# Inflammatory bowel disease

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## Introduction

```
set.seed(123)

source("Baseline/utils.R")

###############
## Packages ##
###############

library(plyr) # Used for mapping values
suppressPackageStartupMessages(library(tidyverse)) # ggplot2, dplyr, and magrittr
library(readxl) # Read in Excel files
library(lubridate) # Handle dates
library(datefixR) # Standardise dates
library(patchwork) # Arrange ggplots

# Generate tables
suppressPackageStartupMessages(library(table1))
library(knitr)
library(pander)

# Generate flowchart of cohort derivation
library(DiagrammeR)
library(DiagrammeRsvg)

# paths to PREdiCCt data
if (file.exists("/docker")) { # If running in docker
  data.path <- "data/final/20221004/"
  redcap.path <- "data/final/20231030/"
  prefix <- "data/end-of-follow-up/"
  outdir <- "data/processed/"
} else { # Run on OS directly
  data.path <- "/Volumes/igmm/cvallejo-predicct/predicct/final/20221004/"
  redcap.path <- "/Volumes/igmm/cvallejo-predicct/predicct/final/20231030/"
  prefix <- "/Volumes/igmm/cvallejo-predicct/predicct/end-of-follow-up/"
  outdir <- "/Volumes/igmm/cvallejo-predicct/predicct/processed/"
}
```

```
demo <- readRDS(paste0(outdir, "demo-demographics.RDS"))
demo.cd <- readRDS(paste0(outdir, "demo-cd.RDS"))
demo.uc <- readRDS(paste0(outdir, "demo-uc.RDS"))

cat_theme <- function(gg) {
  p <- gg +
    scale_fill_manual(values = c("#DA4167", "#F4D35E", "#083D77")) +
    scale_color_manual(values = colorspace::darken(c("#DA4167",
                                                     "#F4D35E",
                                                     "#083D77"),
                                                   0.2)
                       ) +
  theme_minimal()
  p
}
```

This page explores data which describes subjects' IBD, primarily consisting of clinical data.

## IBD type

For this study, we have grouped ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU) into one category. IBD type is self-reported.

Whilst PREdiCCt was designed to recruit an equal number of CD and UC/IBDU subjects, the COVID-19 pandemic halted recruitment which has resulted in there not being an equal balance of CD and UC/IBDU subjects.There are slightly more Crohn's disease (CD) than UC/IBDU subjects in the FC cohort.

```
demo$diagnosis2 <- plyr::mapvalues(demo$diagnosis,
  from = seq(1, 4),
  to = c(1, 2, 2, 2)
) %>%
  factor(levels = c("1", "2"), labels = c("CD", "UC/IBDU"))

demo$diagnosis <- plyr::mapvalues(demo$diagnosis,
  from = seq(1, 4),
  to = c(1, 2, 3, 3)
) %>%
  factor(levels = c("1", "2", "3"), labels = c("CD", "UC", "IBDU"))


demo %>%
```

```
  drop_na(cat) %>%
  ggplot(aes(x = diagnosis2, fill = diagnosis2, color = diagnosis2)) +
  geom_bar() +
  ylab("Frequency") +
  xlab("IBD type") +
  theme_minimal() +
  scale_fill_manual(values = c("#2B2D42", "#92DCE5")) +
  scale_color_manual(values = c("#1E203A", "#1D9BA5")) +
  guides(
    fill = guide_legend(title = "IBD type"),
    color = guide_legend(title = "IBD type")
  )
```

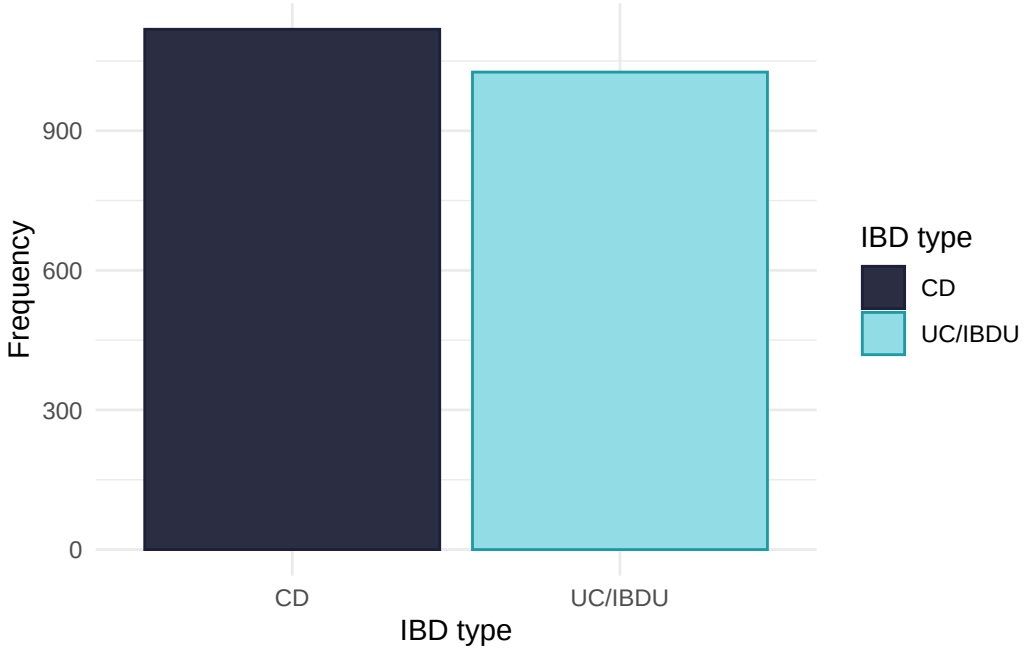



Figure 1: Distribution of IBD type in the FC cohort.

IBD type is significantly associated with FC at recruitment.

```
pander(chisq.test(demo$diagnosis2, demo$cat))
```

Table 1: Chi-squared test between IBD type and FC groups.

Table 1: Pearson's Chi-squared test: `demo$diagnosis2` and `demo$cat`

| Test statistic | df | P value |
|---|---|---|
| 6.815 | 2 | 0.03313 * |

From Figure 2, we can see subjects with UC/IBDU are more likely to have FC $< 50$, whiilst CD subjects are more likely to have FC 50-250. Roughtly the same proportion of subjects with CD and UC/IBDU have FC $> 250$.

```
p <- demo %>%
  drop_na(cat) %>%
  mutate(cat = fct_rev(cat)) %>%
  ggplot(aes(x = diagnosis2, fill = cat, color = cat)) +
  geom_bar(position="fill") +
  scale_y_continuous(labels = scales::percent) +
  labs(x = "IBD subtype",
       y = "Proportion",
       fill = "FC group",
       color = "FC group")
cat_theme(p)
```

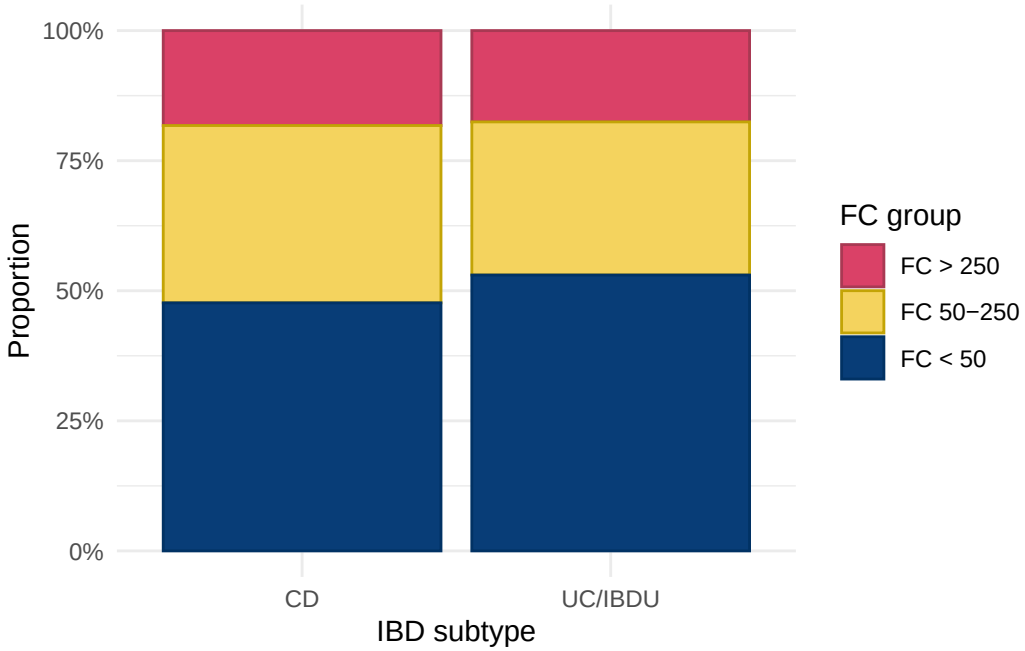



Figure 2: Distribution of FC category by IBD subtype.

## Disease duration

Disease duration has been calculated by subtracting reported date of diagnosis from the date of entry into PREdiCCt. Date of diagnosis has been obtained via REDcap. Where only year was available, the datefixR R package was used to impute the middle of the year. Any disease durations reported to be negative using this method were mapped to 0.

```
redcap <- read_xlsx(paste0(redcap.path, "redcap_clean.xlsx"))
redcap <- distinct(redcap, participantno, .keep_all = TRUE)

diag.date <- redcap[, c("participantno", "date_diag")]
colnames(diag.date)[1] <- "ParticipantNo"
diag.date <- subset(diag.date, (!is.na(date_diag)) &
  (!is.null(date_diag)) &
  date_diag != "")
duration <- merge(diag.date,
  demo,
  by = "ParticipantNo",
  all.x = FALSE,
  all.y = TRUE
```

```
)
duration <- distinct(duration, ParticipantNo, .keep_all = TRUE)

duration <- subset(duration, tolower(date_diag) != "unknown")
duration[duration[, "date_diag"] == "16/032016", "date_diag"] <- "16/03/2016"
duration[duration[, "date_diag"] == "19/04/2017P", "date_diag"] <- "19/04/2017"
duration[duration[, "date_diag"] == "2007 APPROX", "date_diag"] <- "2007"
duration[duration[, "date_diag"] == "approx 1988", "date_diag"] <- "1988"
duration[duration[, "date_diag"] == "?2014", "date_diag"] <- "2014"

duration <- fix_date_df(duration, c("entry_date", "date_diag"))

duration$duration <- as.numeric(with(
  duration,
  (entry_date - date_diag) / 365.25
))

duration[duration[, "duration"] < 0, "duration"] <- 0


duration.cd <- subset(duration, diagnosis == "1")

duration.uc <- subset(duration, diagnosis != "1")

p <- duration %>%
  ggplot(aes(x = duration, color = diagnosis2, fill = diagnosis2)) +
  geom_histogram(bins = 25) +
  theme_minimal() +
  labs(
    x = "Duration (years)",
    y = "Frequency",
    color = "IBD type",
    fill = "IBD type"
  ) +
  scale_fill_manual(
    values = c("#CDEDF6", "#FF6B6B")
  ) +
  scale_color_manual(
    values = c("#5EB1BF", "#C24343")
  )
ggsave("plots/Duration-full-cohort.png",
  p,
```

```
  width = 9,
  height = 6
)
ggsave("plots/Duration-full-cohort.pdf", p, width = 9, height = 6)


duration %>%
  drop_na(duration) %>%
  ggplot(aes(x = duration, color = diagnosis2, fill = diagnosis2)) +
  geom_histogram(bins = 25) +
  theme_minimal() +
  labs(
    x = "Duration (years)",
    y = "Frequency",
    color = "IBD type",
    fill = "IBD type"
  ) +
  scale_fill_manual(
    values = c("#CDEDF6", "#FF6B6B")
  ) +
  scale_color_manual(
    values = c("#5EB1BF", "#C24343")
  )
```

