Mendelian randomisation: Critical Covid-19 as exposure for stroke (Additional analysis)

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20/02/2021

1. Preparation

Load the MendelianRandomization package for the Mendelian randomization (MR) analysis, metafor for the forestplots, cowplot for plotting and knitr and markdown for compilation.

Load the additional data file which is provided as Rdata file available from this github repository.

```
load("additional.data.Rdata")
```

This data file contains three sets of data.

```
#please uncomment to see full details
#str(additional.data$bidirectional.MR)
#str(additional.data$mvMR)
#str(additional.data$c19)
```

2. Bidirectional analysis: Considering ischemic stroke as exposure

Defining the mr_input objects which specify ischemic stroke and its subtypes as exposures for susceptibility to critical Covid-19.

```
iv.ais = additional.data$bidirectional.MR$iv_A2.ais
iv.ces = additional.data$bidirectional.MR$iv_A2.ces
iv.las = additional.data$bidirectional.MR$iv_A2.las
iv.svs = additional.data$bidirectional.MR$iv_A2.svs
mr_ais = mr_input(by = iv.ais$beta_A2,byse = iv.ais$se_A2,
 bx = iv.ais$beta_ais, bxse = iv.ais$se_ais)
mr_ces = mr_input(by = iv.ces$beta_A2,byse = iv.ces$se_A2,
 bx = iv.ces$beta_ces, bxse = iv.ces$se_ces)
mr_las = mr_input(by = iv.las$beta_A2,byse = iv.las$se_A2,
 bx = iv.las$beta_las, bxse = iv.las$se_las)
mr_svs = mr_input(by = iv.svs$beta_A2,byse = iv.svs$se_A2,
 bx = iv.svs$beta_svs, bxse = iv.svs$se_svs)
```

Compute the inverse-variance weighted (IVW) MR estimate.

```
ivw_ais = mr_ivw(mr_ais)
ivw_ces = mr_ivw(mr_ces)
ivw_las = mr_ivw(mr_las)
ivw_svs = mr_ivw(mr_svs)
```

IVW results including MR estimates, their standard error, confidence interval and heterogeneity statistics.

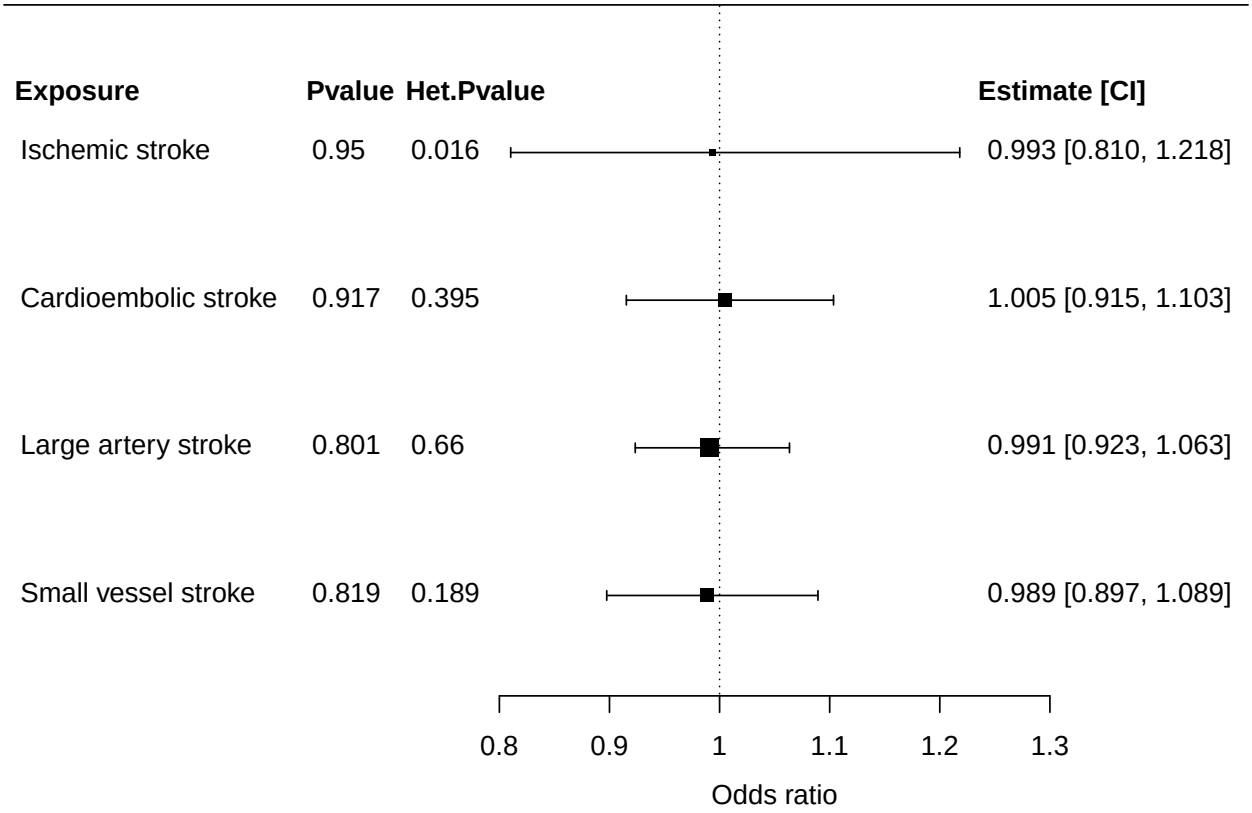
```
##                          Estimate   StdError     CILower    CIUpper    Pvalue
## Ischemic stroke      -0.006532879 0.10399887 -0.21036692 0.19730117 0.9499124
## Cardioembolic stroke  0.004988644 0.04769215 -0.08848625 0.09846354 0.9166925
## Large artery stroke  -0.009090707 0.03602362 -0.07969570 0.06151429 0.8007674
## Small vessel stroke  -0.011281832 0.04941976 -0.10814279 0.08557912 0.8194240
##                        Q-stat Heter.Pvalue
## Ischemic stroke      65.36348   0.01552107
## Cardioembolic stroke 36.59609   0.39456676
## Large artery stroke  31.03460   0.66004184
## Small vessel stroke  39.95006   0.18869552
```

