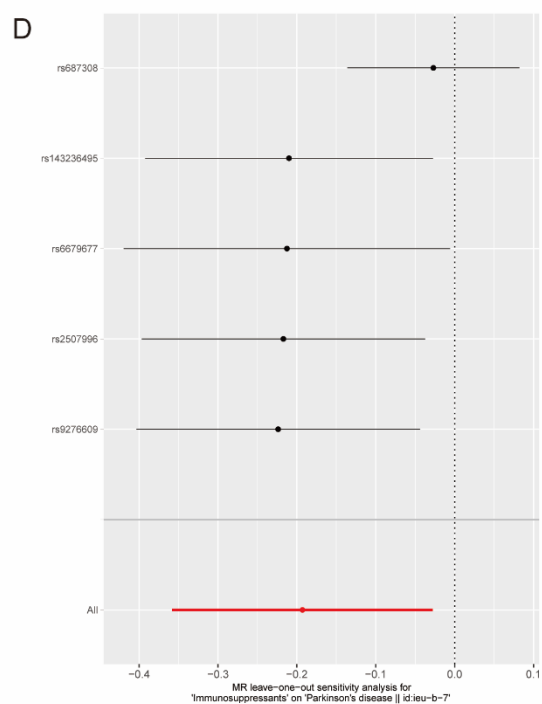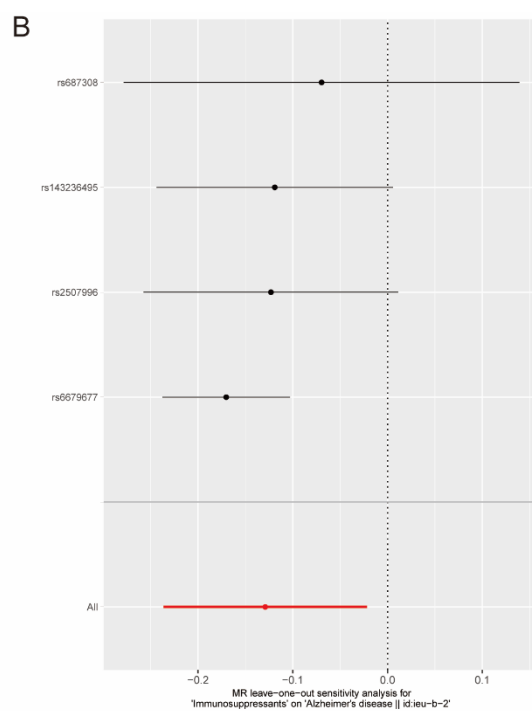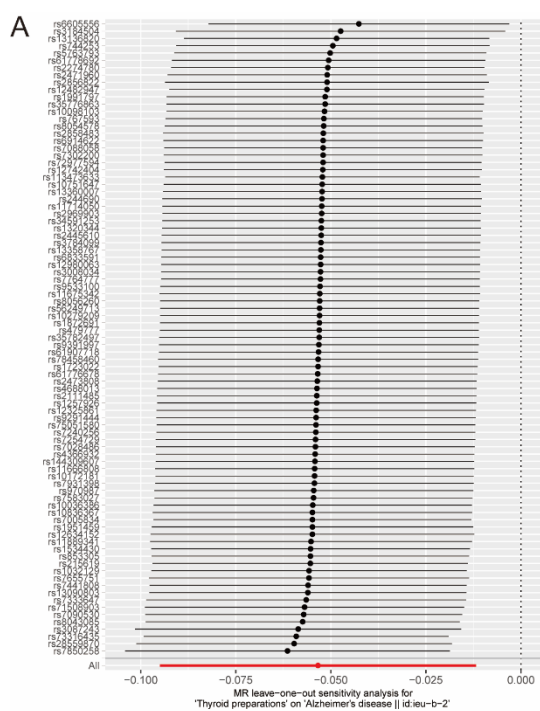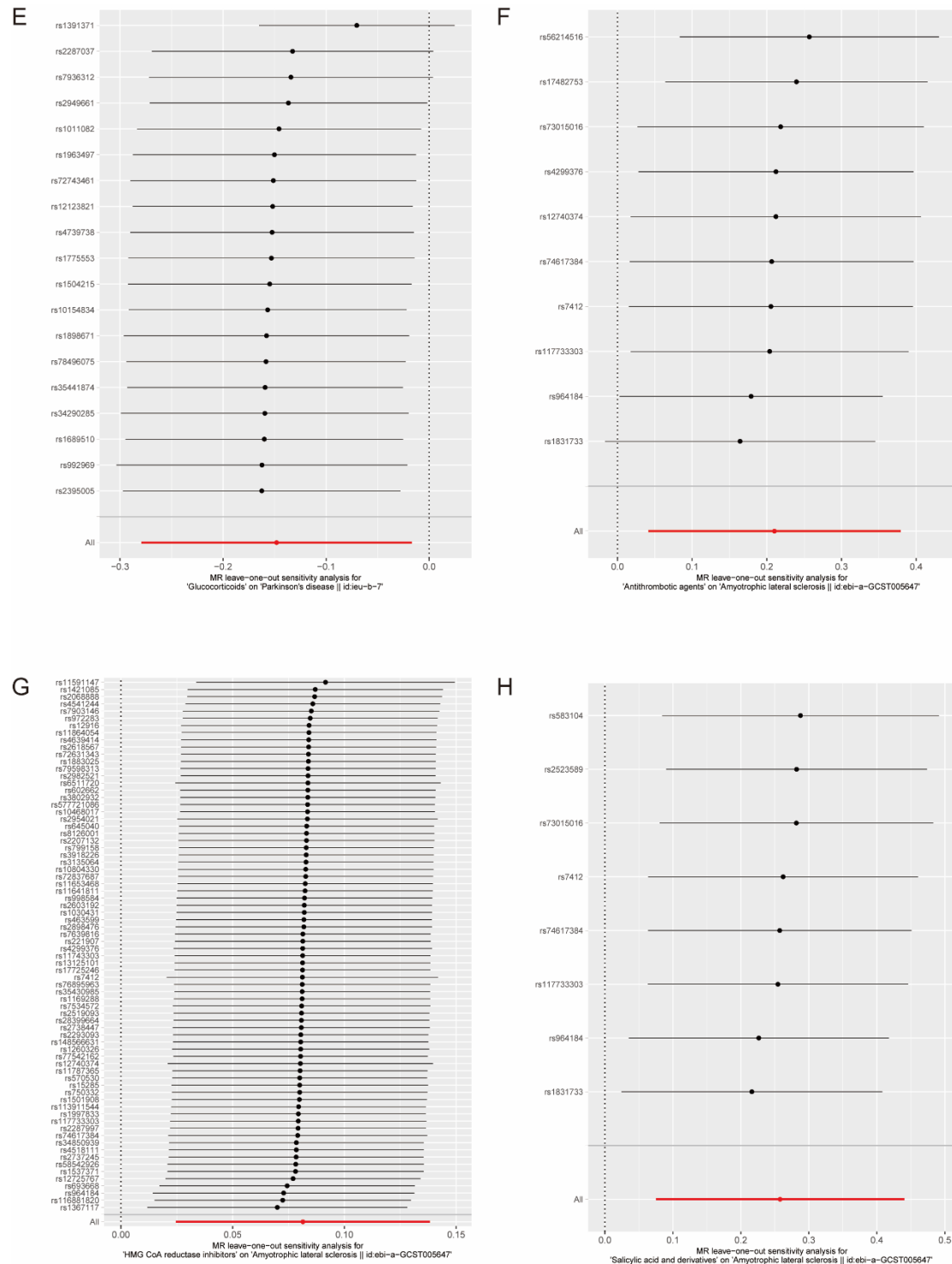**Figure S1. Three possibilities when medication use is associated with NDs:** (1) the primary disease is associated with NDs independent of medication; (2) the association between primary disease is mediated by medication use; (3) the medication is associated with NDs independent of primary disease, for example, through side effects.

