Statin use and brain volume alterations

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This code requires the packages *tidyverse*, *knitr*, *png*, *ggplot2*, *RColorBrewer*, *cowplot*, and *mediation*.

Function used to create the result table:

```
multivarlmR2 <- function (data, outcome, varexpo, varajust,
                          labelexpo = varexpo, decimal = 2) {
  # data        dataset
  # outcome     character vector of outcome names
  # varexpo     character vector of exposure variable (1)
  # varajust    character vector of covariates
  # labelexpo   character vector of labels of the exposure variable, colnames by default
  # decimal     number of digits after the decimal point, 2 by default

  x <- data[,c(varexpo)]
  res <- NULL

  for (i in 1:length(outcome)) {
    # y : variable i to explain
    y <- outcome[i]

    ## Empty matrix which will be used as a table
    mat_res <- matrix(NA, nrow = 0, ncol = 9)
    colnames(mat_res) <- c("Outcome","Exposure","Beta","SE",
                           "Lower CI", "Upper CI" ,"P value", "P.raw",
                           "Adjusted R-squared")

    varexpo <- c(varexpo)

    data2 <- na.omit(data[, c(y, varexpo, varajust)])


    # Writing the equation y ~ x1 + x2 +...+ xp
    formule <- paste(y, "~", varexpo)
    for (k in 1:length(varajust)) {formule <- paste(formule, "+", varajust[k])}
    formule <- as.formula(formule)

    # Model
    mod <- lm(formula = formule, data = data2)

    # Display results of the exposure variable only
```

```r
  # i.e. the second row of coefficients and ICs (the first being the intercept)

  # Coefficients and standard error
  beta <- round(mod$coefficients, decimal)
  se <- round(summary(mod)$coefficients[, 2], decimal)
  CI <- round(confint(mod), decimal)

  # P-value extraction
  pval <- summary(mod)$coefficients[, 4]
  pvalr <- round(pval, 4)
  pvalr[as.double(pval) < 0.0001] <- "<0.0001"

  # Adjusted R-squared value
  adj.r.squared <- round(summary(mod)$adj.r.squared, 4)

  # If the exposure variable is a factor
  if (is.factor(x)) {

    lev <- levels(x)
    nlev <- nlevels(x)

    if (nlev == 2){
      line <- c(y,
                paste(varexpo, "_", lev[2], sep = ""),
                beta[2], se[2],
                CI[2,1], CI[2,2], pvalr[2], pval[2], adj.r.squared)
      mat_res <- rbind(mat_res, line)

    } else if (nlev > 2) {
      line0 <- c(y, paste(varexpo, "_", lev[1], sep = ""), rep("", 6), adj.r.squared)
      mat_res <- rbind(mat_res, line0)

      for (k in 2:nlev) {
        line <- c(y,
                  paste(varexpo, "_", lev[k], sep = ""),
                  beta[k], se[k],
                  CI[k,1], CI[k,2], pvalr[k], pval[k], "")
        mat_res <- rbind(mat_res, line)
      }
    }

  } else if (is.numeric(x)){

    line <- c(y, varexpo, beta[2], se[2],
              CI[2,1], CI[2,2], pvalr[2], pval[2], adj.r.squared)
    mat_res <- rbind(mat_res, line)
  }

  res <- rbind(res, mat_res)
  row.names(res) <- NULL

}
```

```
  return(res)

}
```

MAIN ANALYSES

```
imagsel <- c("GM_vol2", "WM_vol2", "cortical_vol2", "logWMH_vol2")

# Model 1
mmd1 <- multivarlmR2(data = as.data.frame(ukb2),
                     outcome = c(imagsel),
                     varexpo = "statin0b",
                     varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                  "TDI0","APOE4","antidep2","ICV2"),
                     decimal = 2)

mmd1 <- as.data.frame(mmd1)
mmd1$Model <- rep("I",4)

# Model 2
mmd2 <- multivarlmR2(data = as.data.frame(ukb2),
                     outcome = c(imagsel),
                     varexpo = "statin0b",