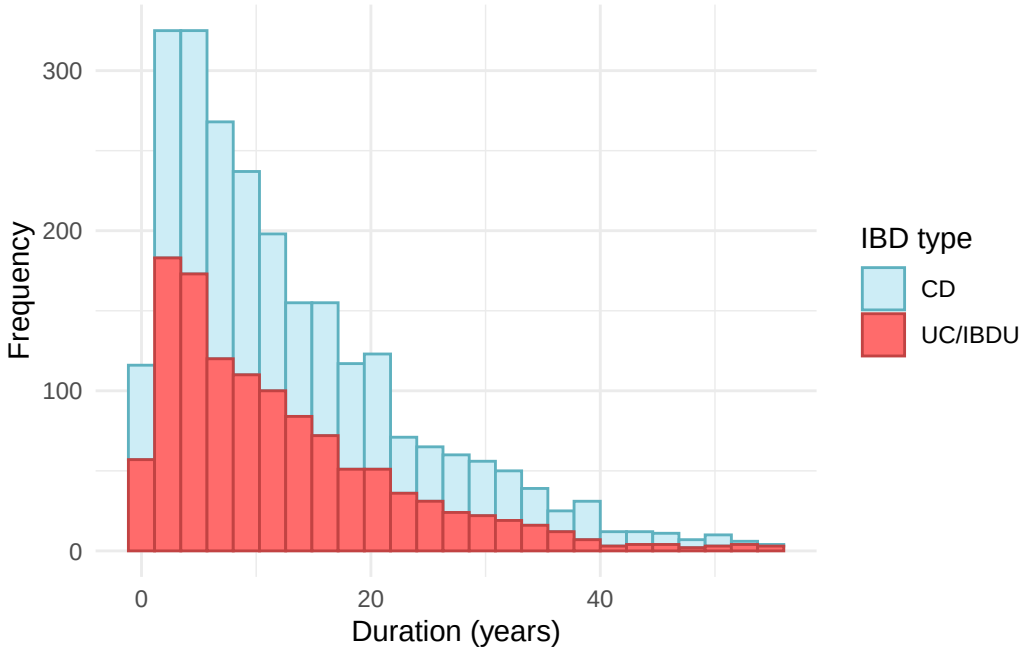



Figure 3

Whilst a low p-value was observed, disease duration was not significantly different between FC groups.

```
demo <- merge(demo, duration[, c("ParticipantNo", "duration")],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

names(demo)[18] <- "IBD Duration"

demo %>%
  aov(formula = `IBD Duration` ~ cat) %>%
  summary() %>%
  pander()
```

Table 2: ANOVA between IBD disease duration and FC groups

Table 2: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 639.6 | 319.8 | 2.708 | 0.06691 |
| **Residuals** | 2021 | 238664 | 118.1 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "CD") %>%
  aov(formula = `IBD Duration` ~ cat) %>%
  summary() %>%
  pander()
```

Table 3: ANOVA between IBD disease duration and FC groups in Crohn's disease.

Table 3: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 162 | 81 | 0.6239 | 0.5361 |
| **Residuals** | 1051 | 136459 | 129.8 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "UC/IBDU") %>%
  aov(formula = `IBD Duration` ~ cat) %>%
  summary() %>%
  pander()
```

Table 4: ANOVA between IBD disease duration and FC groups in UC/IBDU.

Table 4: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 756 | 378 | 3.654 | 0.02626 |
| **Residuals** | 967 | 1e+05 | 103.5 | NA | NA |

```
p <- demo %>%
  filter(diagnosis2 == "UC/IBDU") %>%
  drop_na(cat) %>%
```

```
  mutate(cat = fct_rev(cat)) %>%
  ggplot(aes(x = `IBD Duration`, fill = cat, color = cat)) +
  geom_density() +
  facet_grid(rows = vars(cat)) +
  labs(x = "Disease duration (years)",
       y = "Density",
       fill = "FC group",
       color = "FC group")
cat_theme(p)
```

```
Warning: Removed 56 rows containing non-finite outside the scale range
(`stat_density()`).
```

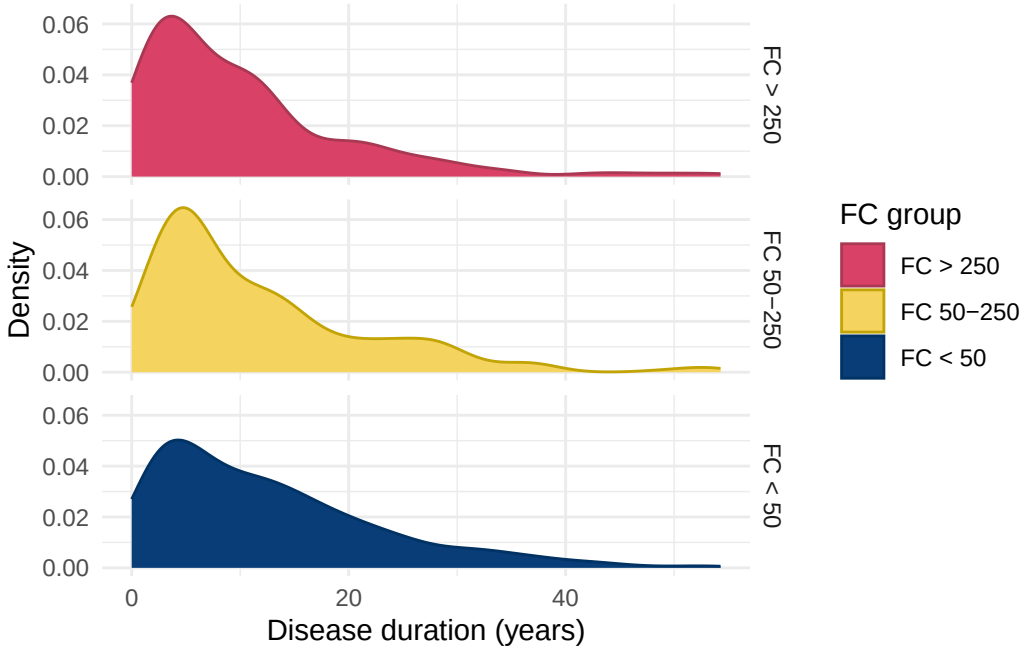



Figure 4: Distribution of disease duration by FC in UC.

## IBD Control

```
IBD <- read_xlsx(paste0(data.path, "Baseline2022/IBD.xlsx"))
```

```r
# create flare_group in IBD_C and make into level
IBD <- IBD %>%
  mutate(flare_group = ifelse(FlaresInPastYear == 0,
    "No Flares",
    "1 or More Flares"
  ))
IBD$flare_group <- factor(IBD$flare_group,
  levels = c("No Flares", "1 or More Flares")
)

IBD <- IBD %>%
  mutate(treatment = ifelse(TreatmentUseful == 4,
    "Not On Treatment",
    "On Treatment"
  ))
IBD$treatment <- factor(IBD$treatment,
  levels = c("Not On Treatment", "On Treatment")
)

# correcting scores where No is favourable and Yes is unfavourable outcomes
# answer options were always YES/NO/Not sure
if (any(IBD$MissPlannedActivities == 3)) {
  IBD <- IBD %>%
    mutate_at(
      vars("MissPlannedActivities":"NewSymptoms"),
      ~ recode(., `3` = 1, `2` = 2, `1` = 0)
    )
}

# correct TreatmentUseful (Yes is favourable, No unfavourable)
# not on treatment was assigned the value 1
if (any(IBD$TreatmentUseful == 3)) {
  IBD <- IBD %>%
    mutate_at(
      "TreatmentUseful",
      ~ recode(., `4` = 2, `3` = 1, `2` = 0, `1` = 2)
    )
}

# exclude rows with missing data, 17 participants excluded for missing IBD-control questionna
IBD <- IBD %>%
  filter(!rowSums(is.na(select(., 17:27))) > 0)
```

```r
# new column with total control score
IBD <- IBD %>%
  mutate(control_score = rowSums(select(., 17:27), na.rm = TRUE))

# new column with IBD-control-8 score
# added 2 to make comparable to future scores where the first question is asked to make compa
IBD <- IBD %>%
  mutate(control_8 = TreatmentUseful +
    MissPlannedActivities +
    WakeUpAtNight +
    SignificantPain +
    OftenLackEnergy +
    AnxiousDepressed +
    NeedChangeTreatment +
    2)

# create groups with cut off of IBD-control-8 scores quiescent (13 or above)/not quiescent
IBD <- IBD %>%
  mutate(control_grouped = ifelse(control_8 >= 13, "13-16", "0-12"))

IBD$control_8 <- as.factor(IBD$control_8)

IBD <- IBD %>%
  mutate(vas_control = ifelse(OverallControl >= 85, "85+", "<85"))

demo <- merge(demo, IBD[, c("ParticipantNo", "control_8", "OverallControl", "vas_control")],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)
```

IBD Control is a validated questionnaire designed to assess disease control from a patient's perspective (Bodger et al. 2013). We considered an eight question subset, IBD-Control-8 which ranges in potential scores from 0 to 16. We also consider the IBD-Control visual analogue scale (VAS). Bodger et al. (2013) found a cut-off of $\geq 13$ for IBD-Control-8 and a cut-off of $\geq 85$ for IBD-Control-VAS to be optimal for identifying quiescent disease.

```r
p1 <- demo %>%
  drop_na(cat) %>%
  ggplot(aes(x = control_8, color = control_8, fill = control_8)) +
  geom_bar() +
```

```
  theme_minimal() +
  theme(legend.position = "none") +
  xlab("Control-8 Scores") +
  ylab("Frequency") +
  scale_color_manual(values = viridis::viridis(15), na.value = "#032B43") +
  scale_fill_manual(values = viridis::viridis(15), na.value = "#032B43") +
  geom_vline(xintercept = 11.5, color = "#FF4B3E")

p2 <- demo %>%
  drop_na(cat) %>%
  ggplot(aes(x = OverallControl)) +
  geom_histogram(binwidth = 5, fill = "#FFD23F", color = "#947805") +
  theme_minimal() +
  xlab("VAS Scores") +
  ylab("Frequency") +
  geom_vline(xintercept = 85, color = "#FF4B3E") +
  scale_x_continuous(breaks = seq(0, 100, 10))
p1 / p2 + plot_annotation(tag_levels = "A")
```