In the manuscript we present the MR estimates and confidence intervalls on the odds ratio scale, where MR estimates represent the odds ratio for critical Covid-19 per unit increase in the log odds ratio of stroke phenotypes.

```
##                         Estimate   StdError   CILower  CIUpper    Pvalue   Q-stat
## Ischemic stroke      0.9934884 0.10399887 0.8102869 1.218111 0.9499124 65.36348
## Cardioembolic stroke 1.0050011 0.04769215 0.9153157 1.103474 0.9166925 36.59609
## Large artery stroke  0.9909505 0.03602362 0.9233973 1.063446 0.8007674 31.03460
## Small vessel stroke  0.9887816 0.04941976 0.8974994 1.089348 0.8194240 39.95006
##                      Heter.Pvalue
## Ischemic stroke        0.01552107
## Cardioembolic stroke   0.39456676
## Large artery stroke    0.66004184
## Small vessel stroke    0.18869552
```

Figure 3: Forest plots of the bidirectional Mendelian randomization analysis illustrating the inverse-variance weighted Mendelian randomization estimate of ischemic stroke phenotypes (ischemic stroke, cardioembolic stroke, large artery stroke and small vessel stroke) as exposures on susceptibility to critical Covid-19.

```
tableIVW = as.data.frame(tableIVW)
tableIVW$Pvalue = round(tableIVW$Pvalue, digits=3)
tableIVW$Heter.Pvalue = round(tableIVW$Heter.Pvalue, digits=3)
forest(x=tableIVW$Estimate,ci.lb=tableIVW$CILower, ci.ub=tableIVW$CIUpper,refline=1,
 xlab="Odds ratio", slab=rownames(tableIVW),transf=exp, digits=3L, top=1,
    ilab=cbind(tableIVW$Pvalue, tableIVW$Heter.Pvalue), ilab.xpos=c(0.615,0.705),
    ilab.pos=4, xlim=c(0.35,1.48))
text(c(0.345,0.61,0.7,1.22), 4.4, pos=4,
 c("Exposure","Pvalue","Het.Pvalue", "Estimate [CI]"),font=2)
```



3. Multivariable MR

Information on potential genetic confounder (smoking, obesity and inflammation) is contained in the following files.

```
mvMR.ais = additional.data$mvMR$mvMR.ais
mvMR.ces = additional.data$mvMR$mvMR.ces
mvMR.las = additional.data$mvMR$mvMR.las
mvMR.svs = additional.data$mvMR$mvMR.svs
```

We performed multivariable MR to adjust for these potential genetic confounder, which we implemented in a multivariable weighted regression.

```
#ais
lm.ais.uni = lm(beta_ais ~ beta_A2 -1, weights = se_ais^-2, data=mvMR.ais)
lm.ais.crp.uni = lm(beta_ais ~ beta_A2 -1, weights = se_ais^-2,
 data = mvMR.ais[-which(is.na(mvMR.ais$beta_crp)==TRUE),])
lm.ais.smoking = lm(beta_ais ~ beta_A2 + beta_smoking -1, weights = se_ais^-2,
 data=mvMR.ais)
lm.ais.bmi = lm(beta_ais ~ beta_A2 + beta_bmi -1, weights = se_ais^-2, data=mvMR.ais)
lm.ais.crp = lm(beta_ais ~ beta_A2 + beta_crp -1, weights = se_ais^-2, data=mvMR.ais)
lm.ais.joint = lm(beta_ais ~ beta_A2 + beta_smoking + beta_bmi + beta_crp -1,
 weights = se_ais^-2, data=mvMR.ais)
#ces
lm.ces.uni = lm(beta_ces ~ beta_A2 -1, weights = se_ces^-2, data=mvMR.ces)
lm.ces.crp.uni = lm(beta_ces ~ beta_A2 -1, weights = se_ces^-2,
 data = mvMR.ces[-which(is.na(mvMR.ces$beta_crp)==TRUE),])
```

```
lm.ces.smoking = lm(beta_ces ~ beta_A2 + beta_smoking -1, weights = se_ces^-2,
 data=mvMR.ces)
lm.ces.bmi = lm(beta_ces ~ beta_A2 + beta_bmi -1, weights = se_ces^-2, data=mvMR.ces)
lm.ces.crp = lm(beta_ces ~ beta_A2 + beta_crp -1, weights = se_ces^-2, data=mvMR.ces)
lm.ces.joint = lm(beta_ces ~ beta_A2 + beta_smoking + beta_bmi + beta_crp -1,
 weights = se_ces^-2, data=mvMR.ces)
#las
lm.las.uni = lm(beta_las ~ beta_A2 -1, weights = se_las^-2, data=mvMR.las)
lm.las.crp.uni = lm(beta_las ~ beta_A2 -1, weights = se_las^-2,
 data = mvMR.las[-which(is.na(mvMR.las$beta_crp)==TRUE),])
lm.las.smoking = lm(beta_las ~ beta_A2 + beta_smoking -1, weights = se_las^-2,
 data=mvMR.las)
lm.las.bmi = lm(beta_las ~ beta_A2 + beta_bmi -1, weights = se_las^-2, data=mvMR.las)
lm.las.crp = lm(beta_las ~ beta_A2 + beta_crp -1, weights = se_las^-2, data=mvMR.las)
lm.las.joint = lm(beta_las ~ beta_A2 + beta_smoking + beta_bmi + beta_crp -1,
 weights = se_las^-2, data=mvMR.las)
#svs
lm.svs.uni = lm(beta_svs ~ beta_A2 -1, weights = se_svs^-2, data=mvMR.svs)
lm.svs.crp.uni = lm(beta_svs ~ beta_A2 -1, weights = se_svs^-2,
 data = mvMR.svs[-which(is.na(mvMR.svs$beta_crp)==TRUE),])
lm.svs.smoking = lm(beta_svs ~ beta_A2 + beta_smoking -1, weights = se_svs^-2,
 data=mvMR.svs)
lm.svs.bmi = lm(beta_svs ~ beta_A2 + beta_bmi -1, weights = se_svs^-2, data=mvMR.svs)
lm.svs.crp = lm(beta_svs ~ beta_A2 + beta_crp -1, weights = se_svs^-2, data=mvMR.svs)
lm.svs.joint = lm(beta_svs ~ beta_A2 + beta_smoking + beta_bmi + beta_crp -1,
 weights = se_svs^-2, data=mvMR.svs)
```