                     varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                  "TDI0","APOE4","antidep2","ICV2",
                                  "frq_alcohol0","smoking0","physact0b"),
                     decimal = 2)

mmd2 <- as.data.frame(mmd2)
mmd2$Model <- rep("II",4)

# Model 3
mmd3 <- multivarlmR2(data = as.data.frame(ukb2),
                     outcome = c(imagsel),
                     varexpo = "statin0b",
                     varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                  "TDI0","APOE4","antidep2","ICV2",
                                  "frq_alcohol0","smoking0","physact0b",
                                  "BMI0","SBP0","DBP0","diabetes0","CHD0","stroke0",
                                  "headinjury0","depression0","insomn0"),
                     decimal = 2)

mmd3 <- as.data.frame(mmd3)
mmd3$Model <- rep("III",4)

res_mmd <- rbind(mmd1, mmd2, mmd3)
res_mmd <- res_mmd %>% arrange(Outcome)
res_mmd <- res_mmd[,-8]

res_mmd
```

```
##          Outcome   Exposure     Beta     SE Lower CI Upper CI P value
```

```
## 1        GM_vol2 statin0b_1 -3703.23 347.78 -4384.88 -3021.57 <0.0001
## 2        GM_vol2 statin0b_1 -3563.44 351.99 -4253.35 -2873.53 <0.0001
## 3        GM_vol2 statin0b_1 -1574.62 399.92 -2358.48  -790.76 <0.0001
## 4        WM_vol2 statin0b_1  1099.53 346.08   421.22  1777.85  0.0015
## 5        WM_vol2 statin0b_1   925.56 351.33   236.95  1614.18  0.0084
## 6        WM_vol2 statin0b_1  -135.14 400.14  -919.43   649.14  0.7356
## 7  cortical_vol2 statin0b_1 -2676.22  344.4 -3351.24 -2001.19 <0.0001
## 8  cortical_vol2 statin0b_1 -2582.38 348.74 -3265.92 -1898.84 <0.0001
## 9  cortical_vol2 statin0b_1 -1447.76 397.76 -2227.38  -668.13   3e-04
## 10   logWMH_vol2 statin0b_1     0.19   0.02     0.16     0.22 <0.0001
## 11   logWMH_vol2 statin0b_1     0.18   0.02     0.15     0.21 <0.0001
## 12   logWMH_vol2 statin0b_1     0.11   0.02     0.07     0.15 <0.0001
##    Adjusted R-squared Model
## 1              0.8925     I
## 2              0.8933    II
## 3              0.8943   III
## 4              0.9129     I
## 5              0.9132    II
## 6              0.9135   III
## 7              0.8464     I
## 8              0.8475    II
## 9              0.8478   III
## 10             0.2774     I
## 11             0.2806    II
## 12             0.3007   III
```

Model III according to statin type

```
ukb2$statintype0 <- as.character(ukb2$statin0b)
ukb2$statintype0[ukb2$fluvastatin0 == "1"] <- "Fluvastatin"
ukb2$statintype0[ukb2$pravastatin0 == "1"] <- "Pravastatin"
ukb2$statintype0[ukb2$rosuvastatin0 == "1"] <- "Rosuvastatin"
ukb2$statintype0[ukb2$atorvastatin0 == "1"] <- "Atorvastatin"
ukb2$statintype0[ukb2$simvastatin0 == "1"] <- "Simvastatin"

ukb2$statintype0 <- factor(ukb2$statintype0,
                           levels = c("0","Simvastatin","Atorvastatin",
                                      "Rosuvastatin","Pravastatin","Fluvastatin"))
table(ukb2$statintype0)
```

```
##
##            0  Simvastatin Atorvastatin Rosuvastatin  Pravastatin  Fluvastatin
##        36217         2486          568          125           96           10
```

```
m.type <- multivarlmR2(data = as.data.frame(ukb2),
                       outcome = c(imagsel),
                       varexpo = "statintype0",
                       varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                    "TDI0","APOE4","antidep2","ICV2",
                                    "frq_alcohol0","smoking0","physact0b",
                                    "BMI0","SBP0","DBP0","diabetes0","CHD0","stroke0",
```

```
