,units='cm',res=400)
layout(matrix(c(1,2),1,2,byrow=FALSE))
#vals=par('usr')
#brem_0interac=N_500[2:26,]
brem_0interac=N_500
brem_0interac=brem_0interac[brem_0interac$mean_betas.data.xm_coeff_y!=0,]
```

```
bpowervals=rbind(brem_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,brem_0inte
rac$z1_coverage.z1_coverage)
bpowervals=as.matrix(bpowervals)
bpowervals=bpowervals/10
bcolnames=cbind(round(brem_0interac$mean_betas.data.x_coeff_m,3),round(brem
_0interac$mean_betas.data.xm_coeff_y,3))
bcolnamesconcat_1=paste('alpha:',bcolnames[,1],sep='')
bcolnamesconcat_2=paste('theta:',bcolnames[,2],sep='')
bcolnamesconcat=paste(bcolnamesconcat_1,bcolnamesconcat_2,sep=', ')
par(las=1)
bspacevec1=c(1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,
            1.5,
            0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5)
bspacevec2=c(1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5,
           1.5,
           0.5,0.5,0.5,0.5)
colnames(bpowervals)=bcolnamesconcat
bfmrpowervals=brem_0interac$fmr_y_int.fmr_y_int
bfmrpowervals=bfmrpowervals/10
barplot(bpowervals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Power and
Coverage of 2sls Estimator of theta (%)',cex.lab=0.4,
        xlim=c(0,100),main="2sls with Z=(Z1,Z2,Z1Z2,Z1Z1)", cex.main="0.5",
        beside=TRUE,col=c('blue','grey'),space=bspacevec1)
#text(x=91,y=65,labels="95%",cex=0.3)
#text(x=91,y=-1,labels="95%",cex=0.3)
mtext("95%",side=1,at=95,cex=0.3)
abline(v=80,lty=2,col='blue')
abline(v=95,lty=2,col='black')
barplot(bfmrpowervals,horiz=TRUE,names.arg=bcolnamesconcat,cex.names=0.3,ce
x.axis=0.4,xlab='Power of FMR to detect non-zero theta
(%)',cex.lab=0.4,col='blue',
        space=bspacevec2,xlim=c(0,100),main="Factorial MR",cex.main="0.5")
abline(v=80,lty=2,col='blue')
legend(x='bottomleft',inset=c(-0.6,-
0.55),legend=c('power','coverage'),col=c('blue','grey'),pch=19,xpd=TRUE,cex
=0.4)
dev.off()



#TYPE I ERROR PLOTS

tiff('50_forestplot_typei.tif',width=12.7,height=9,units='cm',res=400)
#vals=par('usr')
#keep_0interac=N_50[2:26,]
keep_0interac=N_50
keep_0interac=keep_0interac[keep_0interac$mean_betas.data.xm_coeff_y==0,]
typeivals=rbind(keep_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,keep_0inter
ac$fmr_y_int.fmr_y_int)
typeivals=as.matrix(typeivals)
typeivals=typeivals/10
```

```
ticolnames=cbind(round(keep_0interac$mean_betas.data.x_coeff_m,3),round(kee
p_0interac$mean_betas.data.xm_coeff_y,3))
ticolnamesconcat_1=paste('alpha:',ticolnames[,1],sep='')
ticolnamesconcat_2=paste('theta:',ticolnames[,2],sep='')
ticolnamesconcat=paste(ticolnamesconcat_1,ticolnamesconcat_2,sep=', ')
par(las=1)
colnames(typeivals)=ticolnamesconcat
#widthspec=c(0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.
1,0.1,0.1,0.1,1)
barplot(typeivals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Type I Error
Rate',cex.lab=0.4,
        xlim=c(0,6),main='2sls vs FMR: N=50,000', cex.main="0.5",
        beside=TRUE,col=c('blue','red'))
#space=spacevec1
#width=widthspec
#space=spacevec
#names.arg=colnamesconcat
abline(v=5,lty=2,col='black')
legend(x='bottomright',legend=c('2sls','FMR'),col=c('blue','red'),pch=19,xp
d=TRUE,cex=0.4)
dev.off()



tiff('100_forestplot_typei.tif',width=12.7,height=9,units='cm',res=400)
#vals=par('usr')
#ckeep_0interac=N_100[2:26,]
ckeep_0interac=N_100
ckeep_0interac=ckeep_0interac[ckeep_0interac$mean_betas.data.xm_coeff_y==0,
]
ctypeivals=rbind(ckeep_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,ckeep_0in
terac$fmr_y_int.fmr_y_int)
ctypeivals=as.matrix(ctypeivals)
ctypeivals=ctypeivals/10
cticolnames=cbind(round(ckeep_0interac$mean_betas.data.x_coeff_m,3),round(c
keep_0interac$mean_betas.data.xm_coeff_y,3))
cticolnamesconcat_1=paste('alpha:',cticolnames[,1],sep='')
cticolnamesconcat_2=paste('theta:',cticolnames[,2],sep='')
cticolnamesconcat=paste(cticolnamesconcat_1,cticolnamesconcat_2,sep=', ')
par(las=1)
colnames(ctypeivals)=cticolnamesconcat
#widthspec=c(0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.
1,0.1,0.1,0.1,1)
barplot(ctypeivals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Type I Error
Rate',cex.lab=0.4,
        xlim=c(0,6),main='2sls vs FMR: N=100,000', cex.main="0.5",
        beside=TRUE,col=c('blue','red'))
#space=spacevec1
#width=widthspec
#space=spacevec
#names.arg=colnamesconcat
abline(v=5,lty=2,col='black')
legend(x='bottomright',legend=c('2sls','FMR'),col=c('blue','red'),pch=19,xp
d=TRUE,cex=0.4)
dev.off()




tiff('500_forestplot_typei.tif',width=12.7,height=9,units='cm',res=400)
```

```
#vals=par('usr')
#bkeep_0interac=N_500[2:26,]
bkeep_0interac=N_500
bkeep_0interac=bkeep_0interac[bkeep_0interac$mean_betas.data.xm_coeff_y==0,
]
btypeivals=rbind(bkeep_0interac$xm_z1_2sls_detec.xm_z1_2sls_detec,bkeep_0in
terac$fmr_y_int.fmr_y_int)
btypeivals=as.matrix(btypeivals)
btypeivals=btypeivals/10
bticolnames=cbind(round(bkeep_0interac$mean_betas.data.x_coeff_m,3),round(b
keep_0interac$mean_betas.data.xm_coeff_y,3))
bticolnamesconcat_1=paste('alpha:',bticolnames[,1],sep='')
bticolnamesconcat_2=paste('theta:',bticolnames[,2],sep='')
bticolnamesconcat=paste(bticolnamesconcat_1,bticolnamesconcat_2,sep=', ')
par(las=1)
colnames(btypeivals)=bticolnamesconcat
#widthspec=c(0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.1,0.
1,0.1,0.1,0.1,1)
barplot(btypeivals,horiz=TRUE,cex.names=0.3,cex.axis=0.4,xlab='Type I Error
Rate',cex.lab=0.4,
        xlim=c(0,6),main='2sls vs FMR: N=500,000', cex.main="0.5",
        beside=TRUE,col=c('blue','red'))
#space=spacevec1
#width=widthspec
#space=spacevec
#names.arg=colnamesconcat
abline(v=5,lty=2,col='black')
legend(x='bottomright',legend=c('2sls','FMR'),col=c('blue','red'),pch=19,xp
d=TRUE,cex=0.4)
dev.off()
```

4.6.6 Analysis of pleiotropy

```
#script_name: meta_sensitivity_v8.r
#project: 4-way decomp
#script author: Teri North
#script purpose: simulation to examine impact of pleiotropy on performance
of 2sls & FMR
#date created: 10/04/2018
#last edited: 25/01/2019

#read in seed
seedval=commandArgs(6)

print(seedval)
seedval=as.numeric(seedval)

#load packages
library("AER")


sessionInfo()
```

```
#define headers
headers=c("x_coeff_m","x_coeff_y","m_coeff_y","xm_coeff_y",
          "fmr_interac_p","xm_2sls","xm_2sls_se")



set.seed(seedval)

#2 models are run with 1000 repeats for each.
#model 1 - as normal
#model 2 - allow for A2 instrument to also causally affect A1

for (rep in c(1:100)){

  #log session for each sim repeat
  sink(file=paste(seedval,'_rep',rep,"_meta_log.txt",sep=""))

  nval=500000

  #generate data for system
  samp_size=nval
  #error terms
  u=rnorm(samp_size)
  v=rnorm(samp_size)
  e=rnorm(samp_size)
  #confounders
  c=rnorm(samp_size)
  #instruments
  z1=rnorm(samp_size)
  z2=rnorm(samp_size)


  for (model in c(1:2)){
    #write file headers
    #begin with append=FALSE to overwrite current file
    write.table(headers,
file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.txt",sep=""),appen
d=FALSE, quote=FALSE, row.names=FALSE, col.names=FALSE, sep =
"\t",eol="\t")


    for (i in c(0,0.333,0.5,1,-0.333)) {

      for (othcomb in c(1,2,3,4,5)){

        if (othcomb==1){
          j=0
          k=0
          l=0/3
          m=0/3
          n=0/3

        } else if (othcomb==2){
          j=0.333
          k=0.333
          l=0.333/3
          m=0.333/3
          n=0.333/3

        } else if (othcomb==3){
          j=0.5
```

```
      k=0.5
      l=0.5/3
      m=0.5/3
      n=0.5/3

    } else if (othcomb==4){
      j=1
      k=1
      l=1/3
      m=1/3
      n=1/3

    } else if (othcomb==5){
      j=-0.333
      k=-0.333
      l=-0.333/3
      m=-0.333/3
      n=-0.333/3

    }




    print(i)
    print(j)
    print(k)
    print(l)
    coeff_list<- c(i,j,k,l)

    #define models
    #Exposure
    if (model==1){
      a1=c+v+0.14*z1
    } else if (model==2){
      a1=c+v+0.1*z1+0.1*z2
    }
    #Mediator
    a2=i*a1+e+0.18*z2+c
    #Outcome
    y=j*a1+k*a2+u+c+l*a1*a2+m*c*a1+n*c*a2

    a1a2=a1*a2
    z1z2=z1*z2
    z1z1=z1*z1

    #make a dataframe of the required vars
    targ=data.frame(a1,a2,y,a1a2,z1,z2,z1z2,z1z1)


    #split the observations into 4 groups based on median splits of
Instruments
    med_z1=median(targ$z1)
    med_z2=median(targ$z2)


    f0=c(1:length(targ[,1]))
    f1=c(1:length(targ[,1]))
    f2=c(1:length(targ[,1]))
    f3=c(1:length(targ[,1]))
```

```
        for (z in c(1:length(targ[,1]))){

          f0[z]=NA
          f1[z]=NA
          f2[z]=NA
          f3[z]=NA
        }

        for (z in c(1:length(targ[,1]))){
          if ((targ$z1[z]<=med_z1) & (targ$z2[z]<=med_z2)){

            f0[z]=1
            f1[z]=0
            f2[z]=0
            f3[z]=0
          } else if ((targ$z1[z]<=med_z1) & (targ$z2[z]>med_z2)){

            f0[z]=0
            f1[z]=1
            f2[z]=0
            f3[z]=0
          } else if ((targ$z1[z]>med_z1) & (targ$z2[z]<=med_z2)){

            f0[z]=0
            f1[z]=0
            f2[z]=1
            f3[z]=0
          } else if ((targ$z1[z]>med_z1) & (targ$z2[z]>med_z2)){

            f0[z]=0
            f1[z]=0
            f2[z]=0
            f3[z]=1
          }
        }



        #FACTORIAL MR (median split)
        fitfmr <- lm(targ$y ~ f1 + f2 + f3)
        sum_fmr=coef(summary(fitfmr))


        #f0 as the baseline - see fig 2 ference paper

        #reality check on regression coefficients
        mean(targ$y[f1==1]) - fitfmr$coefficients[2]
        mean(targ$y[f2==1]) - fitfmr$coefficients[3]
        mean(targ$y[f3==1]) - fitfmr$coefficients[4]

        mean(targ$y[f0==1]) - fitfmr$coefficients[1] #intercept is mean
outcome for baseline group

        #formal test for interaction using linear contrast of coeffs - use
Wald test comparable to stata's 'test'
        lhyp='1*f1 + 1*f2 - 1*f3 = 0'
        lincon=linearHypothesis(fitfmr,lhyp,test='F')
        int_p=lincon$`Pr(>F)`[2]

        fmr_vec=c(int_p)
```

```
        #instrumental variable 2sls: inst=z1+z2+z1z2+z1z1 [when mediation
expected]
        eq2y<- targ$y ~ targ$a1 + targ$a2 + targ$a1a2 | targ$z1 + targ$z2 +
targ$z1z2 + targ$z1z1
        fitz12sls <- ivreg(eq2y)
        sum_z12sls=coef(summary(fitz12sls))



        tslsz1_vec=c(sum_z12sls[2,1],sum_z12sls[2,2],
                     sum_z12sls[3,1],sum_z12sls[3,2],
                     sum_z12sls[4,1],sum_z12sls[4,2])


        mres=c(coeff_list,fmr_vec,tslsz1_vec[5],tslsz1_vec[6])


        write("",
file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.txt",sep=""),appen
d=TRUE, sep = "\n")
        write.table(mres,
file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.txt",sep=""),appen
d=TRUE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")



      }
    }







  }

  sink()
}
```

4.6.7 Analysis of pleiotropy - pooling estimates across simulation repeats

```
#script_name: Pool_meta_sensitivity_v6.r


#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: pool estimates across simulation repeats by
#                 -taking the mean betahat & SE of betahats (to generate MC
95% CI for betahat)
#                 -take the mean SE and the SD of betahats
#                 -calculate power, type i error and coverage where
applicable
#date created: 09/08/2018
#last edited: 11/10/2018
#notes:
```

```
setwd('') #Folder 1

#number of repeats in each sim
repeats=100
nval=500000

#tracker for erroneous calls - will get two numbers one for model 1 and the
other for model 2

n_z1problem=c(1:2)
for (j in c(1:2)){n_z1problem[j]=0}
n_z1prob_track=1



for (model in c(1:2)){

  xm_z1_2sls_detec=c(1:25)
  for (i in c(1:25)){
    xm_z1_2sls_detec[i]=0
  }


  z1_coverage=c(1:25)
  for (i in c(1:25)){
    z1_coverage[i]=0
  }


  #reality check
  #how many times is the interaction detected (p<0.05), but the estimate is
in the opposite direction to true effect?

  z1problem=c(1:25)
  for (i in c(1:25)){
    z1problem[i]=0
  }



  fmr_y_int=c(1:25)  # counter for # times interaction detected factorial
approach (Wald test 5%)
  for (i in c(1:25)){
    fmr_y_int[i]=0
  }


  #calculating the mean betas
  first=1


  for (seedval in
c(520160447,267639401,37905828,750891730,435580371,945959183,141153971,4562
64979,86129334,119011473)){

    for (rep in c(1:repeats)){

      if (first==1){
```

```
data=read.table(file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.tx
t",sep=''),sep='\t',header=TRUE)
        true_vals=data.frame(data$x_coeff_m,data$x_coeff_y,data$m_coeff_y,
data$xm_coeff_y)
        first=0

        ll=data.frame(
          xm_2sls_ll=data$xm_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_2sls_se
        )

        ul=data.frame(
          xm_2sls_ul=data$xm_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*data$xm_2sls_se
        )


        for (i in c(1:25)){
          if (ll$xm_2sls_ll[i]>0 |
ul$xm_2sls_ul[i]<0){xm_z1_2sls_detec[i]=1}
        }

        for (i in c(1:25)){
          if ((ll$xm_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_2sls_ul[i]>data$xm_coeff_y[i])){z1_coverage[i]=1}
        }


        for (i in c(1:25)){
          if (((ll$xm_2sls_ll[i]>0) &
(data$xm_coeff_y[i]<0))|((ul$xm_2sls_ul[i]<0) & (data$xm_coeff_y[i]>0)))
{z1problem[i]=1}#if interac detec, but coeff wrong direc
        }


        for (i in c(1:25)){
          if (data$fmr_interac_p[i]<0.05){fmr_y_int[i]=1}
        }



      } else if (first==0){


new=read.table(file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.txt
",sep=''),sep='\t',header=TRUE)
        data=data+new

        ll_new=data.frame(
          xm_2sls_ll=new$xm_2sls-(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_2sls_se
        )

        ul_new=data.frame(
          xm_2sls_ul=new$xm_2sls+(qt(0.025,(nval-
4),lower.tail=FALSE))*new$xm_2sls_se
        )


        for (i in c(1:25)){
```

```
          if (ll_new$xm_2sls_ll[i]>0 |
ul_new$xm_2sls_ul[i]<0){xm_z1_2sls_detec[i]=xm_z1_2sls_detec[i]+1}
        }


        for (i in c(1:25)){
          if ((ll_new$xm_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_2sls_ul[i]>new$xm_coeff_y[i])){z1_coverage[i]=z1_coverage[i]+1}
        }


        for (i in c(1:25)){
          if (((ll_new$xm_2sls_ll[i]>0) &
(new$xm_coeff_y[i]<0))|((ul_new$xm_2sls_ul[i]<0) & (new$xm_coeff_y[i]>0)))
{z1problem[i]=z1problem[i]+1}#if interac detec, but coeff wrong direc
        }


        for (i in c(1:25)){
          if (new$fmr_interac_p[i]<0.05){fmr_y_int[i]=fmr_y_int[i]+1}
        }



      }



    }

  }



  #remove true values
  data_est=data.frame(data$xm_2sls,data$xm_2sls_se)



  #mean betas
  mean_denom=repeats*10 #no. rep within seeds * no. seeds
  data_mean=data_est/mean_denom #gives mean beta and mean se
  #add in the true params
  mean_betas=cbind(true_vals,data_mean)



###############################################################################
###############################################################################
######################

  #now for the standard error
  checker=1

  for (seeds in
c(520160447,267639401,37905828,750891730,435580371,945959183,141153971,4562
64979,86129334,119011473)){

    for (rep in c(1:repeats)){

      if (checker==1){
```

```
newdata=read.table(file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res
.txt",sep=''),sep='\t',header=TRUE)
        newdata=(newdata-(data/mean_denom))^2
        checker=0

      } else if (checker==0){


newer=read.table(file=paste(seedval,'_rep',rep,'_model',model,"_pleio_res.t
xt",sep=''),sep='\t',header=TRUE)
        newdata=newdata+(newer-(data/mean_denom))^2
        newdata=data.frame(newdata)
      }

    }
  }


  newdata_est=data.frame(newdata$xm_2sls)



  #divide by n-1 to get s^2
  s2=newdata_est/(repeats*10-1)
  se=sqrt(s2/(repeats*10))



###########################################################################
###########################################################################
############


  xm_z1_2sls_detec=data.frame(xm_z1_2sls_detec)
  z1_coverage=data.frame(z1_coverage)
  fmr_y_int=data.frame(fmr_y_int)

  #results table
  res=data.frame(mean_betas$data.x_coeff_m,
                 mean_betas$data.x_coeff_y,
                 mean_betas$data.m_coeff_y,
                 mean_betas$data.xm_coeff_y,
                 mean_betas$data.xm_2sls,
                 se$newdata.xm_2sls,
                 mean_betas$data.xm_2sls_se,
                 xm_z1_2sls_detec$xm_z1_2sls_detec,
                 z1_coverage$z1_coverage,
                 s2$newdata.xm_2sls,
                 fmr_y_int$fmr_y_int
  )





write.table(res,file=paste('500000_EXTRA_final_res_model_',model,'.txt',sep
=''),sep='\t',row.names=FALSE)
```

```
  #how many times across repeat sims is an interaction detected in the
incorrect direction?
  n_z1problem[n_z1prob_track]=sum(z1problem)
  n_z1prob_track=n_z1prob_track+1



}

write(n_z1problem, file='z1problem.txt',append=FALSE, sep = "\n")



for (model in c(1:2)){

t50=data.frame(read.table(file=paste('500000_EXTRA_final_res_model_',model,
'.txt',sep=''),header=TRUE))

all=t50

headers=c('mediator_coeff','\t','interac_coeff', '\t',
'mean_est','\t','sd(est)','\t','mean(se(est))','\t','se(est)','\t',
          'power','\t','type_i','\t','coverage')

res_l_0=all[round(all$mean_betas.data.xm_coeff_y,3)==0.000,]
res_l_m3=all[round(all$mean_betas.data.xm_coeff_y,3)==-0.111,]
res_l_3=all[round(all$mean_betas.data.xm_coeff_y,3)==0.111,]
res_l_5=all[round(all$mean_betas.data.xm_coeff_y,3)==0.167,]
res_l_1=all[round(all$mean_betas.data.xm_coeff_y,3)==0.333,]

res_l_0=res_l_0[order(res_l_0$mean_betas.data.x_coeff_m),]
res_l_m3=res_l_m3[order(res_l_m3$mean_betas.data.x_coeff_m),]
res_l_3=res_l_3[order(res_l_3$mean_betas.data.x_coeff_m),]
res_l_5=res_l_5[order(res_l_5$mean_betas.data.x_coeff_m),]
res_l_1=res_l_1[order(res_l_1$mean_betas.data.x_coeff_m),]

blank=c(1:5)
for (i in c(1:5)){blank[i]='NA'}

###################################INTERACTION
COEFFICIENT#############################################################
#####################################################

#REMEMBER THAT THE VARIANCE NEEDS TO BE SQRT'D TO CONVERT TO SD
#POWER, TYPE I AND COVERAGE NEED TO BE DIVIDED BY 10 TO CONVERT TO %

###################
#Z=Z1+Z2+Z1Z2+Z1Z1#
###################

editZ1_res_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_be
tas.data.xm_coeff_y,res_l_0$mean_betas.data.xm_2sls,

sqrt(res_l_0$s2.newdata.xm_2sls),res_l_0$mean_betas.data.xm_2sls_se,res_l_0
$se.newdata.xm_2sls,blank,

(res_l_0$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,(res_l_0$z1_coverage.z1_cove
rage)/10)
```

```
editZ1_res_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mean
_betas.data.xm_coeff_y,res_l_m3$mean_betas.data.xm_2sls,

sqrt(res_l_m3$s2.newdata.xm_2sls),res_l_m3$mean_betas.data.xm_2sls_se,res_l
_m3$se.newdata.xm_2sls,(res_l_m3$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,
                           blank, (res_l_m3$z1_coverage.z1_coverage)/10)

editZ1_res_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_be
tas.data.xm_coeff_y,res_l_3$mean_betas.data.xm_2sls,

sqrt(res_l_3$s2.newdata.xm_2sls),res_l_3$mean_betas.data.xm_2sls_se,res_l_3
$se.newdata.xm_2sls,(res_l_3$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,
                          blank, (res_l_3$z1_coverage.z1_coverage)/10)

editZ1_res_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_be
tas.data.xm_coeff_y,res_l_5$mean_betas.data.xm_2sls,

sqrt(res_l_5$s2.newdata.xm_2sls),res_l_5$mean_betas.data.xm_2sls_se,res_l_5
$se.newdata.xm_2sls,(res_l_5$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,
                          blank, (res_l_5$z1_coverage.z1_coverage)/10)

editZ1_res_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_be
tas.data.xm_coeff_y,res_l_1$mean_betas.data.xm_2sls,

sqrt(res_l_1$s2.newdata.xm_2sls),res_l_1$mean_betas.data.xm_2sls_se,res_l_1
$se.newdata.xm_2sls,(res_l_1$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,
                          blank, (res_l_1$z1_coverage.z1_coverage)/10)


#interaction coefficient=0
write.table(headers, file=paste('TSLS_MED_L0_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('TSLS_MED_L0_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editZ1_res_l_0,
file=paste('TSLS_MED_L0_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers,
file=paste('TSLS_MED_LM3_',model,'_.txt'),append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('TSLS_MED_LM3_',model,'_.txt'),append=TRUE, sep =
"\n")
write.table(editZ1_res_l_m3,
file=paste('TSLS_MED_LM3_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers, file=paste('TSLS_MED_L3_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('TSLS_MED_L3_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editZ1_res_l_3,
file=paste('TSLS_MED_L3_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=5
write.table(headers, file=paste('TSLS_MED_L5_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('TSLS_MED_L5_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editZ1_res_l_5,
file=paste('TSLS_MED_L5_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
```

```
write.table(headers, file=paste('TSLS_MED_L1_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('TSLS_MED_L1_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editZ1_res_l_1,
file=paste('TSLS_MED_L1_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)



#####
#FMR#
#####

headers2=c('mediator_coeff','\t','interac_coeff', '\t',
'power','\t','type_i')


editfmr_res_l_0=data.frame(res_l_0$mean_betas.data.x_coeff_m,res_l_0$mean_b
etas.data.xm_coeff_y,blank,(res_l_0$fmr_y_int.fmr_y_int)/10)
editfmr_res_l_m3=data.frame(res_l_m3$mean_betas.data.x_coeff_m,res_l_m3$mea
n_betas.data.xm_coeff_y,(res_l_m3$fmr_y_int.fmr_y_int)/10,blank)
editfmr_res_l_3=data.frame(res_l_3$mean_betas.data.x_coeff_m,res_l_3$mean_b
etas.data.xm_coeff_y,(res_l_3$fmr_y_int.fmr_y_int)/10,blank)
editfmr_res_l_5=data.frame(res_l_5$mean_betas.data.x_coeff_m,res_l_5$mean_b
etas.data.xm_coeff_y,(res_l_5$fmr_y_int.fmr_y_int)/10,blank)
editfmr_res_l_1=data.frame(res_l_1$mean_betas.data.x_coeff_m,res_l_1$mean_b
etas.data.xm_coeff_y,(res_l_1$fmr_y_int.fmr_y_int)/10,blank)