A. MR leave-one-out sensitivity analysis for 'Thyroid preparations' on 'Alzheimer's disease || id:ieu-b-2'

B. MR leave-one-out sensitivity analysis for 'Immunosuppressants' on 'Alzheimer's disease || id:ieu-b-2'

C. MR leave-one-out sensitivity analysis for 'Thyroid preparations' on 'Parkinson's disease || id:ieu-b-7'

D. MR leave-one-out sensitivity analysis for 'Immunosuppressants' on 'Parkinson's disease || id:ieu-b-7'

Figure S2. Forest plots of leave-one out sensitivity analysis between medications and neurodegenerative diseases. A-B shows the causal effect between thyroid preparations, immunosuppressants and Alzheimer's disease (AD); C-E shows the causal effect between thyroid preparations, immunosuppressants, glucocorticoids and Parkinson's disease (PD); F-H shows the causal effect between antithrombotic agents, HMG CoA reductase inhibitors, salicylic acid and derivatives and Amyotrophic Lateral Sclerosis (ALS).

#The codes for MR test on associations between medications and AD

```
library(TwoSampleMR)
library(MRInstruments)
setwd("C:\\Users\\Wenjing Wang\\Documents")
```

Taking the medication category C07 as an example:

##Obtain Genetic Instruments

```
C07_exp_dat <- read_exposure_data(
    filename = "C07_summary.csv",
    sep = ",",
    snp_col = "rsid",
    phenotype_col= "Traits",
    beta_col = "effect",
    se_col = "se",
    effect_allele_col = "a1",
    other_allele_col = "a2",
    eaf_col = "a1_freq",
    pval_col = "p-value",
    samplesize_col = "n"
)
head(C07_exp_dat)


C07_exp_dat <- clump_data(C07_exp_dat)
```
or
```
C07_exp_dat <- clump_data(
    C07_exp_dat,
    clump_kb = 10000,
    clump_r2 = 0.001,
    clump_p1 = 1,
    clump_p2 = 1,
    pop = "EUR"
)
```

Extract Exposure IVs from Outcome GWAS and Harmonize

```
AD_out_dat <- extract_outcome_data(snps=C07_exp_dat$SNP,outcomes='ieu-b-2')
AD2_out_dat <- AD_out_dat[!duplicated(AD_out_dat$SNP), ]
dat <- harmonise_data(C07_exp_dat, AD2_out_dat)
```

Perform MR Analysis

```
res <- mr(dat)
res
OR <- generate_odds_ratios(res)
OR
```

Pleiotropy

```
pleiotropy <- mr_pleiotropy_test(dat)#Horizontal pleiotropy
pleiotropy

mr_presso(BetaOutcome = "beta.outcome", BetaExposure = "beta.exposure", SdOutcome = "se.outcome",
SdExposure = "se.exposure", OUTLIERtest = TRUE, DISTORTIONtest = TRUE, data = dat, NbDistribution = 1000,
SignifThreshold = 0.05)
```

Scatter plot

```
p1 <- mr_scatter_plot(res, dat)
p1[[1]]
```

Leaveoneout

```
res_loo <- mr_leaveoneout(dat)
p3 <- mr_leaveoneout_plot(res_loo)
p3[[1]]
```

Forest plot

```
dt <- read.csv("ADMedicationForest.csv")
dt$"<- paste(rep(" ",20), collapse =" ")
dt$'OR (95% CI)' <- ifelse(is.na(dt$OR), "",
                                   sprintf("%.3f (%.3f - %.3f)",
                                           dt$OR, dt$ORlci, dt$ORuci))
forest(dt[,c(1, 2, 3, 7, 8)],
        est = dt$OR,
        lower = dt$ORlci,
        upper = dt$ORuci,
        ci_column = 4,
        ref_line = 1)
```

#The codes for MR test on associations between medications and PD

```
library(TwoSampleMR)
library(MRInstruments)
setwd("C:\\Users\\Wenjing Wang\\Documents")
```

Taking the medication category C07 as an example:

##Obtain Genetic Instruments

```
C07_exp_dat <- read_exposure_data(
    filename = "C07_summary.csv",
    sep = ",",
    snp_col = "rsid",
    phenotype_col= "Traits",
```

```
    beta_col = "effect",
    se_col = "se",
    effect_allele_col = "a1",
    other_allele_col = "a2",
    eaf_col = "a1_freq",
    pval_col = "p-value",
    samplesize_col = "n"
)
head(C07_exp_dat)

C07_exp_dat <- clump_data(C07_exp_dat)
```
or
```
C07_exp_dat <- clump_data(
    C07_exp_dat,
    clump_kb = 10000,
    clump_r2 = 0.001,
    clump_p1 = 1,
    clump_p2 = 1,
    pop = "EUR"
)
```