Create the overview table for the multivariable MR analysis.

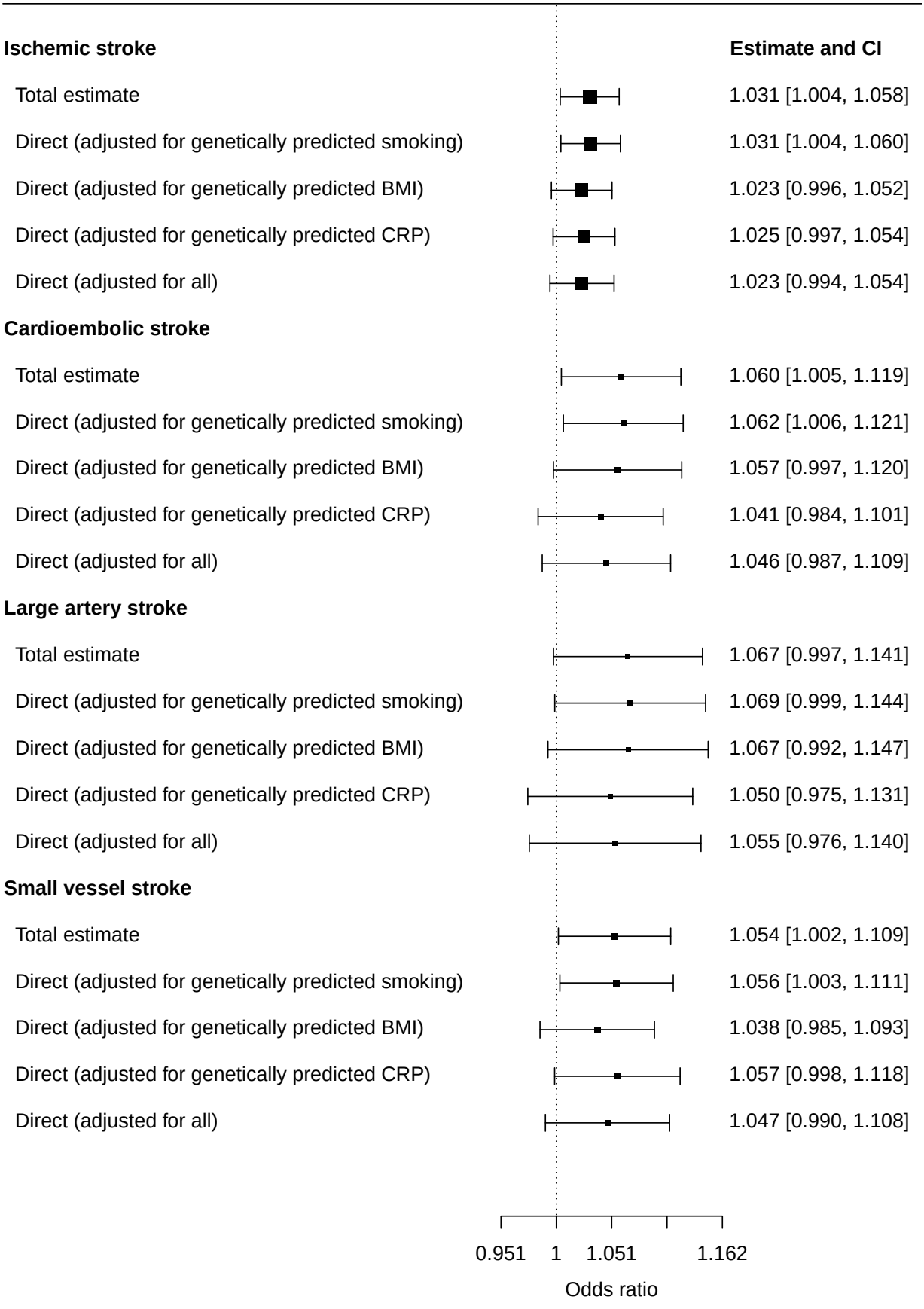
```
mvMR.out = rbind(
summary(lm.ais.uni)$coefficients,summary(lm.ais.smoking)$coefficients[1,],
 summary(lm.ais.bmi)$coefficients[1,],summary(lm.ais.crp)$coefficients[1,],
 summary(lm.ais.joint)$coefficients[1,],
 #
 summary(lm.ces.uni)$coefficients,summary(lm.ces.smoking)$coefficients[1,],
 summary(lm.ces.bmi)$coefficients[1,],summary(lm.ces.crp)$coefficients[1,],
 summary(lm.ces.joint)$coefficients[1,],
 #
 summary(lm.las.uni)$coefficients,summary(lm.las.smoking)$coefficients[1,],
 summary(lm.las.bmi)$coefficients[1,],summary(lm.las.crp)$coefficients[1,],
 summary(lm.las.joint)$coefficients[1,],
 #
 summary(lm.svs.uni)$coefficients,summary(lm.svs.smoking)$coefficients[1,],
 summary(lm.svs.bmi)$coefficients[1,],summary(lm.svs.crp)$coefficients[1,],
 summary(lm.svs.joint)$coefficients[1,]
)
rownames(mvMR.out) = c(
 "ais.total","ais.direct.adj.smoking","ais.direct.adj.bmi",
 "ais.direct.adj.crp","ais.direct.adj.all",
 "ces.total","ces.direct.adj.smoking","ces.direct.adj.bmi",
 "ces.direct.adj.crp","ces.direct.adj.all",
 "las.total","las.direct.adj.smoking","las.direct.adj.bmi",
 "las.direct.adj.crp","las.direct.adj.all",
 "svs.total","svs.direct.adj.smoking","svs.direct.adj.bmi",
```

```
 "svs.direct.adj.crp","svs.direct.adj.all"
)
#mvMR.out
mvMR.out = as.data.frame(mvMR.out)
mvMR.OR = as.data.frame(mvMR.out)
mvMR.OR$Estimate = exp(mvMR.out$Estimate)
mvMR.OR$CILower = exp(mvMR.out$Estimate-1.96*mvMR.out$"Std. Error")
mvMR.OR$CIUpper = exp(mvMR.out$Estimate+1.96*mvMR.out$"Std. Error")
mvMR.OR$Pvalue = mvMR.OR$"Pr(>|t|)"
mvMR.OR$"Std. Error" = NULL
mvMR.OR$"t value" = NULL
mvMR.OR$"Pr(>|t|)" = NULL
mvMR.OR
```

```
##                          Estimate   CILower  CIUpper     Pvalue
## ais.total                1.030588 1.0035138 1.058392 0.03425213
## ais.direct.adj.smoking   1.031465 1.0040919 1.059585 0.03167421
## ais.direct.adj.bmi       1.023163 0.9955215 1.051571 0.11206699
## ais.direct.adj.crp       1.025310 0.9970764 1.054342 0.09028762
## ais.direct.adj.all       