#interaction coefficient=0
write.table(headers2, file=paste('fmr_L0_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('fmr_L0_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editfmr_res_l_0,
file=paste('fmr_L0_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=m3
write.table(headers2, file=paste('fmr_LM3_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('fmr_LM3_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editfmr_res_l_m3,
file=paste('fmr_LM3_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=3
write.table(headers2, file=paste('fmr_L3_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('fmr_L3_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editfmr_res_l_3,
file=paste('fmr_L3_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=5
write.table(headers2, file=paste('fmr_L5_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('fmr_L5_',model,'_.txt'),append=TRUE, sep = "\n")
write.table(editfmr_res_l_5,
file=paste('fmr_L5_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)
#interaction coefficient=1
write.table(headers2, file=paste('fmr_L1_',model,'_.txt'),append=FALSE,
quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")
write("", file=paste('fmr_L1_',model,'_.txt'),append=TRUE, sep = "\n")
```

```
write.table(editfmr_res_l_1,
file=paste('fmr_L1_',model,'_.txt'),append=TRUE, quote=FALSE,
row.names=FALSE, col.names=FALSE)

}
```

4.6.8 Variance explained by IVs

```
#script_name: factorial_mr_varex_sens.r

#project: 4-way decomp

#script author: Teri North

#script purpose: simulation to experiment with diff % variance explained at N=50K

#date created: 25/10/2018

#last edited: 26/10/2018

#notes:

#edited from factoria_mr_v4_f_vi.r




#read in seed

seedval=commandArgs(6)

print(seedval)

seedval=as.numeric(seedval)


#install.packages("systemfit")

library("systemfit")


sessionInfo()


#define headers

headers=c("x_coeff_m","x_coeff_y","m_coeff_y","xm_coeff_y",

	"x_obs", "x_obs_se",

	"m_obs", "m_obs_se",

	"xm_obs", "xm_obs_se",
```

```
        "f1", "f1_se",
        "f2", "f2_se",
        "f3","f3_se",
        "fmr_interac_p",
        "x_2sls", "x_2sls_se",
        "m_2sls", "m_2sls_se",
        "xm_2sls", "xm_2sls_se",
        "x_z1_2sls", "x_z1_2sls_se",
        "m_z1_2sls", "m_z1_2sls_se",
        "xm_z1_2sls", "xm_z1_2sls_se",
        "x_z2_2sls", "x_z2_2sls_se",
        "m_z2_2sls", "m_z2_2sls_se",
        "xm_z2_2sls", "xm_z2_2sls_se")



set.seed(seedval)

for (nval in c(50000)){
  for (rep in c(1:1000)){
    #log session for each seed, sample size and sim repeat
    sink(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRlog.txt",sep=""))

    #write file headers
    #begin with append=FALSE to overwrite current file
    write.table(headers,
file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=FALSE, quote=FALSE,
row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")

    #generate data for system
    samp_size=nval
    #error terms
```

```
u=rnorm(samp_size)
v=rnorm(samp_size)
e=rnorm(samp_size)
#confounders
c=rnorm(samp_size)
#instruments
z1=rnorm(samp_size)
z2=rnorm(samp_size)


#begin looping over coefficient combinations

for (i in c(0,0.333,0.5,1,-0.333)) {

 for (othcomb in c(1,2,3,4,5)){

  if (othcomb==1){
   j=0
   k=0
   l=0/3
   m=0/3
   n=0/3

  } else if (othcomb==2){
   j=0.333
   k=0.333
   l=0.333/3
   m=0.333/3
   n=0.333/3

  } else if (othcomb==3){
```

```
 j=0.5
 k=0.5
 l=0.5/3
 m=0.5/3
 n=0.5/3

} else if (othcomb==4){
 j=1
 k=1
 l=1/3
 m=1/3
 n=1/3

} else if (othcomb==5){
 j=-0.333
 k=-0.333
 l=-0.333/3
 m=-0.333/3
 n=-0.333/3

}

print(i)
print(j)
print(k)
print(l)
coeff_list<- c(i,j,k,l)

#define models
```

```
#Exposure
a1=c+v+0.32*z1
#Mediator
a2=i*a1+e+0.39*z2+c
#Outcome
y=j*a1+k*a2+u+c+l*a1*a2+m*c*a1+n*c*a2

a1a2=a1*a2
z1z2=z1*z2
z1z1=z1*z1
z2z2=z2*z2

#observational
eqy <- y ~ a1 + a2 + a1a2
fitols <- systemfit(eqy)
print(fitols)
conf_ols <- confint(fitols) #95% CI for observational betas
print(conf_ols)
sum_ols=coef(summary(fitols))
obs_vec=c(fitols$coefficients[2],sum_ols[2,2],
    fitols$coefficients[3],sum_ols[3,2],
    fitols$coefficients[4],sum_ols[4,2])



#split the observations into 4 groups based on median splits of Instruments
med_z1=median(z1)
med_z2=median(z2)

fact_group=c(1:nval)
f0=c(1:nval)
```

```
f1=c(1:nval)
f2=c(1:nval)
f3=c(1:nval)

for (z in c(1:nval)){
 fact_group[z]=NA
 f0[z]=NA
 f1[z]=NA
 f2[z]=NA
 f3[z]=NA
}

for (z in c(1:nval)){
 if ((z1[z]<=med_z1) & (z2[z]<=med_z2)){
   fact_group[z]=0
   f0[z]=1
   f1[z]=0
   f2[z]=0
   f3[z]=0
 } else if ((z1[z]<=med_z1) & (z2[z]>med_z2)){
   fact_group[z]=1
   f0[z]=0
   f1[z]=1
   f2[z]=0
   f3[z]=0
 } else if ((z1[z]>med_z1) & (z2[z]<=med_z2)){
   fact_group[z]=2
   f0[z]=0
   f1[z]=0
   f2[z]=1
   f3[z]=0
```

```
  } else if ((z1[z]>med_z1) & (z2[z]>med_z2)){
    fact_group[z]=3
    f0[z]=0
    f1[z]=0
    f2[z]=0
    f3[z]=1
  }
}



#FACTORIAL MR (median split)
feqy <- y ~ f1 + f2 + f3
fitfmr <- systemfit(feqy)
print(fitfmr)
conf_fmr <- confint(fitfmr) #95% CI for fmr betas
print(conf_fmr)
sum_fmr=coef(summary(fitfmr))


#f0 as the baseline - see fig 2 ference paper

#reality check on regression coefficients
mean(y[f1==1]) - fitfmr$coefficients[2]
mean(y[f2==1]) - fitfmr$coefficients[3]
mean(y[f3==1]) - fitfmr$coefficients[4]

mean(y[f0==1]) - fitfmr$coefficients[1] #intercept is mean outcome for baseline group

#formal test for interaction using linear contrast of coeffs - use Wald test comparable to stata's
'test'
```

```
lhyp='1*eq1_f1 + 1*eq1_f2 - 1*eq1_f3 = 0'

lincon=linearHypothesis(fitfmr,lhyp,test='F')

int_p=lincon$`Pr(>F)`[2]


fmr_vec=c(fitfmr$coefficients[2],sum_fmr[2,2], #f1 vs f0

        fitfmr$coefficients[3],sum_fmr[3,2], #f2 vs f0

        fitfmr$coefficients[4],sum_fmr[4,2], #f3 vs f0

        int_p)


#instrumental variable 2sls: inst=z1+z2+z1z2 [when no mediation expected]

inst1<- ~ z1 + z2 + z1z2

fit2sls <-systemfit(eqy,"2SLS",inst=inst1)

conf_2sls <- confint(fit2sls)

sum_2sls=coef(summary(fit2sls))

print(fit2sls)

print(conf_2sls)

print(sum_2sls)


tsls_vec=c(fit2sls$coefficients[2],sum_2sls[2,2],

         fit2sls$coefficients[3],sum_2sls[3,2],

         fit2sls$coefficients[4],sum_2sls[4,2])



#instrumental variable 2sls: inst=z1+z2+z1z2+z1z1 [when mediation expected]

inst2<- ~ z1 + z2 + z1z2 + z1z1

fitz12sls <-systemfit(eqy,"2SLS",inst=inst2)

conf_z12sls <- confint(fitz12sls)

sum_z12sls=coef(summary(fitz12sls))

print(fitz12sls)

print(conf_z12sls)

print(sum_z12sls)
```

```
tslsz1_vec=c(fitz12sls$coefficients[2],sum_z12sls[2,2],
            fitz12sls$coefficients[3],sum_z12sls[3,2],
            fitz12sls$coefficients[4],sum_z12sls[4,2])


#instrumental variable 2sls: inst=z1+z2+z1z2+z1z1+z2z2
inst3<- ~ z1 + z2 + z1z2 + z1z1 + z2z2
fitz22sls <-systemfit(eqy,"2SLS",inst=inst3)
conf_z22sls <- confint(fitz22sls)
sum_z22sls=coef(summary(fitz22sls))
print(fitz22sls)
print(conf_z22sls)
print(sum_z22sls)

tslsz2_vec=c(fitz22sls$coefficients[2],sum_z22sls[2,2],
            fitz22sls$coefficients[3],sum_z22sls[3,2],
            fitz22sls$coefficients[4],sum_z22sls[4,2])


#all results
res_vec=c(coeff_list,obs_vec,fmr_vec,tsls_vec,tslsz1_vec,tslsz2_vec)
write("", file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=TRUE, sep = "\n")
write.table(res_vec, file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=""),append=TRUE, row.names=FALSE, col.names=FALSE, sep = "\t",eol="\t")
```

```
    }

  }

  sink()
 }
}
```

4.6.9 Variance explained by IVs – pooling simulation results

```
#script_name: pool_sim_pap1_varex_sens.r
#project: 4-way decomp: paper 1
#script author: Teri North
#script purpose: pool estimates across simulation repeats by
#		-taking the mean betahat & SE of betahats (to generate MC 95% CI for betahat)
#		-take the mean SE and the SD of betahats
#		-calculate power, type i error and coverage where applicable
#date created: 26/10/2018
#last edited: 04/02/2019
#notes:
#code edited from pool_sim_pap1_obs_and_other_est_SC_1krep_v6.R

setwd('VAREX_SENS/')

#number of repeats in each sim
repeats=1000

#tracker for erroneous calls
n_problem=0
```

```
n_prob_track=1

n_z1problem=0
n_z1prob_track=1

n_z2problem=0
n_z2prob_track=1

for (nval in c(50000)){

 xm_2sls_detec=c(1:25) # counter for # times interaction is detected (null is rejected) at 5% level
 for (i in c(1:25)){
  xm_2sls_detec[i]=0
 }
 xm_z1_2sls_detec=c(1:25)
 for (i in c(1:25)){
  xm_z1_2sls_detec[i]=0
 }
 xm_z2_2sls_detec=c(1:25)
 for (i in c(1:25)){
  xm_z2_2sls_detec[i]=0
 }
 xm_obs_detec=c(1:25) # counter for # times interaction is detected (null is rejected) at 5% level
 for (i in c(1:25)){
  xm_obs_detec[i]=0
 }


 coverage=c(1:25) # counter for # times 95% CI contains true value
 for (i in c(1:25)){
  coverage[i]=0
```

```
}
z1_coverage=c(1:25)
for (i in c(1:25)){
  z1_coverage[i]=0
}
z2_coverage=c(1:25)
for (i in c(1:25)){
  z2_coverage[i]=0
}
obscoverage=c(1:25)
for (i in c(1:25)){
  obscoverage[i]=0
}

#reality check
#how many times is the interaction detected (p<0.05), but the estimate is in the opposite direction to true effect?
problem=c(1:25)
for (i in c(1:25)){
  problem[i]=0
}
z1problem=c(1:25)
for (i in c(1:25)){
  z1problem[i]=0
}
z2problem=c(1:25)
for (i in c(1:25)){
  z2problem[i]=0
}
```

```
fmr_y_int=c(1:25)  # counter for # times interaction detected factorial approach (Wald test 5%)
for (i in c(1:25)){
  fmr_y_int[i]=0
}


#calculating the mean betas
first=1


for (seedval in c(48595837)){

  for (rep in c(1:repeats)){

    if (first==1){


data=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=''),sep='\t',header=TRUE)
      true_vals=data.frame(data$x_coeff_m,data$x_coeff_y,data$m_coeff_y, data$xm_coeff_y)
      first=0

      ll=data.frame(
        xm_2sls_ll=data$xm_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_2sls_se,
        xm_z1_2sls_ll=data$xm_z1_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_z1_2sls_se,
        xm_z2_2sls_ll=data$xm_z2_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_z2_2sls_se,
        xm_obs_ll=data$xm_obs-(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_obs_se
      )

      ul=data.frame(
        xm_2sls_ul=data$xm_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_2sls_se,
        xm_z1_2sls_ul=data$xm_z1_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_z1_2sls_se,
```

```
  xm_z2_2sls_ul=data$xm_z2_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_z2_2sls_se,
  xm_obs_ul=data$xm_obs+(qt(0.025,(nval-4),lower.tail=FALSE))*data$xm_obs_se
 )



 for (i in c(1:25)){
  if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
   xm_2sls_detec[i]=NA
  } else if (ll$xm_2sls_ll[i]>0 | ul$xm_2sls_ul[i]<0){xm_2sls_detec[i]=1}
 }

 for (i in c(1:25)){
  if (ll$xm_z1_2sls_ll[i]>0 | ul$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=1}
 }

 for (i in c(1:25)){
  if (ll$xm_z2_2sls_ll[i]>0 | ul$xm_z2_2sls_ul[i]<0){xm_z2_2sls_detec[i]=1}
 }

 for (i in c(1:25)){
  if (ll$xm_obs_ll[i]>0 | ul$xm_obs_ul[i]<0){xm_obs_detec[i]=1}
 }



 for (i in c(1:25)){
  if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
   coverage[i]=NA
  } else if ((ll$xm_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_2sls_ul[i]>data$xm_coeff_y[i])){coverage[i]=1}
 }
```

```
for (i in c(1:25)){
  if ((ll$xm_z1_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_z1_2sls_ul[i]>data$xm_coeff_y[i])){z1_coverage[i]=1}
}

for (i in c(1:25)){
  if ((ll$xm_z2_2sls_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_z2_2sls_ul[i]>data$xm_coeff_y[i])){z2_coverage[i]=1}
}

for (i in c(1:25)){
  if ((ll$xm_obs_ll[i]<data$xm_coeff_y[i]) &
(ul$xm_obs_ul[i]>data$xm_coeff_y[i])){obscoverage[i]=1}
}



for (i in c(1:25)){
  if (is.na(ll$xm_2sls_ll[i])|is.na(ul$xm_2sls_ul[i])){
    problem[i]=NA
  } else if (((ll$xm_2sls_ll[i]>0) & (data$xm_coeff_y[i]<0))|((ul$xm_2sls_ul[i]<0) &
(data$xm_coeff_y[i]>0))) {problem[i]=1}#if interac detec, but coeff wrong direc
}

for (i in c(1:25)){
  if (((ll$xm_z1_2sls_ll[i]>0) & (data$xm_coeff_y[i]<0))|((ul$xm_z1_2sls_ul[i]<0) &
(data$xm_coeff_y[i]>0))) {z1problem[i]=1}#if interac detec, but coeff wrong direc
}

for (i in c(1:25)){
  if (((ll$xm_z2_2sls_ll[i]>0) & (data$xm_coeff_y[i]<0))|((ul$xm_z2_2sls_ul[i]<0) &
(data$xm_coeff_y[i]>0))) {z2problem[i]=1}#if interac detec, but coeff wrong direc
}
```

```
for (i in c(1:25)){
  if (data$fmr_interac_p[i]<0.05){fmr_y_int[i]=1}
}

} else if (first==0){

new=read.table(file=paste(seedval,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=''),sep='\t',header=TR
UE)
data=data+new

ll_new=data.frame(
  xm_2sls_ll=new$xm_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_2sls_se,
  xm_z1_2sls_ll=new$xm_z1_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_z1_2sls_se,
  xm_z2_2sls_ll=new$xm_z2_2sls-(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_z2_2sls_se,
  xm_obs_ll=new$xm_obs-(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_obs_se
)

ul_new=data.frame(
  xm_2sls_ul=new$xm_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_2sls_se,
  xm_z1_2sls_ul=new$xm_z1_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_z1_2sls_se,
  xm_z2_2sls_ul=new$xm_z2_2sls+(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_z2_2sls_se,
  xm_obs_ul=new$xm_obs+(qt(0.025,(nval-4),lower.tail=FALSE))*new$xm_obs_se
)

for (i in c(1:25)){
  if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){
    xm_2sls_detec[i]=NA
```

```
    } else if (ll_new$xm_2sls_ll[i]>0 |
ul_new$xm_2sls_ul[i]<0){xm_2sls_detec[i]=xm_2sls_detec[i]+1}

  }


  for (i in c(1:25)){

    if (ll_new$xm_z1_2sls_ll[i]>0 |
ul_new$xm_z1_2sls_ul[i]<0){xm_z1_2sls_detec[i]=xm_z1_2sls_detec[i]+1}

  }


  for (i in c(1:25)){

    if (ll_new$xm_z2_2sls_ll[i]>0 |
ul_new$xm_z2_2sls_ul[i]<0){xm_z2_2sls_detec[i]=xm_z2_2sls_detec[i]+1}

  }


  for (i in c(1:25)){

    if (ll_new$xm_obs_ll[i]>0 | ul_new$xm_obs_ul[i]<0){xm_obs_detec[i]=xm_obs_detec[i]+1}

  }




  for (i in c(1:25)){

    if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){

      coverage[i]=NA

    } else if ((ll_new$xm_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_2sls_ul[i]>new$xm_coeff_y[i])){coverage[i]=coverage[i]+1}

  }


  for (i in c(1:25)){

    if ((ll_new$xm_z1_2sls_ll[i]<new$xm_coeff_y[i]) &
(ul_new$xm_z1_2sls_ul[i]>new$xm_coeff_y[i])){z1_coverage[i]=z1_coverage[i]+1}

  }


  for (i in c(1:25)){
```

```
  if ((ll_new$xm_z2_2sls_ll[i]<new$xm_coeff_y[i]) & (ul_new$xm_z2_2sls_ul[i]>new$xm_coeff_y[i])){z2_coverage[i]=z2_coverage[i]+1}
}

for (i in c(1:25)){
  if ((ll_new$xm_obs_ll[i]<new$xm_coeff_y[i]) & (ul_new$xm_obs_ul[i]>new$xm_coeff_y[i])){obscoverage[i]=obscoverage[i]+1}
}

for (i in c(1:25)){
  if (is.na(ll_new$xm_2sls_ll[i])|is.na(ul_new$xm_2sls_ul[i])){
    problem[i]=NA
  } else if (((ll_new$xm_2sls_ll[i]>0) & (new$xm_coeff_y[i]<0))|((ul_new$xm_2sls_ul[i]<0) & (new$xm_coeff_y[i]>0))) {problem[i]=problem[i]+1}#if interac detec, but coeff wrong direc
}

for (i in c(1:25)){
  if (((ll_new$xm_z1_2sls_ll[i]>0) & (new$xm_coeff_y[i]<0))|((ul_new$xm_z1_2sls_ul[i]<0) & (new$xm_coeff_y[i]>0))) {z1problem[i]=z1problem[i]+1}#if interac detec, but coeff wrong direc
}

for (i in c(1:25)){
  if (((ll_new$xm_z2_2sls_ll[i]>0) & (new$xm_coeff_y[i]<0))|((ul_new$xm_z2_2sls_ul[i]<0) & (new$xm_coeff_y[i]>0))) {z2problem[i]=z2problem[i]+1}#if interac detec, but coeff wrong direc
}

for (i in c(1:25)){
  if (new$fmr_interac_p[i]<0.05){fmr_y_int[i]=fmr_y_int[i]+1}
}
```

```
    }

  }

}

#remove true values
data_est=data.frame(data$x_obs,data$x_obs_se,
                data$m_obs,data$m_obs_se,
                data$xm_obs,data$xm_obs_se,
                data$x_2sls,data$x_2sls_se,
                data$x_z1_2sls,data$x_z1_2sls_se,
                data$x_z2_2sls,data$x_z2_2sls_se,
                data$m_2sls,data$m_2sls_se,
                data$m_z1_2sls,data$m_z1_2sls_se,
                data$m_z2_2sls,data$m_z2_2sls_se,
                data$xm_2sls,data$xm_2sls_se,
                data$xm_z1_2sls,data$xm_z1_2sls_se,
                data$xm_z2_2sls,data$xm_z2_2sls_se
)

#mean betas
```

```
  mean_denom=repeats
  data_mean=data_est/mean_denom #gives mean beta and mean se
  #add in the true params
  mean_betas=cbind(true_vals,data_mean)



##########################################################################################
##########################################################################################
#########

  #now for the standard error
  checker=1

  for (seeds in c(48595837)){

    for (rep in c(1:repeats)){

      if (checker==1){


newdata=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=''),sep='\t',header=T
RUE)
        newdata=(newdata-(data/mean_denom))^2
        checker=0

      } else if (checker==0){



newer=read.table(file=paste(seeds,'_rep',rep,'_samp',nval,"_FMRres.txt",sep=''),sep='\t',header=TR
UE)
        newdata=newdata+(newer-(data/mean_denom))^2
```

```
    newdata=data.frame(newdata)


   }

  }
}


newdata_est=data.frame(newdata$x_obs,
                  newdata$m_obs,
                  newdata$xm_obs,
                  newdata$x_2sls,
                  newdata$x_z1_2sls,
                  newdata$x_z2_2sls,
                  newdata$m_2sls,
                  newdata$m_z1_2sls,
                  newdata$m_z2_2sls,
                  newdata$xm_2sls,
                  newdata$xm_z1_2sls,
                  newdata$xm_z2_2sls
)


#divide by n-1 to get s^2
s2=newdata_est/(repeats-1)
se=sqrt(s2/(repeats))
```

```
######################################################################################
####################################################################################


xm_2sls_detec=data.frame(xm_2sls_detec)
xm_z1_2sls_detec=data.frame(xm_z1_2sls_detec)
xm_z2_2sls_detec=data.frame(xm_z2_2sls_detec)
xm_obs_detec=data.frame(xm_obs_detec)
coverage=data.frame(coverage)
z1_coverage=data.frame(z1_coverage)
z2_coverage=data.frame(z2_coverage)
obscoverage=data.frame(obscoverage)
fmr_y_int=data.frame(fmr_y_int)


#results table
res=data.frame(mean_betas$data.x_coeff_m,
        mean_betas$data.x_coeff_y,
        mean_betas$data.m_coeff_y,
        mean_betas$data.xm_coeff_y,
        mean_betas$data.x_obs,
        se$newdata.x_obs,
        mean_betas$data.m_obs,
        se$newdata.m_obs,
        mean_betas$data.xm_obs,
        se$newdata.xm_obs,
        mean_betas$data.x_2sls,
        se$newdata.x_2sls,
        mean_betas$data.x_z1_2sls,
        se$newdata.x_z1_2sls,
        mean_betas$data.x_z2_2sls,
        se$newdata.x_z2_2sls,
        mean_betas$data.m_2sls,
```

```
se$newdata.m_2sls,
mean_betas$data.m_z1_2sls,
se$newdata.m_z1_2sls,
mean_betas$data.m_z2_2sls,
se$newdata.m_z2_2sls,
mean_betas$data.xm_2sls,
se$newdata.xm_2sls,
mean_betas$data.xm_z1_2sls,
se$newdata.xm_z1_2sls,
mean_betas$data.xm_z2_2sls,
se$newdata.xm_z2_2sls,
mean_betas$data.xm_obs_se,
mean_betas$data.xm_2sls_se,
mean_betas$data.xm_z1_2sls_se,
mean_betas$data.xm_z2_2sls_se,
xm_obs_detec$xm_obs_detec,
xm_2sls_detec$xm_2sls_detec,
xm_z1_2sls_detec$xm_z1_2sls_detec,
xm_z2_2sls_detec$xm_z2_2sls_detec,
coverage$coverage,
z1_coverage$z1_coverage,
z2_coverage$z2_coverage,
obscoverage$obscoverage,
s2$newdata.xm_obs,
s2$newdata.xm_2sls,
s2$newdata.xm_z1_2sls,
s2$newdata.xm_z2_2sls,
fmr_y_int$fmr_y_int
)
```

```
  write.table(res,file=paste(nval,'_EXTRA_final_res.txt',sep=''),sep='\t',row.names=FALSE)

  #how many times across all models and repeat sims is an interaction detected in the incorrect direction?
  n_problem[n_prob_track]=sum(problem)
  n_prob_track=n_prob_track+1

  n_z1problem[n_z1prob_track]=sum(z1problem)
  n_z1prob_track=n_z1prob_track+1

  n_z2problem[n_z2prob_track]=sum(z2problem)
  n_z2prob_track=n_z2prob_track+1

}

write(n_problem, file='problem.txt',append=FALSE, sep = "\n")
write(n_z1problem, file='z1problem.txt',append=FALSE, sep = "\n")
write(n_z2problem, file='z2problem.txt',append=FALSE, sep = "\n")