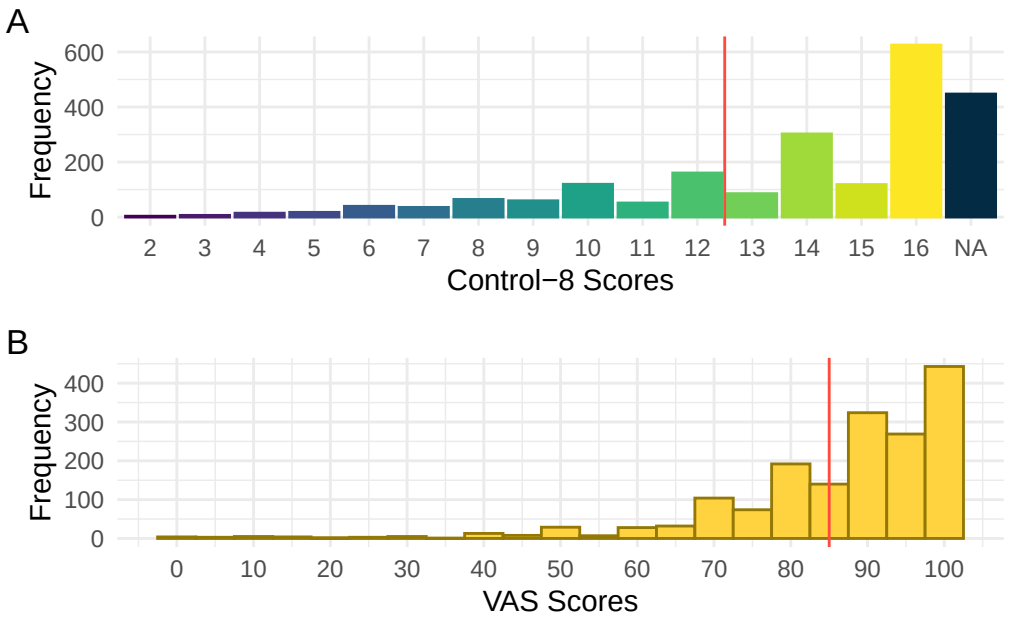



Figure 5: Distributiuon of IBD Control scores for (A) Control-8 and (B) Visual analogue scale. The vertical red lines denote the cut-offs for quiescent disease reported by Bodger et al. (2013).

IBD-Control-8 scores and VAS were both found to be significantly associated with FC.

```
demo %>%
  aov(formula = as.numeric(control_8) ~ cat) %>%
  summary() %>%
  pander()
```

Table 5: ANOVA between control-8 and FC groups across the FC cohort.

Table 5: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 65.25 | 32.63 | 3.335 | 0.03586 |
| **Residuals** | 1694 | 16574 | 9.784 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "CD") %>%
  aov(formula = as.numeric(control_8) ~ cat) %>%
  summary() %>%
  pander()
```

Table 6: ANOVA between control-8 and FC groups in Crohn's disease.

Table 6: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 29.06 | 14.53 | 1.373 | 0.254 |
| **Residuals** | 867 | 9179 | 10.59 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "UC/IBDU") %>%
  aov(formula = as.numeric(control_8) ~ cat) %>%
  summary() %>%
  pander()
```

Table 7: ANOVA between control-8 and FC groups in UC/IBDU.

Table 7: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 73.18 | 36.59 | 4.166 | 0.01584 |
| **Residuals** | 824 | 7238 | 8.783 | NA | NA |

```
demo %>%
  aov(formula = OverallControl ~ cat) %>%
  summary() %>%
  pander()
```

Table 8: ANOVA between control VAS and FC groups across the FC cohort.

Table 8: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 4692 | 2346 | 9.996 | 4.836e-05 |
| **Residuals** | 1687 | 395921 | 234.7 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "CD") %>%
  aov(formula = OverallControl ~ cat) %>%
  summary() %>%
  pander()
```

Table 9: ANOVA between control VAS and FC groups in Crohn's disease.

Table 9: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 1632 | 815.8 | 3.4 | 0.03383 |
| **Residuals** | 862 | 206848 | 240 | NA | NA |

```
demo %>%
  filter(diagnosis2 == "UC/IBDU") %>%
  aov(formula = OverallControl ~ cat) %>%
  summary() %>%
  pander()
```

Table 10: ANOVA between control VAS and FC groups in UC/IBDU.

Table 10: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 2933 | 1467 | 6.448 | 0.001665 |
| **Residuals** | 822 | 186983 | 227.5 | NA | NA |

Instead to treating VAS as a continuous value, going forward, VAS will be discretised into below 85 and 85 and above as a VAS of 85 was found by Bodger et al. (2013) to be predictive of quiescent disease.

```
demo <- demo %>%
  select(-OverallControl)
demo %>%
  drop_na(cat) %>%
  ggplot(aes(x = vas_control, color = vas_control, fill = vas_control)) +
  geom_bar() +
  theme_minimal() +
  theme(legend.position = "none") +
  xlab("Visual analogue scores") +
  ylab("Frequency") +
  scale_color_manual(values = c("#D00000", "#447604"), na.value = "#032B43") +
  scale_fill_manual(values = c("#D00000", "#447604"), na.value = "#032B43")
```

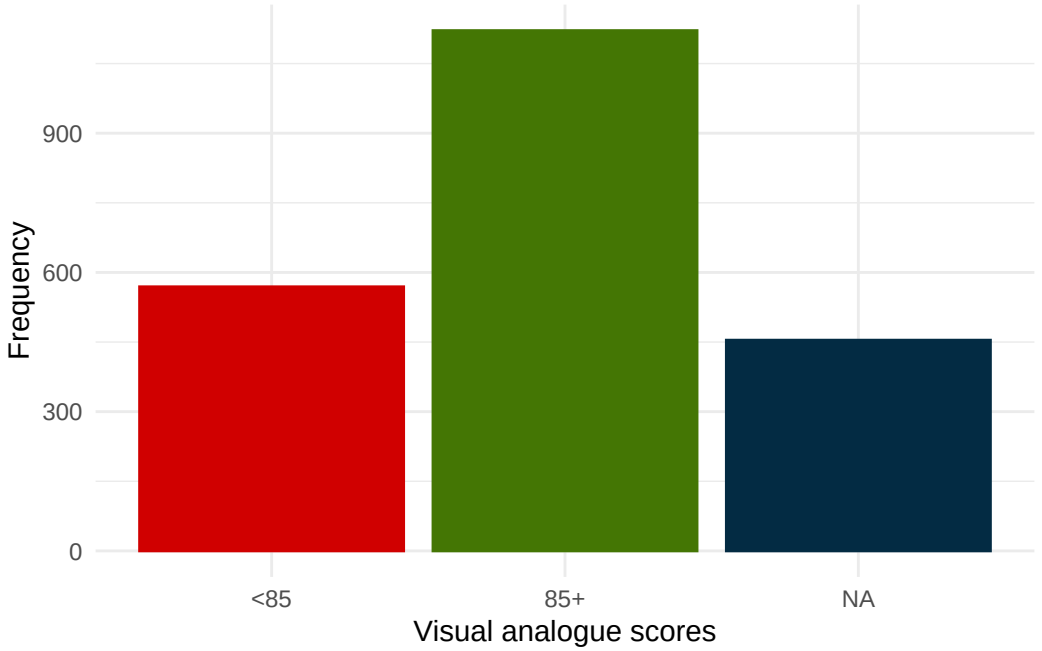



Figure 6: Distribution of discretised IBD-Control-VAS scores.

The discretised VAS is continued to be significantly associated with FC.

```
pander(chisq.test(demo$vas_control, demo$cat))
```

Table 11: Chi squared test between VAS and FC groups.

Table 11: Pearson's Chi-squared test: `demo$vas_control` and `demo$cat`

| Test statistic | df | P value |
|---|---|---|
| 16.89 | 2 | 0.0002153 * * * |

## Medication use

This section is concerned with medication used by study participants. Current treatment strategy, bio-naive status and antibiotic use are considered.

### IBD treatment strategy

```
drugs <- data.frame(ParticipantNo = demo$ParticipantNo)

drugs$ASA <- FALSE
drugs$imm <- FALSE
drugs$bio <- FALSE
drugs$category <- NA

redcap <- redcap %>% mutate(
  curr_on_mesa = ifelse(is.na(curr_on_mesa),
    0,
    curr_on_mesa
  ),
  curr_on_aza = ifelse(is.na(curr_on_aza),
    0,
    curr_on_aza
  ),
  curr_on_merc = ifelse(is.na(curr_on_merc),
    0,
    curr_on_merc
  ),
  curr_on_metho = ifelse(is.na(curr_on_metho),
    0,
    curr_on_metho
  ),
  curr_on_ciclo = ifelse(is.na(curr_on_ciclo),
    0,
    curr_on_ciclo
  ),
  curr_on_inflix = ifelse(is.na(curr_on_inflix),
    0,
    curr_on_inflix
  ),
  curr_on_ada = ifelse(is.na(curr_on_ada),
    0,
    curr_on_ada
  ),
  curr_on_goli = ifelse(is.na(curr_on_goli),
    0,
    curr_on_goli
  ),
```

```
  curr_on_vedo = ifelse(is.na(curr_on_vedo),
    0,
    curr_on_vedo
  ),
  curr_on_ust = ifelse(is.na(curr_on_ust),
    0,
    curr_on_ust
  )
)

for (i in 1:nrow(drugs)) {
  if (drugs[i, "ParticipantNo"] %in% redcap$participantno) {
    subject.data <- subset(redcap, participantno == drugs[i, "ParticipantNo"])[1, ]
    if (subject.data$curr_on_mesa == 1) drugs[i, "ASA"] <- TRUE

    # Immunosuppressants
    if (subject.data$curr_on_aza == 1 |
      subject.data$curr_on_merc == 1 |
      subject.data$curr_on_metho == 1 |
      subject.data$curr_on_ciclo == 1) {
      drugs[i, "imm"] <- TRUE
    }

    # Biologics
    if (subject.data$curr_on_inflix == 1 |
      subject.data$curr_on_ada == 1 |
      subject.data$curr_on_goli == 1 |
      subject.data$curr_on_vedo == 1 |
      subject.data$curr_on_ust == 1) {
      drugs[i, "bio"] <- TRUE
    }
    if (drugs[i, "imm"] & drugs[i, "bio"]) {
      drugs[i, "category"] <- 4
    } else if (drugs[i, "imm"]) {
      drugs[i, "category"] <- 2
    } else if (drugs[i, "bio"]) {
      drugs[i, "category"] <- 3
    } else if (drugs[i, "ASA"]) {
      drugs[i, "category"] <- 1
    }
  }
}
```

```r
drugs$category <- factor(drugs$category,
  levels = 1:4,
  labels = c(
    "5-ASA",
    "Mono immunotherapy",
    "Mono biologic",
    "Combo therapy"
  )
)

drugs <- merge(drugs, demo[, c("ParticipantNo", "cat", "diagnosis2")], by = "ParticipantNo")
colnames(drugs)[5] <- "Treatment"
```

For IBD treatment, subjects are categorised as being on either a 5-ASA, mono immunotherapy, mono biologic, or immuno-biologic combination treatment strategy based upon REDCap data provided by participants' IBD care teams.

Treatments. in REDCap were selected via check boxes. As such, `NA` (unticked) is assumed to mean the participant is not on a given medication.

Immunosuppressants are defined as:

- Azathioprine
- Mercaptopurine
- Methotrexate
- Ciclosporin

Biologics are defined as:

- Infliximab
- Adalimumab
- Golimumab
- Vedolizumab
- Ustekinumab

Patients are only categorised as receiving a 5-ASA treatment plan if 5-ASA is the only IBD treatment they are receiving (I.E no immunotherapy or biologics).

As should be expected given poor efficacy in CD, a 5-ASA treatment strategy is much more common for UC/IBDU participants (Figure 7). Mono biologic therapy is the most common treatment strategy for CD subjects.