1.023443 0.9942095 1.053536 0.12915199
## ces.total                1.060252 1.0045302 1.119064 0.04201793
## ces.direct.adj.smoking   1.062324 1.0063549 1.121406 0.03676331
## ces.direct.adj.bmi       1.056872 0.9973522 1.119943 0.07155953
## ces.direct.adj.crp       1.040824 0.9836324 1.101341 0.17618398
## ces.direct.adj.all       1.046269 0.9873142 1.108745 0.13845213
## las.total                1.066872 0.9974258 1.141153 0.06915720
## las.direct.adj.smoking   1.068976 0.9985798 1.144334 0.06485996
## las.direct.adj.bmi       1.066925 0.9924350 1.147007 0.08993311
## las.direct.adj.crp       1.049911 0.9745407 1.131110 0.21053970
## las.direct.adj.all       1.054553 0.9758596 1.139593 0.19106506
## svs.total                1.053982 1.0018415 1.108837 0.05119026
## svs.direct.adj.smoking   1.055899 1.0031795 1.111390 0.04632535
## svs.direct.adj.bmi       1.037611 0.9853329 1.092663 0.17217999
## svs.direct.adj.crp       1.056672 0.9984336 1.118307 0.06699006
## svs.direct.adj.all       1.047268 0.9901331 1.107700 0.11869423
```

Supplementary Figure 2: Forest plot contrasting the Mendelian randomization estimates and confidence intervals (CI) from univariable Mendelian randomization (total estimate) and multivariable Mendelian randomization accounting for potential pleiotropic pathways (direct estimate).

```
mvMR.out = mvMR.out[20:1,]
outcomes = c("Ischemic stroke","Cardioembolic stroke",
 "Large artery stroke","Small vessel stroke")
labels = rep(c("Total estimate", "Direct (adjusted for genetically predicted smoking)",
 "Direct (adjusted for genetically predicted BMI)",
 "Direct (adjusted for genetically predicted CRP)",
 "Direct (adjusted for all)"),4)[20:1]
data.rma = rma(yi=mvMR.out$Estimate,sei=mvMR.out$"Std. Error")
forest(data.rma,addfit=FALSE, rows=c(1:5, 7:11, 13:17, 19:23), ylim=c(0, 25),
 slab=labels, atransf=exp,top=1, xlab="Odds ratio", digits=3L, xlim=c(-0.5,0.33))
 text(-0.51, c(24,18,12,6), pos=4, outcomes,font=2)
#points(rep(-0.495,4), c(24.04,18.04,12.04,6.04), pch=21,bg="black")
text(0.146, c(24), pos=4, c("Estimate and CI"),font=2)
```