#Now read back in so that we have all the data across all sample sizes
n_t5=c(1:25)
for (i in c(1:25)){
  n_t5[i]=50000
}
```

```
sampsize=n_t5

t5=data.frame(sampsize,read.table(file=paste(50000,'_EXTRA_final_res.txt',sep=''),header=TRUE))



headers=c('mediator_coeff','\t','interac_coeff', '\t', 'sample_size','\t','mean_est','\t',
        'sd(est)','\t','mean(se(est))','\t','se(est)','\t',
        'power','\t','type_i','\t','coverage')

blank=c(1:25)
for (i in c(1:25)){blank[i]='NA'}

####################################INTERACTION
COEFFICIENT###########################################################################
#################################################

#REMEMBER THAT THE VARIANCE NEEDS TO BE SQRT'D TO CONVERT TO SD
#POWER, TYPE I AND COVERAGE NEED TO BE DIVIDED BY 10 TO CONVERT TO %
##############
#Z=Z1+Z2+Z1Z2#
##############
edit_res_t5=data.frame(t5$mean_betas.data.x_coeff_m,t5$mean_betas.data.xm_coeff_y,t5$samps
ize,t5$mean_betas.data.xm_2sls,

sqrt(t5$s2.newdata.xm_2sls),t5$mean_betas.data.xm_2sls_se,t5$se.newdata.xm_2sls,blank,
            (t5$xm_2sls_detec.xm_2sls_detec)/10,(t5$coverage.coverage)/10)

edit_res_t5=edit_res_t5[order(t5$mean_betas.data.xm_coeff_y,t5$mean_betas.data.x_coeff_m),]

#write results table
write.table(headers, file='TSLS_NOMED.txt',append=FALSE, quote=FALSE, row.names=FALSE,
col.names=FALSE, sep = "",eol="")
write("", file='TSLS_NOMED.txt',append=TRUE, sep = "\n")
```

```
write.table(edit_res_t5, file='TSLS_NOMED.txt',append=TRUE, quote=FALSE, row.names=FALSE, col.names=FALSE)



###################

#Z=Z1+Z2+Z1Z2+Z1Z1#

###################


editZ1_res_t5=data.frame(t5$mean_betas.data.x_coeff_m,t5$mean_betas.data.xm_coeff_y,t5$sampsize,t5$mean_betas.data.xm_z1_2sls,


sqrt(t5$s2.newdata.xm_z1_2sls),t5$mean_betas.data.xm_z1_2sls_se,t5$se.newdata.xm_z1_2sls, blank,

                    (t5$xm_z1_2sls_detec.xm_z1_2sls_detec)/10,(t5$z1_coverage.z1_coverage)/10)


editZ1_res_t5=editZ1_res_t5[order(t5$mean_betas.data.xm_coeff_y,t5$mean_betas.data.x_coeff_m),]


#write results table

write.table(headers, file='TSLS_MED.txt',append=FALSE, quote=FALSE, row.names=FALSE, col.names=FALSE, sep = "",eol="")

write("", file='TSLS_MED.txt',append=TRUE, sep = "\n")