                                    "headinjury0","depression0","insomn0"),
                      decimal = 2)

m.type <- as.data.frame(m.type)
m.type$Exposure <- rep(c("No statin","Simvastatin","Atorvastatin",
                         "Rosuvastatin","Pravastatin","Fluvastatin"), 4)
m.type <- m.type[,-8]
m.type
```

```
##          Outcome     Exposure     Beta      SE  Lower CI Upper CI P value
## 1        GM_vol2    No statin
## 2        GM_vol2  Simvastatin -1494.61  432.23  -2341.79  -647.43   5e-04
## 3        GM_vol2 Atorvastatin -1933.71  859.37  -3618.11  -249.31  0.0244
## 4        GM_vol2 Rosuvastatin  -807.58 1695.41  -4130.64  2515.48  0.6338
## 5        GM_vol2  Pravastatin -2527.38 1973.94  -6396.36  1341.61  0.2004
## 6        GM_vol2  Fluvastatin -7221.76 6063.78 -19106.94  4663.43  0.2337
## 7        WM_vol2    No statin
## 8        WM_vol2  Simvastatin  -260.76  432.45  -1108.38   586.87  0.5465
## 9        WM_vol2 Atorvastatin   653.72  859.83  -1031.56     2339  0.4471
## 10       WM_vol2 Rosuvastatin  -221.26  1696.3  -3546.06  3103.54  0.8962
## 11       WM_vol2  Pravastatin -1219.65 1974.98  -5090.67  2651.36  0.5369
## 12       WM_vol2  Fluvastatin   7603.7 6066.96  -4287.71 19495.12  0.2101
## 13 cortical_vol2    No statin
## 14 cortical_vol2  Simvastatin -1391.74  429.89  -2234.34  -549.14  0.0012
## 15 cortical_vol2 Atorvastatin -1067.58  854.73  -2742.86   607.71  0.2117
## 16 cortical_vol2 Rosuvastatin -2556.51 1686.24  -5861.59   748.58  0.1295
## 17 cortical_vol2  Pravastatin -2735.75 1963.27  -6583.81  1112.31  0.1635
## 18 cortical_vol2  Fluvastatin -7620.75 6030.99 -19441.66  4200.16  0.2064
## 19   logWMH_vol2    No statin
## 20   logWMH_vol2  Simvastatin      0.1    0.02      0.06     0.14 <0.0001
## 21   logWMH_vol2 Atorvastatin     0.14    0.04      0.06     0.22   5e-04
## 22   logWMH_vol2 Rosuvastatin     0.14    0.08     -0.02     0.29  0.0888
## 23   logWMH_vol2  Pravastatin     0.24    0.09      0.06     0.42  0.0095
## 24   logWMH_vol2  Fluvastatin    -0.45    0.28        -1      0.1  0.1086
##    Adjusted R-squared
## 1              0.8943
## 2
## 3
## 4
## 5
## 6
## 7              0.9135
## 8
## 9
## 10
## 11
## 12
## 13             0.8478
## 14
## 15
## 16
## 17
## 18
```

```
## 19             0.3008
## 20
## 21
## 22
## 23
## 24
```

```r
m.type.p <- subset(m.type, m.type$Exposure != "No statin")
colnames(m.type.p)[5:7] <- c("Lower_CI","Upper_CI","P")
m.type.p$Beta <- as.numeric(m.type.p$Beta)
m.type.p$Lower_CI <- as.numeric(m.type.p$Lower_CI)
m.type.p$Upper_CI <- as.numeric(m.type.p$Upper_CI)
m.type.p$Exposure <- factor(m.type.p$Exposure,
                            levels = c("Fluvastatin","Pravastatin","Rosuvastatin",
                                       "Atorvastatin","Simvastatin"))


p1 <- m.type.p %>% subset(m.type.p$Outcome == "GM_vol2") %>%
  ggplot(aes(x = Exposure , y = Beta, color = Exposure)) +
  geom_point(size = 0.9) +
  geom_hline(yintercept = 0, lty = 1, lwd = 1, color = "grey90") +
  geom_errorbar(aes(ymin = Lower_CI, ymax = Upper_CI), width=.2) +
  scale_color_discrete(type = rev(brewer.pal(n = 5, name = "Dark2"))) +
  xlab("") +
  ylab(expression(Beta)) +
  ylim(c(-20000,20000)) +
  ggtitle("Grey matter") +
  coord_flip() +
  guides(fill = "none", color = "none", linetype = "none", shape = "none") +
  theme_minimal()


p2 <- m.type.p %>% subset(m.type.p$Outcome== "WM_vol2") %>%
  ggplot(aes(x = Exposure, y = Beta, color = Exposure)) +
  geom_point(size = 0.9) +
  geom_hline(yintercept = 0, lty = 1, lwd = 1, color = "grey90") +
  geom_errorbar(aes(ymin = Lower_CI, ymax = Upper_CI), width= 0.2) +