Ischemic stroke
Estimate and CI
Total estimate
1.031 [1.004, 1.058]
Direct (adjusted for genetically predicted smoking)
1.031 [1.004, 1.060]
Direct (adjusted for genetically predicted BMI)
1.023 [0.996, 1.052]
Direct (adjusted for genetically predicted CRP)
1.025 [0.997, 1.054]
Direct (adjusted for all)
1.023 [0.994, 1.054]
Cardioembolic stroke
Total estimate
1.060 [1.005, 1.119]
Direct (adjusted for genetically predicted smoking)
1.062 [1.006, 1.121]
Direct (adjusted for genetically predicted BMI)
1.057 [0.997, 1.120]
Direct (adjusted for genetically predicted CRP)
1.041 [0.984, 1.101]
Direct (adjusted for all)
1.046 [0.987, 1.109]
Large artery stroke
Total estimate
1.067 [0.997, 1.141]
Direct (adjusted for genetically predicted smoking)
1.069 [0.999, 1.144]
Direct (adjusted for genetically predicted BMI)
1.067 [0.992, 1.147]
Direct (adjusted for genetically predicted CRP)
1.050 [0.975, 1.131]
Direct (adjusted for all)
1.055 [0.976, 1.140]
Small vessel stroke
Total estimate
1.054 [1.002, 1.109]
Direct (adjusted for genetically predicted smoking)
1.056 [1.003, 1.111]
Direct (adjusted for genetically predicted BMI)
1.038 [0.985, 1.093]
Direct (adjusted for genetically predicted CRP)
1.057 [0.998, 1.118]
Direct (adjusted for all)
1.047 [0.990, 1.108]
0.951
1
1.051
1.162
Odds ratio

In order to compare the model fit, we computed a likelihood ratio test which contrasts the residual sum of squares of the univariable with the multivariable MR model.

```
#ais
lrt.ais.smoking = anova(lm.ais.uni, lm.ais.smoking)
lrt.ais.bmi = anova(lm.ais.uni, lm.ais.bmi)
lrt.ais.crp = anova(lm.ais.crp.uni, lm.ais.crp)
#ces
lrt.ces.smoking = anova(lm.ces.uni, lm.ces.smoking)
lrt.ces.bmi = anova(lm.ces.uni, lm.ces.bmi)
lrt.ces.crp = anova(lm.ces.crp.uni, lm.ces.crp)
#las
lrt.las.smoking = anova(lm.las.uni, lm.las.smoking)
lrt.las.bmi = anova(lm.las.uni, lm.las.bmi)
lrt.las.crp = anova(lm.las.crp.uni, lm.las.crp)
#svs
lrt.svs.smoking = anova(lm.svs.uni, lm.svs.smoking)
lrt.svs.bmi = anova(lm.svs.uni, lm.svs.bmi)
lrt.svs.crp = anova(lm.svs.crp.uni, lm.svs.crp)
```

Create the table to summarize the likelihood ratio test.

```
lrt.test = rbind(
c(lrt.ais.smoking$RSS, lrt.ais.smoking$Df[2], lrt.ais.smoking$F[2],
 lrt.ais.smoking$"Pr(>F)"[2]),
c(lrt.ais.bmi$RSS, lrt.ais.bmi$Df[2], lrt.ais.bmi$F[2],
 lrt.ais.bmi$"Pr(>F)"[2]),
c(lrt.ais.crp$RSS, lrt.ais.crp$Df[2], lrt.ais.crp$F[2],
 lrt.ais.crp$"Pr(>F)"[2]),
c(lrt.ces.smoking$RSS, lrt.ces.smoking$Df[2], lrt.ces.smoking$F[2],
 lrt.ces.smoking$"Pr(>F)"[2]),
c(lrt.ces.bmi$RSS, lrt.ces.bmi$Df[2], lrt.ces.bmi$F[2],
 lrt.ces.bmi$"Pr(>F)"[2]),
c(lrt.ces.crp$RSS, lrt.ces.crp$Df[2], lrt.ces.crp$F[2],
 lrt.ces.crp$"Pr(>F)"[2]),
c(lrt.las.smoking$RSS, lrt.las.smoking$Df[2], lrt.las.smoking$F[2],
 lrt.las.smoking$"Pr(>F)"[2]),
c(lrt.las.bmi$RSS, lrt.las.bmi$Df[2], lrt.las.bmi$F[2],
 lrt.las.bmi$"Pr(>F)"[2]),
c(lrt.las.crp$RSS, lrt.las.crp$Df[2], lrt.las.crp$F[2],
 lrt.las.crp$"Pr(>F)"[2]),
c(lrt.svs.smoking$RSS, lrt.svs.smoking$Df[2], lrt.svs.smoking$F[2],
 lrt.svs.smoking$"Pr(>F)"[2]),
c(lrt.svs.bmi$RSS, lrt.svs.bmi$Df[2], lrt.svs.bmi$F[2],
 lrt.svs.bmi$"Pr(>F)"[2]),
c(lrt.svs.crp$RSS, lrt.svs.crp$Df[2], lrt.svs.crp$F[2],
 lrt.svs.crp$"Pr(>F)"[2])
)
colnames(lrt.test) = c("RSS1", "RSS2","DF","F","p-val")
rownames(lrt.test) = rep(c("smoking","bmi","crp"),4)
lrt.test
```

```
##             RSS1     RSS2 DF            F      p-val
## smoking 40.23033 39.43582  1 5.842541e-01 0.45082478
## bmi     40.23033 36.91926  1 2.600835e+00 0.11763845
## crp     37.45699 34.84059  1 2.102699e+00 0.15814954
```

```
## smoking 43.89899 42.43902  1 9.976437e-01 0.32614312
## bmi     43.89899 43.73320  1 1.099393e-01 0.74259762
## crp     42.76479 37.54370  1 3.893879e+00 0.05840663
## smoking 41.28956 40.61249  1 4.834721e-01 0.49238831
## bmi     41.28956 41.28954  1 1.754007e-05 0.99668708
## crp     40.87216 39.64796  1 8.645500e-01 0.36041604
## smoking 26.74162 26.15000  1 6.561007e-01 0.42453698
## bmi     26.74162 23.99289  1 3.322362e+00 0.07866962
## crp     26.17666 26.17591  1 8.043158e-04 0.97757584
```