write.table(editZ1_res_t5, file='TSLS_MED.txt',append=TRUE, quote=FALSE, row.names=FALSE, col.names=FALSE)
```

4.6.10 Seeds used

4.6.10.1 Main analysis:

7821897

8376154

649384402

238140535

170379645

312006101

713795870

169378934

456561608

28335714

4.6.10.2 Pleiotropy sensitivity analysis:

520160447

267639401

37905828

750891730

435580371

945959183

141153971

456264979

86129334

119011473

4.6.10.3 Variance explained sensitivity analysis

48595837

5 METHODS FOR ILLUSTRATIVE EXAMPLE

We used data from the UK Biobank (17), a cohort of middle aged to older individuals, to estimate the interactive effect of body mass index (BMI) and educational attainment on systolic blood pressure using ordinary least squares regression, 2SLS (with both $Z=(Z_1,Z_2,Z_1Z_2)$ and $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$) and factorial MR.

UK Biobank is a population-based health research resource consisting of approximately 500,000 people, aged between 38 years and 73 years, who were recruited between the years 2006 and 2010 from across the UK(17). Particularly focused on identifying determinants of human diseases in middle-aged and older individuals, participants provided a range of information (such as demographics, health status, lifestyle measures, cognitive testing, personality self-report, and physical and mental health measures) via questionnaires and interviews; anthropometric measures, BP readings and samples of blood, urine and saliva were also taken (data available at www.ukbiobank.ac.uk). A full description of the study design, participants and quality control (QC) methods have been described in detail previously(18). UK Biobank received ethical approval from the Research Ethics Committee (REC reference for UK Biobank is 11/NW/0382).

The full data release contains the cohort of successfully genotyped samples (n=488,377). 49,979 individuals were genotyped using the UK BiLEVE array and 438,398 using the UK Biobank axiom array. Pre-imputation QC, phasing and imputation are described elsewhere(19). In brief, prior to phasing, multiallelic SNPs or those with MAF ≤1% were removed. Phasing of genotype data was performed using a modified version of the

SHAPEIT2 algorithm(20). Genotype imputation to a reference set combining the UK10K haplotype and HRC reference panels(21) was performed using IMPUTE2 algorithms(22). The analyses presented here were restricted to autosomal variants within the HRC site list using a graded filtering with varying imputation quality for different allele frequency ranges. Therefore, rarer genetic variants are required to have a higher imputation INFO score (Info>0.3 for MAF >3%; Info>0.6 for MAF 1-3%; Info>0.8 for MAF 0.5-1%; Info>0.9 for MAF 0.1-0.5%) with MAF and Info scores having been recalculated on an in house derived 'European' subset.

Individuals with sex-mismatch (derived by comparing genetic sex and reported sex) or individuals with sex-chromosome aneuploidy were excluded from the analysis (n=814). We restricted the sample to individuals of white British ancestry who self-report as "White British" and who have very similar ancestral backgrounds according to the PCA (n=409,703), as described by Bycroft(19).

Estimated kinship coefficients using the KING toolset(23) identified 107,162 pairs of individuals(19). An in-house algorithm was then applied to this list and preferentially removed the individuals related to the greatest number of other individuals until no related pairs remain. These individuals were excluded (n=79,448). Additionally 2 individuals were removed due to them relating to a very large number (>200) of individuals.

Quality Control filtering of the UK Biobank data was conducted by R.Mitchell, G.Hemani, T.Dudding, L.Paternoster as described in the published protocol (doi: 10.5523/bris.3074krb6t2frj29yh2b03x3wxj)(24).

We assumed a causal effect of years of education on BMI. All phenotype measures were taken from the baseline assessment clinic in 2006-2010. Educational attainment was used as a continuous variable of years of completed education (data field 845). BMI was calculated as weight in kilograms divided by height in metres squared. Systolic blood pressure was taken from the second reading, generally measured using an Omron 705 IT electronic blood pressure monitor (OMRON Healthcare Europe B. V. Kruisweg 577 2132 NA Hoofddorp).

Pregnant (or possibly pregnant) women (n=372) were removed from the analysis because of changes to both BMI and blood pressure during pregnancy. We created genetic risk scores for BMI and years of schooling for all UK Biobank participants using the results of recent GWAS studies (25, 26). The discovery datasets excluded UK Biobank (the SNPs for years of schooling were taken from the dataset EduYears_Discovery_5000.txt available on the SSGAC website https://www.thessgac.org/data). We selected SNPs from each study with a P value below genome-wide significance (P ≤ 5 x 10-8). We pruned SNPs from the BMI genetic risk score to only include those independent from the education genetic risk score. Prior to pruning, the BMI genetic risk score included 69 SNPs and after pruning, this reduced to 67, while the education genetic risk score included 74 SNPs. Each genetic risk score was calculated as the sum of the effect alleles for all SNPs associated with BMI or education, with each SNP weighted by the regression coefficient from the GWAS from which the SNP was identified. We searched for proxy SNPs with an R^2 above 0.8 for any SNP missing from UK Biobank using genotype data from European individuals (CEU) from phase 3 (version 5) of the 1000 Genomes project (27).

Age in whole years during baseline assessment centre attendance and sex were used as covariates in all analyses. Genetic analyses were also adjusted for the first 40 principal components to minimise the effects of population stratification. Sensitivity analyses were run with and without adjusting for genotyping array.

Instrumental variable regression was implemented in Stata (StataCorp, Texas) (28) using ivreg2 (29). Factorial MR and observational analyses were implemented using -regress-. STATA's -lincom- command was used to combine coefficients for the purposes of interaction detection assessment for the factorial MR approach. The main effects for BMI and years of schooling were included in the linear regression and instrumental variable models.

The models tested are listed below. Principal components refer to principal components of population stratification.

1. Linear regression of systolic blood pressure on BMI, years of schooling, BMI*years of schooling, age and sex
2. Instrumental variable regression with
    a. Outcome: systolic blood pressure
    b. Instrumented variables: BMI, years of schooling, BMI*years of schooling
    c. Included instruments: age, sex, 40 principal components
    d. Excluded instruments: years of schooling PRS, BMI PRS, years of schooling PRS*BMI PRS, years of schooling PRS* years of schooling PRS

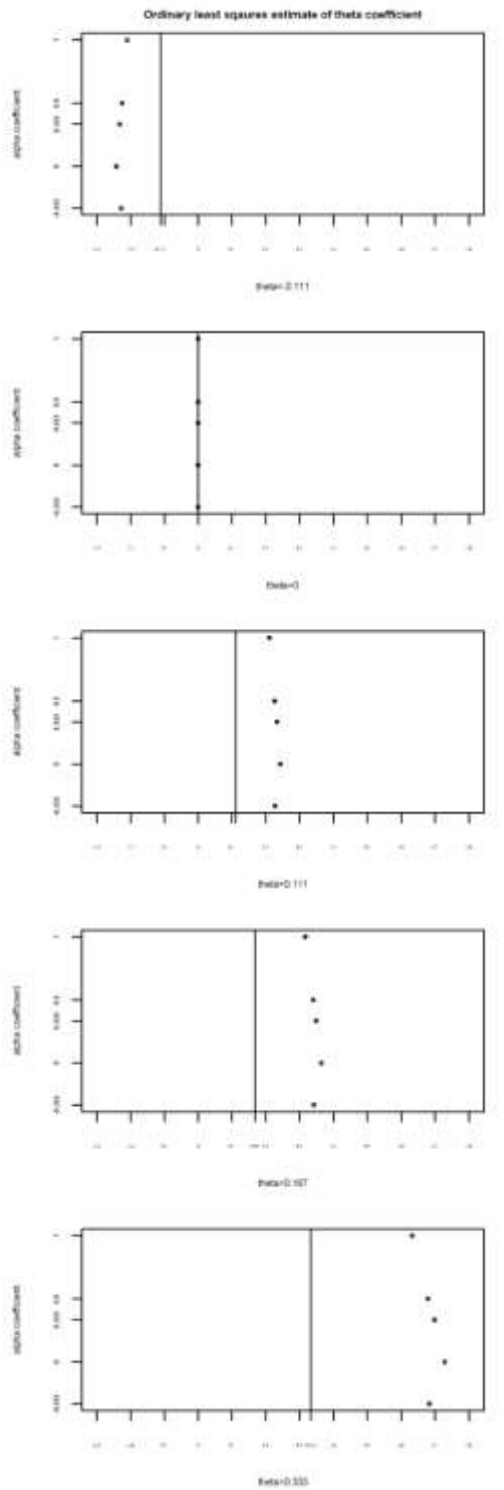
3. Instrumental variable regression with
    a. Outcome: systolic blood pressure
    b. Instrumented variables: BMI, years of schooling, BMI*years of schooling
    c. Included instruments: age, sex, 40 principal components, genotyping array
    d. Excluded instruments: years of schooling PRS, BMI PRS, years of schooling PRS*BMI PRS, years of schooling PRS* years of schooling PRS
4. Instrumental variable regression with
    a. Outcome: systolic blood pressure
    b. Instrumented variables: BMI, years of schooling, BMI*years of schooling
    c. Included instruments: age, sex, 40 principal components
    d. Excluded instruments: years of schooling PRS, BMI PRS, years of schooling PRS*BMI PRS
5. Instrumental variable regression with
    a. Outcome: systolic blood pressure
    b. Instrumented variables: BMI, years of schooling, BMI*years of schooling
    c. Included instruments: age, sex, 40 principal components, genotyping array
    d. Excluded instruments: years of schooling PRS, BMI PRS, years of schooling PRS*BMI PRS
6. Instrumental variable regression with
    a. Outcome: systolic blood pressure
    b. Instrumented variables: BMI, years of schooling
    c. Included instruments: age, sex, 40 principal components
    d. Excluded instruments: years of schooling PRS, BMI PRS
7. Instrumental variable regression with

   a. Outcome: systolic blood pressure
   b. Instrumented variables: BMI, years of schooling
   c. Included instruments: age, sex, 40 principal components, genotyping array
   d. Excluded instruments: years of schooling PRS, BMI PRS
8. Linear regression of systolic blood pressure on the three non-reference categories of FMR (low-high, high-low and high-high PRS scores), adjusted for age, sex, 40 principal components, followed by test of linear combination of FMR category coefficients
9. Linear regression of systolic blood pressure on the three non-reference categories of FMR (low-high, high-low and high-high PRS scores), adjusted for age, sex, 40 principal components and genotyping array, followed by test of linear combination of FMR category coefficients

6 FIGURES: BIAS IN ESTIMATES OF THE INTERACTION TERM

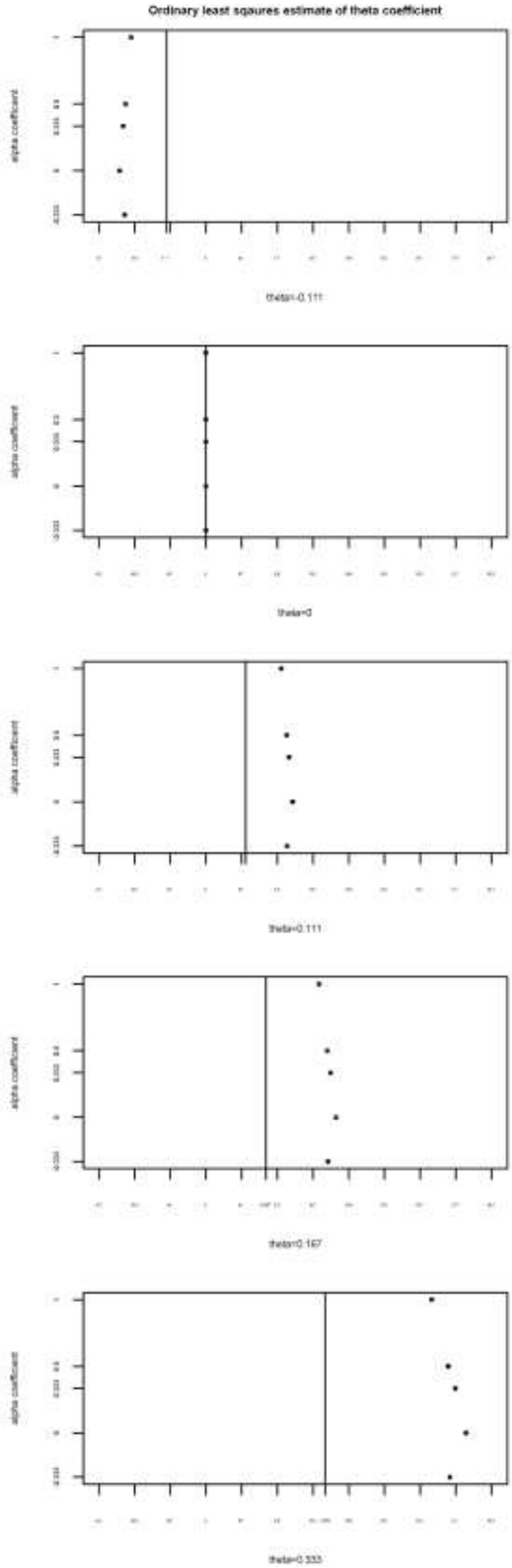
6.1 Coefficient estimates for ordinary least squares when N=50,000.

Theta is the interaction coefficient (A1A2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the OLS estimates with their Monte Carlo 95% confidence interval are overlaid.



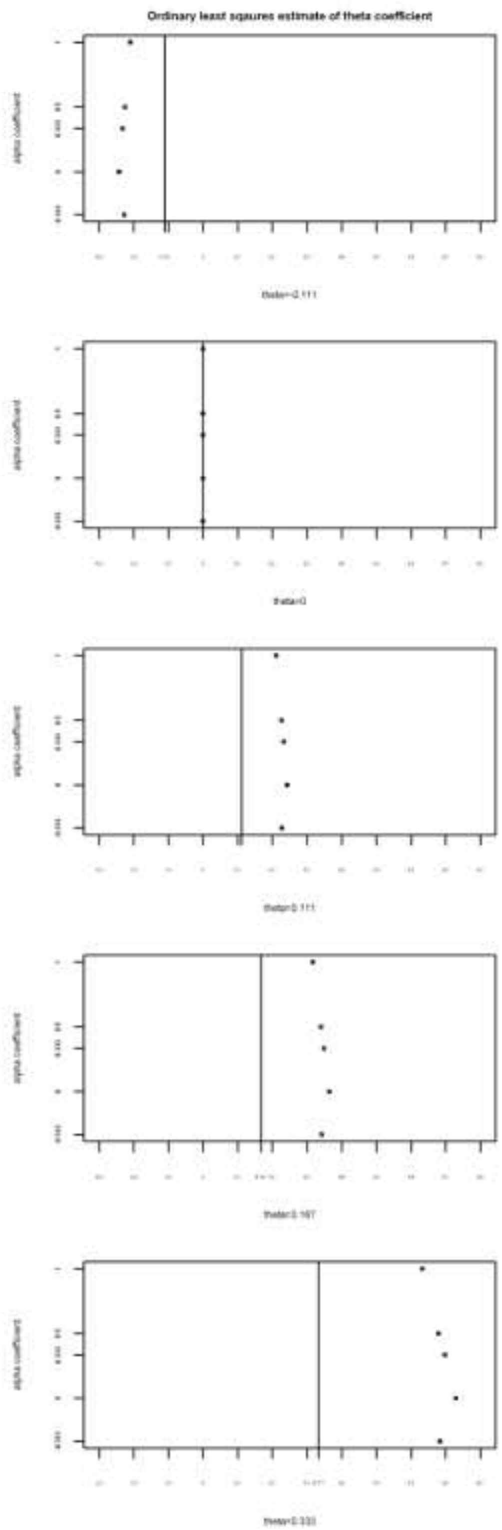
6.2 Coefficient estimates for ordinary least squares when N=100,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the OLS estimates with their Monte Carlo 95% confidence interval are overlaid.



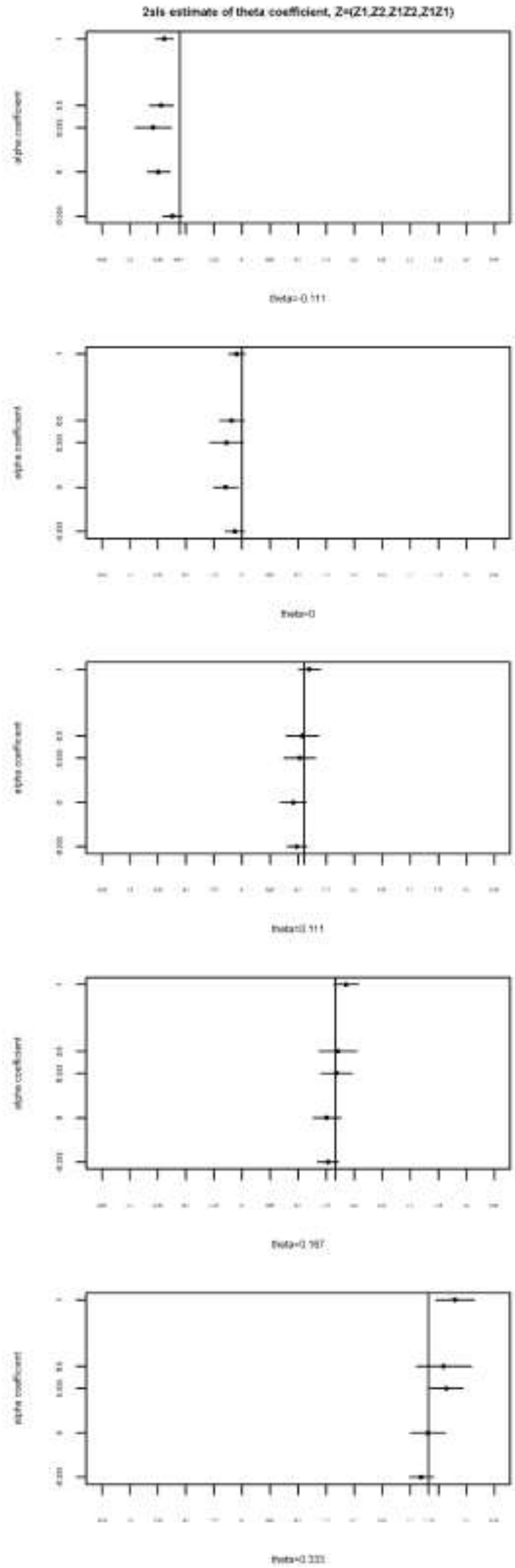
6.3 Coefficient estimates for ordinary least squares when N=500,000

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the OLS estimates with their Monte Carlo 95% confidence interval are overlaid.



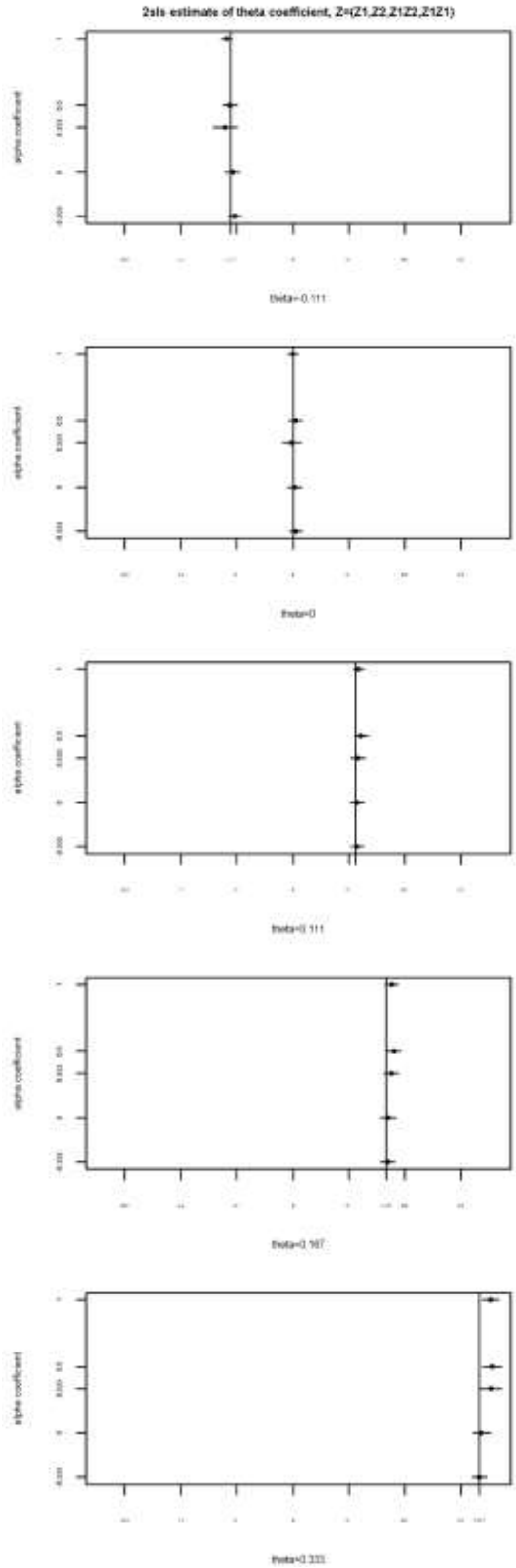
6.4 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ when N=50,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



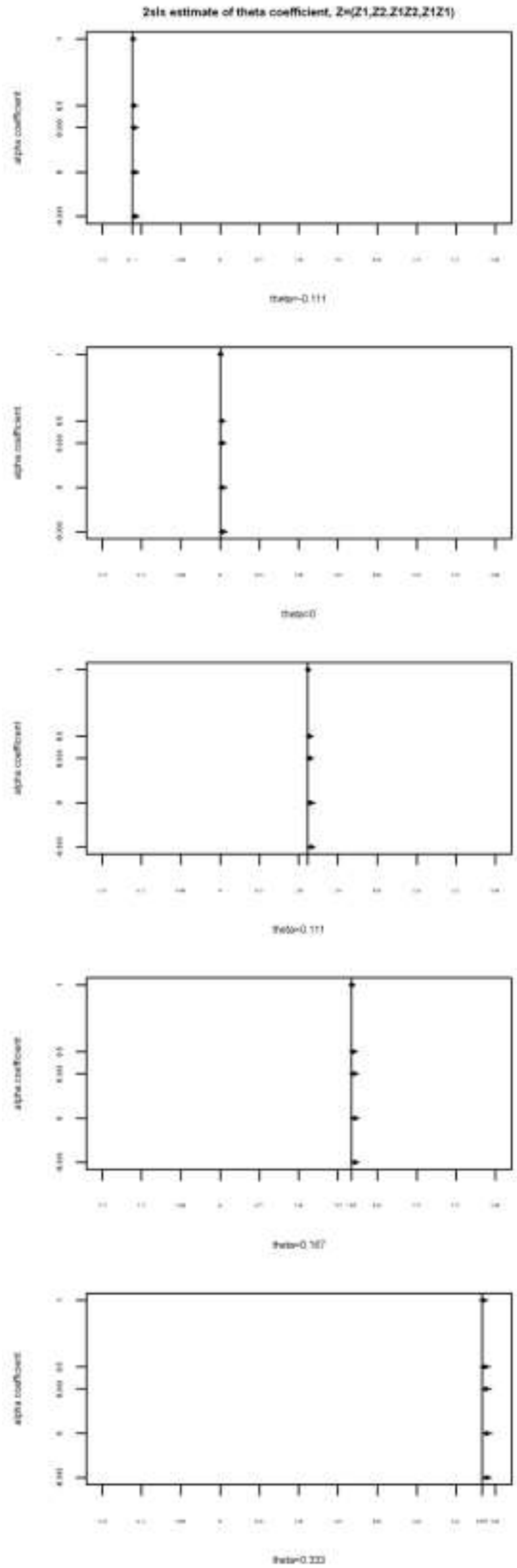
6.5 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ when N=100,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



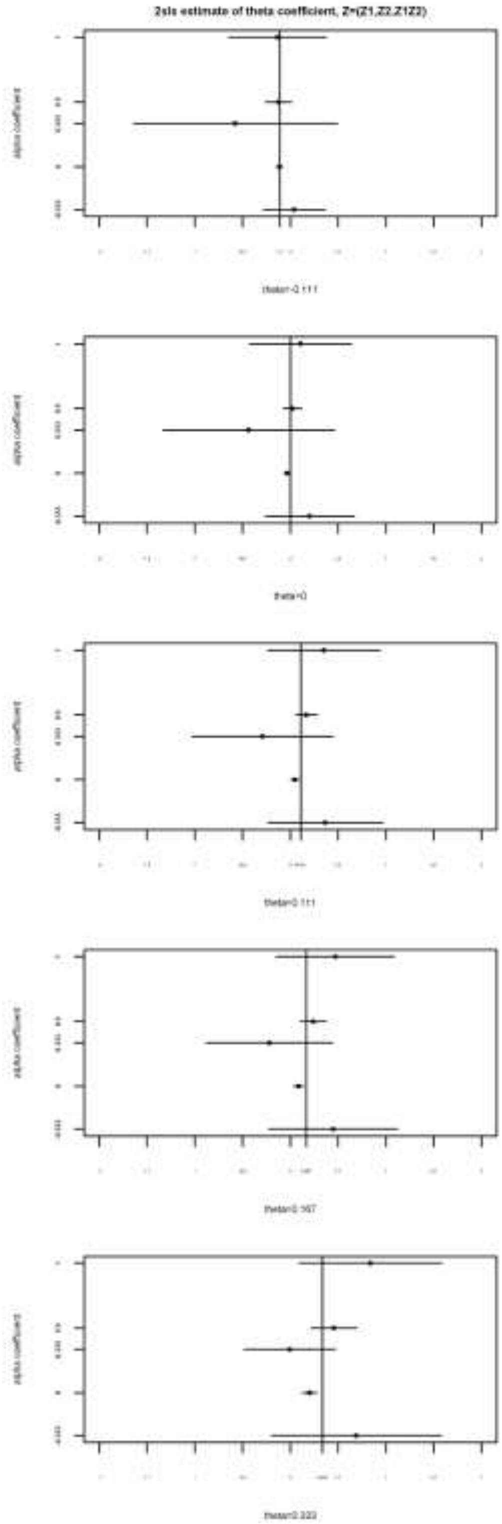
6.6 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ when N=500,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



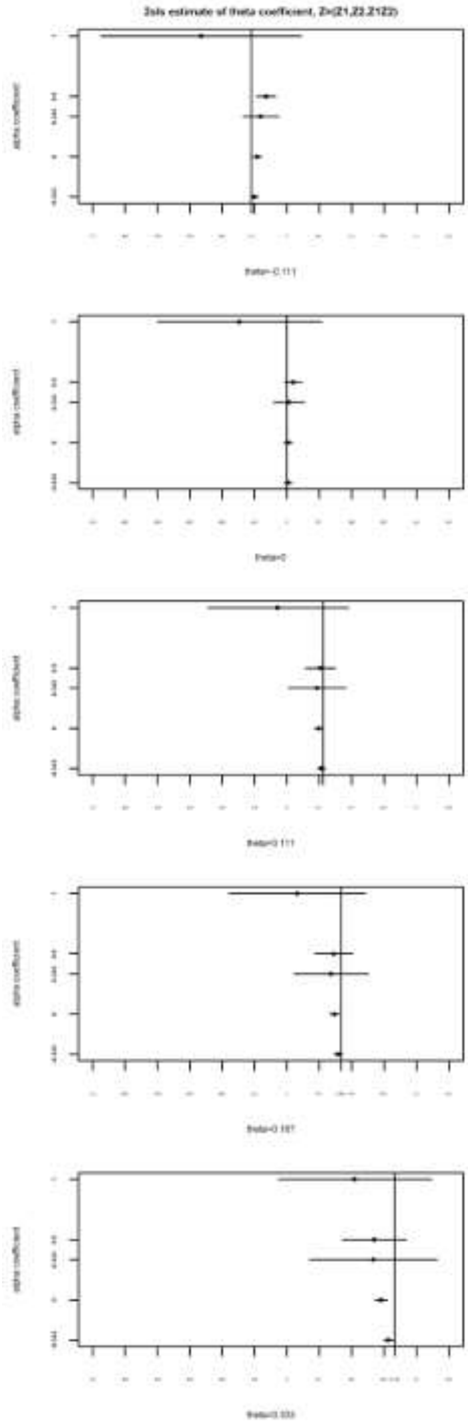
6.7 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2)$ when N=50,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



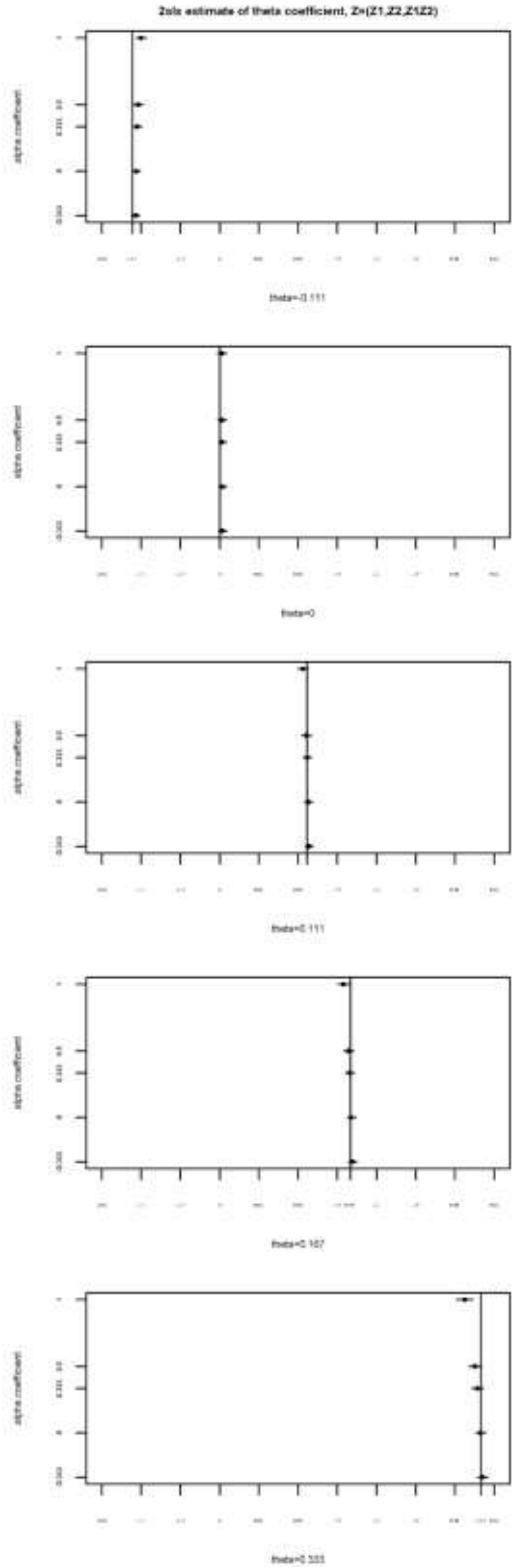
6.8 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2)$ when N=100,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



6.9 Coefficient estimates for 2SLS using $Z=(Z_1,Z_2,Z_1Z_2)$ when N=500,000.

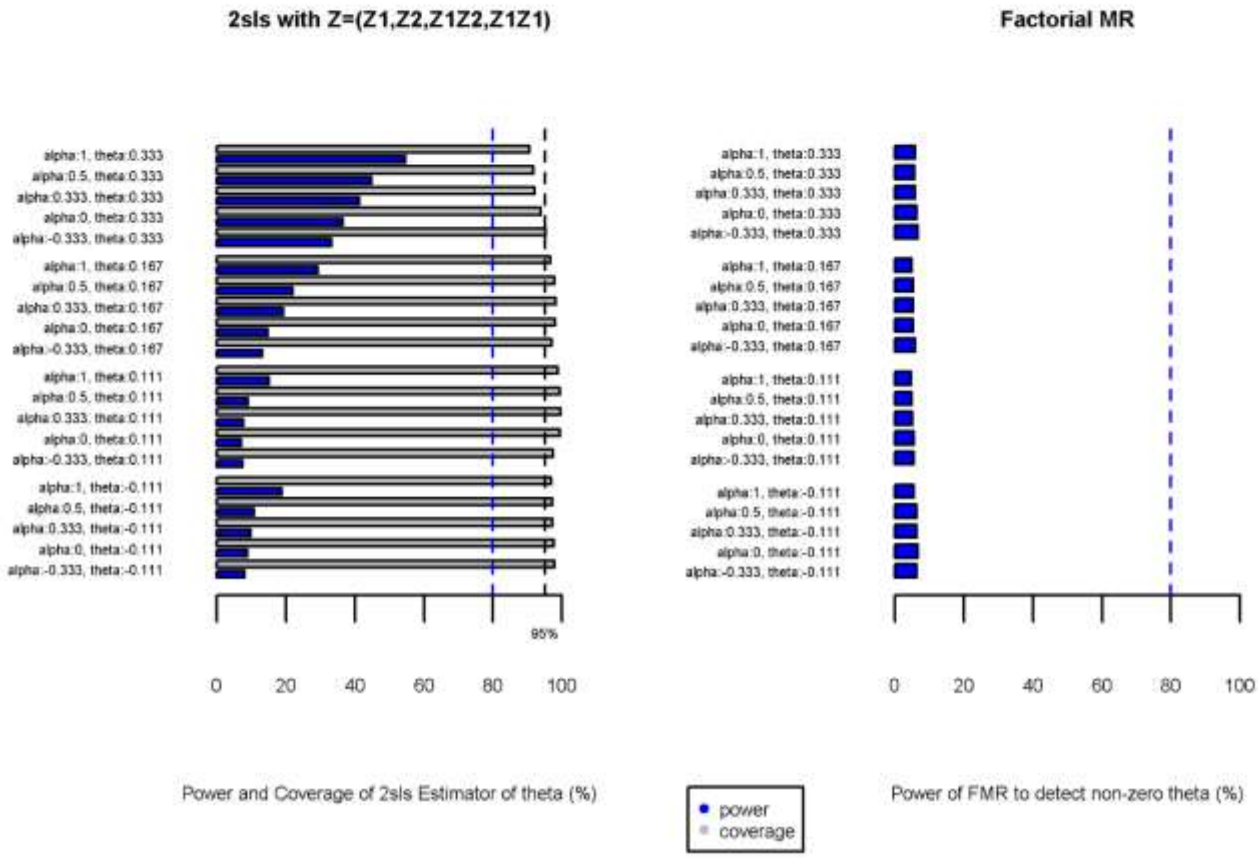
Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2. The vertical lines show the true theta (interaction) coefficient and the 2SLS estimates with their Monte Carlo 95% confidence interval are overlaid.



7 FIGURES: POWER, COVERAGE AND TYPE 1 ERROR

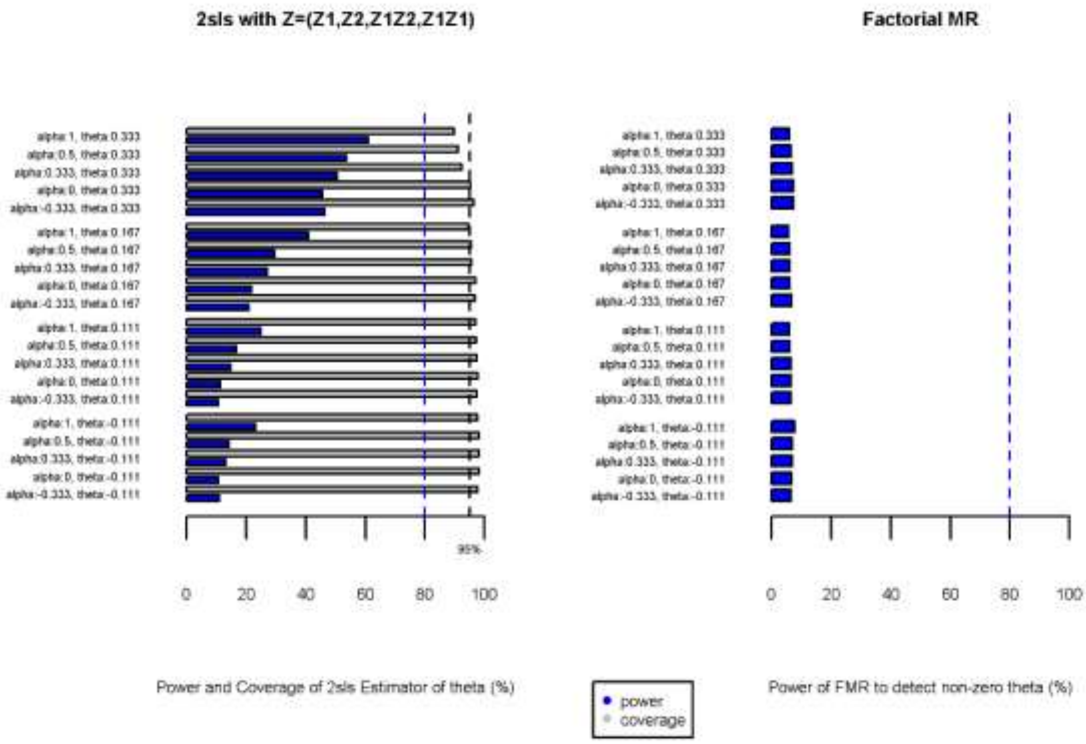
7.1 2SLS (power and coverage) versus factorial MR (power) when N=50,000.

Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2.

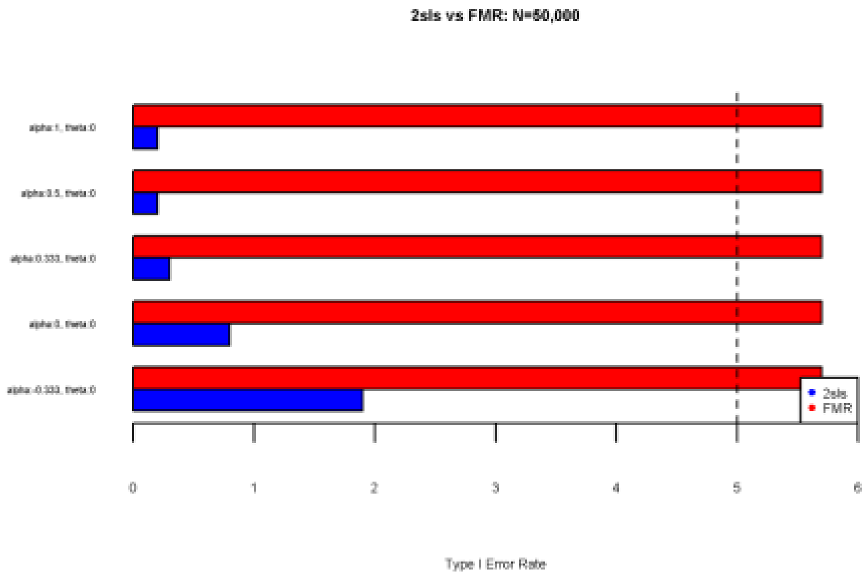


7.2 2SLS (power and coverage) versus factorial MR (power) when N=100,000

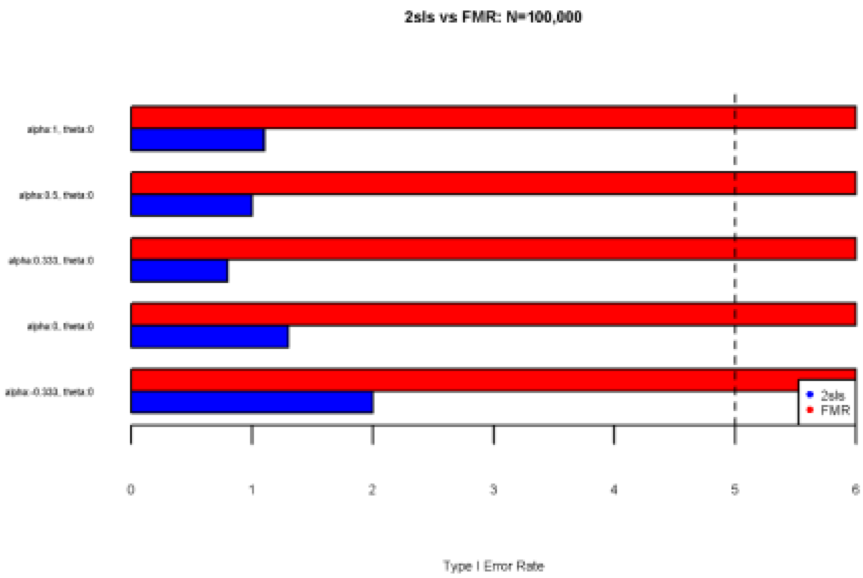
Theta is the interaction coefficient (A_1A_2), and alpha is the effect of A1 on A2.



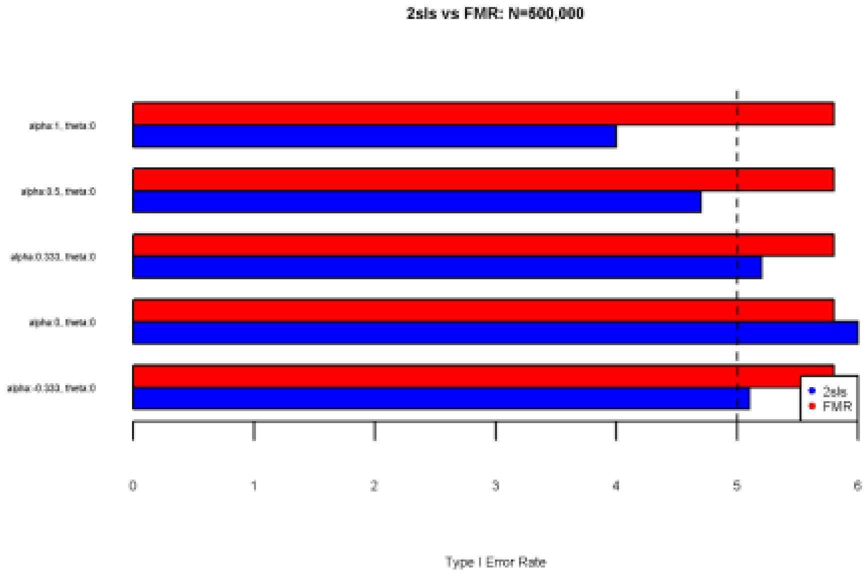
7.3 Type I error rate of 2SLS using Z=Z1,Z2,Z1Z2,Z1Z1 versus factorial MR at N=50,000



7.4 Type I error rate of 2SLS using Z=Z1,Z2,Z1Z2,Z1Z1 versus factorial MR at N=100,000



7.5 Type I error rate of 2SLS using Z=Z1,Z2,Z1Z2,Z1Z1 versus factorial MR at N=500,000



8 SUMMARY OF RESULTS OF SENSITIVITY ANALYSES

An additional simulation was run at N=500,000 where A_2's instrument had a pleiotropic effect on A_1. Under some parameter combinations the existence of pleiotropy negatively affected the performance of the 2SLS using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ and factorial MR estimators, potentially because the instruments were weaker. We also increased the instrument coefficients in the data generating model in a further simulation at N=50,000 to mimic stronger instrumental variables. As expected, the power of 2SLS using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ to detect the interaction was higher with greater instrumental variable strength. Repeating the main observational and 2SLS (using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$) using robust standard errors did not materially affect the results. Examination of the Sanderson-Windmeijer F-statistic revealed that in smaller sample sizes the instruments were weak to predict the interaction term.

9 SUMMARY OF RESULTS OF ILLUSTRATIVE EXAMPLE

Data were available for all variables for N=306,593 participants. Neither factorial MR nor the 2SLS approaches (using $Z=(Z_1,Z_2,Z_1Z_2,Z_1Z_1)$ or $Z=(Z_1,Z_2,Z_1Z_2)$) detected an interaction between BMI and years of schooling on systolic blood pressure, in contrast to the (age and sex adjusted) observational linear regression analysis which suggested a positive additive interaction; $\beta=0.029$ mmHg higher systolic blood pressure per unit increase in BMI (kg/m^2)*years of schooling ($p<0.0005$). The genetic risk score for BMI explained 1.6% of the variance in BMI, and the education genetic risk score explained 0.5% of the variance in years of education.

10 FULL NUMERICAL RESULTS FOR ALL ANALYSES

11 ORDINARY LEAST SQUARES ASSOCIATION

11.1 THETA=-0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean observational interaction effect estimate	Standard deviation of observational estimate	Mean estimated standard error of observational estimate	Standard error of the bias (standard deviation of observational estimate/sqrt(1000))	Power of observational estimator (%)	Coverage of observational estimator (%)
α = -0.333	θ = -0.111	10,000	-0.22741	0.00702	0.006463	0.000222	100	0
		20,000	-0.22765	0.004721	0.004562	0.000149	100	0
		30,000	-0.22775	0.003883	0.003726	0.000123	100	0
		40,000	-0.22761	0.003451	0.003225	0.000109	100	0
		50,000	-0.22743	0.003007	0.002885	9.51E-05	100	0
		60,000	-0.22752	0.002805	0.002633	8.87E-05	100	0
		70,000	-0.22744	0.002672	0.002438	8.45E-05	100	0
		80,000	-0.22748	0.002503	0.00228	7.92E-05	100	0
		90,000	-0.22742	0.00222	0.002149	7.02E-05	100	0
		100,000	-0.22743	0.002063	0.00204	6.52E-05	100	0
		500,000	-0.22747	0.000959	0.000912	3.03E-05	100	0
		1,000,000	-0.22753	0.000681	0.000645	2.15E-05	100	0
α = 0	θ = -0.111	10,000	-0.24269	0.005632	0.0052	0.000178	100	0

No mediation		20,000	-0.24272	0.003767	0.00367	0.000119	100	0
		30,000	-0.24283	0.003072	0.002997	9.72E-05	100	0
		40,000	-0.24274	0.002693	0.002594	8.52E-05	100	0
		50,000	-0.24255	0.002369	0.002321	7.49E-05	100	0
		60,000	-0.24261	0.00223	0.002119	7.05E-05	100	0
		70,000	-0.24255	0.002094	0.001962	6.62E-05	100	0
		80,000	-0.24262	0.00196	0.001835	6.20E-05	100	0
		90,000	-0.24256	0.001761	0.00173	5.57E-05	100	0
		100,000	-0.24256	0.001677	0.001641	5.30E-05	100	0
		500,000	-0.2426	0.000763	0.000734	2.41E-05	100	0
		1,000,000	-0.24263	0.000534	0.000519	1.69E-05	100	0
α = 0.333	θ = -0.111	10,000	-0.23253	0.004377	0.003991	0.000138	100	0
		20,000	-0.2325	0.002953	0.002817	9.34E-05	100	0
		30,000	-0.23258	0.002394	0.002301	7.57E-05	100	0
		40,000	-0.23254	0.002085	0.001991	6.59E-05	100	0
		50,000	-0.23239	0.001827	0.001782	5.78E-05	100	0
		60,000	-0.23243	0.001707	0.001626	5.40E-05	100	0
		70,000	-0.23239	0.00161	0.001506	5.09E-05	100	0
		80,000	-0.23246	0.001513	0.001409	4.78E-05	100	0

		90,000	-0.23241	0.001382	0.001328	4.37E-05	100	0
		100,000	-0.23241	0.001335	0.00126	4.22E-05	100	0
		500,000	-0.23243	0.000595	0.000563	1.88E-05	100	0
		1,000,000	-0.23244	0.000413	0.000398	1.31E-05	100	0
α = 0.5	θ = -0.111	10,000	-0.22614	0.003901	0.003527	0.000123	100	0
		20,000	-0.22611	0.002642	0.00249	8.35E-05	100	0
		30,000	-0.22618	0.00214	0.002033	6.77E-05	100	0
		40,000	-0.22615	0.001861	0.00176	5.89E-05	100	0
		50,000	-0.22602	0.001625	0.001575	5.14E-05	100	0
		60,000	-0.22605	0.001512	0.001437	4.78E-05	100	0
		70,000	-0.22602	0.001432	0.001331	4.53E-05	100	0
		80,000	-0.22608	0.001349	0.001245	4.27E-05	100	0
		90,000	-0.22604	0.001237	0.001174	3.91E-05	100	0
		100,000	-0.22604	0.001201	0.001114	3.80E-05	100	0
		500,000	-0.22605	0.000533	0.000498	1.68E-05	100	0