```r
plt.cols <- c("#52528C", "#DD6E42", "#048A81", "#C585B3")


p <- drugs %>%
  drop_na(cat) %>%
  ggplot(aes(x = Treatment, fill = Treatment, color = Treatment)) +
  geom_bar() +
  theme_minimal() +
  theme(legend.position = "none") +
  xlab("Treatment strategy") +
  ylab("Frequency") +
  scale_fill_manual(values = plt.cols, na.value = "#032B43") +
  scale_colour_manual(
    values = colorspace::darken(plt.cols, 0.3),
    na.value = "#032B43"
  ) +
  facet_grid(rows = vars(diagnosis2))

ggsave("plots/baseline/treat_strat.pdf" , p, width = 10, height = 8)
ggsave("plots/baseline/treat_strat.png" , p, width = 10, height = 8)
p
```

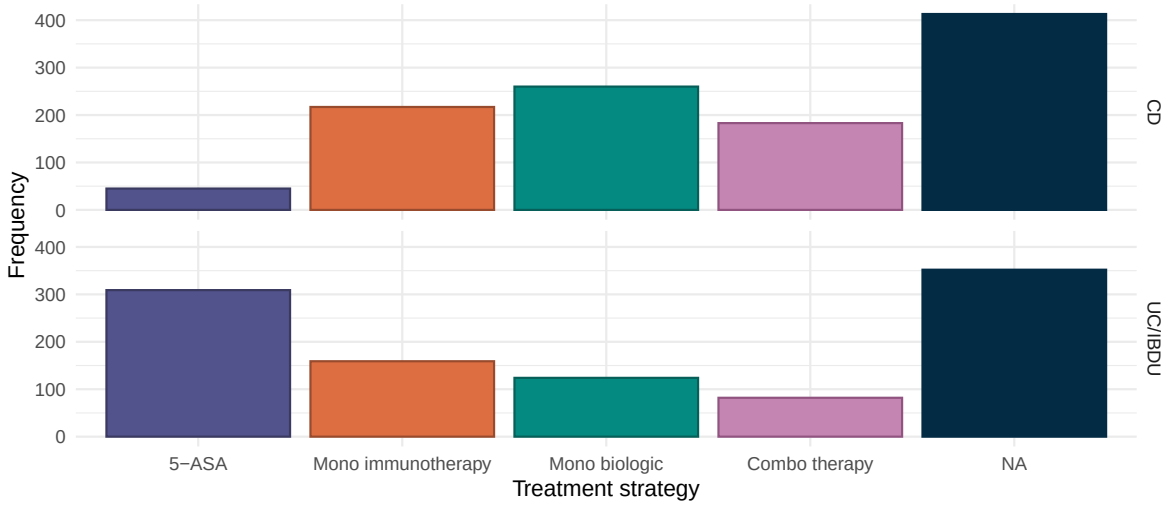



Figure 7: Reported treatment strategies for the FC cohort.

As we are unable to differentiate between participants which are are no treatment and those for whom treatment data is missing, we will instead use a `None reported` category.

```
drugs <- drugs %>%
  mutate(Treatment = if_else(is.na(Treatment),
                             "None reported",
                             Treatment))
demo <- merge(demo,
              drugs[, c("ParticipantNo", "Treatment")],
              by = "ParticipantNo",
              all.x = TRUE,
              all.y = FALSE,
              sort = FALSE)
```

```
pander(with(subset(drugs, diagnosis2 == "CD"), chisq.test(Treatment, cat)))
```

Table 12: Chi-squared test between treatment strategy and FC groups for participants with Crohn's disease.

Table 12: Pearson's Chi-squared test: `Treatment` and `cat`

| Test statistic | df | P value |
|---|---|---|
| 7.571 | 8 | 0.4765 |

```
pander(with(subset(drugs, diagnosis2 == "UC/IBDU"), chisq.test(Treatment, cat)))
```

Table 13: Chi-squared test between treatment strategy and FC groups for participants with Ulcerative colitis/IBDU.

Table 13: Pearson's Chi-squared test: `Treatment` and `cat`

| Test statistic | df | P value |
|---|---|---|
| 12.26 | 8 | 0.1401 |

### Current medications

```
findCurrent <- function(x) {
  sum(x == 1)
}
```

```
drug.cols <- c("participantno",
               "curr_on_mesa",
               "curr_on_aza",
               "curr_on_merc",
               "curr_on_metho",
               "curr_on_ciclo",
               "curr_on_inflix",
               "curr_on_ada",
               "curr_on_goli",
               "curr_on_vedo",
               "curr_on_ust")

drug.tab <- redcap[, drug.cols]

drug.available <- c()
for (i in 1:nrow(drug.tab)) {
  if (any(drug.tab[i, -1] != 0)) {
    drug.available <- c(drug.available, "yes")
  } else(drug.available <- c(drug.available, "no"))
}

drug.tab$available <- drug.available
```

### Whole cohort

```
drug.tab.cd <- subset(drug.tab,
                      participantno %in%
                        subset(demo, diagnosis2 == "CD")$ParticipantNo)
drug.tab.uc <- subset(drug.tab,
                      participantno %in%
                        subset(demo, diagnosis2 == "UC/IBDU")$ParticipantNo)




cd.rx.counts <- sapply(drug.tab.cd[, -1], findCurrent)
uc.rx.counts <- sapply(drug.tab.uc[, -1], findCurrent)

rx.counts <- cbind(cd.rx.counts, uc.rx.counts)
rx.counts <- rx.counts[-nrow(rx.counts), ] # remove available row
rownames(rx.counts) <- c("5-ASA",
```

```
                          "Azathioprine",
                          "Mercaptopurine",
                          "Methotrexate",
                          "Ciclosporin",
                          "Infliximab",
                          "Adalimumab",
                          "Golimumab",
                          "Vedolizumab",
                          "Ustekinumab")
colnames(rx.counts) <- c("Crohn's disease",
                          "Ulcerative colitis/IBDU")


knitr::kable(rx.counts)
```

| | Crohn's disease | Ulcerative colitis/IBDU |
|---|---|---|
| 5-ASA | 89 | 551 |
| Azathioprine | 325 | 218 |
| Mercaptopurine | 93 | 64 |
| Methotrexate | 61 | 14 |
| Ciclosporin | 1 | 1 |
| Infliximab | 286 | 104 |
| Adalimumab | 164 | 29 |
| Golimumab | 0 | 6 |
| Vedolizumab | 65 | 102 |
| Ustekinumab | 14 | 3 |

### FC cohort

```
fc.ids <- demo %>%
  filter(!is.na(cat)) %>%
  pull(ParticipantNo)


drug.tab.fc <- subset(drug.tab,
                      participantno %in% fc.ids)

drug.tab.fc.cd <- subset(drug.tab.fc,
                     participantno %in%
                       subset(demo, diagnosis2 == "CD")$ParticipantNo)
```

```r
drug.tab.fc.uc <- subset(drug.tab.fc,
                      participantno %in%
                        subset(demo, diagnosis2 == "UC/IBDU")$ParticipantNo)



cd.rx.counts <- sapply(drug.tab.fc.cd[, -1], findCurrent)
uc.rx.counts <- sapply(drug.tab.fc.uc[, -1], findCurrent)

rx.counts <- cbind(cd.rx.counts, uc.rx.counts)
rx.counts <- rx.counts[-nrow(rx.counts), ] # remove available row
rownames(rx.counts) <- c("5-ASA",
                         "Azathioprine",
                         "Mercaptopurine",
                         "Methotrexate",
                         "Ciclosporin",
                         "Infliximab",
                         "Adalimumab",
                         "Golimumab",
                         "Vedolizumab",
                         "Ustekinumab")
colnames(rx.counts) <- c("Crohn's disease",
                         "Ulcerative colitis/IBDU")

knitr::kable(rx.counts)
```

| | Crohn's disease | Ulcerative colitis/IBDU |
|---|---|---|
| 5-ASA | 75 | 436 |
| Azathioprine | 270 | 177 |
| Mercaptopurine | 78 | 51 |
| Methotrexate | 52 | 12 |
| Ciclosporin | 1 | 1 |
| Infliximab | 241 | 87 |
| Adalimumab | 137 | 21 |
| Golimumab | 0 | 5 |
| Vedolizumab | 55 | 90 |
| Ustekinumab | 10 | 3 |

### FFQ Cohort

```r
FFQ <- read_xlsx(paste0(
  prefix,
  "predicct ffq_nutrientfood groupDQI all foods_data (n1092)Nov2022.xlsx"
))

FFQ <- FFQ %>%
  filter(!is.na(fibre))

ffq.ids <- fc.ids[fc.ids %in% FFQ$participantno]




drug.tab.ffq <- subset(drug.tab,
                       participantno %in% ffq.ids)

drug.tab.ffq.cd <- subset(drug.tab.ffq,
                      participantno %in%
                        subset(demo, diagnosis2 == "CD")$ParticipantNo)
drug.tab.ffq.uc <- subset(drug.tab.ffq,
                      participantno %in%
                        subset(demo, diagnosis2 == "UC/IBDU")$ParticipantNo)




cd.rx.counts <- sapply(drug.tab.ffq.cd[, -1], findCurrent)
uc.rx.counts <- sapply(drug.tab.ffq.uc[, -1], findCurrent)

rx.counts <- cbind(cd.rx.counts, uc.rx.counts)
rx.counts <- rx.counts[-nrow(rx.counts), ] # remove available row
rownames(rx.counts) <- c("5-ASA",
                         "Azathioprine",
                         "Mercaptopurine",
                         "Methotrexate",
                         "Ciclosporin",
                         "Infliximab",
                         "Adalimumab",
                         "Golimumab",
                         "Vedolizumab",
                         "Ustekinumab")
colnames(rx.counts) <- c("Crohn's disease",
```

```
                          "Ulcerative colitis/IBDU")

knitr::kable(rx.counts)
```

| | Crohn's disease | Ulcerative colitis/IBDU |
|---|---|---|
| 5-ASA | 30 | 223 |
| Azathioprine | 111 | 79 |
| Mercaptopurine | 32 | 23 |
| Methotrexate | 16 | 4 |
| Ciclosporin | 0 | 0 |
| Infliximab | 81 | 27 |
| Adalimumab | 69 | 13 |
| Golimumab | 0 | 4 |
| Vedolizumab | 19 | 29 |
| Ustekinumab | 3 | 2 |

**Bio-naive status**