  scale_color_discrete(type = rev(brewer.pal(n = 5, name = "Dark2"))) +
  xlab("") +
  ylab(expression(Beta)) +
  ylim(c(-20000,20000)) +
  ggtitle("White matter") +
  coord_flip() +
  guides(fill = "none", color = "none", linetype = "none", shape = "none") +
  theme_minimal()

p3 <- m.type.p %>% subset(m.type.p$Outcome == "cortical_vol2") %>%
  ggplot(aes(x = Exposure, y = Beta, color = Exposure)) +
  geom_point(size = 0.9)+
  geom_hline(yintercept = 0, lty = 1, lwd = 1, color = "grey90") +
  geom_errorbar(aes(ymin = Lower_CI, ymax = Upper_CI), width=.2) +
```

```
  scale_color_discrete(type = rev(brewer.pal(n = 5, name = "Dark2"))) +
  xlab("") +
  ylab(expression(Beta)) +
  ylim(c(-20000,20000)) +
  ggtitle("Peripheral cortical grey matter") +
  coord_flip() +
  guides(fill = "none", color = "none", linetype = "none", shape = "none") +
  theme_minimal()


p4 <- m.type.p %>% subset(m.type.p$Outcome == "logWMH_vol2") %>%
  ggplot(aes(x = Exposure, y = Beta, color = Exposure)) +
  geom_point(size = 0.9)+
  geom_hline(yintercept = 0, lty = 1, lwd = 1, color = "grey90") +
  geom_errorbar(aes(ymin = Lower_CI, ymax = Upper_CI), width = .2) +
  scale_color_discrete(type = rev(brewer.pal(n = 5, name = "Dark2"))) +
  xlab("") +
  ylab(expression(Beta)) +
  ylim(c(-1,1)) +
  ggtitle("White matter hyperintensities") +
  coord_flip() +
  guides(fill = "none", color = "none", linetype = "none", shape = "none") +
  theme_minimal()

# plot_grid(p1, p2, p3, p4, ncol = 1)
```

Figure: Associations between statin type and the volumes of grey matter, white matter, peripheral cortical grey matter and white matter hyperintensity.

MEDIATION ANALYSIS

Statin, total cholesterol, and grey matter

```
GM <- lm(GM_vol2 ~ statin0b + chol0 + centre2 + age0 + sex + ethnic0b + qualif0b +
           TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
           BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
           depression0 + insomn0,
         data = ukb2)

GM.med1 <- lm(chol0 ~ statin0b + centre2 + age0 + sex + ethnic0b + qualif0b +
           TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
             BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
             depression0 + insomn0,
              data = ukb2)


GM.chol <- mediate(GM.med1, GM, treat = "statin0b", mediator = "chol0",
                     robustSE = T, sims = 1000)

summary(GM.chol)
```

```
##
## Causal Mediation Analysis
##
## Quasi-Bayesian Confidence Intervals
##
##                 Estimate 95% CI Lower 95% CI Upper p-value
## ACME           -3.02e+02    -5.48e+02       -65.38   0.012 *
## ADE            -1.27e+03    -2.23e+03      -437.46   0.004 **
## Total Effect   -1.57e+03    -2.48e+03      -769.63  <2e-16 ***
## Prop. Mediated  1.95e-01     4.31e-02         0.47   0.012 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 35222
##
##
## Simulations: 1000
```

Statin, total cholesterol, and white matter

```
WM <- lm(WM_vol2 ~ statin0b + chol0 + centre2 + age0 + sex + ethnic0b + qualif0b +
           TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
           BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
           depression0 + insomn0,
         data = ukb2)

WM.med1 <- lm(chol0 ~ statin0b + centre2 + age0 + sex + ethnic0b + qualif0b +
                TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
                BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
                depression0 + insomn0,
              data = ukb2)


WM.chol <- mediate(WM.med1, WM, treat = "statin0b", mediator = "chol0",
                   robustSE = T, sims = 1000)
summary(WM.chol)
```