		1,000,000	-0.22606	0.000369	0.000352	1.17E-05	100	0
α = 1	θ = -0.111	10,000	-0.21067	0.002929	0.002577	9.26E-05	100	0
		20,000	-0.21064	0.002004	0.001819	6.34E-05	100	0
		30,000	-0.21068	0.001622	0.001486	5.13E-05	100	0
		40,000	-0.21067	0.001408	0.001286	4.45E-05	100	0

50,000	-0.21058	0.00122	0.001151	3.86E-05	100	0
60,000	-0.21061	0.001124	0.00105	3.56E-05	100	0
70,000	-0.21059	0.001075	0.000972	3.40E-05	100	0
80,000	-0.21063	0.001019	0.00091	3.22E-05	100	0
90,000	-0.2106	0.000936	0.000858	2.96E-05	100	0
100,000	-0.2106	0.00092	0.000814	2.91E-05	100	0
500,000	-0.21061	0.000404	0.000364	1.28E-05	100	0
1,000,000	-0.21061	0.00028	0.000257	8.85E-06	100	0

11.2 THETA=0

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean observational interaction effect estimate	Standard deviation of observational estimate	Mean estimated standard error of observational estimate	Standard error of the bias (standard deviation of observational estimate/sqrt(1000))	Type I error of observational estimator (%)	Coverage of observational estimator (%)
α = -0.333	θ = 0	10,000	-6.49E-05	0.006435	0.006363834	0.000203	4.8	95.2
		20,000	-0.00016	0.004422	0.004492431	0.00014	4.6	95.4
		30,000	-0.00026	0.003624	0.003668848	0.000115	4.8	95.2
		40,000	-0.00015	0.003227	0.003175481	0.000102	5	95
		50,000	5.13E-05	0.002801	0.002840981	8.86E-05	4.6	95.4
		60,000	-3.77E-06	0.002648	0.002593147	8.37E-05	4.7	95.3
		70,000	6.02E-05	0.002449	0.002401261	7.74E-05	4.7	95.3
		80,000	5.83E-06	0.002283	0.002245631	7.22E-05	5.4	94.6
		90,000	5.13E-05	0.002105	0.00211651	6.66E-05	4.8	95.2
		100,000	8.12E-05	0.001922	0.002008939	6.08E-05	4	96
		500,000	8.71E-06	0.000888	0.0008983	2.81E-05	4.5	95.5
		1,000,000	-3.41E-05	0.000631	0.000635118	2.00E-05	4.7	95.3
α = 0	θ = 0	10,000	-0.0002	0.005286	0.005132689	0.000167	4.9	95.1
No mediation		20,000	-0.00011	0.003601	0.003622746	0.000114	4.1	95.9

		30,000	-0.0002	0.002952	0.002958611	9.34E-05	5.3	94.7
		40,000	-0.00015	0.002574	0.002560852	8.14E-05	4.5	95.5
		50,000	4.61E-05	0.002298	0.002290979	7.27E-05	5.1	94.9
		60,000	7.78E-06	0.002122	0.00209099	6.71E-05	4.6	95.4
		70,000	6.08E-05	0.001948	0.001936354	6.16E-05	4.4	95.6
		80,000	-1.88E-05	0.001813	0.001811084	5.73E-05	4.5	95.5
		90,000	2.14E-05	0.001691	0.001707118	5.35E-05	5.7	94.3
		100,000	4.96E-05	0.001594	0.001619927	5.04E-05	4.5	95.5
		500,000	-6.20E-06	0.000716	0.00072437	2.27E-05	3.7	96.3
		1,000,000	-2.47E-05	0.000504	0.000512135	1.59E-05	4.9	95.1
α = 0.333	θ = 0	10,000	-0.00021	0.004084	0.003931463	0.000129	5.3	94.7
		20,000	-6.96E-05	0.002789	0.002775045	8.82E-05	5.3	94.7
		30,000	-0.00014	0.002281	0.002266252	7.21E-05	5.2	94.8
		40,000	-0.00012	0.001977	0.001961668	6.25E-05	5.4	94.6
		50,000	3.44E-05	0.001773	0.001754907	5.61E-05	5.2	94.8
		60,000	1.09E-05	0.001606	0.001601776	5.08E-05	4.3	95.7
		70,000	4.84E-05	0.001484	0.00148331	4.69E-05	4.5	95.5
		80,000	-2.44E-05	0.001378	0.001387465	4.36E-05	4.7	95.3
		90,000	5.53E-06	0.001298	0.00130794	4.10E-05	5.4	94.6
		100,000	2.72E-05	0.001254	0.001240929	3.97E-05	5.5	94.5

		500,000	-1.06E-05	0.000551	0.000554875	1.74E-05	4.4	95.6
		1,000,000	-1.60E-05	0.000384	0.000392306	1.21E-05	4.6	95.4
α = 0.5	θ = 0	10,000	-0.0002	0.003609	0.003467276	0.000114	5.2	94.8
		20,000	-5.53E-05	0.00247	0.002447499	7.81E-05	5.1	94.9
		30,000	-0.00011	0.002017	0.001998734	6.38E-05	5	95
		40,000	-0.0001	0.001748	0.001730134	5.53E-05	5.8	94.2
		50,000	2.96E-05	0.001566	0.001547774	4.95E-05	5.2	94.8
		60,000	1.10E-05	0.00141	0.001412752	4.46E-05	4.5	95.5
		70,000	4.26E-05	0.001307	0.001308257	4.13E-05	4.8	95.2
		80,000	-2.42E-05	0.001214	0.001223753	3.84E-05	4.4	95.6
		90,000	1.59E-06	0.001146	0.001153647	3.62E-05	5	95
		100,000	2.05E-05	0.001116	0.00109449	3.53E-05	5.3	94.7
		500,000	-1.10E-05	0.000486	0.000489386	1.54E-05	4.3	95.7
		1,000,000	-1.31E-05	0.000338	0.000346007	1.07E-05	3.7	96.3
α = 1	θ = 0	10,000	-0.00016	0.002617	0.002509598	8.28E-05	5.2	94.8
		20,000	-3.08E-05	0.001801	0.001771684	5.70E-05	4.8	95.2
		30,000	-7.01E-05	0.001467	0.00144679	4.64E-05	4.9	95.1
		40,000	-7.36E-05	0.001273	0.001252403	4.03E-05	6	94
		50,000	1.99E-05	0.001135	0.001120399	3.59E-05	4.9	95.1
		60,000	9.74E-06	0.001011	0.001022722	3.20E-05	4.2	95.8

70,000	3.02E-05	0.000945	0.000947055	2.99E-05	5.6	94.4
80,000	-2.08E-05	0.000877	0.000885915	2.77E-05	4.2	95.8
90,000	-3.39E-06	0.000833	0.000835211	2.63E-05	4.9	95.1
100,000	9.59E-06	0.000821	0.000792326	2.60E-05	5.7	94.3
500,000	-1.00E-05	0.000353	0.000354261	1.12E-05	5.2	94.8
1,000,000	-7.77E-06	0.000245	0.000250475	7.74E-06	3.6	96.4

11.3 THETA=0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean observational interaction effect estimate	Standard deviation of observational estimate	Mean estimated standard error of observational estimate	Standard error of the bias (standard deviation of observational estimate/sqrt(1000))	Power of observational estimator (%)	Coverage of observational estimator (%)
α = -0.333	θ = 0.111	10,000	0.227283	0.006788	0.006461	0.000215	100	0
		20,000	0.227317	0.00484	0.004562	0.000153	100	0
		30,000	0.227234	0.003946	0.003726	0.000125	100	0
		40,000	0.227303	0.003475	0.003225	0.00011	100	0
		50,000	0.227529	0.003052	0.002885	9.65E-05	100	0
		60,000	0.227517	0.002883	0.002633	9.12E-05	100	0
		70,000	0.227557	0.002598	0.002438	8.22E-05	100	0
		80,000	0.227489	0.002392	0.00228	7.57E-05	100	0
		90,000	0.227522	0.00232	0.002149	7.34E-05	100	0
		100,000	0.227596	0.002102	0.00204	6.65E-05	100	0
		500,000	0.227489	0.000949	0.000912	3.00E-05	100	0
		1,000,000	0.227459	0.000678	0.000645	2.14E-05	100	0
α = 0	θ = 0.111	10,000	0.24229	0.005457	0.0052	0.000173	100	0
No mediation		20,000	0.24249	0.003812	0.00367	0.000121	100	0

		30,000	0.242427	0.003171	0.002998	0.0001	100	0
		40,000	0.242437	0.002732	0.002595	8.64E-05	100	0
		50,000	0.242646	0.002481	0.002321	7.85E-05	100	0
		60,000	0.242627	0.002239	0.002118	7.08E-05	100	0
		70,000	0.242671	0.00202	0.001962	6.39E-05	100	0
		80,000	0.242578	0.001868	0.001835	5.91E-05	100	0
		90,000	0.242598	0.001818	0.00173	5.75E-05	100	0
		100,000	0.242658	0.001681	0.001641	5.32E-05	100	0
		500,000	0.242587	0.00075	0.000734	2.37E-05	100	0
		1,000,000	0.242576	0.00053	0.000519	1.67E-05	100	0
α = 0.333	θ = 0.111	10,000	0.232112	0.004266	0.003991	0.000135	100	0
		20,000	0.232361	0.002975	0.002817	9.41E-05	100	0
		30,000	0.232313	0.002487	0.002301	7.86E-05	100	0
		40,000	0.232301	0.002131	0.001991	6.74E-05	100	0
		50,000	0.23246	0.001947	0.001781	6.16E-05	100	0
		60,000	0.232453	0.001711	0.001626	5.41E-05	100	0
		70,000	0.232486	0.001563	0.001506	4.94E-05	100	0
		80,000	0.232408	0.001442	0.001408	4.56E-05	100	0
		90,000	0.232422	0.001402	0.001328	4.43E-05	100	0
		100,000	0.23246	0.00133	0.00126	4.21E-05	100	0

		500,000	0.232408	0.00058	0.000563	1.83E-05	100	0
		1,000,000	0.232411	0.00041	0.000398	1.30E-05	100	0
α = 0.5	θ = 0.111	10,000	0.225745	0.003811	0.003528	0.000121	100	0
		20,000	0.225997	0.002663	0.00249	8.42E-05	100	0
		30,000	0.225954	0.002225	0.002034	7.04E-05	100	0
		40,000	0.225938	0.001905	0.00176	6.02E-05	100	0
		50,000	0.226076	0.00174	0.001575	5.50E-05	100	0
		60,000	0.226075	0.001519	0.001437	4.80E-05	100	0
		70,000	0.226103	0.001396	0.001331	4.41E-05	100	0
		80,000	0.226032	0.001287	0.001245	4.07E-05	100	0
		90,000	0.226044	0.001251	0.001174	3.96E-05	100	0
		100,000	0.226076	0.001195	0.001114	3.78E-05	100	0
		500,000	0.226029	0.000516	0.000498	1.63E-05	100	0
		1,000,000	0.226037	0.000366	0.000352	1.16E-05	100	0
α = 1	θ = 0.111	10,000	0.210343	0.002878	0.002577	9.10E-05	100	0
		20,000	0.210576	0.002028	0.001819	6.41E-05	100	0
		30,000	0.210544	0.001686	0.001486	5.33E-05	100	0
		40,000	0.210524	0.001443	0.001286	4.56E-05	100	0
		50,000	0.210618	0.001313	0.001151	4.15E-05	100	0
		60,000	0.210629	0.001138	0.00105	3.60E-05	100	0

70,000	0.210647	0.00106	0.000973	3.35E-05	100	0
80,000	0.210593	0.000974	0.00091	3.08E-05	100	0
90,000	0.210597	0.00095	0.000858	3.00E-05	100	0
100,000	0.210623	0.000915	0.000814	2.89E-05	100	0
500,000	0.210585	0.000388	0.000364	1.23E-05	100	0
1,000,000	0.210599	0.000276	0.000257	8.74E-06	100	0

11.4 THETA=0.167

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean observational interaction effect estimate	Standard deviation of observational estimate	Mean estimated standard error of observational estimate	Standard error of the bias (standard deviation of observational estimate/sqrt(1000))	Power of observational estimator	Coverage of observational estimator
α = -0.333	θ = 0.167	10,000	0.341299	0.00729	0.006582	0.000231	100	0
		20,000	0.341399	0.005277	0.004647	0.000167	100	0
		30,000	0.341322	0.004296	0.003796	0.000136	100	0
		40,000	0.341371	0.003755	0.003285	0.000119	100	0
		50,000	0.341609	0.003325	0.002939	0.000105	100	0
		60,000	0.34162	0.003126	0.002683	9.89E-05	100	0
		70,000	0.341648	0.0028	0.002484	8.86E-05	100	0
		80,000	0.341572	0.002563	0.002323	8.11E-05	100	0
		90,000	0.341599	0.00253	0.00219	8.00E-05	100	0
		100,000	0.341696	0.002295	0.002078	7.26E-05	100	0
		500,000	0.341571	0.001025	0.000929	3.24E-05	100	0
		1,000,000	0.341547	0.000733	0.000657	2.32E-05	100	0
α = 0	θ = 0.167	10,000	0.363898	0.005728	0.005283	0.000181	100	0
No mediation		20,000	0.364156	0.004045	0.003729	0.000128	100	0

		30,000	0.364104	0.003392	0.003046	0.000107	100	0
		40,000	0.364094	0.002905	0.002636	9.19E-05	100	0
		50,000	0.36431	0.002656	0.002358	8.40E-05	100	0
		60,000	0.3643	0.002374	0.002152	7.51E-05	100	0
		70,000	0.36434	0.002133	0.001993	6.75E-05	100	0
		80,000	0.364241	0.001968	0.001864	6.22E-05	100	0
		90,000	0.364251	0.001945	0.001757	6.15E-05	100	0
		100,000	0.364327	0.001784	0.001668	5.64E-05	100	0
		500,000	0.364248	0.000795	0.000746	2.51E-05	100	0
		1,000,000	0.364241	0.000562	0.000527	1.78E-05	100	0
α = 0.333	θ = 0.167	10,000	0.348622	0.004524	0.004064	0.000143	100	0
		20,000	0.348926	0.003185	0.002869	0.000101	100	0
		30,000	0.348885	0.002693	0.002343	8.51E-05	100	0
		40,000	0.34886	0.002294	0.002028	7.25E-05	100	0
		50,000	0.349021	0.002105	0.001814	6.66E-05	100	0
		60,000	0.349023	0.001832	0.001656	5.79E-05	100	0
		70,000	0.349054	0.001674	0.001534	5.29E-05	100	0
		80,000	0.348973	0.001544	0.001434	4.88E-05	100	0
		90,000	0.34898	0.001515	0.001352	4.79E-05	100	0
		100,000	0.349026	0.001422	0.001283	4.50E-05	100	0

		500,000	0.348966	0.00062	0.000574	1.96E-05	100	0
		1,000,000	0.348974	0.000442	0.000406	1.40E-05	100	0
α = 0.5	θ = 0.167	10,000	0.339057	0.004082	0.003602	0.000129	100	0
		20,000	0.339363	0.002879	0.002542	9.10E-05	100	0
		30,000	0.339327	0.002433	0.002076	7.69E-05	100	0
		40,000	0.339298	0.002071	0.001797	6.55E-05	100	0
		50,000	0.339438	0.001897	0.001608	6.00E-05	100	0
		60,000	0.339447	0.001644	0.001468	5.20E-05	100	0
		70,000	0.339473	0.001513	0.001359	4.78E-05	100	0
		80,000	0.3394	0.001395	0.001271	4.41E-05	100	0
		90,000	0.339405	0.001366	0.001198	4.32E-05	100	0
		100,000	0.339444	0.00129	0.001137	4.08E-05	100	0
		500,000	0.339389	0.000557	0.000508	1.76E-05	100	0
		1,000,000	0.339401	0.000399	0.000359	1.26E-05	100	0
α = 1	θ = 0.167	10,000	0.315911	0.003193	0.002659	0.000101	100	0
		20,000	0.316195	0.002272	0.001877	7.19E-05	100	0
		30,000	0.316167	0.001904	0.001533	6.02E-05	100	0
		40,000	0.316138	0.001619	0.001327	5.12E-05	100	0
		50,000	0.316234	0.001477	0.001187	4.67E-05	100	0
		60,000	0.316255	0.001276	0.001084	4.03E-05	100	0

70,000	0.316271	0.001194	0.001004	3.78E-05	100	0
80,000	0.316216	0.0011	0.000939	3.48E-05	100	0
90,000	0.316213	0.001075	0.000885	3.40E-05	100	0
100,000	0.316246	0.001023	0.00084	3.24E-05	100	0
500,000	0.316199	0.000434	0.000375	1.37E-05	100	0
1,000,000	0.316218	0.000313	0.000265	9.88E-06	100	0

11.5 THETA=0.333

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean observational interaction effect estimate	Standard deviation of observational estimate	Mean estimated standard error of observational estimate	Standard error of the bias (standard deviation of observational estimate/sqrt(1000))	Power of observational estimator	Coverage of observational estimator
α = -0.333	θ = 0.333	10,000	0.682663	0.009651	0.007199	0.000305	100	0
		20,000	0.682963	0.007144	0.005085	0.000226	100	0
		30,000	0.682903	0.005803	0.004153	0.000184	100	0
		40,000	0.682894	0.004991	0.003594	0.000158	100	0
		50,000	0.683167	0.004502	0.003215	0.000142	100	0
		60,000	0.683243	0.00417	0.002935	0.000132	100	0
		70,000	0.683235	0.003737	0.002718	0.000118	100	0
		80,000	0.683138	0.003384	0.002542	0.000107	100	0
		90,000	0.683147	0.00341	0.002396	0.000108	100	0
		100,000	0.68331	0.00312	0.002274	9.87E-05	100	0
		500,000	0.683132	0.001364	0.001017	4.31E-05	100	0
		1,000,000	0.683128	0.000981	0.000719	3.10E-05	100	0
α = 0	θ = 0.333	10,000	0.727997	0.007092	0.005711	0.000224	100	0
No mediation		20,000	0.728426	0.005103	0.004032	0.000161	100	0

		30,000	0.728408	0.004353	0.003293	0.000138	100	0
		40,000	0.72834	0.003681	0.00285	0.000116	100	0
		50,000	0.728575	0.0034	0.00255	0.000108	100	0
		60,000	0.728593	0.002998	0.002327	9.48E-05	100	0
		70,000	0.728619	0.002699	0.002155	8.54E-05	100	0
		80,000	0.7285	0.002481	0.002016	7.85E-05	100	0
		90,000	0.728481	0.002501	0.0019	7.91E-05	100	0
		100,000	0.728604	0.002255	0.001803	7.13E-05	100	0
		500,000	0.728502	0.001007	0.000806	3.19E-05	100	0
		1,000,000	0.728507	0.000713	0.00057	2.25E-05	100	0
α = 0.333	θ = 0.333	10,000	0.697454	0.005767	0.004439	0.000182	100	0
		20,000	0.697921	0.004128	0.003134	0.000131	100	0
		30,000	0.697906	0.003566	0.00256	0.000113	100	0
		40,000	0.697838	0.003005	0.002216	9.50E-05	100	0
		50,000	0.698008	0.002758	0.001982	8.72E-05	100	0
		60,000	0.698036	0.002381	0.001809	7.53E-05	100	0
		70,000	0.69806	0.002198	0.001675	6.95E-05	100	0
		80,000	0.69797	0.002037	0.001567	6.44E-05	100	0
		90,000	0.697954	0.002012	0.001477	6.36E-05	100	0
		100,000	0.698024	0.00184	0.001401	5.82E-05	100	0

		500,000	0.697942	0.000809	0.000627	2.56E-05	100	0
		1,000,000	0.697964	0.000585	0.000443	1.85E-05	100	0
α = 0.5	θ = 0.333	10,000	0.678314	0.005351	0.003978	0.000169	100	0
		20,000	0.678781	0.003833	0.002808	0.000121	100	0
		30,000	0.678766	0.003304	0.002293	0.000104	100	0
		40,000	0.678702	0.002782	0.001985	8.80E-05	100	0
		50,000	0.678847	0.002543	0.001776	8.04E-05	100	0
		60,000	0.678883	0.002194	0.001621	6.94E-05	100	0
		70,000	0.678904	0.002046	0.001501	6.47E-05	100	0
		80,000	0.678824	0.0019	0.001404	6.01E-05	100	0
		90,000	0.678808	0.001862	0.001324	5.89E-05	100	0
		100,000	0.678867	0.001714	0.001256	5.42E-05	100	0
		500,000	0.678788	0.000747	0.000561	2.36E-05	100	0
		1,000,000	0.678816	0.000544	0.000397	1.72E-05	100	0
α = 1	θ = 0.333	10,000	0.631984	0.004546	0.003065	0.000144	100	0
		20,000	0.632421	0.003283	0.002164	0.000104	100	0
		30,000	0.632404	0.002781	0.001767	8.80E-05	100	0
		40,000	0.63235	0.00234	0.00153	7.40E-05	100	0
		50,000	0.632448	0.002124	0.001368	6.72E-05	100	0
		60,000	0.632501	0.001843	0.001249	5.83E-05	100	0

70,000	0.632512	0.001752	0.001157	5.54E-05	100	0
80,000	0.632453	0.001632	0.001082	5.16E-05	100	0
90,000	0.632429	0.001582	0.00102	5.00E-05	100	0
100,000	0.632482	0.001476	0.000968	4.67E-05	100	0
500,000	0.632409	0.000631	0.000433	1.99E-05	100	0
1,000,000	0.632445	0.000463	0.000306	1.46E-05	100	0

12 2SLS INSTRUMENT DOES NOT ASSUME MEDIATION, Z=(Z1,Z2,Z1Z2)

12.1 THETA=-0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = -0.111	10,000	-0.21775	6.214008	43.15983	0.196504	1.2	100
		20,000	-0.069	1.723318	6.548343	0.054496	1.7	99.7
		30,000	0.016721	3.693011	32.8285	0.116783	3.2	99.1
		40,000	-0.10449	0.405008	0.441858	0.012807	5.9	97.7
		50,000	0.03879	5.227974	33.43623	0.165323	7.2	97.9
		60,000	-0.10669	0.274416	0.282685	0.008678	6.7	98.2
		70,000	-0.10058	0.250272	0.259073	0.007914	8	97.8
		80,000	-0.10868	0.243907	0.236284	0.007713	7.5	97.3
		90,000	-0.08746	0.227107	0.220484	0.007182	7.1	98
		100,000	-0.1003	0.202746	0.202602	0.006411	9.8	98.6
		500,000	-0.10677	0.084521	0.082203	0.002673	28.1	94.2
		1,000,000	-0.11088	0.056678	0.057986	0.001792	48.7	95.3
α = 0	θ = -0.111	10,000	0.246957	6.568474	62.61536	0.207713	1.5	99.6
No mediation		20,000	1.096622	39.55999	1464.155	1.250997	2.1	99.6

		30,000	-0.02826	2.979395	42.48063	0.094217	3.7	98.9
		40,000	-0.09496	1.219632	2.056836	0.038568	6.3	98.4
		50,000	-0.11402	0.51638	0.66536	0.016329	7.4	97.5
		60,000	-0.08589	0.505889	0.614479	0.015998	6.7	98.5
		70,000	-0.08715	0.355384	0.370698	0.011238	8.4	98.6
		80,000	-0.10475	1.033444	3.087159	0.03268	8.3	97.5
		90,000	-0.06191	0.441419	0.376284	0.013959	7.7	98.5
		100,000	-0.09253	0.220696	0.222076	0.006979	10.1	99
		500,000	-0.10599	0.086511	0.083838	0.002736	27.8	94.3
		1,000,000	-0.1103	0.057625	0.058942	0.001822	47.7	95.7
α = 0.333	θ = -0.111	10,000	-0.36033	6.508636	90.21198	0.205821	1.9	99.6