4. Other Covid-19 definitions from the Covid-19 host genetics initiative

For the main analysis we considered the most severe definition of Covid-19 from the 5th release of the Covid-19 host genetics initiative https://www.covid19hg.org/results/r5/, which is defined as critical ill Covid-19, where a critical case is defined as an individual who was hospitalized with laboratory confirmed SARS-CoV-2 infection and required respiratory support or died. Here we present the following Covid-19 definitions: - B1: Hospitalized for Covid-19 versus controls with laboratory-confirmed Covid-19 - B2: Hospitalized for Covid-19 versus population controls - C2: Reported Covid-19 infection versus population controls

Next we read in the data and define the mr_input objects for all three Covid-19 definitions.

```
iv_B1 = additional.data$c19$iv_B1
iv_B2 = additional.data$c19$iv_B2
iv_C2 = additional.data$c19$iv_C2
#
mr_B1.ais = mr_input(bx = iv_B1$beta_B1,bxse = iv_B1$se_B1,
 by = iv_B1$beta_ais, byse = iv_B1$se_ais)
mr_B1.ces = mr_input(bx = iv_B1$beta_B1,bxse = iv_B1$se_B1,
 by = iv_B1$beta_ces, byse = iv_B1$se_ces)
mr_B1.las = mr_input(bx = iv_B1$beta_B1,bxse = iv_B1$se_B1,
 by = iv_B1$beta_las, byse = iv_B1$se_las)
mr_B1.svs = mr_input(bx = iv_B1$beta_B1,bxse = iv_B1$se_B1,
 by = iv_B1$beta_svs, byse = iv_B1$se_svs)
#
mr_B2.ais = mr_input(bx = iv_B2$beta_B2,bxse = iv_B2$se_B2,
 by = iv_B2$beta_ais, byse = iv_B2$se_ais)
mr_B2.ces = mr_input(bx = iv_B2$beta_B2,bxse = iv_B2$se_B2,
 by = iv_B2$beta_ces, byse = iv_B2$se_ces)
mr_B2.las = mr_input(bx = iv_B2$beta_B2,bxse = iv_B2$se_B2,
 by = iv_B2$beta_las, byse = iv_B2$se_las)
mr_B2.svs = mr_input(bx = iv_B2$beta_B2,bxse = iv_B2$se_B2,
 by = iv_B2$beta_svs, byse = iv_B2$se_svs)
#
mr_C2.ais = mr_input(bx = iv_C2$beta_C2,bxse = iv_C2$se_C2,
 by = iv_C2$beta_ais, byse = iv_C2$se_ais)
mr_C2.ces = mr_input(bx = iv_C2$beta_C2,bxse = iv_C2$se_C2,
 by = iv_C2$beta_ces, byse = iv_C2$se_ces)
mr_C2.las = mr_input(bx = iv_C2$beta_C2,bxse = iv_C2$se_C2,
 by = iv_C2$beta_las, byse = iv_C2$se_las)
mr_C2.svs = mr_input(bx = iv_C2$beta_C2,bxse = iv_C2$se_C2,
 by = iv_C2$beta_svs, byse = iv_C2$se_svs)
```

Perform inverse-variance weighted MR.

```
ivw_B1.ais = mr_ivw(mr_B1.ais)
ivw_B1.ces = mr_ivw(mr_B1.ces)
ivw_B1.las = mr_ivw(mr_B1.las)
ivw_B1.svs = mr_ivw(mr_B1.svs)
#
ivw_B2.ais = mr_ivw(mr_B2.ais)
ivw_B2.ces = mr_ivw(mr_B2.ces)
ivw_B2.las = mr_ivw(mr_B2.las)
ivw_B2.svs = mr_ivw(mr_B2.svs)
#
ivw_C2.ais = mr_ivw(mr_C2.ais)
ivw_C2.ces = mr_ivw(mr_C2.ces)
ivw_C2.las = mr_ivw(mr_C2.las)
ivw_C2.svs = mr_ivw(mr_C2.svs)
```