```
##
## Causal Mediation Analysis
##
## Quasi-Bayesian Confidence Intervals
##
##                 Estimate 95% CI Lower 95% CI Upper p-value
## ACME             204.449      -19.111       458.64   0.074 .
## ADE             -307.248    -1200.456       649.35   0.524
## Total Effect    -102.799    -1037.802       784.52   0.856
## Prop. Mediated    -0.132       -6.093         6.58   0.870
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 35222
##
```

```
##
## Simulations: 1000
```

Statin, total cholesterol, and peripheral cortical grey matter

```
cortical <- lm(cortical_vol2 ~ statin0b + chol0 + centre2 + age0 + sex + ethnic0b +
                 qualif0b + TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 +
                 physact0b + BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 +
                 headinjury0 + depression0 + insomn0,
          data = ukb2)

cortical.med1 <- lm(chol0 ~ statin0b + centre2 + age0 + sex + ethnic0b +
                 qualif0b + TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 +
                 physact0b + BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 +
                 headinjury0 + depression0 + insomn0,
               data = subset(ukb2, is.na(ukb2$cortical_vol2) == F))


cortical.chol <- mediate(cortical.med1, cortical, treat = "statin0b", mediator = "chol0",
                    robustSE = T, sims = 1000)
summary(cortical.chol)
```

```
##
## Causal Mediation Analysis
##
## Quasi-Bayesian Confidence Intervals
##
##                  Estimate 95% CI Lower 95% CI Upper p-value
## ACME           -1.55e+02    -3.94e+02        94.68   0.204
## ADE            -1.22e+03    -2.14e+03      -318.90   0.012 *
## Total Effect   -1.37e+03    -2.23e+03      -503.32  <2e-16 ***
## Prop. Mediated  1.11e-01    -7.44e-02         0.43   0.204
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 35222
##
##
## Simulations: 1000
```

Statin, total cholesterol, and WMH

```
WMH <- lm(logWMH_vol2 ~ statin0b + chol0 + centre2 + age0 + sex + ethnic0b + qualif0b +
            TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
            BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
            depression0 + insomn0,
          data = ukb2)

WMH.med1 <- lm(chol0 ~ statin0b + centre2 + age0 + sex + ethnic0b + qualif0b +
                 TDI0 + APOE4 + antidep2 + ICV2 + frq_alcohol0 + smoking0 + physact0b +
```

```
                BMI0 + SBP0 + DBP0 + diabetes0 + CHD0 + stroke0 + headinjury0 +
                depression0 + insomn0,
              data = subset(ukb2, is.na(ukb2$logWMH_vol2) == F))


WMH.chol <- mediate(WMH.med1, WMH, treat = "statin0b", mediator = "chol0",
                        robustSE = T, sims = 1000)
summary(WMH.chol)
```

```
##
## Causal Mediation Analysis
##
## Quasi-Bayesian Confidence Intervals
##
##                Estimate 95% CI Lower 95% CI Upper p-value
## ACME            0.00817     -0.00316         0.02    0.17
## ADE             0.10805      0.07135         0.15  <2e-16 ***
## Total Effect    0.11622      0.07912         0.15  <2e-16 ***
## Prop. Mediated  0.07191     -0.02831         0.18    0.17
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Sample Size Used: 34102
##
##
## Simulations: 1000
```

SECONDARY ANALYSIS

```
# Cortical structures with FAST and sub-cortical structures with FIRST
imag <- colnames(ukb2)[c(337:360,362:371,373:380,382:388,390:392,394:396)]
# length(imag)
# 55 imaging variables


# Model 3
mod3 <- multivarlmR2(data = as.data.frame(ukb2),
                     outcome = imag,
                     varexpo = "statin0b",
                     varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                  "TDI0","APOE4","antidep2","ICV2",
                                  "frq_alcohol0","smoking0","physact0b",
                                  "BMI0","SBP0","DBP0","diabetes0","CHD0","stroke0",