		20,000	0.515166	11.8878	251.7985	0.375925	3	99.5
		30,000	-0.32242	4.218115	172.7044	0.133388	4.4	99.1
		40,000	-0.04793	1.584554	7.390424	0.050108	6	98.8
		50,000	-0.57867	17.22369	381.2039	0.544661	7.6	97.7
		60,000	-0.16338	1.162284	2.872041	0.036755	6.9	98.5
		70,000	1.031644	35.24122	1722.213	1.114425	8.4	99.1
		80,000	0.053764	3.430512	12.64235	0.108482	8.6	98.4
		90,000	-0.18281	4.12814	24.30278	0.130543	7.5	98.6
		100,000	-0.08139	0.897594	2.551107	0.028384	10.1	99.3

		500,000	-0.10473	0.089978	0.086718	0.002845	27.6	95
		1,000,000	-0.10955	0.058984	0.060322	0.001865	47.1	96.4
α = 0.5	θ = -0.111	10,000	-0.32521	5.340703	57.00212	0.168888	2.2	99.7
		20,000	-0.17623	6.479462	85.99288	0.204899	3.1	99.6
		30,000	-0.12533	3.023454	42.98291	0.09561	4.8	99.1
		40,000	-0.15743	2.543494	25.46778	0.080432	6.4	98.8
		50,000	-0.12348	2.230048	10.55006	0.07052	7.9	97.8
		60,000	-0.32028	7.239807	272.1581	0.228943	7	98.8
		70,000	-0.20027	2.297505	11.57199	0.072653	8.5	99.3
		80,000	-0.22864	2.213789	16.7742	0.070006	9.1	98.5
		90,000	-0.04359	1.285722	3.771445	0.040658	7.7	98.7
		100,000	-0.06435	0.473639	0.781673	0.014978	10.3	99.3
		500,000	-0.10388	0.092499	0.088789	0.002925	27.5	95.8
		1,000,000	-0.10911	0.059847	0.061197	0.001893	46.3	96.8
α = 1	θ = -0.111	10,000	-0.29284	5.188695	88.12826	0.164081	3.2	99.7
		20,000	-0.46863	9.160373	294.736	0.289676	4.1	99.6
		30,000	-0.22865	2.631471	47.38844	0.083214	5.6	99.1
		40,000	-1.63516	69.79232	30492.19	2.207027	7.1	99.1
		50,000	-0.13721	8.255129	166.3684	0.26105	8.6	98
		60,000	-0.20744	2.236071	11.54497	0.070711	8.8	99.1

70,000	-0.29327	4.868044	42.68373	0.153941	8.2	99.3
80,000	0.01058	22.58778	4609.322	0.714288	9.5	98.8
90,000	-0.25879	4.325907	55.24257	0.136797	8.8	98.6
100,000	-0.26527	4.998768	28.97802	0.158075	10.5	99
500,000	-0.09994	0.106611	0.099948	0.003371	27.9	96.9
1,000,000	-0.10742	0.063393	0.064744	0.002005	46.2	97.7

12.2 THETA=0

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Type I error of 2sls estimator	Coverage of 2sls estimator
α = -0.333	θ = 0	10,000	-0.06625	6.257886	45.53554	0.197892	0	100
		20,000	-0.05187	1.652465	5.91879	0.052256	0.2	99.8
		30,000	0.031233	4.999218	40.59871	0.158089	0.4	99.6
		40,000	-0.019	0.425931	0.452861	0.013469	1	99
		50,000	0.201257	7.493741	48.00768	0.236973	1.1	98.9
		60,000	-0.0058	0.265096	0.275365	0.008383	1.2	98.8
		70,000	-0.00454	0.238511	0.250518	0.007542	2	98
		80,000	-0.00648	0.235611	0.230215	0.007451	2.6	97.4
		90,000	0.011816	0.214749	0.213654	0.006791	2.1	97.9
		100,000	0.002848	0.199567	0.198006	0.006311	1.6	98.4
		500,000	0.003615	0.083695	0.080411	0.002647	6.3	93.7
		1,000,000	-0.00108	0.055738	0.056762	0.001763	4.7	95.3
α = 0	θ = 0	10,000	0.302075	6.575332	61.31404	0.20793	0	100
No mediation		20,000	0.521476	36.51752	1523.227	1.154785	0.2	99.8

		30,000	-0.16634	4.580503	94.23084	0.144848	0.2	99.8
		40,000	-0.01389	1.045202	2.085443	0.033052	0.7	99.3
		50,000	-0.03516	0.585904	0.805202	0.018528	0.7	99.3
		60,000	-0.00411	0.452345	0.553792	0.014304	0.4	99.6
		70,000	-0.00557	0.318206	0.331378	0.010063	0.8	99.2
		80,000	0.003372	0.337123	0.651364	0.010661	1.3	98.7
		90,000	0.020326	0.297559	0.291984	0.00941	1.1	98.9
		100,000	0.003015	0.215195	0.214225	0.006805	1	99
		500,000	0.003522	0.085028	0.081221	0.002689	5.7	94.3
		1,000,000	-0.00113	0.056278	0.057176	0.00178	4.7	95.3
α = 0.333	θ = 0	10,000	-0.16879	5.890676	130.6215	0.18628	0	100
		20,000	0.551993	9.280967	200.6147	0.29349	0.1	99.9
		30,000	-0.22368	8.6254	455.9818	0.272759	0.1	99.9
		40,000	-0.00494	0.965853	3.107193	0.030543	0.3	99.7
		50,000	-0.43591	14.5223	318.9475	0.459236	0.2	99.8
		60,000	-0.04154	0.826501	1.953673	0.026136	0.1	99.9
		70,000	0.777269	24.56081	1200.354	0.776681	0.4	99.6
		80,000	0.091533	2.358262	8.581851	0.074575	0.3	99.7
		90,000	-0.01449	3.532681	24.83627	0.111713	0.5	99.5
		100,000	0.005468	0.766312	1.995738	0.024233	0.7	99.3

		500,000	0.003446	0.087553	0.082996	0.002769	4.7	95.3
		1,000,000	-0.0012	0.057109	0.057865	0.001806	4.4	95.6
α = 0.5	θ = 0	10,000	-0.18757	5.736502	58.64873	0.181404	0	100
		20,000	-0.13307	5.868711	82.26659	0.185585	0.1	99.9
		30,000	-0.10436	4.484523	68.65502	0.141813	0.1	99.9
		40,000	-0.19128	2.822528	21.53514	0.089256	0.3	99.7
		50,000	0.020761	1.54377	6.689685	0.048818	0.1	99.9
		60,000	-0.21769	4.632296	198.8609	0.146486	0.1	99.9
		70,000	-0.05389	1.171219	5.266748	0.037037	0.4	99.6
		80,000	-0.0534	1.451717	7.088886	0.045907	0.2	99.8
		90,000	0.014493	1.110803	3.291321	0.035127	0.5	99.5
		100,000	0.018968	0.434499	0.628817	0.01374	0.5	99.5
		500,000	0.003409	0.089473	0.084375	0.002829	4.3	95.7
		1,000,000	-0.00123	0.057656	0.058328	0.001823	4.1	95.9
α = 1	θ = 0	10,000	-0.13832	5.399892	91.33763	0.17076	0	100
		20,000	-0.45335	13.82701	444.3984	0.437248	0.1	99.9
		30,000	0.014092	1.989054	29.79733	0.062899	0.1	99.9
		40,000	-0.61841	40.9668	17496.97	1.295484	0.1	99.9
		50,000	0.105713	8.622337	173.8918	0.272662	0	100
		60,000	-0.07933	2.378191	11.51237	0.075205	0	100

70,000	-0.14894	5.168856	43.18671	0.163454	0	100
80,000	-1.55432	33.823	5414.013	1.069577	0.1	99.9
90,000	-0.11091	2.640426	37.04351	0.083498	0.2	99.8
100,000	-0.14681	4.102587	25.07565	0.129735	0.3	99.7
500,000	0.00305	0.102249	0.092846	0.003233	2.6	97.4
1,000,000	-0.00137	0.059998	0.060316	0.001897	3.4	96.6

12.3 THETA=0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator	Coverage of 2sls estimator
α = -0.333	θ = 0.111	10,000	0.085238	6.562822	49.52134	0.207535	1.7	100
		20,000	-0.03474	2.442886	11.2895	0.077251	2.8	99.4
		30,000	0.045745	6.9286	48.51535	0.219102	3.6	99.2
		40,000	0.066495	0.506448	0.519387	0.016015	4.5	98.2
		50,000	0.363723	9.771656	62.66634	0.309007	4.6	98.8
		60,000	0.095085	0.27349	0.282726	0.008649	5.7	98.3
		70,000	0.091487	0.244835	0.257173	0.007742	5.3	97.8
		80,000	0.095728	0.241232	0.235719	0.007628	8.5	96.5
		90,000	0.111088	0.215324	0.217744	0.006809	9.1	97.6
		100,000	0.105991	0.205774	0.202752	0.006507	10	97.7
		500,000	0.114003	0.086158	0.0821	0.002725	30.7	94.1
		1,000,000	0.108718	0.057131	0.058006	0.001807	46.1	95.3
α = 0	θ = 0.111	10,000	0.357192	7.15916	64.34084	0.226393	1.6	99.9
No mediation		20,000	-0.05367	37.16733	1600.504	1.175334	3.6	99.1

		30,000	-0.30441	9.394095	213.2775	0.297067	3.6	99.4
		40,000	0.067182	1.255177	2.625237	0.039692	4.4	98.6
		50,000	0.0437	0.757077	1.02221	0.023941	5.5	99.5
		60,000	0.077682	0.634207	0.803016	0.020055	6	98.3
		70,000	0.076	0.34817	0.338319	0.01101	5.7	98.2
		80,000	0.111494	1.171376	3.544879	0.037042	9.5	97.2
		90,000	0.102563	0.275337	0.287034	0.008707	9.3	98.3
		100,000	0.098559	0.229209	0.223779	0.007248	10.1	98.1
		500,000	0.113035	0.08841	0.083676	0.002796	30.5	94.5
		1,000,000	0.108036	0.058265	0.058983	0.001842	46.4	95.5
α = 0.333	θ = 0.111	10,000	0.02275	6.381498	181.659	0.201801	2.1	99.8
		20,000	0.58882	7.255711	150.1406	0.229446	3.7	99.3
		30,000	-0.12494	14.10819	754.1116	0.44614	3.7	99.6
		40,000	0.038054	1.322966	6.185259	0.041836	4.7	98.6
		50,000	-0.29315	11.95199	260.83	0.377955	5.2	99.6
		60,000	0.080297	1.026853	2.613358	0.032472	7.1	99
		70,000	0.522894	13.89466	678.7721	0.439388	5.8	98.9
		80,000	0.129303	1.401817	4.726981	0.044329	10.4	97.9
		90,000	0.153821	4.041784	25.48676	0.127812	9.5	98.9
		100,000	0.092321	1.437649	4.349528	0.045462	10.4	98.4

		500,000	0.111627	0.092241	0.086503	0.002917	30.7	95
		1,000,000	0.107164	0.059868	0.060399	0.001893	45.6	95.6
α = 0.5	θ = 0.111	10,000	-0.04992	6.317666	62.13505	0.199782	2.5	99.8
		20,000	-0.0899	5.804687	79.92608	0.18356	3.7	99.3
		30,000	-0.08339	6.90051	102.1386	0.218213	4	99.6
		40,000	-0.22512	4.708213	50.31435	0.148887	5.2	98.8
		50,000	0.165003	1.792945	7.415969	0.056698	5	99.7
		60,000	-0.1151	7.856869	258.1645	0.248456	7.5	99
		70,000	0.092482	1.30247	6.030621	0.041188	5.8	99.2
		80,000	0.121836	2.911936	21.92397	0.092083	10.3	98.2
		90,000	0.072576	1.545835	5.012182	0.048884	9.9	98.8
		100,000	0.102284	0.748443	1.187633	0.023668	10.4	98.6
		500,000	0.110696	0.095083	0.08857	0.003007	31.2	95.5
		1,000,000	0.106644	0.060886	0.061301	0.001925	44.8	95.8
α = 1	θ = 0.111	10,000	0.016191	5.706895	95.16416	0.180468	3.2	99.7
		20,000	-0.43807	18.57751	594.795	0.587472	4.6	99.5
		30,000	0.256829	4.11468	85.66557	0.130118	5.7	99.6
		40,000	0.398352	16.43501	4503.089	0.519721	5.8	99.1
		50,000	0.348632	9.45311	190.2508	0.298934	6.3	99.7
		60,000	0.048776	2.693678	12.41903	0.085182	8.3	99.5

70,000	-0.00461	5.685566	47.0415	0.179793	6.9	99.5
80,000	-3.11921	70.25019	13769.61	2.221506	10	98.4
90,000	0.036976	2.762198	22.36578	0.087348	9.9	99.3
100,000	-0.02836	3.518813	22.27361	0.111275	11.2	98.6
500,000	0.10604	0.115306	0.10096	0.003646	31.7	96.4
1,000,000	0.104675	0.065148	0.064984	0.00206	43.3	96.6

12.4 THETA=0.167

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator	Coverage of 2sls estimator
α = -0.333	θ = 0.167	10,000	0.161211	6.804202	51.68335	0.215168	3.1	99.6
		20,000	-0.02615	2.983269	14.40362	0.094339	6.6	99
		30,000	0.053023	7.996032	52.58625	0.252857	6.9	98.8
		40,000	0.109369	0.562013	0.561665	0.017772	9.3	98
		50,000	0.4452	10.91622	70.02417	0.345201	9.9	98.7
		60,000	0.14568	0.284006	0.291775	0.008981	11.5	98.1
		70,000	0.139648	0.254543	0.266112	0.008049	10.9	97.7
		80,000	0.146983	0.249086	0.242707	0.007877	16.5	96.1
		90,000	0.160873	0.220538	0.223801	0.006974	15.2	97.8
		100,000	0.157717	0.212212	0.208499	0.006711	17.9	97.5
		500,000	0.169364	0.088559	0.084209	0.0028	52.8	94.5
		1,000,000	0.163782	0.058667	0.059522	0.001855	78.5	95.3
α = 0	θ = 0.167	10,000	0.384834	7.632824	66.67638	0.241371	4.5	99.6
No mediation		20,000	-0.34211	38.86641	1659.691	1.229064	6.9	98.6

		30,000	-0.37366	11.94794	273.6259	0.377827	7.9	99.2
		40,000	0.107839	1.46571	2.949423	0.04635	10.7	98.1
		50,000	0.083248	0.8638	1.166297	0.027316	11.3	99.3
		60,000	0.118699	0.771383	0.946173	0.024393	13.4	97.9
		70,000	0.116908	0.384944	0.369013	0.012173	11.9	98.1
		80,000	0.165717	1.684155	5.070107	0.053258	17.4	96.5
		90,000	0.143806	0.323509	0.328469	0.01023	17.4	98
		100,000	0.146475	0.242708	0.23457	0.007675	19.4	97.4
		500,000	0.167956	0.091799	0.086716	0.002903	51.9	94.4
		1,000,000	0.162784	0.060435	0.061158	0.001911	75.9	95.6
α = 0.333	θ = 0.167	10,000	0.118808	6.992638	210.8103	0.221127	5.6	99.2
		20,000	0.607289	6.63452	125.3148	0.209802	8.1	98.6
		30,000	-0.07542	16.94599	904.9135	0.535879	10	99.2
		40,000	0.059614	1.749855	8.837436	0.055335	12.3	98
		50,000	-0.22155	10.74209	236.7258	0.339695	11.9	99.2
		60,000	0.141399	1.27745	3.261332	0.040397	14.5	98.4
		70,000	0.395325	8.56771	417.2397	0.270935	12	98.4
		80,000	0.148244	1.069799	2.941633	0.03383	17.9	96.8
		90,000	0.238232	4.630255	25.86044	0.146422	17.7	98.2
		100,000	0.135878	1.856925	5.776062	0.058721	19.9	97.7

		500,000	0.16588	0.097008	0.090787	0.003068	50.9	94.8
		1,000,000	0.161506	0.062844	0.063408	0.001987	71.8	96.1
α = 0.5	θ = 0.167	10,000	0.019104	6.664308	64.97602	0.210744	6.1	99.1
		20,000	-0.06825	5.989795	78.92715	0.189414	8.4	98.5
		30,000	-0.07288	8.224195	124.1627	0.260072	10	99.3
		40,000	-0.2421	5.837098	64.99095	0.184585	12.6	98
		50,000	0.237341	2.21805	10.19671	0.070141	12.8	99.2
		60,000	-0.06365	10.42808	390.4894	0.329765	14.7	98.3
		70,000	0.165889	1.858064	9.151722	0.058757	12.6	98.6
		80,000	0.209719	3.889168	30.41479	0.122986	18.1	97.1
		90,000	0.101705	1.887371	6.084278	0.059684	18.3	98
		100,000	0.144068	0.948483	1.494762	0.029994	21	97.7
		500,000	0.164501	0.100782	0.093644	0.003187	49.8	94.8
		1,000,000	0.160744	0.064345	0.064802	0.002035	68.9	96.3
α = 1	θ = 0.167	10,000	0.09368	5.892411	97.23889	0.186334	9.8	98.8
		20,000	-0.4304	20.97362	671.0983	0.663244	10.6	98.2
		30,000	0.378562	5.425829	114.4574	0.17158	12.8	99
		40,000	0.908258	15.35535	2832.478	0.485579	15.2	98.6
		50,000	0.470457	10.01062	198.9186	0.316564	13.8	98.8
		60,000	0.113022	2.900672	13.53292	0.091727	16.9	98.3

70,000	0.067771	6.009432	50.98357	0.190035	13.9	98.9
80,000	-3.90401	89.58272	17960.33	2.832854	19.4	97.1
90,000	0.111139	3.553606	39.86445	0.112375	20.1	98.4
100,000	0.031041	3.398025	21.44655	0.107455	20.8	97.2
500,000	0.157689	0.127015	0.109916	0.004017	48.1	95.3
1,000,000	0.157859	0.070483	0.070328	0.002229	63.7	97.1

12.5 THETA=0.333

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator	Coverage of 2sls estimator
α = -0.333	θ = 0.333	10,000	0.388677	7.81111	59.5645	0.247009	10.1	98.2
		20,000	-0.00044	4.786057	23.87388	0.151348	16.9	96.9
		30,000	0.074812	11.36517	66.83278	0.359398	20.9	97.3
		40,000	0.237734	0.761812	0.713607	0.024091	24.2	97.1
		50,000	0.689144	14.34763	92.07353	0.453712	25.6	97.8
		60,000	0.297163	0.335516	0.33689	0.01061	30.5	97.2
		70,000	0.28384	0.304217	0.30987	0.00962	31	97.8
		80,000	0.300442	0.289113	0.278051	0.009143	35.8	95.4
		90,000	0.309931	0.253031	0.255318	0.008002	38.5	97.3
		100,000	0.312586	0.242481	0.237091	0.007668	39.5	96.6
		500,000	0.335112	0.099686	0.09483	0.003152	90.5	94.1
		1,000,000	0.328643	0.066105	0.0671	0.00209	99.3	96
α = 0	θ = 0.333	10,000	0.467593	9.547763	77.35779	0.301927	14.3	96.8
No mediation		20,000	-1.20569	48.13992	1841.103	1.522318	18.9	95.5

		30,000	-0.58098	19.72037	454.804	0.623613	23.3	96.1
		40,000	0.229565	2.276794	4.355157	0.071999	26.8	95.6
		50,000	0.201656	1.222505	1.663323	0.038659	27.2	96.2
		60,000	0.241504	1.243631	1.478072	0.039327	32.4	95.8
		70,000	0.23939	0.544596	0.509121	0.017222	29.6	96.6
		80,000	0.328062	3.247758	9.683401	0.102703	35.7	94.2
		90,000	0.267286	0.575975	0.480611	0.018214	37	96.9
		100,000	0.289935	0.30158	0.284954	0.009537	38	95.9
		500,000	0.33239	0.107332	0.101637	0.003394	85.4	93.9
		1,000,000	0.326701	0.070686	0.071743	0.002235	98	96.3
α = 0.333	θ = 0.333	10,000	0.406406	9.692701	300.7414	0.30651	17.3	96.3
		20,000	0.662585	7.127646	114.5098	0.225396	21	95.4
		30,000	0.072835	25.56029	1356.877	0.808287	24.7	96.1
		40,000	0.124167	3.254435	16.93763	0.102914	27.6	95.2
		50,000	-0.0072	7.734129	167.1191	0.244575	28.3	95.8
		60,000	0.324337	2.218865	6.158413	0.070167	32.5	95.1
		70,000	0.013381	7.669513	370.5341	0.242531	29.9	96.2
		80,000	0.204955	1.616596	5.710002	0.051121	35.2	93.6
		90,000	0.490959	7.026869	39.10739	0.222209	36.3	96
		100,000	0.266289	3.183921	10.13468	0.100684	37.8	95.2

		500,000	0.328315	0.118434	0.111204	0.003745	79.8	93.7
		1,000,000	0.324207	0.076521	0.077616	0.00242	94.9	96.5
α = 0.5	θ = 0.333	10,000	0.225774	7.86307	74.85897	0.248652	18.8	96
		20,000	-0.00343	7.254742	76.93808	0.229415	21.7	94.8
		30,000	-0.04139	12.34687	192.8554	0.390442	25	95.9
		40,000	-0.29291	9.424248	109.2822	0.298021	28.9	95.1
		50,000	0.45392	3.894822	19.33617	0.123165	29	95.6
		60,000	0.090382	18.88432	787.2233	0.597175	33.4	95.1
		70,000	0.38567	3.882381	20.04184	0.122772	29.5	95.8
		80,000	0.472839	6.986196	55.97751	0.220923	35.3	93.3
		90,000	0.188918	3.072642	9.509641	0.097165	36.3	95.6
		100,000	0.269167	1.589925	2.490781	0.050278	37.5	94.8
		500,000	0.325593	0.126034	0.117429	0.003986	76.2	93.6
		1,000,000	0.32272	0.080001	0.081074	0.00253	92.8	96.5
α = 1	θ = 0.333	10,000	0.325684	6.551942	104.6608	0.207191	23.5	94.5
		20,000	-0.40745	28.17452	901.663	0.890957	25	94.3
		30,000	0.743033	9.53234	203.269	0.301439	27.1	93.8
		40,000	2.434921	53.07075	22498.55	1.678245	30.9	94.3
		50,000	0.835201	12.08151	225.2215	0.382051	30.7	95.1
		60,000	0.305374	3.647052	18.05817	0.11533	34.1	94

70,000	0.28448	7.165697	64.43737	0.226599	29.7	95
80,000	-6.2537	148.4059	30556.66	4.693005	35.4	92.8
90,000	0.333184	6.799938	93.15192	0.215033	36.6	94.6
100,000	0.208895	3.823617	19.64807	0.120913	38.5	94.1
500,000	0.312328	0.173982	0.149289	0.005502	67.8	92.5
1,000,000	0.317093	0.093453	0.093978	0.002955	84.8	96.3

13 FACTORIAL MR

13.1 THETA=-0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Power of FMR to detect an interaction (%)
α = -0.333	θ = -0.111	10,000	5.1
		20,000	4.4
		30,000	4.2
		40,000	7.1
		50,000	6.3
		60,000	7.8
		70,000	6.3
		80,000	6.5
		90,000	7.7
		100,000	6.5
		500,000	16.6
		1,000,000	29.2
α = 0	θ = -0.111	10,000	5.6
No mediation		20,000	4.5
		30,000	4.2
		40,000	6.9
		50,000	6.6
		60,000	7.4
		70,000	6.3
		80,000	6.7
		90,000	7.7
		100,000	6.7
		500,000	16.2
		1,000,000	28.9
α = 0.333	θ = -0.111	10,000	5.5
		20,000	4.9

		30,000	4.6
		40,000	6.5
		50,000	6.2
		60,000	7.2
		70,000	6.4
		80,000	6.7
		90,000	7.4
		100,000	6.9
		500,000	14.9
		1,000,000	26.9
α = 0.5	θ = -0.111	10,000	5.4
		20,000	4.5
		30,000	4.7
		40,000	6.2
		50,000	6.2
		60,000	7.7
		70,000	6.5
		80,000	6.6
		90,000	7.2
		100,000	6.8
		500,000	14.5
		1,000,000	24.8
α = 1	θ = -0.111	10,000	5.6
		20,000	4.2
		30,000	4.5
		40,000	5.9