Create the output table.

```
tableC19 = matrix(nrow=12, ncol=7)
colnames(tableC19) = c("Estimate","StdError","CILower","CIUpper",
 "Pvalue","Q-stat", "Heter.Pvalue")
rownames(tableC19) = rep(c("Ischemic stroke","Cardioembolic stroke",
 "Large artery stroke","Small vessel stroke"),3)
#B1
tableC19[1,] = c(ivw_B1.ais$Estimate, ivw_B1.ais$StdError,
 ivw_B1.ais$CILower, ivw_B1.ais$CIUpper, ivw_B1.ais$Pvalue, ivw_B1.ais$Heter.Stat)
tableC19[2,] = c(ivw_B1.ces$Estimate, ivw_B1.ces$StdError,
 ivw_B1.ces$CILower, ivw_B1.ces$CIUpper, ivw_B1.ces$Pvalue, ivw_B1.ces$Heter.Stat)
tableC19[3,] = c(ivw_B1.las$Estimate, ivw_B1.las$StdError,
 ivw_B1.las$CILower, ivw_B1.las$CIUpper, ivw_B1.las$Pvalue, ivw_B1.las$Heter.Stat)
tableC19[4,] = c(ivw_B1.svs$Estimate, ivw_B1.svs$StdError,
 ivw_B1.svs$CILower, ivw_B1.svs$CIUpper, ivw_B1.svs$Pvalue, ivw_B1.svs$Heter.Stat)
#B2
tableC19[5,] = c(ivw_B2.ais$Estimate, ivw_B2.ais$StdError,
 ivw_B2.ais$CILower, ivw_B2.ais$CIUpper, ivw_B2.ais$Pvalue, ivw_B2.ais$Heter.Stat)
tableC19[6,] = c(ivw_B2.ces$Estimate, ivw_B2.ces$StdError,
 ivw_B2.ces$CILower, ivw_B2.ces$CIUpper, ivw_B2.ces$Pvalue, ivw_B2.ces$Heter.Stat)
tableC19[7,] = c(ivw_B2.las$Estimate, ivw_B2.las$StdError,
 ivw_B2.las$CILower, ivw_B2.las$CIUpper, ivw_B2.las$Pvalue, ivw_B2.las$Heter.Stat)
tableC19[8,] = c(ivw_B2.svs$Estimate, ivw_B2.svs$StdError,
 ivw_B2.svs$CILower, ivw_B2.svs$CIUpper, ivw_B2.svs$Pvalue, ivw_B2.svs$Heter.Stat)
#C2
tableC19[ 9,] = c(ivw_C2.ais$Estimate, ivw_C2.ais$StdError,
 ivw_C2.ais$CILower, ivw_C2.ais$CIUpper, ivw_C2.ais$Pvalue, ivw_C2.ais$Heter.Stat)
tableC19[10,] = c(ivw_C2.ces$Estimate, ivw_C2.ces$StdError,
 ivw_C2.ces$CILower, ivw_C2.ces$CIUpper, ivw_C2.ces$Pvalue, ivw_C2.ces$Heter.Stat)
tableC19[11,] = c(ivw_C2.las$Estimate, ivw_C2.las$StdError,
 ivw_C2.las$CILower, ivw_C2.las$CIUpper, ivw_C2.las$Pvalue, ivw_C2.las$Heter.Stat)
tableC19[12,] = c(ivw_C2.svs$Estimate, ivw_C2.svs$StdError,
 ivw_C2.svs$CILower, ivw_C2.svs$CIUpper, ivw_C2.svs$Pvalue, ivw_C2.svs$Heter.Stat)
#
#tableC19
```

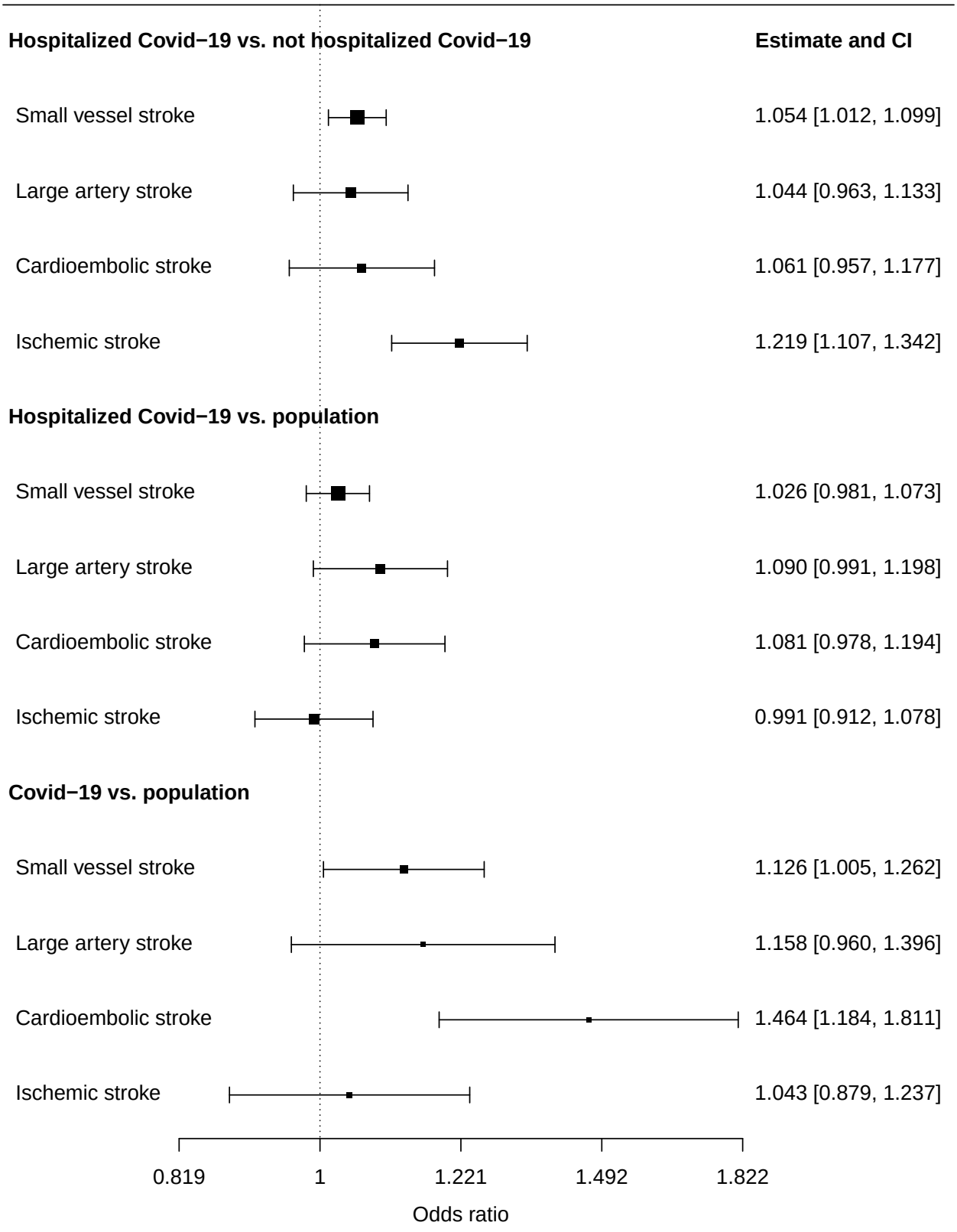
In the manuscript we present the MR estimates and confidence intervalls on the odds ratio scale, where MR estimates represent the odds ratio for critical Covid-19 per unit increase in the log odds ratio of stroke