```
bio.naive <- data.frame(ParticipantNo = redcap$participantno)
bio.naive <- subset(bio.naive, ParticipantNo %in% demo$ParticipantNo)
bio.naive <- merge(bio.naive,
  demo[, c("ParticipantNo", "diagnosis")],
  all.y = TRUE,
  all.x = FALSE
)
bio.naive <- distinct(bio.naive, ParticipantNo, .keep_all = TRUE)
bio.naive$naive <- "yes"

bio.vars <- c("inflix", "ada", "goli", "vedo", "ust")

for (i in 1:nrow(bio.naive)) {
  temp.df <- as.data.frame(subset(redcap, participantno == bio.naive[i, 1]))
  temp.df <- temp.df[, paste0("curr_on_", bio.vars)]
  temp.df <- temp.df[, !is.na(temp.df[1, ])]

  if (any(temp.df == 1)) {
    bio.naive[i, "naive"] <- "no-using"
  } else if (any(temp.df == 2)) {
    bio.naive[i, "naive"] <- "no-not-using"
```

```
  } # else naive
}

drugs.eof <- read_xlsx(paste0(prefix, "EOF_drugs.xlsx"))
using <- subset(drugs.eof, AtRecruitmentYN == 1)
bio.list <- seq(4, 8)
using <- subset(using, DrugType %in% bio.list)
using <- subset(demo, ParticipantId %in% using$ParticipantId)
using <- using[, c("ParticipantNo", "diagnosis")]
using$naive <- c("no-using")

drugs <- rbind(bio.naive, using)

for (i in unique(drugs$ParticipantNo)) {
  temp <- subset(drugs, ParticipantNo == i)
  # if "no-using" in either extract then report using
  if (nrow(temp) > 1) {
    if (any(temp$naive == "no-using")) {
      drugs <- subset(drugs, ParticipantNo != i)
      drugs <- rbind(
        drugs,
        data.frame(
          ParticipantNo = i,
          diagnosis = temp[1, "diagnosis"],
          naive = "no-using"
        )
      )
    }
  }
}

drugs <- distinct(drugs, ParticipantNo, .keep_all = TRUE)

demo <- merge(demo,
  drugs[, c(1, 3)],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

demo$naive <- factor(demo$naive,
  levels = c("no-using", "no-not-using", "yes"),
```

```
  labels = c("Current", "Previously", "Never prescribed")
)

colnames(demo)[colnames(demo) == "naive"] <- "Biologic"
```

Bio-naive status has been determined using REDCap and EoS data. As clinical teams were not explicitly asked if a subject was bio-naive, the subject is instead defined as being bio-naive if there are no recorded biologics for the subject (which may bias subjects with missing data towards incorrectly being reported as bio-naive). Non bio-naive subjects are categorised further into either "currently using" or "previously used".

Biologic treatments are defined as infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab.

Small molecule treatments are not considered in this report due to their low prescribing rates during the recruitment period (which ended March 2020).

```
demo %>%
  drop_na(cat) %>%
  ggplot(aes(x = Biologic, fill = Biologic, color = Biologic)) +
  geom_bar() +
  xlab("Biologic status") +
  ylab("Frequency") +
  theme_minimal() +
  theme(legend.position = "none") +
  scale_fill_manual(values = c("#CACF85", "#8CBA80", "#E58F65")) +
  scale_color_manual(values = c("#747825", "#4A6E3F", "#934D1B")) +
  guides(
    fill = guide_legend(title = "Biologic status"),
    color = guide_legend(title = "Biologic status")
  ) +
  facet_grid(rows = vars(diagnosis2))
```

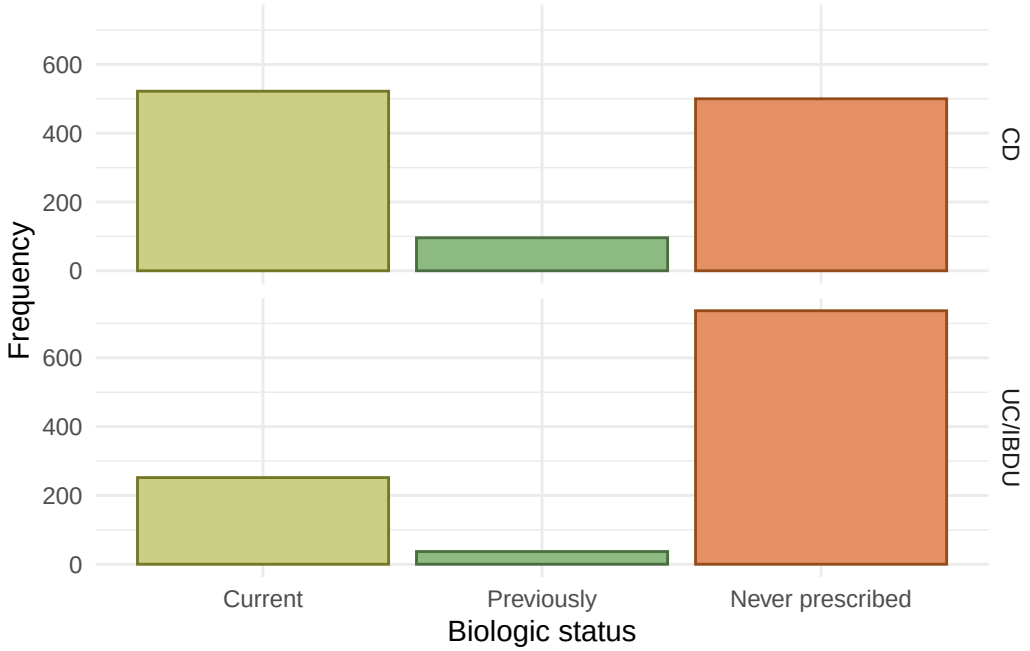



Figure 8: Bio-naivety in the FC cohort.

Bio-naive status was found to be associated with FC groups which may be due to patients with more active disease being more likely to be prescribed a biologic.

```
pander(chisq.test(demo$Biologic, demo$cat))
```

Table 17: Chi-squared test between bio-naive status and FC groups.

Table 17: Pearson's Chi-squared test: `demo$Biologic` and `demo$cat`

| Test statistic | df | P value |
|---|---|---|
| 16.51 | 4 | 0.002406 * * |

## Smoking

```
smoking <- read_xlsx(paste0(data.path, "Baseline2022/lifestyle.xlsx")) %>%
  select(ParticipantNo, Smoke, SmokedInPast)
smoking$Smoke <- plyr::mapvalues(smoking$Smoke, from = 2, to = 3)
```

```r
for (i in 1:nrow(smoking)) {
  if ((!is.na(smoking[i, "SmokedInPast"]) & smoking[i, "SmokedInPast"] == 1) & (!is.na(smoki
    smoking[i, "Smoke"] <- 2
  }
}

smoking$Smoke <- factor(smoking$Smoke,
  levels = seq(1, 3),
  labels = c("Current", "Previous", "Never")
)

smoking <- smoking[, -3]


demo <- merge(demo,
  smoking,
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

esmoking <- read_xlsx(paste0(data.path, "Baseline2022/lifestyle.xlsx")) %>%
  select(ParticipantNo, ECigs, ECigsPast)
esmoking$ECigs <- plyr::mapvalues(esmoking$ECigs, from = 2, to = 3)

for (i in 1:nrow(esmoking)) {
  if ((!is.na(esmoking[i, "ECigsPast"] == 1) & esmoking[i, "ECigsPast"] == 1) &
      (!is.na(esmoking[i, "ECigs"]) & esmoking[i, "ECigs"] == 3)) {
    esmoking[i, "ECigs"] <- 2
  }
}

esmoking$ECigs <- factor(esmoking$ECigs,
  levels = seq(1, 3),
  labels = c("Current", "Previous", "Never")
)

esmoking <- esmoking[, -3]


demo <- merge(demo,
  esmoking,
```

```
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)
```

```
demo %>%
  drop_na(cat) %>%
  ggplot(aes(x = Smoke, fill = Smoke, color = Smoke)) +
  geom_bar() +
  xlab("Smoking status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Smoking status"),
    color = guide_legend(title = "Smoking status")
  )
```

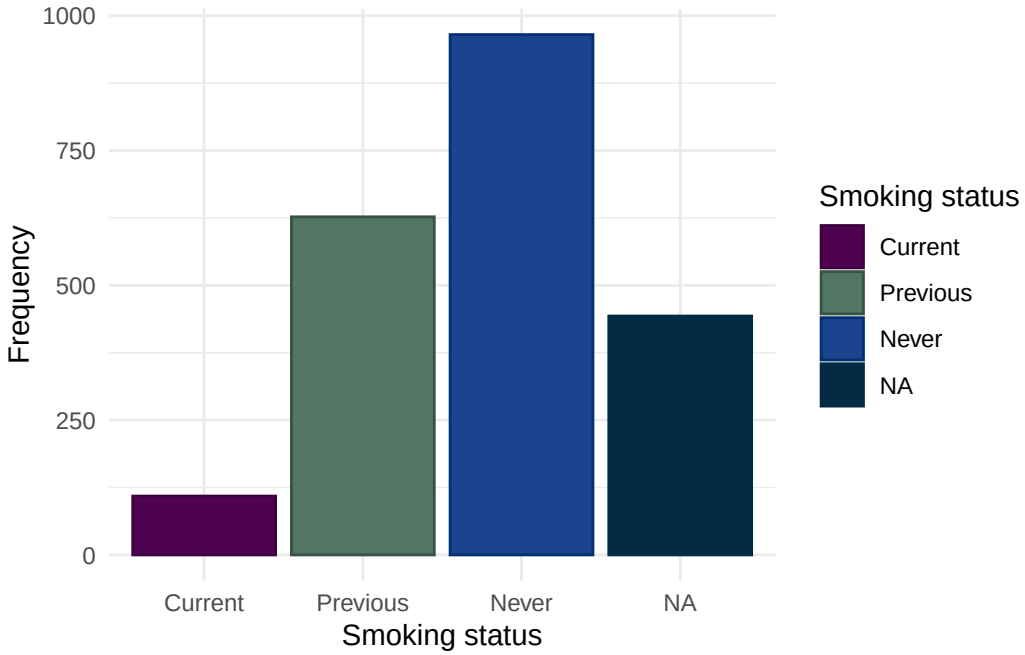



Figure 9: Smoking status for subjects in the FC cohort.

Smoking status is not associated with FC at recruitment across the entire FC cohort.