                                  "headinjury0","depression0","insomn0"),
                     decimal = 2)


mod3 <- as.data.frame(mod3)
mod3$P.adjust <- p.adjust(mod3$P.raw, method = "fdr")
mod3 <- mod3[,c("Outcome","Beta","Lower CI","Upper CI",
                "P value","P.adjust","Adjusted R-squared")]
```

```
mod3
```

```
##                       Outcome    Beta Lower CI Upper CI P value     P.adjust
## 1                  thalam_vol2 -101.53  -142.11   -60.96 <0.0001 3.002218e-05
## 2                    caud_vol2   26.61    -2.77    55.99  0.0758 1.544668e-01
## 3                    puta_vol2   -8.94   -45.36    27.49  0.6306 7.078280e-01
## 4                   palli_vol2  -21.72   -38.72    -4.73  0.0122 4.831096e-02
## 5                    hipp_vol2  -43.25   -76.18   -10.33    0.01 4.721198e-02
## 6                    amyg_vol2  -20.88   -38.21    -3.55  0.0182 5.723677e-02
## 7                   accum_vol2  -17.99   -25.65   -10.34 <0.0001 7.556033e-05
## 8            TemporalPole_vol2 -134.11  -210.78   -57.44   6e-04 5.403626e-03
## 9          SupTemporalAnt_vol2  -34.83    -53.3   -16.36   2e-04 2.413594e-03
## 10        SupTemporalPost_vol2   -6.75   -37.33    23.84  0.6654 7.126323e-01
## 11         MidTemporalAnt_vol2  -42.57   -64.56   -20.58   1e-04 2.042123e-03
## 12        MidTemporalPost_vol2  -14.61   -65.21    35.99  0.5714 6.687145e-01
## 13        MidTemporalOcci_vol2   -21.4   -73.43    30.63  0.4201 5.373579e-01
## 14         InfTemporalAnt_vol2  -24.46   -43.61    -5.31  0.0123 4.831096e-02
## 15        InfTemporalPost_vol2   11.13   -37.16    59.42  0.6515 7.126323e-01
## 16        InfTemporalOcci_vol2   17.53   -24.75     59.8  0.4165 5.373579e-01
## 17     ParahippocampalAnt_vol2  -43.12   -72.19   -14.05  0.0036 2.230255e-02
## 18    ParahippocampalPost_vol2    -8.2   -21.95     5.55  0.2427 3.813378e-01
## 19    TemporalFusiformAnt_vol2  -38.12   -53.45    -22.8 <0.0001 3.002218e-05
## 20   TemporalFusiformPost_vol2   -1.99   -34.08     30.1  0.9032 9.062174e-01
## 21       TempOcciFusiform_vol2   23.79    -8.46    56.04  0.1482 2.629131e-01
## 22           PlanumPolare_vol2   -9.11   -22.56     4.34  0.1842 3.166750e-01
## 23                 Heschl_vol2  -14.11   -28.62      0.4  0.0567 1.299913e-01
## 24        PlanumTemporale_vol2   -11.5   -35.85    12.86  0.3549 5.027525e-01
## 25             SupFrontal_vol2  -23.16  -130.99    84.67  0.6738 7.126323e-01
## 26             MidFrontal_vol2  120.14    15.59    224.7  0.0243 6.685854e-02
## 27        Parsopercularis_vol2  -31.62    -64.5     1.26  0.0594 1.307697e-01
## 28       Parstriangularis_vol2  -13.91   -48.65    20.84  0.4328 5.409831e-01
## 29         FrontalOrbital_vol2  -80.29  -126.65   -33.93   7e-04 5.403626e-03
## 30             Precentral_vol2 -128.24  -235.16   -21.32  0.0187 5.723677e-02
## 31          FrontalMedial_vol2  -10.84   -34.32    12.64  0.3656 5.027525e-01
## 32                Frontalpole  -60.85  -203.94    82.25  0.4046 5.373579e-01
## 33            Subcallosal_vol2  -23.32   -47.11     0.46  0.0546 1.299913e-01
## 34       FrontalOperculum_vol2  -22.08   -37.98    -6.18  0.0065 3.565007e-02
## 35            Postcentral_vol2  -42.46  -133.93    49.02   0.363 5.027525e-01
## 36      SupParietalLobule_vol2   -49.2  -107.33     8.93  0.0972 1.842594e-01
## 37       SupramarginalAnt_vol2   19.03   -20.45    58.52  0.3447 5.027525e-01
## 38      SupramarginalPost_vol2   18.75   -38.53    76.03  0.5211 6.369409e-01
## 39                Angular_vol2   39.52   -19.86     98.9  0.1921 3.201451e-01
## 40         Intracalcarine_vol2   -2.63   -46.46    41.19  0.9062 9.062174e-01
## 41             Precuneous_vol2   -54.3  -137.46    28.85  0.2006 3.244327e-01
## 42      ParietalOperculum_vol2   -8.01   -34.74    18.71  0.5567 6.656378e-01
## 