Extract Exposure IVs from Outcome GWAS and Harmonize
```
PD_out_dat <- extract_outcome_data(snps=C07_exp_dat$SNP,outcomes='ieu-b-7')
PD2_out_dat <- PD_out_dat[!duplicated(PD_out_dat$SNP), ]
dat <- harmonise_data(C07_exp_dat, PD2_out_dat)
```

Perform MR Analysis
```
res <- mr(dat)
res
OR <- generate_odds_ratios(res)
OR
```

Pleiotropy
```
pleiotropy <- mr_pleiotropy_test(dat)#Horizontal pleiotropy
pleiotropy
```

Scatter plot
```
p1 <- mr_scatter_plot(res, dat)
p1[[1]]
```

Leaveoneout
```
res_loo <- mr_leaveoneout(dat)
p3 <- mr_leaveoneout_plot(res_loo)
p3[[1]]
```

Forest plot

```r
dt <- read.csv("PDMedicationForest.csv")
dt$"<- paste(rep(" ",20), collapse =" ")
dt$'OR (95% CI)' <- ifelse(is.na(dt$OR), "",
                           sprintf("%.3f (%.3f - %.3f)",
                                   dt$OR, dt$ORlci, dt$ORuci))

forest(dt[,c(1, 2, 3, 7, 8)],
       est = dt$OR,
       lower = dt$ORlci,
       upper = dt$ORuci,
       ci_column = 4,
       ref_line = 1)
```

#The codes for MR test on associations between medications and ALS

```r
library(TwoSampleMR)
library(MRInstruments)
setwd("C:\\Users\\Wenjing Wang\\Documents")
```

Taking the medication category C07 as an example:

##Obtain Genetic Instruments

```r
C07_exp_dat <- read_exposure_data(
    filename = "C07_summary.csv",
    sep = ",",
    snp_col = "rsid",
    phenotype_col= "Traits",
    beta_col = "effect",
    se_col = "se",
    effect_allele_col = "a1",
    other_allele_col = "a2",
    eaf_col = "a1_freq",
    pval_col = "p-value",
    samplesize_col = "n"
)
head(C07_exp_dat)


C07_exp_dat <- clump_data(C07_exp_dat)
```
or
```r
C07_exp_dat <- clump_data(
    C07_exp_dat,
    clump_kb = 10000,
    clump_r2 = 0.001,
```

```
    clump_p1 = 1,
    clump_p2 = 1,
    pop = "EUR"
)
```

Extract Exposure IVs from Outcome GWAS and Harmonize
```
ALS_out_dat <- extract_outcome_data(snps=C07_exp_dat$SNP,outcomes=' ebi-a-GCST005647')
ALS2_out_dat <- ALS_out_dat[!duplicated(ALS_out_dat$SNP), ]
dat <- harmonise_data(C07_exp_dat, ALS2_out_dat)
```

Perform MR Analysis
```
res <- mr(dat)
res
OR <- generate_odds_ratios(res)
OR
```

Pleiotropy
```
pleiotropy <- mr_pleiotropy_test(dat)#Horizontal pleiotropy
pleiotropy
```

Scatter plot
```
p1 <- mr_scatter_plot(res, dat)
p1[[1]]
```

Leaveoneout
```
res_loo <- mr_leaveoneout(dat)
p3 <- mr_leaveoneout_plot(res_loo)
p3[[1]]
```

Forest plot
```
dt <- read.csv("ALSMedicationForest.csv")
dt$" "<- paste(rep(" ",20), collapse =" ")
dt$'OR (95% CI)' <- ifelse(is.na(dt$OR), "",
                           sprintf("%.3f (%.3f - %.3f)",
                                   dt$OR, dt$ORlci, dt$ORuci))
forest(dt[,c(1, 2, 3, 7, 8)],
       est = dt$OR,
       lower = dt$ORlci,
       upper = dt$ORuci,
       ci_column = 4,
       ref_line = 1)
```