```
pander(chisq.test(demo$Smoke, demo$cat))
```

Table 18: Chi-squared test between between smoking status and FC groups.

Table 18: Pearson's Chi-squared test: `demo$Smoke` and `demo$cat`

| Test statistic | df | P value |
|---|---|---|
| 8.662 | 4 | 0.07013 |

## E-cigarette use

The vast majority of participants do not report using some form of e-cigarettes. It should be noted that as recruitment ended March 2020, these day may not reflect more modern trends.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = ECigs, fill = ECigs, color = ECigs)) +
```

```
  geom_bar() +
  xlab("E-cigarette status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "E-cigarette status"),
    color = guide_legend(title = "E-cigarette status")
  )
```

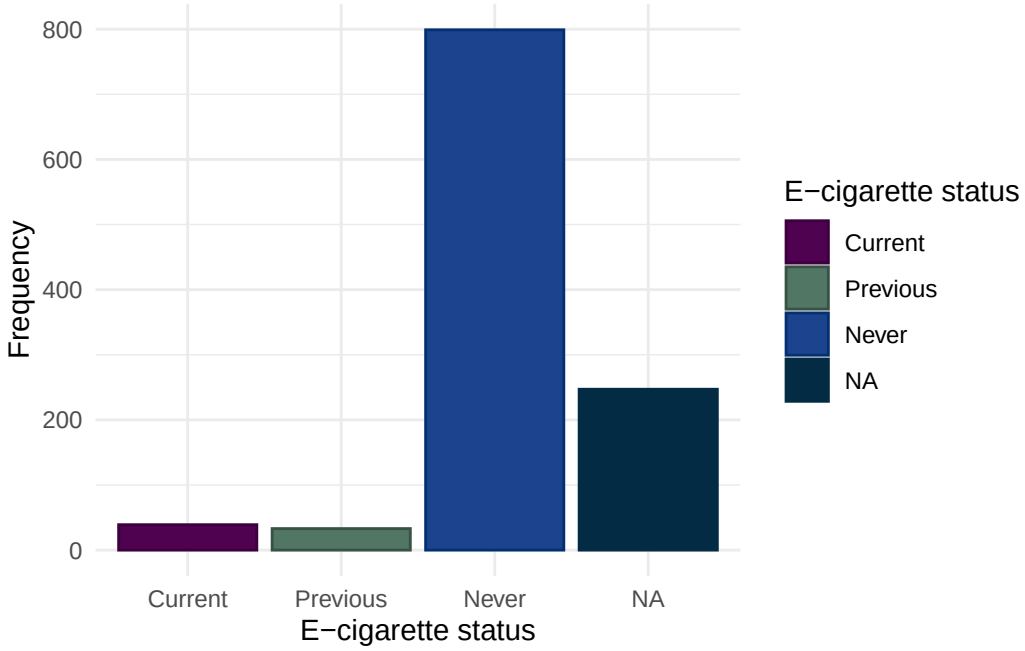



Figure 10: E-cigarette usage for subjects in the FC cohort.

```
pander(chisq.test(demo.cd$ECigs, demo.cd$cat))
```

Table 19: Chi-squared test between between E-cigarettte usage and FC groups.

Table 19: Pearson's Chi-squared test: `demo.cd$ECigs` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 5.96 | 4 | 0.2022 |

## Variables only relevant to Crohn's disease subjects

This section looks at data only applicable to subjects with CD. The following variables are considered: surgery, Montreal location, Montreal behaviour, Harvey-Bradshaw index, and smoking.

### Surgery

```
predicct.surgery <- read_xlsx(paste0(
  data.path,
  "Baseline2022/IBD.xlsx"
))[, c("ParticipantNo", "HadSurgeryForIBD")]
colnames(predicct.surgery)[2] <- "Surgery"


redcap.surgery <- redcap[, c("participantno", "surgery")]


names(redcap.surgery) <- c("ParticipantNo", "Surgery")

surgery <- rbind(redcap.surgery, predicct.surgery)
surgery <- subset(surgery, !is.na(surgery$Surgery))

# As REDCap is first, this will be prioritised over subject (if not NA)
surgery <- distinct(surgery, ParticipantNo, .keep_all = TRUE)

demo.cd <- subset(demo, diagnosis2 == "CD")
demo.cd <- merge(demo.cd, surgery, all.x = TRUE, all.y = FALSE)
demo.cd$Surgery <- factor(demo.cd$Surgery,
  levels = c(2, 1),
  labels = c("No", "Yes")
)
```

Surgical data has been obtained from both REDCap and patient-completed questionnaires. Where data are available from both data sources, REDCap is the preferred data source.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = Surgery, fill = Surgery, color = Surgery)) +
  geom_bar() +
  xlab("Previous surgery") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(values = c("#F9B9B7", "#96C9DC"), na.value = "#032B43") +
  scale_color_manual(values = c("#D06965", "#448CA2"), na.value = "#032B43")
```

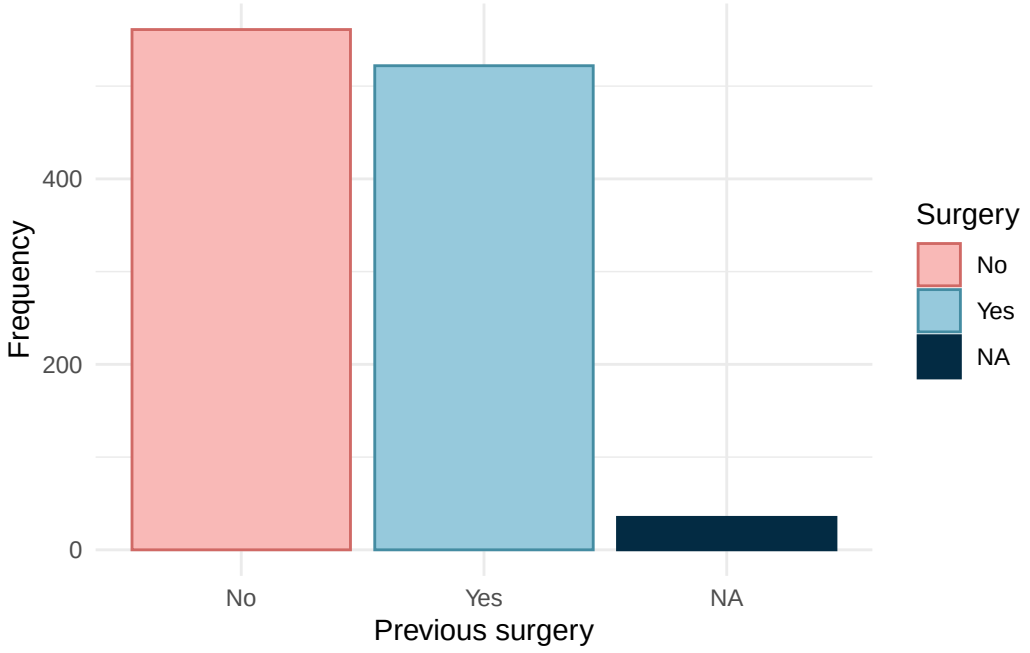



Figure 11: Previous surgery for Crohn's disease subjects in the FC cohort.

FC at study recruitment is significantly associated with having previously undergone surgery for CD.

```
pander(chisq.test(demo.cd$Surgery, demo.cd$cat))
```

Table 20: Chi-squared test between previous surgery and FC groups.

Table 20: Pearson's Chi-squared test: `demo.cd$Surgery` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 7.389 | 2 | 0.02486 * |

### Montreal location

```
mapping <- data.frame(
  code = seq(1, 6),
  definition = c(
    "Oesophago-gastric",
    "Duodenal",
    "Jejunal",
    "Ileal",
    "Colonic",
    "Rectal"
  )
)

cd.location <- redcap[, c("participantno", paste0("mac_extent___", 1:6))]
L4 <- rep(0, nrow(cd.location))
Location <- rep(NA, nrow(cd.location))

for (i in 1:nrow(cd.location)) {
  # If Oesophago-gastric, Duodenal, Jejunal, then L4 is present
  if (any(cd.location[i, 2:4] == 1)) L4[i] <- 1
  if (cd.location[i, 5] == 1 & cd.location[i, 6] == 1) {
    Location[i] <- 3 # Ileal-colonic
  } else if (cd.location[i, 5] == 1 & cd.location[i, 6] == 0) {
    Location[i] <- 1 # Ileal only
  } else if (cd.location[i, 5] == 0 & cd.location[i, 6] == 1) {
    Location[i] <- 2 # Colonic only
  }
  if (is.na(Location[i]) & L4[i] == 1) {
    Location[i] <- 4 # L4 Only
  }
}
```

```
L4[is.na(Location) & L4 == 0] <- NA

mont.df <- data.frame(
  cd.location[, "participantno"],
  Location,
  L4
)
colnames(mont.df)[1] <- "ParticipantNo"
demo.cd <- merge(demo.cd, mont.df,
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

demo.cd$Location <- factor(demo.cd$Location,
  levels = c(1, 2, 3, 4),
  labels = c("L1", "L2", "L3", "L4 only")
)

demo.cd$L4 <- factor(demo.cd$L4,
  levels = c(0, 1),
  labels = c("Not present", "Present")
)
```

Montreal location has been obtained from REDcap data. Rather than being asked for Montreal location directly, clinical teams were asked to provide more granular detail by ticking boxes if inflammation was in any of the following areas Oesophago-gastric, Duodenal, Jejunal, Ileal, Colonic, Rectal. If only any of the first 3 were reported then the subject was assigned "L4 only". L1-L3 were assigned as per convention (Silverberg et al. 2005). If no location was reported then location was assigned `NA`.

As can be seen in Figure 12, L3 is the most common Montreal location in this cohort with roughly an equal amount of subjects having either L1 or L2.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = Location, fill = Location, color = Location)) +
  geom_bar() +
  xlab("Montreal location") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
```

```
    values = c("#33CA7F", "#96C9DC", "#C33C54", "#FCB97D"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#318859", "#448CA2", "#80333E", "#BD7700"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Montreal location"),
    color = guide_legend(title = "Montreal location")
  )
```

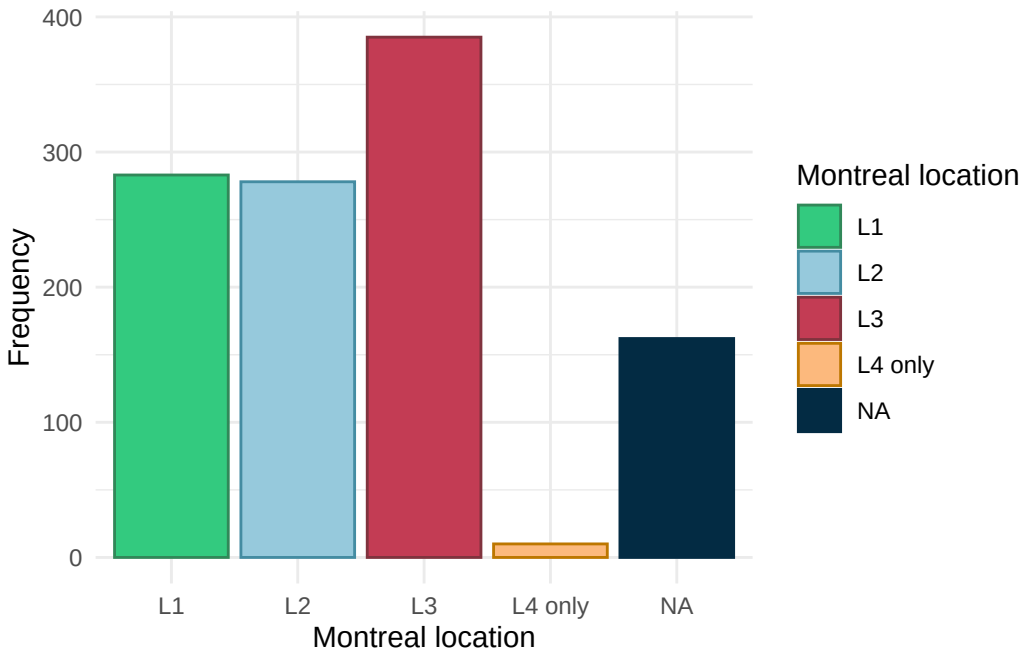



Figure 12: Montreal location for CD subjects in the FC cohort.