43                Lingual_vol2  -56.44  -107.97    -4.91  0.0318 8.332089e-02
## 44   LateralOccipitalSup_vol2 -199.16  -327.35   -70.97  0.0023 1.600031e-02
## 45   LateralOccipitalInf_vol2    6.79   -66.01     79.6  0.8549 8.871252e-01
## 46                 Cuneal_vol2   -7.65   -36.57    21.26  0.6039 6.919344e-01
## 47      OccipitalFusiform_vol2  -32.98   -69.25     3.29  0.0747 1.544668e-01
## 48         Supracalcarine_vol2   12.43     2.93    21.92  0.0103 4.721198e-02
## 49          OccipitalPole_vol2   -70.2  -156.62    16.23  0.1114 2.042434e-01
## 50          Paracingulate_vol2     -66  -120.18   -11.82   0.017 5.723677e-02
```

```
## 51          CingulateAnt_vol2   68.85    -9.17   146.88  0.0837 1.644066e-01
## 52         CingulatePost_vol2   46.52      2.3    90.73  0.0392 9.804213e-02
## 53               Insular_vol2  -49.93   -90.19    -9.66  0.0151 5.533674e-02
## 54      CentralOpercular_vol2  -39.22   -72.86    -5.59  0.0223 6.446338e-02
## 55 JuxtapositionalLobule_vol2  -21.51   -62.45    19.43  0.3032 4.632047e-01
##    Adjusted R-squared
## 1              0.6027
## 2              0.3546
## 3              0.4701
## 4              0.2786
## 5              0.2644
## 6              0.1601
## 7              0.2948
## 8              0.4246
## 9              0.3069
## 10             0.3715
## 11             0.3222
## 12             0.4344
## 13             0.3014
## 14             0.2293
## 15             0.3293
## 16             0.3082
## 17             0.3696
## 18             0.2448
## 19             0.3331
## 20             0.4247
## 21             0.3859
## 22             0.4282
## 23             0.3942
## 24             0.3868
## 25             0.3579
## 26             0.4171
## 27             0.2434
## 28             0.1957
## 29             0.5038
## 30             0.4319
## 31             0.2218
## 32              0.654
## 33             0.5011
## 34             0.3029
## 35             0.3829
## 36             0.2362
## 37              0.241
## 38             0.2833
## 39             0.2632
## 40             0.2506
## 41             0.5358
## 42             0.3769
## 43             0.5295
## 44             0.4892
## 45             0.4049
## 46             0.3091
## 47             0.3811
## 48             0.2981
```

```
## 49             0.3833
## 50             0.4144
## 51             0.2691
## 52             0.5487
## 53             0.5092
## 54             0.4996
## 55               0.21
```

SENSITIVITY ANALYSIS

Never users versus long-term statin users

```
## Create a variable for long-term statin users

ukb2$statin_t02 <- rep(NA, dim(ukb2)[1])
# 0: never used statin
ukb2$statin_t02[ukb2$statin0b == 0 & ukb2$statin2b == 0] <- 0
# 1: started using statin at the imaging visit (removed)
ukb2$statin_t02[ukb2$statin0b == 0 & ukb2$statin2b == 1] <- 1
# 2: reported using statin at recruitment but not at the imaging visit (removed)
ukb2$statin_t02[ukb2$statin0b == 1 & ukb2$statin2b == 0] <- 2
# 3: continuously used statin between recruitment and imaging visit
ukb2$statin_t02[ukb2$statin0b == 1 & ukb2$statin2b == 1] <- 3

ukb2$statin_t02 <- as.factor(ukb2$statin_t02)
table(ukb2$statin_t02)
```

```
##
##     0     1     2     3
## 31400  4817   828  2457
```

```
ukb3 <- ukb2 %>% filter(ukb2$statin_t02 == "0" | ukb2$statin_t02 == "3")
table(ukb3$statin0b)
```

```
##
##     0     1
## 31400  2457
```

```
# Model 1
m.longt1 <- multivarlmR2(data = as.data.frame(ukb3),
                         outcome = imagsel,
                         varexpo = "statin0b",
                         varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                      "TDI0","APOE4","antidep2","ICV2"),
                         decimal = 2)

m.longt1 <- as.data.frame(m.longt1)
m.longt1$Model <- rep("I",4)

# Model 2
m.longt2 <- multivarlmR2(data = as.data.frame(ukb3),
```