phenotypes.

```
##                          Estimate   CILower  CIUpper       Pvalue    Q-stat
## Ischemic.stroke        1.0543969 1.0120623 1.098502 1.129510e-02  5.311137
## Cardioembolic.stroke   1.0444962 0.9628737 1.133038 2.943382e-01  5.061964
## Large.artery.stroke    1.0612851 0.9573448 1.176510 2.580344e-01  5.080008
## Small.vessel.stroke    1.2189058 1.1071316 1.341965 5.486583e-05  7.963956
## Ischemic.stroke.1      1.0257022 0.9806918 1.072778 2.676891e-01 46.405610
## Cardioembolic.stroke.1 1.0895516 0.9905898 1.198400 7.750438e-02 56.522798
## Large.artery.stroke.1  1.0806794 0.9780492 1.194079 1.275068e-01 37.369324
## Small.vessel.stroke.1  0.9914841 0.9117823 1.078153 8.414617e-01 30.301629
## Ischemic.stroke.2      1.1263516 1.0049231 1.262453 4.091959e-02 59.810782
## Cardioembolic.stroke.2 1.1577283 0.9601726 1.395931 1.249752e-01 44.238478
## Large.artery.stroke.2  1.4643369 1.1842596 1.810653 4.293080e-04 33.982150
## Small.vessel.stroke.2  1.0428979 0.8793853 1.236814 6.292779e-01 25.092586
##                        Heter.Pvalue
## Ischemic.stroke        0.9151672066
## Cardioembolic.stroke   0.9281286076
## Large.artery.stroke    0.9272299684
## Small.vessel.stroke    0.7165289538
## Ischemic.stroke.1      0.0213754949
## Cardioembolic.stroke.1 0.0016383696
## Large.artery.stroke.1  0.1370114003
## Small.vessel.stroke.1  0.3990612222
## Ischemic.stroke.2      0.0001110187
## Cardioembolic.stroke.2 0.0101977324
## Large.artery.stroke.2  0.1082899431
## Small.vessel.stroke.2  0.4571944850
```

Supplementary Figure 4: Forest plot for other Covid-19 definitions

```
data = tableC19[12:1,]
data = as.data.frame(data)
data$Pvalue = round(data$Pvalue, digits=3)
data$Heter.Pvalue = round(data$Heter.Pvalue, digits=3)
data.rma = rma(yi=as.numeric(data$Estimate),sei=as.numeric(data$StdError))
forest(data.rma,addfit=FALSE, rows=c(1:4, 6:9, 11:14), ylim=c(1, 15.5),
 slab=rownames(tableC19), atransf=exp,top=1, xlab="Odds ratio", digits=3L, xlim=c(-0.45,0.9))
text(-0.46, c(15,10,5), pos=4,
c("Hospitalized Covid-19 vs. not hospitalized Covid-19",
 "Hospitalized Covid-19 vs. population","Covid-19 vs. population"),font=2)
text(c(0.6), 15, pos=4, c("Estimate and CI"),font=2)
```


Hospitalized Covid−19 vs. not hospitalized Covid−19
Estimate and CI
Small vessel stroke
1.054 [1.012, 1.099]
Large artery stroke
1.044 [0.963, 1.133]
Cardioembolic stroke
1.061 [0.957, 1.177]
Ischemic stroke
1.219 [1.107, 1.342]
Hospitalized Covid−19 vs. population
Small vessel stroke
1.026 [0.981, 1.073]
Large artery stroke
1.090 [0.991, 1.198]
Cardioembolic stroke
1.081 [0.978, 1.194]
Ischemic stroke
0.991 [0.912, 1.078]
Covid−19 vs. population
Small vessel stroke
1.126 [1.005, 1.262]
Large artery stroke
1.158 [0.960, 1.396]
Cardioembolic stroke
1.464 [1.184, 1.811]
Ischemic stroke
1.043 [0.879, 1.237]
0.819
1
1.221
1.492
1.822
Odds ratio