Due to the low number of subjects with L4-only, Fisher's exact test has been used to compare with FC.

```
pander(fisher.test(demo.cd$Location, demo.cd$cat, workspace = 20000000))
```

Table 21: Fisher's exact test between Montreal location and FC groups.

Table 21: Fisher's Exact Test for Count Data: `demo.cd$Location` and `demo.cd$cat`

| P value | Alternative hypothesis |
|---|---|
| 0.6059 | two.sided |

In addition to L4-only being considered, we also investigate L4 as a modifier.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = L4, fill = L4, color = L4)) +
  geom_bar() +
  xlab("Presence of L4") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(values = c("#51E5FF", "#EC368D"), na.value = "#032B43") +
  scale_color_manual(values = c("#079DB1", "#AF0863"), na.value = "#032B43") +
  guides(
    fill = guide_legend(title = "Presence of L4"),
    color = guide_legend(title = "Presence of L4")
  )
```

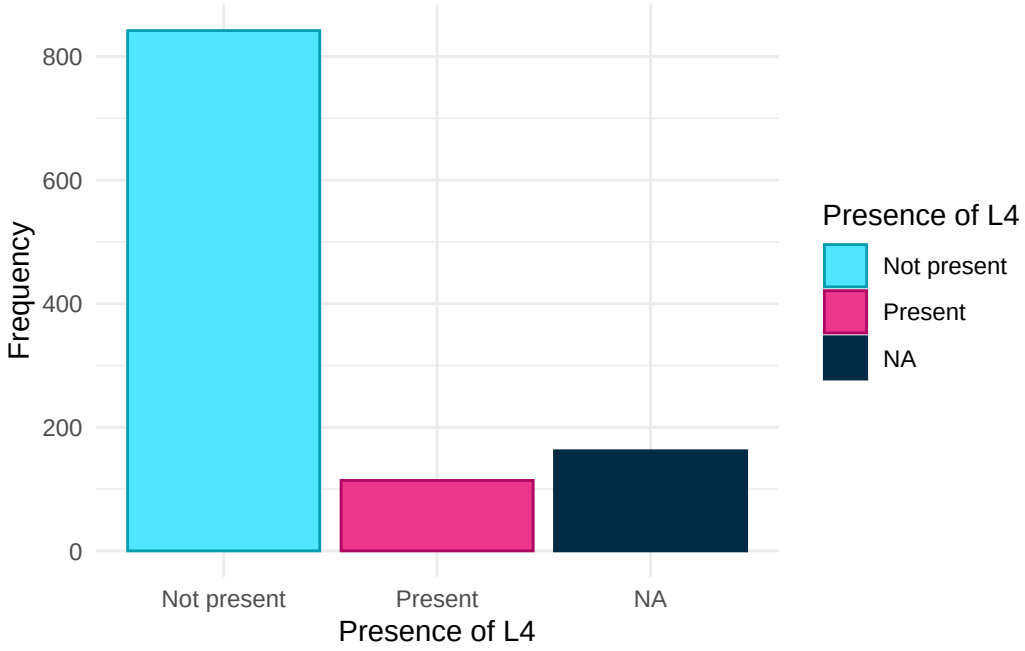



Figure 13: L4 (upper GI involvement) in the FC cohort.

```
pander(chisq.test(demo.cd$L4, demo.cd$cat))
```

Table 22: Chi-squared test between L4 and FC groups.

Table 22: Pearson's Chi-squared test: `demo.cd$L4` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 5.611 | 2 | 0.06047 |

### Montreal behaviour

```
cd.behaviour <- redcap[, c("participantno", "behaviour", "perianal")]
colnames(cd.behaviour) <- c("ParticipantNo", "Behaviour", "Perianal")
cd.behaviour$Perianal[!is.na(cd.behaviour$Perianal) & cd.behaviour$Perianal == 3] <- NA


demo.cd <- merge(demo.cd,
  cd.behaviour,
```

```
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

demo.cd$Behaviour <- factor(demo.cd$Behaviour,
  levels = c(1, 2, 3),
  labels = c("B1", "B2", "B3")
)
```

Montreal behaviour has been obtained from REDCap data and was recorded conventionally. The majority of CD subjects have the B1 (inflammatory) phenotype.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = Behaviour, fill = Behaviour, color = Behaviour)) +
  geom_bar() +
  xlab("Montreal behaviour") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#7AE7C7", "#440381", "#D64045"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#07A282", "#340165", "#942E31"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Montreal behaviour"),
    color = guide_legend(title = "Montreal behaviour")
  )
```

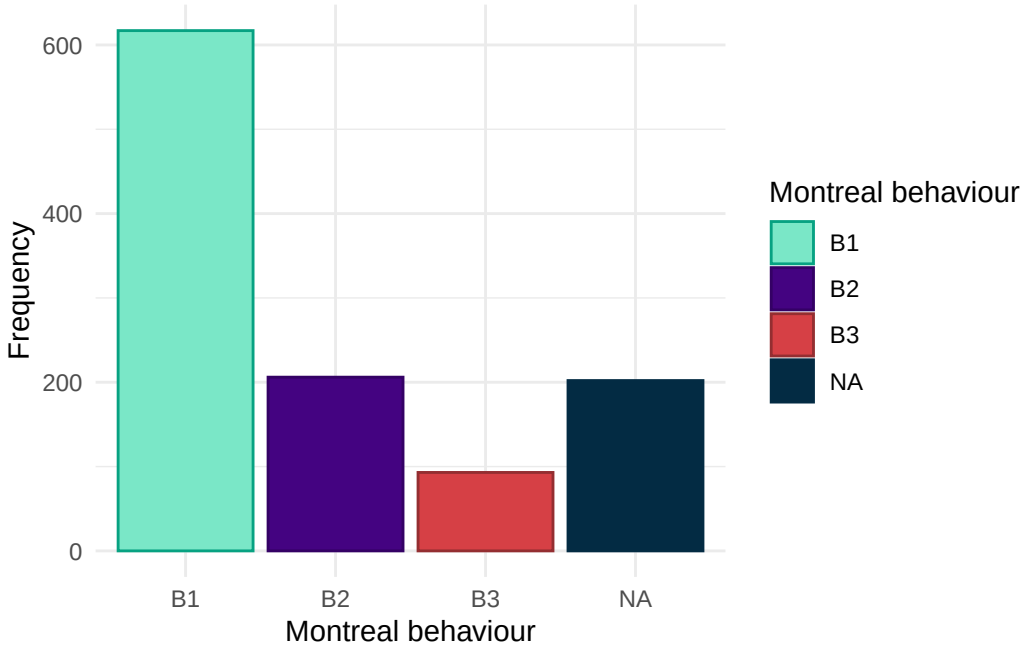



Figure 14: Montreal behaviour for CD subjects in the FC cohort.

Montreal behaviour is not significantly associated with FC at recruitment.

```
pander(chisq.test(demo.cd$Behaviour, demo.cd$cat))
```

Table 23: Chi-squared test between Montreal behaviour and FC groups.

Table 23: Pearson's Chi-squared test: `demo.cd$Behaviour` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 5.136 | 4 | 0.2736 |

Approximately a third of CD subjects are reported to have perianal disease.

```
demo.cd$Perianal <- factor(demo.cd$Perianal,
  levels = c(2, 1),
  labels = c("No", "Yes")
)

demo.cd %>%
```

```
  drop_na(cat) %>%
  ggplot(aes(x = Perianal, fill = Perianal, color = Perianal)) +
  geom_bar() +
  xlab("Perianal disease") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(values = c("#023C40", "#AF5B5B"), na.value = "#032B43") +
  scale_color_manual(values = c("#002C30", "#754242"), na.value = "#032B43") +
  guides(
    fill = guide_legend(title = "Perianal disease"),
    color = guide_legend(title = "Perianal disease")
  )
```

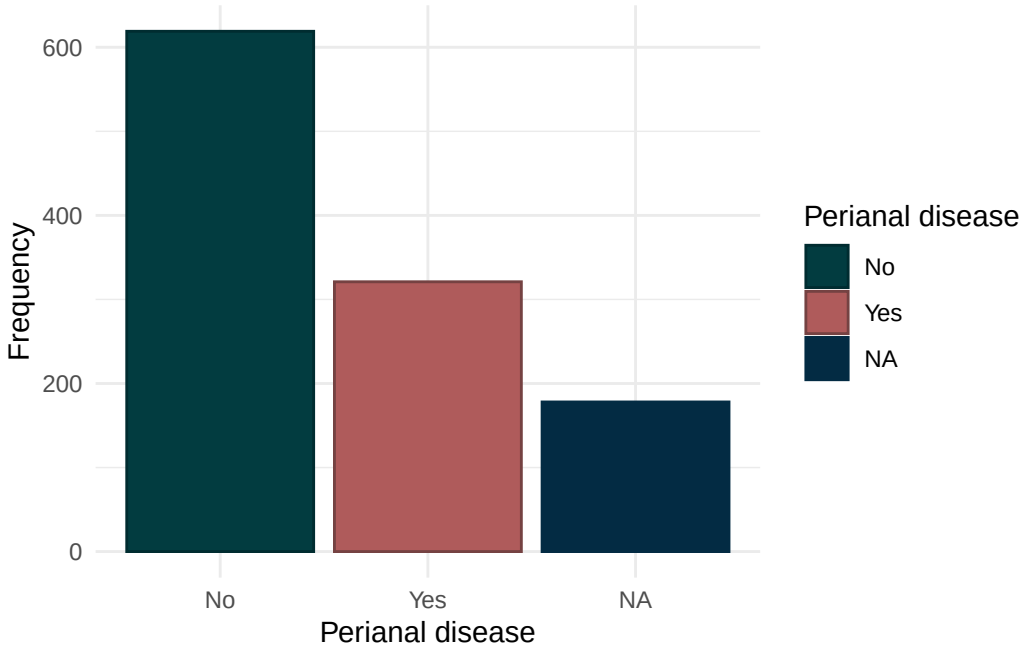



Figure 15: Perianal disease for CD subjects in the FC cohort.

Perianal disease is not associated with FC at recruitment.

```
pander(chisq.test(demo.cd$Perianal, demo.cd$cat))
```

Table 24: Chi-squared test between between perianal disease and FC groups.