		50,000	5.4
		60,000	7
		70,000	6
		80,000	6.7
		90,000	6.6

100,000	7.7
500,000	12.8
1,000,000	20

Power and type I error defined using F statistic and Wald test

13.2 THETA=0

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Type I error of FMR to detect an interaction (%)
α = -0.333	θ = 0	10,000	5.2
		20,000	4.7
		30,000	5.8
		40,000	5.9
		50,000	5.7
		60,000	5.1
		70,000	4.2
		80,000	4.6
		90,000	4.5
		100,000	6
		500,000	5.8
		1,000,000	4.7
α = 0	θ = 0	10,000	5.2
No mediation		20,000	4.7
		30,000	5.8
		40,000	5.9
		50,000	5.7
		60,000	5.1
		70,000	4.2
		80,000	4.6
		90,000	4.5
		100,000	6
		500,000	5.8
		1,000,000	4.7
α = 0.333	θ = 0	10,000	5.2
		20,000	4.7

		30,000	5.8
		40,000	5.9
		50,000	5.7
		60,000	5.1
		70,000	4.2
		80,000	4.6
		90,000	4.5
		100,000	6
		500,000	5.8
		1,000,000	4.7
α = 0.5	θ = 0	10,000	5.2
		20,000	4.7
		30,000	5.8
		40,000	5.9
		50,000	5.7
		60,000	5.1
		70,000	4.2
		80,000	4.6
		90,000	4.5
		100,000	6
		500,000	5.8
		1,000,000	4.7
α = 1	θ = 0	10,000	5.2
		20,000	4.7
		30,000	5.8
		40,000	5.9
		50,000	5.7
		60,000	5.1
		70,000	4.2
		80,000	4.6
		90,000	4.5

100,000	6
500,000	5.8
1,000,000	4.7

Power and type I error defined using F statistic and Wald test

13.3 THETA=0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Power of FMR to detect an interaction (%)
α = -0.333	θ = 0.111	10,000	5.2
		20,000	6.3
		30,000	6.3
		40,000	5.7
		50,000	5.4
		60,000	6.1
		70,000	4.8
		80,000	5.8
		90,000	5.8
		100,000	6.5
		500,000	11
		1,000,000	15.2
α = 0	θ = 0.111	10,000	5.1
No mediation		20,000	6.3
		30,000	6.4
		40,000	5.7
		50,000	5.5
		60,000	5.6
		70,000	4.8
		80,000	5.7
		90,000	5.7
		100,000	6.4
		500,000	10
		1,000,000	13.1
α = 0.333	θ = 0.111	10,000	4.7
		20,000	6.4

		30,000	6.1
		40,000	5.5
		50,000	5
		60,000	5.4
		70,000	4.9
		80,000	5.6
		90,000	5.3
		100,000	6.5
		500,000	9.6
		1,000,000	11.5
α = 0.5	θ = 0.111	10,000	4.5
		20,000	6.5
		30,000	6
		40,000	5.6
		50,000	4.9
		60,000	5.5
		70,000	4.9
		80,000	5.6
		90,000	5.3
		100,000	6
		500,000	9.1
		1,000,000	10.5
α = 1	θ = 0.111	10,000	4.5
		20,000	6
		30,000	6.2
		40,000	5.2
		50,000	4.6
		60,000	5.1
		70,000	4.7
		80,000	5.6
		90,000	4.5

100,000	5.8
500,000	8
1,000,000	9.1

Power and type I error defined using F statistic and Wald test

13.4 THETA=0.167

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Power of FMR to detect an interaction (%)
α = -0.333	θ = 0.167	10,000	4.9
		20,000	6.5
		30,000	6.6
		40,000	6
		50,000	5.9
		60,000	6.4
		70,000	5.9
		80,000	6.5
		90,000	5.8
		100,000	6.6
		500,000	13.8
		1,000,000	21.7
α = 0	θ = 0.167	10,000	4.9
No mediation		20,000	6.2
		30,000	6.6
		40,000	5.7
		50,000	5.3
		60,000	5.9
		70,000	5.3
		80,000	6.2
		90,000	5.6
		100,000	6
		500,000	11.8
		1,000,000	18.8
α = 0.333	θ = 0.167	10,000	4.4
		20,000	5.9

		30,000	6.7
		40,000	5.4
		50,000	5.3
		60,000	5.3
		70,000	5.4
		80,000	5.7
		90,000	5.3
		100,000	6
		500,000	10.2
		1,000,000	15.8
α = 0.5	θ = 0.167	10,000	4.5
		20,000	5.8
		30,000	6.3
		40,000	5.8
		50,000	5.3
		60,000	5.5
		70,000	5.2
		80,000	5.9
		90,000	5.4
		100,000	6.1
		500,000	9.9
		1,000,000	14.1
α = 1	θ = 0.167	10,000	4.8
		20,000	5.9
		30,000	6.2
		40,000	5.8
		50,000	4.9
		60,000	5.4
		70,000	5.5
		80,000	5.8
		90,000	5.5

100,000	5.7
500,000	8.4
1,000,000	11.5

Power and type I error defined using F statistic and Wald test

13.5 THETA=0.333

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Power of FMR to detect an interaction (%)
α = -0.333	θ = 0.333	10,000	4.8
		20,000	6.7
		30,000	6.8
		40,000	6.2
		50,000	6.7
		60,000	7.2
		70,000	6.3
		80,000	6.5
		90,000	7.1
		100,000	7.3
		500,000	22.5
		1,000,000	37
α = 0	θ = 0.333	10,000	4.5
No mediation		20,000	6.1
		30,000	6.4
		40,000	5.9
		50,000	6.3
		60,000	6.9
		70,000	6.2
		80,000	6.3
		90,000	7
		100,000	7.2
		500,000	17.4
		1,000,000	28.1
α = 0.333	θ = 0.333	10,000	4.5
		20,000	5.9

		30,000	6.5
		40,000	5.8
		50,000	5.8
		60,000	6.5
		70,000	5.8
		80,000	6
		90,000	6.7
		100,000	6.8
		500,000	14.1
		1,000,000	21.8
α = 0.5	θ = 0.333	10,000	4.8
		20,000	5.4
		30,000	6.7
		40,000	5.7
		50,000	5.6
		60,000	6.5
		70,000	6
		80,000	5.7
		90,000	6.8
		100,000	6.5
		500,000	13.2
		1,000,000	20.3
α = 1	θ = 0.333	10,000	4.9
		20,000	5.4
		30,000	6.7
		40,000	5.7
		50,000	5.8
		60,000	6.4
		70,000	5
		80,000	5.2
		90,000	6.2

100,000	5.9
500,000	10.4
1,000,000	14.8

Power and type I error defined using F statistic and Wald test

14 2SLS INSTRUMENT ASSUMES MEDIATION, Z=(Z1,Z2,Z1Z2,Z1Z1)

14.1 THETA=-0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = -0.111	10,000	-0.18706	1.076519	1.48131	0.034043	2.3	99.5
		20,000	-0.11597	0.598166	0.646303	0.018916	3.4	99.4
		30,000	-0.10924	0.454739	0.465493	0.01438	5.2	98.4
		40,000	-0.12039	0.316235	0.320225	0.01	8.8	97.6
		50,000	-0.12401	0.279135	0.281334	0.008827	8.1	97.8
		60,000	-0.11514	0.2304	0.239271	0.007286	9.1	98
		70,000	-0.11283	0.220268	0.224387	0.006965	9.5	97.3
		80,000	-0.11624	0.216432	0.206372	0.006844	10.1	97.5
		90,000	-0.10729	0.195853	0.19348	0.006193	9.3	97.3
		100,000	-0.10355	0.183141	0.18348	0.005791	10.9	97.6
		500,000	-0.10763	0.079258	0.076689	0.002506	30.9	94.8
		1,000,000	-0.11182	0.053775	0.054206	0.001701	56.4	95.4
α = 0	θ = -0.111	10,000	-0.20216	0.986655	1.498846	0.031201	3.7	99.1
No mediation		20,000	-0.12065	0.74251	0.979235	0.02348	4.1	99

		30,000	-0.13328	0.72618	0.786817	0.022964	5.7	98.3
		40,000	-0.14241	0.433761	0.456131	0.013717	8.1	97.9
		50,000	-0.14925	0.334484	0.339586	0.010577	8.8	97.7
		60,000	-0.12349	0.295504	0.306463	0.009345	8.9	98.1
		70,000	-0.11151	0.255225	0.267764	0.008071	9.9	98.1
		80,000	-0.11771	0.304805	0.27821	0.009639	10.2	98.3
		90,000	-0.10535	0.229623	0.223587	0.007261	8.9	98.2
		100,000	-0.10737	0.208313	0.205176	0.006587	10.5	98.1
		500,000	-0.10839	0.086107	0.083045	0.002723	29.7	94.5
		1,000,000	-0.11173	0.057225	0.05864	0.00181	49.6	96
α = 0.333	θ = -0.111	10,000	-0.21154	0.765203	1.298475	0.024198	5.1	99
		20,000	-0.16806	0.575466	0.806974	0.018198	5.8	99.2
		30,000	-0.15945	0.840079	1.161619	0.026566	6.8	98.3
		40,000	-0.14832	0.417362	0.511085	0.013198	10	98.7
		50,000	-0.15869	0.52521	0.466656	0.016609	9.8	97.3
		60,000	-0.1373	0.353551	0.368441	0.01118	10.6	98.6
		70,000	-0.11488	0.340849	0.356105	0.010779	12	98
		80,000	-0.12547	0.227594	0.245195	0.007197	11.4	98.5
		90,000	-0.10681	0.255881	0.259467	0.008092	12	97.9
		100,000	-0.12069	0.357219	0.293045	0.011296	13.1	98.2

		500,000	-0.10922	0.081828	0.079741	0.002588	32.8	95.6
		1,000,000	-0.11149	0.054341	0.055932	0.001718	53	95.2
α = 0.5	θ = -0.111	10,000	-0.1875	0.699966	1.109288	0.022135	5.5	99.1
		20,000	-0.16198	0.465365	0.593426	0.014716	6.5	98.7
		30,000	-0.16132	0.604987	0.789674	0.019131	8.7	98.2
		40,000	-0.14376	0.358825	0.423346	0.011347	10.7	98.8
		50,000	-0.14444	0.34384	0.382541	0.010873	10.8	97.2
		60,000	-0.14044	0.279346	0.309524	0.008834	12.2	98.5
		70,000	-0.11983	0.287092	0.290708	0.009079	12.5	97.9
		80,000	-0.12279	0.242507	0.267138	0.007669	13.5	98.8
		90,000	-0.1048	0.223925	0.234768	0.007081	13.4	97.7
		100,000	-0.1122	0.206471	0.199921	0.006529	14.2	98.1
		500,000	-0.10963	0.076283	0.075222	0.002412	35.8	95.8
		1,000,000	-0.11126	0.051235	0.052565	0.00162	59.5	95.2
α = 1	θ = -0.111	10,000	-0.18726	0.490068	0.950795	0.015497	9.8	98.6
		20,000	-0.14977	0.397464	0.608196	0.012569	10.5	98.3
		30,000	-0.14452	0.364937	0.491593	0.01154	15	97.8
		40,000	-0.13845	0.305051	0.36495	0.009647	15.6	98
		50,000	-0.13884	0.25266	0.3258	0.00799	18.8	96.9
		60,000	-0.12785	0.262517	0.296885	0.008302	17.4	98

70,000	-0.12724	0.495161	0.495209	0.015658	17.9	97.8
80,000	-0.12058	0.228902	0.234561	0.007239	19.9	97.9
90,000	-0.10064	0.249745	0.248568	0.007898	20.9	96.7
100,000	-0.11763	0.162328	0.163181	0.005133	23.2	97.7
500,000	-0.11067	0.058644	0.059315	0.001854	52	95.3
1,000,000	-0.11069	0.040609	0.041169	0.001284	76.9	95.7

14.2 THETA=0

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Type I error of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = 0	10,000	-0.03339	1.028665	1.436209	0.032529	0.1	99.9
		20,000	0.005382	0.601347	0.642348	0.019016	0.3	99.7
		30,000	0.001548	0.441551	0.454041	0.013963	0.8	99.2
		40,000	-0.00575	0.310096	0.312888	0.009806	1.6	98.4
		50,000	-0.01317	0.276796	0.276383	0.008753	1.9	98.1
		60,000	-5.92E-05	0.224856	0.23396	0.007111	1.6	98.4
		70,000	-0.00413	0.214716	0.219423	0.00679	2	98
		80,000	-0.0034	0.20984	0.201842	0.006636	2.5	97.5
		90,000	0.001843	0.188239	0.188744	0.005953	2.4	97.6
		100,000	0.005428	0.179205	0.179321	0.005667	2	98
		500,000	0.003899	0.078714	0.075032	0.002489	5.1	94.9
		1,000,000	-0.00128	0.052679	0.05307	0.001666	4.5	95.5
α = 0	θ = 0	10,000	-0.01961	1.010714	1.537807	0.031962	0	100
No mediation		20,000	0.024202	0.689174	0.90307	0.021794	0.4	99.6

		30,000	-0.00248	0.67781	0.752259	0.021434	0.2	99.8
		40,000	-0.01519	0.43524	0.456942	0.013763	0.7	99.3
		50,000	-0.02921	0.344766	0.343028	0.010902	0.8	99.2
		60,000	-0.00605	0.306988	0.308644	0.009708	0.8	99.2
		70,000	-0.00076	0.239685	0.253623	0.007579	1.2	98.8
		80,000	-0.00409	0.281678	0.264636	0.008907	1.3	98.7
		90,000	0.005483	0.21645	0.214791	0.006845	1.7	98.3
		100,000	0.003484	0.203867	0.198973	0.006447	1.3	98.7
		500,000	0.003411	0.084527	0.080513	0.002673	6	94
		1,000,000	-0.0014	0.056028	0.056911	0.001772	4.6	95.4
α = 0.333	θ = 0	10,000	-0.01446	0.773106	1.325373	0.024448	0.1	99.9
		20,000	-0.00123	0.533524	0.757063	0.016871	0.4	99.6
		30,000	-0.00839	0.790478	1.116682	0.024997	0	100
		40,000	-0.00612	0.444997	0.536436	0.014072	0.4	99.6
		50,000	-0.02799	0.483952	0.445904	0.015304	0.3	99.7
		60,000	-0.01033	0.336787	0.353051	0.01065	0.4	99.6
		70,000	0.002013	0.264741	0.299273	0.008372	0.3	99.7
		80,000	-0.00888	0.230955	0.237422	0.007303	0.9	99.1
		90,000	0.007127	0.257261	0.255802	0.008135	0.4	99.6
		100,000	-0.00234	0.265298	0.249449	0.008389	0.8	99.2

		500,000	0.002546	0.078625	0.076435	0.002486	5.2	94.8
		1,000,000	-0.00113	0.0529	0.053714	0.001673	4.7	95.3
α = 0.5	θ = 0	10,000	0.004062	0.664833	1.066352	0.021024	0.1	99.9
		20,000	0.004738	0.439981	0.557946	0.013913	0.4	99.6
		30,000	-0.01706	0.531479	0.720319	0.016807	0	100
		40,000	-0.00276	0.346847	0.402602	0.010968	0.2	99.8
		50,000	-0.01849	0.357505	0.486435	0.011305	0.2	99.8
		60,000	-0.01426	0.270824	0.296974	0.008564	0.4	99.6
		70,000	0.000592	0.253393	0.269395	0.008013	0.3	99.7
		80,000	-0.00565	0.23951	0.260929	0.007574	0.7	99.3
		90,000	0.010253	0.206037	0.21955	0.006515	0.5	99.5
		100,000	0.004624	0.192501	0.189997	0.006087	1	99
		500,000	0.001997	0.072593	0.071647	0.002296	4.7	95.3
		1,000,000	-0.00083	0.049471	0.050173	0.001564	4.7	95.3
α = 1	θ = 0	10,000	-0.0037	0.467823	0.905348	0.014794	0.1	99.9
		20,000	0.018115	0.35524	0.513046	0.011234	0.4	99.6
		30,000	0.003369	0.373595	0.510629	0.011814	0	100
		40,000	-0.00253	0.306245	0.35916	0.009684	0.4	99.6
		50,000	-0.00935	0.23839	0.295923	0.007539	0.2	99.8
		60,000	-0.00144	0.239451	0.279512	0.007572	0.3	99.7

70,000	-0.00055	0.391558	0.40733	0.012382	0.6	99.4
80,000	-0.00416	0.207396	0.209482	0.006558	0.7	99.3
90,000	0.012204	0.197349	0.211747	0.006241	0.5	99.5
100,000	-0.00019	0.150885	0.152935	0.004771	1.1	98.9
500,000	0.000492	0.055034	0.05541	0.00174	4	96
1,000,000	-3.96E-05	0.037923	0.038476	0.001199	4.1	95.9

14.3 THETA=0.111

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = 0.111	10,000	0.120269	1.010892	1.417101	0.031967	2.4	99.5
		20,000	0.126731	0.628127	0.658104	0.019863	3.7	99.2
		30,000	0.112331	0.451049	0.464658	0.014263	4.3	98.9
		40,000	0.108884	0.318172	0.319714	0.010061	6.6	97.8
		50,000	0.097668	0.290143	0.287094	0.009175	7.5	97.5
		60,000	0.115022	0.230645	0.239489	0.007294	7.8	97.6
		70,000	0.104572	0.21962	0.224498	0.006945	6.8	98
		80,000	0.109442	0.213109	0.206112	0.006739	10.5	97.2
		90,000	0.110973	0.190894	0.192683	0.006037	10.4	97
		100,000	0.114406	0.183568	0.183199	0.005805	10.6	97.5
		500,000	0.115423	0.081204	0.07659	0.002568	35.8	94.4
		1,000,000	0.109258	0.053775	0.054225	0.001701	51.9	95.4
α = 0	θ = 0.111	10,000	0.162937	1.06187	1.605094	0.033579	3	99.5
No mediation		20,000	0.169053	0.680691	0.876537	0.021525	4.7	99

		30,000	0.128316	0.67302	0.75667	0.021283	4.9	98.9
		40,000	0.112028	0.464982	0.481922	0.014704	6.7	98.4
		50,000	0.090828	0.378685	0.365357	0.011975	7.1	99.4
		60,000	0.11139	0.341494	0.327837	0.010799	8	98.1
		70,000	0.11	0.253138	0.265954	0.008005	6.7	98.5
		80,000	0.109532	0.274905	0.266797	0.008693	11.3	96.9
		90,000	0.11632	0.217853	0.22034	0.006889	11	97.9
		100,000	0.114334	0.211933	0.205414	0.006702	11.4	97.9
		500,000	0.115209	0.087647	0.082886	0.002772	32.3	94.4
		1,000,000	0.108941	0.058118	0.058694	0.001838	46.9	95
$\alpha = 0.333$	$\theta = 0.111$	10,000	0.182614	0.823528	1.381805	0.026042	4	99.6
		20,000	0.165589	0.529343	0.752904	0.016739	5.2	98.9
		30,000	0.142673	0.76978	1.102976	0.024343	6.6	99
		40,000	0.13608	0.499585	0.584051	0.015798	7.8	98.4
		50,000	0.102723	0.460935	0.44649	0.014576	7.7	99.6
		60,000	0.116631	0.34323	0.363245	0.010854	9.6	98.2
		70,000	0.118904	0.246106	0.27617	0.007783	9.1	98.7
		80,000	0.107707	0.25778	0.257697	0.008152	14	97.6
		90,000	0.121068	0.291152	0.275773	0.009207	12.2	98
		100,000	0.11602	0.213249	0.223246	0.006744	14.6	97.5

		500,000	0.114313	0.081735	0.079503	0.002585	34.4	94.9
		1,000,000	0.10923	0.055636	0.056011	0.001759	51.1	94.9
α = 0.5	θ = 0.111	10,000	0.195619	0.655741	1.049814	0.020736	5	99.2
		20,000	0.171457	0.454953	0.587361	0.014387	5.9	98.7
		30,000	0.127195	0.518937	0.704378	0.01641	8.2	99
		40,000	0.138243	0.366566	0.418836	0.011592	9.5	98.4
		50,000	0.107457	0.466333	0.629951	0.014747	9	99.3
		60,000	0.11191	0.294334	0.32035	0.009308	11.1	98.3
		70,000	0.121018	0.250276	0.271187	0.007914	10.9	98.6
		80,000	0.111488	0.262529	0.281733	0.008302	15.3	97
		90,000	0.125309	0.208127	0.223658	0.006582	14.9	98
		100,000	0.121444	0.199154	0.197452	0.006298	16.7	97.2
		500,000	0.113621	0.075993	0.074991	0.002403	38.7	95.2
		1,000,000	0.109603	0.052219	0.05263	0.001651	56.7	95.4
α = 1	θ = 0.111	10,000	0.179866	0.479524	0.92671	0.015164	9	99.1
		20,000	0.186004	0.383159	0.591125	0.012117	11.1	98.3
		30,000	0.151255	0.418301	0.57858	0.013228	15.2	98.7
		40,000	0.133393	0.331091	0.390104	0.01047	16.8	98.3
		50,000	0.120147	0.308455	0.394251	0.009754	15.1	98.8
		60,000	0.124971	0.269574	0.295066	0.008525	17.3	98.2

70,000	0.126138	0.323431	0.355051	0.010228	17.4	98.4
80,000	0.112269	0.225509	0.228095	0.007131	21.4	96.5
90,000	0.125045	0.194023	0.217156	0.006136	22.1	97.1
100,000	0.117242	0.163908	0.164104	0.005183	24.9	97.1
500,000	0.111657	0.060065	0.059355	0.001899	52.5	96.4
1,000,000	0.110615	0.040422	0.041157	0.001278	74.7	95.8

14.4 THETA=0.167

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = 0.167	10,000	0.197331	1.013906	1.416338	0.032063	5.4	99.2
		20,000	0.187588	0.649627	0.673347	0.020543	8.1	98.4
		30,000	0.167889	0.464047	0.477021	0.014674	9.3	98.4
		40,000	0.166374	0.327316	0.328466	0.010351	12.1	97.3
		50,000	0.153254	0.302185	0.297196	0.009556	13.1	97.1
		60,000	0.172735	0.237619	0.246105	0.007514	15.6	97.5
		70,000	0.159085	0.225859	0.230669	0.007142	14	97.9
		80,000	0.166032	0.218373	0.211477	0.006906	18.7	96.7
		90,000	0.165702	0.196023	0.197819	0.006199	17.8	96.7
		100,000	0.169058	0.188743	0.188055	0.005969	20.7	96.9
		500,000	0.171353	0.083522	0.078537	0.002641	60.1	94.3
		1,000,000	0.164694	0.05512	0.055633	0.001743	84.4	95.7
α = 0	θ = 0.167	10,000	0.254486	1.096615	1.650447	0.034678	7.7	98.8
No mediation		20,000	0.241696	0.694182	0.884161	0.021952	9.7	98.3

		30,000	0.193913	0.687636	0.787755	0.021745	11.9	98.2
		40,000	0.175827	0.489114	0.502759	0.015467	14.4	97.3
		50,000	0.151028	0.402886	0.382987	0.01274	14.7	98
		60,000	0.170286	0.365595	0.343382	0.011561	16.5	97
		70,000	0.165544	0.269808	0.27966	0.008532	14.8	98.1
		80,000	0.166513	0.278154	0.274003	0.008796	19.4	95.9
		90,000	0.171905	0.22407	0.228294	0.007086	21.1	97.7
		100,000	0.169925	0.220342	0.213114	0.006968	21.8	97.1
		500,000	0.171276	0.090857	0.085828	0.002873	53.7	94.2
		1,000,000	0.164275	0.060318	0.060837	0.001907	77.3	95.4
$\alpha = 0.333$	$\theta = 0.167$	10,000	0.281449	0.862732	1.423515	0.027282	9.7	98.5
		20,000	0.24925	0.542047	0.767064	0.017141	13	97.7
		30,000	0.218431	0.771141	1.106324	0.024386	16.8	97.8
		40,000	0.207394	0.534682	0.617173	0.016908	18.8	97
		50,000	0.168274	0.45721	0.454628	0.014458	19.3	98.1
		60,000	0.180303	0.35498	0.376225	0.011225	19.8	96.8
		70,000	0.177525	0.263748	0.30285	0.00834	18.4	97.8
		80,000	0.166177	0.278174	0.275033	0.008797	23.7	95.4
		90,000	0.178209	0.317524	0.292757	0.010041	24.6	96.8