```
                          outcome = imagsel,
                          varexpo = "statin0b",
                          varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                       "TDI0","APOE4","antidep2","ICV2",
                                       "frq_alcohol0","smoking0","physact0b"),
                          decimal = 2)

m.longt2 <- as.data.frame(m.longt2)
m.longt2$Model <- rep("II",4)

# Model 3
m.longt3 <- multivarlmR2(data = as.data.frame(ukb3),
                          outcome = imagsel,
                          varexpo = "statin0b",
                          varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                       "TDI0","APOE4","antidep2","ICV2",
                                       "frq_alcohol0","smoking0","physact0b","BMI0",
                                       "SBP0","DBP0","diabetes0","CHD0","stroke0",
                                       "headinjury0","depression0","insomn0"),
                          decimal = 2)

m.longt3 <- as.data.frame(m.longt3)
m.longt3$Model <- rep("III",4)

m.longt <- rbind(m.longt1, m.longt2, m.longt3)
m.longt <- m.longt %>% arrange(Outcome)
m.longt <- m.longt[,-8]

m.longt
```

```
##          Outcome   Exposure     Beta     SE Lower CI Upper CI P value
## 1        GM_vol2 statin0b_1 -3647.08 395.56 -4422.39 -2871.78 <0.0001
## 2        GM_vol2 statin0b_1 -3455.04 399.91 -4238.88 -2671.19 <0.0001
## 3        GM_vol2 statin0b_1 -1795.79 457.85 -2693.19  -898.39 <0.0001
## 4        WM_vol2 statin0b_1  1173.29 393.63   401.75  1944.83  0.0029
## 5        WM_vol2 statin0b_1   973.78 399.32   191.11  1756.46  0.0147
## 6        WM_vol2 statin0b_1    60.23 458.05  -837.56   958.02  0.8954
## 7  cortical_vol2 statin0b_1 -2374.54 393.39 -3145.59 -1603.49 <0.0001
## 8  cortical_vol2 statin0b_1 -2234.11 398.02 -3014.24 -1453.97 <0.0001
## 9  cortical_vol2 statin0b_1 -1379.86 457.13 -2275.84  -483.87  0.0025
## 10   logWMH_vol2 statin0b_1     0.17   0.02     0.13     0.21 <0.0001
## 11   logWMH_vol2 statin0b_1     0.16   0.02     0.12      0.2 <0.0001
## 12   logWMH_vol2 statin0b_1      0.1   0.02     0.06     0.14 <0.0001
##    Adjusted R-squared Model
## 1               0.896     I
## 2              0.8969    II
## 3              0.8977   III
## 4              0.9158     I
## 5               0.916    II
## 6              0.9163   III
## 7              0.8508     I
## 8              0.8518    II
## 9              0.8521   III
```

```
## 10             0.2749     I
## 11             0.2773    II
## 12             0.2956   III
```

Replace self-reported medical history variables with variables based on ICD10 diagnoses

```
mod3ICD <- multivarlmR2(data = as.data.frame(ukb2),
                        outcome = imagsel,
                        varexpo = "statin0b",
                        varajust = c("centre2","age0","sex","ethnic0b","qualif0b",
                                     "TDI0","APOE4","antidep2","ICV2",
                                     "frq_alcohol0","smoking0","physact0b","BMI0",
                                     "SBP0","DBP0","diabetesICD0","CHD_ICD0",
                                     "stroke_ICD0","headinjuryICD0","depressionICD0"),
                    decimal = 2)

mod3ICD <- as.data.frame(mod3ICD)
mod3ICD$Model <- rep("III",4)
mod3ICD <- mod3ICD[,-8]

mod3ICD
```

```
##         Outcome   Exposure     Beta     SE Lower CI Upper CI P value
## 1       GM_vol2 statin0b_1 -2596.81 380.35 -3342.31 -1851.32 <0.0001
## 2       WM_vol2 statin0b_1   222.54 380.17  -522.61   967.69  0.5583
## 3 cortical_vol2 statin0b_1 -2303.73 378.14 -3044.89 -1562.58 <0.0001
## 4   logWMH_vol2 statin0b_1     0.14   0.02     0.11     0.18 <0.0001
##   Adjusted R-squared Model
## 1              0.894   III
## 2             0.9135   III
## 3             0.8475   III
## 4             0.3001   III
```