		100,000	0.175376	0.212486	0.218545	0.006719	27.1	95.7

		500,000	0.170365	0.08551	0.083281	0.002704	56.3	94.7
		1,000,000	0.164576	0.058432	0.058739	0.001848	79.2	95.3
α = 0.5	θ = 0.167	10,000	0.291685	0.661444	1.050285	0.020917	11.7	98.5
		20,000	0.255066	0.476864	0.614482	0.01508	15.6	97.5
		30,000	0.199539	0.537757	0.711098	0.017005	18.8	97.6
		40,000	0.208956	0.387175	0.444912	0.012244	22.2	97
		50,000	0.17062	0.540904	0.719625	0.017105	21.9	97.9
		60,000	0.175187	0.316329	0.342877	0.010003	21.7	97.1
		70,000	0.181411	0.260993	0.28036	0.008253	20.9	97.1
		80,000	0.170233	0.282157	0.299607	0.008923	25.6	95
		90,000	0.183009	0.216731	0.233047	0.006854	26.1	96.5
		100,000	0.180029	0.209878	0.207586	0.006637	29.4	95.4
		500,000	0.1696	0.080158	0.079073	0.002535	61.2	95.3
		1,000,000	0.164985	0.055127	0.055536	0.001743	82.4	95.4
α = 1	θ = 0.167	10,000	0.271922	0.497693	0.95017	0.015738	18.8	97.7
		20,000	0.2702	0.420568	0.645974	0.0133	23.7	96.4
		30,000	0.22542	0.451278	0.623109	0.014271	27.6	96.7
		40,000	0.201557	0.351069	0.416972	0.011102	29.9	96.5
		50,000	0.185087	0.362523	0.455346	0.011464	29.2	96.7
		60,000	0.188366	0.300819	0.319382	0.009513	31	96.7

70,000	0.189674	0.310527	0.337741	0.00982	33.4	97
80,000	0.170657	0.247531	0.252153	0.007828	35.5	94.8
90,000	0.181635	0.21289	0.228958	0.006732	36.6	95.6
100,000	0.176135	0.178366	0.177016	0.00564	40.8	94.7
500,000	0.167407	0.06535	0.06394	0.002067	74.4	96.1
1,000,000	0.166108	0.043419	0.044296	0.001373	92.9	95.7

14.5 THETA=0.333

Modelled mediator coefficient	Modelled interaction coefficient	Sample size	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power of 2sls estimator (%)	Coverage of 2sls estimator (%)
α = -0.333	θ = 0.333	10,000	0.428057	1.069232	1.458777	0.033812	16.6	97.1
		20,000	0.369795	0.740297	0.749296	0.02341	22.4	95.5
		30,000	0.334231	0.53054	0.53955	0.016777	27.1	96.8
		40,000	0.338499	0.371777	0.373049	0.011757	31.8	95.6
		50,000	0.319681	0.354974	0.342252	0.011225	33.1	95.3
		60,000	0.34553	0.272033	0.278466	0.008602	37.8	96.1
		70,000	0.322296	0.257233	0.261428	0.008134	37.8	97.1
		80,000	0.335462	0.246562	0.238683	0.007797	42.4	95.2
		90,000	0.329562	0.224228	0.223987	0.007091	44.2	96.9
		100,000	0.332689	0.214283	0.212504	0.006776	46.3	96.5
		500,000	0.338807	0.094062	0.088349	0.002975	92.9	94.2
		1,000,000	0.330671	0.061866	0.062674	0.001956	99.7	95.9
α = 0	θ = 0.333	10,000	0.528586	1.23056	1.833369	0.038914	22	94.1
No mediation		20,000	0.45919	0.796727	0.981171	0.025195	28	93.2

		30,000	0.39031	0.79043	0.924352	0.024996	31.8	94.7
		40,000	0.366844	0.58864	0.59584	0.018614	35.8	94
		50,000	0.331268	0.495326	0.457067	0.015664	36.5	93.9
		60,000	0.346623	0.45599	0.408503	0.01442	38.5	93.2
		70,000	0.331844	0.347033	0.341126	0.010974	38.6	95.3
		80,000	0.337116	0.312211	0.314922	0.009873	41.4	92.4
		90,000	0.338328	0.261122	0.268376	0.008257	43.8	94.7
		100,000	0.336367	0.259293	0.250686	0.0082	45.6	95.2
		500,000	0.339141	0.105754	0.100298	0.003344	87.4	93.2
		1,000,000	0.329946	0.070574	0.071263	0.002232	98.2	95.8
α = 0.333	θ = 0.333	10,000	0.577363	1.022258	1.624879	0.032327	30.9	92.8
		20,000	0.499734	0.630736	0.848212	0.019946	36.4	92.3
		30,000	0.44525	0.820973	1.148082	0.025961	40	91.9
		40,000	0.420911	0.660508	0.747598	0.020887	41	92.9
		50,000	0.364533	0.478234	0.51281	0.015123	41.3	92.1
		60,000	0.370939	0.41781	0.436842	0.013212	42.5	91.9
		70,000	0.353037	0.389211	0.42966	0.012308	43	93.6
		80,000	0.341237	0.357078	0.345618	0.011292	46.1	90.3
		90,000	0.34929	0.419244	0.365197	0.013258	48.1	92.4
		100,000	0.353088	0.304584	0.306412	0.009632	50.5	92.4

		500,000	0.338183	0.10356	0.101379	0.003275	84.2	93.3
		1,000,000	0.330284	0.071051	0.071642	0.002247	97.2	95.1
α = 0.5	θ = 0.333	10,000	0.579308	0.716971	1.088362	0.022673	34.8	91.7
		20,000	0.505395	0.585861	0.735026	0.018527	41.6	92
		30,000	0.41614	0.674192	0.859305	0.02132	42.1	91.1
		40,000	0.420671	0.479873	0.554046	0.015175	44.5	91.5
		50,000	0.359729	0.798667	1.031265	0.025256	44.8	91.7
		60,000	0.36464	0.409033	0.433782	0.012935	45.3	91.3
		70,000	0.362229	0.330984	0.343779	0.010467	45.7	92.8
		80,000	0.346116	0.362177	0.377255	0.011453	47.8	90.1
		90,000	0.355765	0.266053	0.285936	0.008413	51.3	91.4
		100,000	0.355435	0.263591	0.258795	0.008335	53.6	91.1
		500,000	0.337203	0.099789	0.098314	0.003156	86	93.5
		1,000,000	0.330799	0.06827	0.069106	0.002159	97.5	94.9
α = 1	θ = 0.333	10,000	0.547539	0.591245	1.054379	0.018697	43.7	88.8
		20,000	0.522284	0.587953	0.879207	0.018593	51.3	89.3
		30,000	0.447471	0.577175	0.791724	0.018252	51.9	87.6
		40,000	0.40564	0.432167	0.523054	0.013666	53.5	88.5
		50,000	0.37952	0.555151	0.665846	0.017555	54.5	90.6
		60,000	0.37817	0.429324	0.456015	0.013576	54.8	90.2

70,000	0.379901	0.369908	0.418037	0.011698	55.6	91.1
80,000	0.34547	0.344038	0.351551	0.010879	55.2	89.1
90,000	0.351067	0.318713	0.339428	0.010079	59.4	90.5
100,000	0.352462	0.241217	0.235006	0.007628	60.8	89.7
500,000	0.334322	0.087996	0.084452	0.002783	90.8	93.7
1,000,000	0.332255	0.057	0.058392	0.001802	98.9	95.3

15 ALLOWING FOR PLEIOTROPIC EFFECTS OF THE INSTRUMENTS: Z=(Z1,Z2,Z1Z2,Z1Z1), N=500,000

15.1 Standalone model – no pleiotropic effect

Modelled mediator coefficient, α	Modelled interaction coefficient, θ	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power/ Type I error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	-0.105	0.064	0.077	0.002	29.8	95.7
0		-0.104	0.073	0.084	0.002	27.8	95.9
0.333		-0.105	0.071	0.081	0.002	31.8	96.2
0.5		-0.105	0.067	0.076	0.002	35.6	96.2
1		-0.108	0.052	0.060	0.002	50.7	96
-0.333	0	0.005	0.065	0.075	0.002	4.2 [type I error]	95.8
0		0.006	0.074	0.081	0.002	4 [type I error]	96
0.333		0.005	0.071	0.077	0.002	3.8 [type I error]	96.2
0.5		0.004	0.065	0.073	0.002	3.8 [type I error]	96.2
1		0.002	0.048	0.056	0.002	3.2 [type I error]	96.8
-0.333	0.111	0.115	0.069	0.077	0.002	33.8	95.5
0		0.116	0.080	0.083	0.003	32.4	95.6
0.333		0.115	0.075	0.080	0.002	34.9	96.6
0.5		0.114	0.068	0.076	0.002	39.2	96.6
1		0.111	0.050	0.060	0.002	51.8	96.4
-0.333	0.167	0.171	0.072	0.079	0.002	59.7	95.1

0		0.171	0.084	0.086	0.003	54.3	96.3
0.333		0.170	0.078	0.084	0.002	56.4	96.6
0.5		0.169	0.071	0.080	0.002	60.3	96.1
1		0.166	0.054	0.065	0.002	72.4	96.4
-0.333	0.333	0.337	0.085	0.089	0.003	94.5	94.2
0		0.336	0.101	0.101	0.003	85.7	95
0.333		0.334	0.094	0.103	0.003	84.3	95.7
0.5		0.333	0.086	0.100	0.003	85.3	95.7
1		0.331	0.071	0.086	0.002	89.6	94.8

15.2 Standalone model – pleiotropic effect

Modelled mediator coefficient, α	Modelled interaction coefficient, θ	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power/ Type I error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	-0.099	0.142	0.176	0.004	10.7	97.9
0		-0.101	0.105	0.120	0.003	18.5	96.9
0.333		-0.104	0.076	0.087	0.002	29.2	96
0.5		-0.105	0.066	0.076	0.002	34.8	96.4
1		-0.106	0.048	0.055	0.002	54	96.2
-0.333	0	0.010	0.143	0.172	0.005	2 [type I error]	98
0		0.009	0.108	0.116	0.003	3.2 [type I error]	96.8
0.333		0.006	0.077	0.083	0.002	3.4 [type I error]	96.6
0.5		0.005	0.067	0.072	0.002	3.5 [type I error]	96.5
1		0.003	0.047	0.051	0.001	3.6 [type I error]	96.4
-0.333	0.111	0.120	0.154	0.175	0.005	13.8	97.3
0		0.118	0.116	0.119	0.004	20.1	96.6
0.333		0.116	0.083	0.086	0.003	32.4	96.8
0.5		0.115	0.072	0.075	0.002	39.3	96.7
1		0.113	0.051	0.055	0.002	58.5	96.5
-0.333	0.167	0.176	0.163	0.180	0.005	22.5	96.3

0		0.173	0.123	0.123	0.004	36.4	96.7
0.333		0.171	0.088	0.090	0.003	52.2	96.8
0.5		0.170	0.076	0.080	0.002	59.9	96.5
1		0.168	0.054	0.059	0.002	78.1	96.6
-0.333	0.333	0.341	0.197	0.203	0.006	48.3	94.8
0		0.338	0.147	0.145	0.005	67.8	94.7
0.333		0.335	0.107	0.111	0.003	80.7	95.1
0.5		0.334	0.093	0.099	0.003	84.9	95.1
1		0.333	0.069	0.078	0.002	93.9	95.1

16 ALLOWING FOR PLEIOTROPIC EFFECTS OF THE INSTRUMENTS: FACTORIAL MR, N=500,000

16.1 Standalone model – no pleiotropic effect

Modelled mediator coefficient, α	Modelled interaction coefficient, θ	Power/Type I error of FMR to detect an interaction (%)
-0.333	-0.111	17.7
0		15.3
0.333		13.2
0.5		12.7
1		10.2
-0.333	0	5.5 [type I error]
0		5.5 [type I error]
0.333		5.5 [type I error]
0.5		5.5 [type I error]
1		5.5 [type I error]
-0.333	0.111	11.7
0		11
0.333		9.7
0.5		9.1
1		8.4
-0.333	0.167	15.4
0		13.7
0.333		11.8
0.5		10.8
1		9.4
-0.333	0.333	22.3
0		17.8
0.333		15.1
0.5		13.8
1		10.6

Power and type I error defined using F statistic and Wald test

16.2 Standalone model – pleiotropic effect

Modelled mediator coefficient, α	Modelled interaction coefficient, θ	Power/Type I error of FMR to detect an interaction (%)
-0.333	-0.111	6.4
0		10.1
0.333		13.3
0.5		15
1		19.1
-0.333	0	5.5 [type I error]
0		5.5 [type I error]
0.333		5.5 [type I error]
0.5		5.5 [type I error]
1		5.5 [type I error]
-0.333	0.111	6.2
0		7.9
0.333		9.5
0.5		10.2
1		12.5
-0.333	0.167	7.3
0		8.8
0.333		11.2
0.5		12.6
1		15.3
-0.333	0.333	9.1
0		12.1
0.333		14.4
0.5		15.6
1		18.2

Power and type I error defined using F statistic and Wald test

17 INCREASING THE VARIANCE EXPLAINED BY THE INSTRUMENTS, N=50,000, 2SLS INSTRUMENT ASSUMES MEDIATION

Modelled mediator coefficient, α	Modelled interaction coefficient, θ	Mean 2sls interaction effect estimate	Standard deviation of 2sls estimate	Mean estimated standard error of 2sls estimate	Standard error of the bias (standard deviation of 2sls estimate/sqrt(1000))	Power/ Type I error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	-0.109	0.050	0.049	0.002	61.9	94.9
0		-0.109	0.055	0.053	0.002	55.6	94.9
0.333		-0.109	0.052	0.051	0.002	58.8	95.8
0.5		-0.109	0.049	0.047	0.002	64	95.4
1		-0.109	0.038	0.036	0.001	81.2	95.1
-0.333	0	0.001	0.048	0.048	0.002	4.4	95.6
0		0.001	0.052	0.052	0.002	4.6	95.4
0.333		0.001	0.049	0.048	0.002	4.8	95.2
0.5		0.001	0.046	0.045	0.001	4.9	95.1
1		0.001	0.034	0.034	0.001	4.8	95.2
-0.333	0.111	0.112	0.049	0.049	0.002	63.6	95.4
0		0.112	0.053	0.053	0.002	56	95.1
0.333		0.112	0.050	0.050	0.002	61.4	95.9
0.5		0.111	0.047	0.047	0.001	66.6	95.9
1		0.111	0.036	0.036	0.001	83.2	95.6
-0.333	0.167	0.167	0.050	0.050	0.002	89.5	95.3

0		0.167	0.055	0.055	0.002	84.5	95.5
0.333		0.167	0.053	0.053	0.002	84.3	95.5
0.5		0.167	0.050	0.050	0.002	87.1	95.7
1		0.166	0.039	0.039	0.001	95.2	96
-0.333	0.333	0.333	0.057	0.057	0.002	99.8	95.6
0		0.333	0.065	0.065	0.002	98.9	95.3
0.333		0.332	0.065	0.065	0.002	98.6	95.6
0.5		0.332	0.062	0.062	0.002	99	95.3
1		0.332	0.052	0.052	0.002	99.8	94.6

18 HETEROSKEDASTIC ROBUST STANDARD ERRORS

18.1 OLS REGRESSION, N=50,000

Modelled mediator coefficient	Modelled interaction coefficient	Mean estimated standard error of 2sls estimate	Power/Type I Error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	0.00305	100	0
-0.333	0.000	0.00284	4.6	95.4
-0.333	0.111	0.00305	100	0
-0.333	0.167	0.00330	100	0
-0.333	0.333	0.00441	100	0
0	-0.111	0.00241	100	0
0	0.000	0.00229	5.1	94.9
0	0.111	0.00241	100	0
0	0.167	0.00256	100	0
0	0.333	0.00324	100	0
0.333	-0.111	0.00187	100	0
0.333	0.000	0.00175	5.2	94.8
0.333	0.111	0.00187	100	0
0.333	0.167	0.00201	100	0
0.333	0.333	0.00262	100	0

0.5	-0.111	0.00167	100	0
0.5	0.000	0.00155	5.1	94.9
0.5	0.111	0.00167	100	0
0.5	0.167	0.00181	100	0
0.5	0.333	0.00243	100	0
1	-0.111	0.00126	100	0
1	0.000	0.00112	4.7	95.3
1	0.111	0.00126	100	0
1	0.167	0.00141	100	0
1	0.333	0.00205	100	0

18.2 OLS REGRESSION, N=500,000

Modelled mediator coefficient	Modelled interaction coefficient	Mean estimated standard error of 2sls estimate	Power/Type I Error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	0.00097	100	0
-0.333	0.000	0.00090	4.5	95.5
-0.333	0.111	0.00097	100	0
-0.333	0.167	0.00105	100	0
-0.333	0.333	0.00140	100	0

0	-0.111	0.00076	100	0
0	0.000	0.00072	3.6	96.4
0	0.111	0.00076	100	0
0	0.167	0.00081	100	0
0	0.333	0.00102	100	0
0.333	-0.111	0.00059	100	0
0.333	0.000	0.00055	4.3	95.7
0.333	0.111	0.00059	100	0
0.333	0.167	0.00063	100	0
0.333	0.333	0.00083	100	0
0.5	-0.111	0.00053	100	0
0.5	0.000	0.00049	4	96
0.5	0.111	0.00053	100	0
0.5	0.167	0.00057	100	0
0.5	0.333	0.00077	100	0
1	-0.111	0.00040	100	0
1	0.000	0.00035	5.2	94.8
1	0.111	0.00040	100	0
1	0.167	0.00045	100	0
1	0.333	0.00065	100	0

18.3 2SLS INSTRUMENT ASSUMES MEDIATION, Z=(Z1,Z2,Z1Z2,Z1Z1),N=50,000

Modelled mediator coefficient	Modelled interaction coefficient	Mean estimated standard error of 2sls estimate	Power/Type I Error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	0.283	8.1	98.1
-0.333	0.000	0.278	1.8	98.2
-0.333	0.111	0.289	7.3	97.8
-0.333	0.167	0.299	12.9	97.6
-0.333	0.333	0.344	33.5	95.5
0	-0.111	0.342	8.7	97.7
0	0.000	0.345	0.7	99.3
0	0.111	0.368	7	99.5
0	0.167	0.385	14.7	98.1
0	0.333	0.460	36.8	94.1
0.333	-0.111	0.472	9.4	97.6
0.333	0.000	0.450	0.2	99.8
0.333	0.111	0.451	7.4	99.6
0.333	0.167	0.459	19	98.4
0.333	0.333	0.517	41	92.1
0.5	-0.111	0.383	10.3	97.3

0.5	0.000	0.490	0.2	99.8
0.5	0.111	0.635	8.3	99.3
0.5	0.167	0.726	21.3	98
0.5	0.333	1.041	44.2	91.9
1	-0.111	0.328	18.2	97.1
1	0.000	0.298	0.2	99.8
1	0.111	0.397	15	98.8
1	0.167	0.459	28.9	96.8
1	0.333	0.671	54.6	90.8

18.4 2SLS INSTRUMENT ASSUMES MEDIATION, Z=(Z1,Z2,Z1Z2,Z1Z1),N=500,000

Modelled mediator coefficient	Modelled interaction coefficient	Mean estimated standard error of 2sls estimate	Power/Type I Error of 2sls estimator (%)	Coverage of 2sls estimator (%)
-0.333	-0.111	0.0768	30.9	95
-0.333	0.000	0.0751	5	95
-0.333	0.111	0.0766	35.9	94.4
-0.333	0.167	0.0786	60.1	94.3
-0.333	0.333	0.0885	92.9	94.4

0	-0.111	0.0831	29.9	94.5
0	0.000	0.0806	5.9	94.1
0	0.111	0.0830	32.3	94.4
0	0.167	0.0859	53.5	94.2
0	0.333	0.1005	87.3	93.2
0.333	-0.111	0.0799	32.5	95.6
0.333	0.000	0.0765	5	95
0.333	0.111	0.0796	34.3	94.9
0.333	0.167	0.0834	56.3	94.6
0.333	0.333	0.1017	84.2	93.4
0.5	-0.111	0.0753	35.9	95.8
0.5	0.000	0.0717	4.7	95.3
0.5	0.111	0.0751	38.8	95.5
0.5	0.167	0.0792	61.1	95.3
0.5	0.333	0.0987	86	93.5
1	-0.111	0.0594	52.1	95.4
1	0.000	0.0555	3.9	96.1
1	0.111	0.0595	52.3	96.5
1	0.167	0.0641	74.2	96
1	0.333	0.0849	90.7	93.9

19 Examination of Sanderson-Windmeijer F Statistics

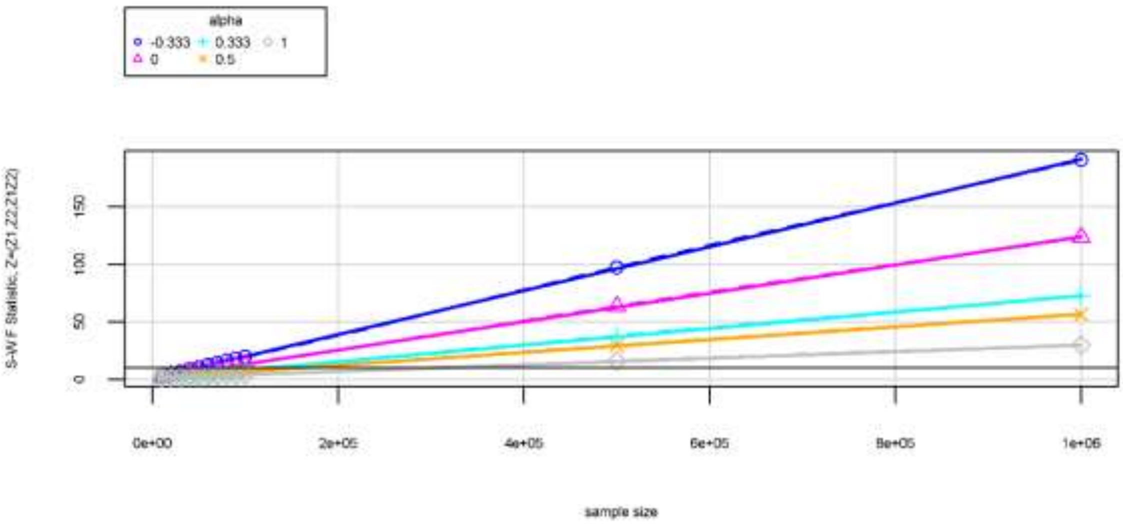
Modelled mediator coefficient	F_statistic_2SLS_assuming_no_mediation	F_statistic_2SLS_assuming_mediation	N
-0.333	2.68	1.94	10000
-0.333	4.88	3.20	20000
-0.333	6.53	4.12	30000
-0.333	9.10	5.50	40000
-0.333	10.59	6.45	50000
-0.333	12.64	7.66	60000
-0.333	14.36	8.47	70000
-0.333	16.56	9.76	80000
-0.333	17.99	10.69	90000
-0.333	19.76	11.55	1.00E+05
-0.333	97.46	55.64	5.00E+05
-0.333	191.17	109.02	1.00E+06
0	2.12	1.55	10000
0	3.54	2.28	20000
0	4.63	2.84	30000
0	6.29	3.64	40000
0	7.23	4.14	50000
0	8.60	4.81	60000
0	9.51	5.27	70000
0	11.18	6.09	80000
0	12.08	6.58	90000
0	13.28	7.13	1.00E+05

0	63.61	32.34	5.00E+05
0	123.87	62.49	1.00E+06
0.333	1.69	1.38	10000
0.333	2.51	1.87	20000
0.333	3.16	2.28	30000
0.333	4.12	2.78	40000
0.333	4.67	3.12	50000
0.333	5.48	3.50	60000
0.333	5.90	3.84	70000
0.333	7.02	4.39	80000
0.333	7.53	4.78	90000
0.333	8.27	5.20	1.00E+05
0.333	37.67	21.85	5.00E+05
0.333	72.64	41.85	1.00E+06
0.5	1.55	1.35	10000
0.5	2.18	1.78	20000
0.5	2.69	2.16	30000
0.5	3.43	2.59	40000
0.5	3.87	2.91	50000
0.5	4.49	3.22	60000
0.5	4.77	3.54	70000
0.5	5.70	4.02	80000
0.5	6.09	4.40	90000
0.5	6.68	4.80	1.00E+05
0.5	29.51	19.62	5.00E+05

0.5	56.55	37.54	1.00E+06
1	1.32	1.32	10000
1	1.63	1.71	20000
1	1.91	2.06	30000
1	2.29	2.40	40000
1	2.54	2.72	50000
1	2.85	2.94	60000
1	2.92	3.27	70000
1	3.50	3.64	80000
1	3.70	4.08	90000
1	4.03	4.47	1.00E+05
1	15.91	17.55	5.00E+05
1	29.83	33.69	1.00E+06

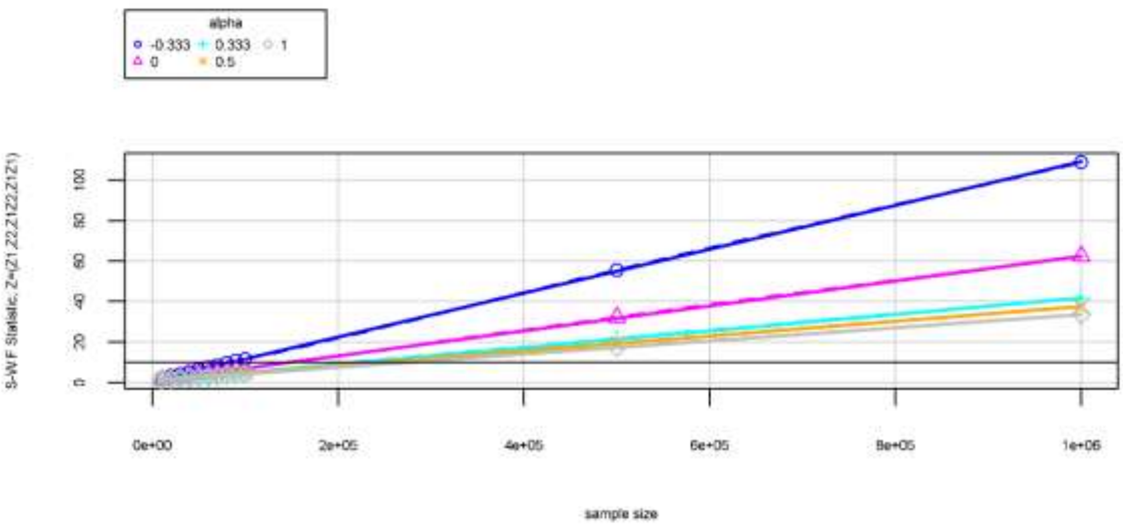
19.1 F Statistic 2SLS using Z=Z1,Z2,Z1Z2 against sample size

A plot showing the correlation of the Sanderson-Windmeijer F statistic(16) and sample size for the 2SLS estimator using Z=Z1,Z2,Z1Z2. Plot created using the *scatterplot* function from the *car* R package(9).



19.2 F statistic 2SLS using Z=Z1,Z2,Z1Z2,Z1Z1 against sample size

A plot showing the correlation of the Sanderson-Windmeijer F statistic(16) and sample size for the 2SLS estimator assuming mediation. Plot created using the *scatterplot* function from the *car* R package(9)



20 BIOBANK ILLUSTRATION

Models are described in detail in a subsequent section.

(*) adjusted for genotyping array

Model	Estimated interactive effect (kg/m2 *years)	95% Confidence interval	P-VALUE
1 OLS	0.029	(0.026,0.031)	<0.0005
2 Instrument assumes mediation Z=(Z1,Z2,Z1Z2,Z1Z1)	-0.037	(-0.357, 0.283)	0.820
3 Instrument assumes mediation Z=(Z1,Z2,Z1Z2,Z1Z1)*	-0.037	(-0.357, 0.283)	0.820
4 Instrument does not assume mediation Z=(Z1,Z2,Z1Z2)	-0.050	(-0.371,0.271)	0.761
5 Instrument does not assume mediation Z=(Z1,Z2,Z1Z2)*	-0.050	(-0.371,0.271)	0.761
8 FMR	NA	NA	0.250
9 FMR*	NA	NA	0.251

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