Table 24: Pearson's Chi-squared test: `demo.cd$Perianal` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 1.305 | 2 | 0.5207 |

### Harvey-Bradshaw Index

```
HBI.df <- redcap[, c("participantid", "current_hb")]
colnames(HBI.df) <- c("ParticipantId", "HBI")
HBI.df <- subset(HBI.df, ParticipantId %in% demo.cd$ParticipantId)

demo.cd <- merge(demo.cd, HBI.df, by = "ParticipantId", all.x = TRUE)

temp <- demo.cd %>%
  drop_na(cat)
percHBI <- round(sum(is.na(temp$HBI)) / nrow(temp), 2) * 100
```

Whilst HBI was collected via REDCap, substantial missingness is observed with 60% of CD subjects in the FC sub-cohort missing HBI.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = as.factor(HBI))) +
  geom_bar(fill = "#A167A5", color = "#4A306D") +
  theme_minimal() +
  ylab("Frequency") +
  xlab("Harvey-Bradshaw index at time of recruitment")
```


Figure 16: Harvey-Bradshaw index for CD subjects in the FC cohort.

```
pander(summary(aov(HBI ~ cat, data = demo.cd)))
```

Table 25: ANOVA between between Harvey-Bradshaw index and FC groups.

Table 25: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 13.1 | 6.548 | 1.174 | 0.3102 |
| **Residuals** | 441 | 2461 | 5.579 | NA | NA |

### PRO-2 in Crohn's disease

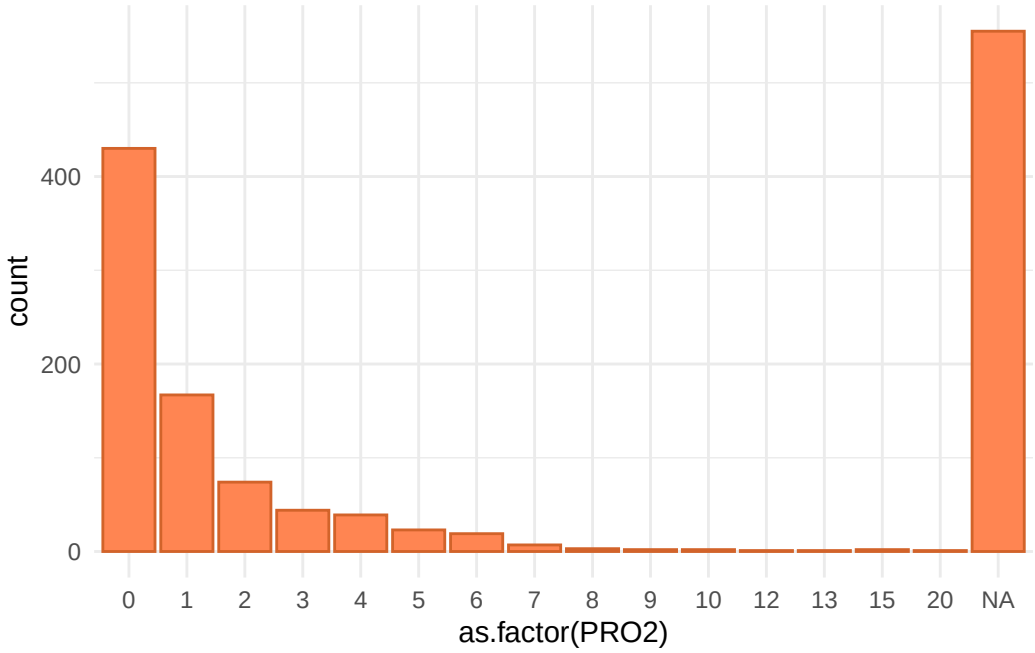
Sum of liquid stools per day and abdominal pain.

```
PRO2 <- redcap[, c("participantno", "liq_stool_day", "abdo_pain")]
PRO2$liq_stool_day <- as.numeric(PRO2$liq_stool_day) # Drop ileostomies

PRO2$PRO2 <- with(PRO2, liq_stool_day + abdo_pain)
```

```r
PRO2$ParticipantNo <- PRO2$participantno
demo.cd <- merge(demo.cd,
  PRO2[, c("ParticipantNo", "PRO2")],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

demo.cd %>%
  ggplot(aes(x = as.factor(PRO2))) +
  geom_bar(fill = "#FF8552", color = "#D2632A") +
  scale_fill_manual(na.value = "#032B43") +
  scale_color_manual(na.value = "#032B43") +
  theme_minimal()
```




```r
pander(summary(aov(PRO2 ~ cat, data = demo.cd)))
```

Table 26: ANOVA between between PRO2 and FC groups in Crohn's disease.

Table 26: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 4.8 | 2.4 | 0.6194 | 0.5386 |
| **Residuals** | 669 | 2592 | 3.875 | NA | NA |

### Smoking

```
percPrev <- round(sum(temp$Smoke == "Previous", na.rm = TRUE) / nrow(temp), 2) * 100
```

We consider smoking for CD and UC separately as smoking is often reported to worsen outcomes in CD but is possibly protective in UC. Smoking status is self-reported by study participants.

Whilst most subjects have never been a smoker, a substantial proportion of subjects (27%) have previously been smokers.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = Smoke, fill = Smoke, color = Smoke)) +
  geom_bar() +
  xlab("Smoking status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Smoking status"),
    color = guide_legend(title = "Smoking status")
  )
```

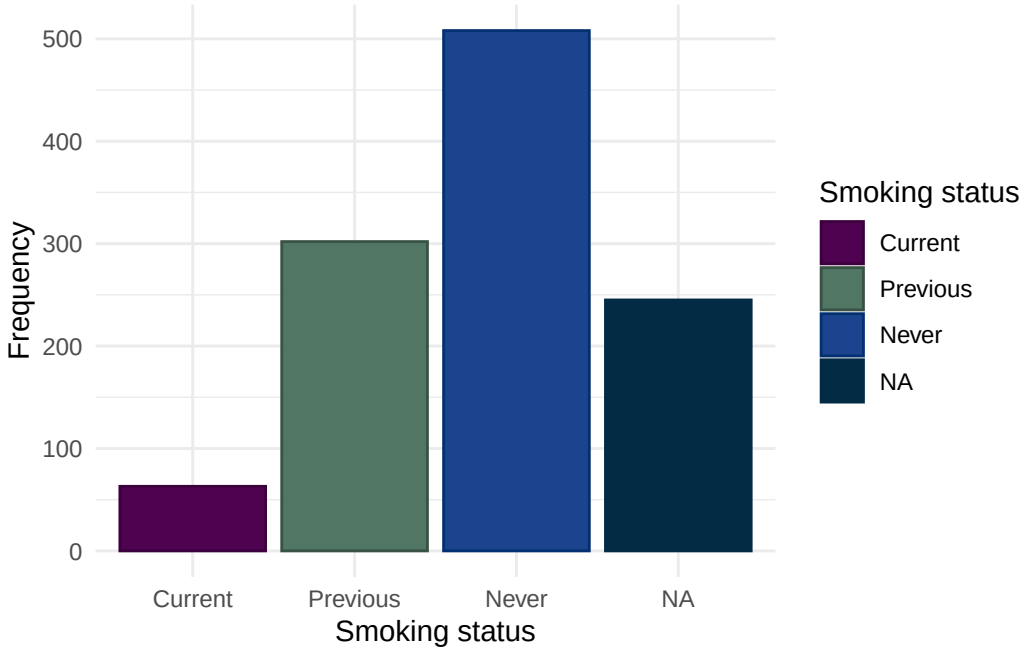



Figure 17: Smoking status for CD subjects in the FC cohort.

Smoking status is associated with FC at recruitment for CD subjects.

```
pander(chisq.test(demo.cd$Smoke, demo.cd$cat))
```

Table 27: Chi-squared test between between smoking status and FC groups for CD subjects.

Table 27: Pearson's Chi-squared test: `demo.cd$Smoke` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 11.08 | 4 | 0.02572 * |

### E-cigarette use

The vast majority of participants do not report using some form of e-cigarettes. It should be noted that as recruitment ended March 2020, these day may not reflect more modern trends.

```
demo.cd %>%
  drop_na(cat) %>%
  ggplot(aes(x = ECigs, fill = ECigs, color = ECigs)) +
```

```
  geom_bar() +
  xlab("E-cigarette status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "E-cigarette status"),
    color = guide_legend(title = "E-cigarette status")
  )
```

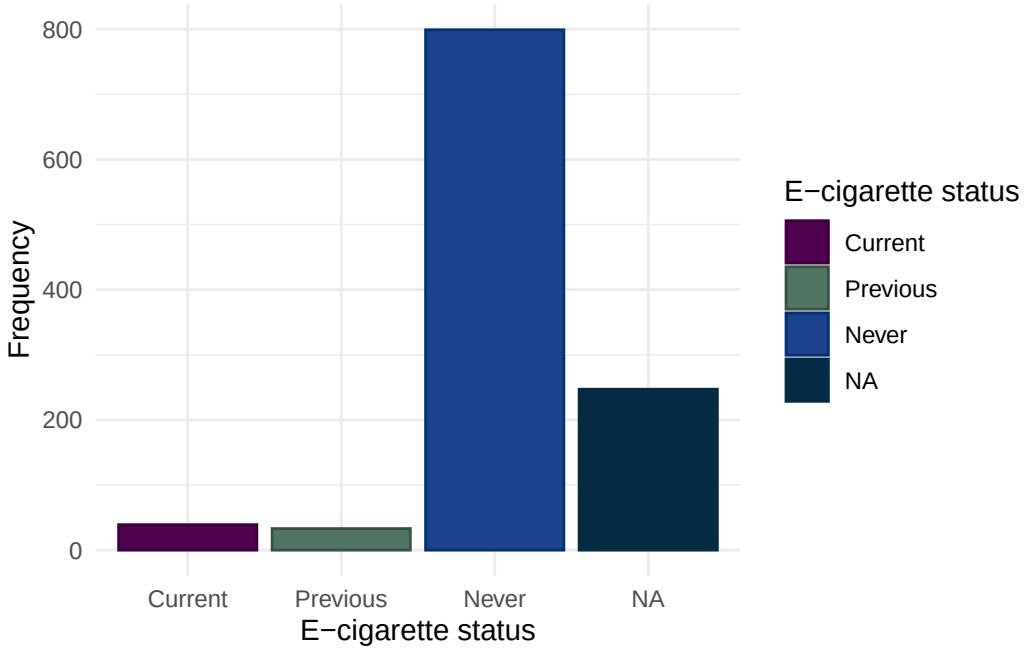



Figure 18: E-cigarette usage for CD subjects in the FC cohort.

```
pander(chisq.test(demo.cd$ECigs, demo.cd$cat))
```

Table 28: Chi-squared test between between E-cigarettte usage and FC groups for CD subjects.

Table 28: Pearson's Chi-squared test: `demo.cd$ECigs` and `demo.cd$cat`

| Test statistic | df | P value |
|---|---|---|
| 5.96 | 4 | 0.2022 |

### Variables only relevant to ulcerative colitis/IBDU subjects

This section looks at variables only relevant to UC/IBDU subjects: Montreal extent, Mayo score, Smoking status and E-cigarette use.

As PREdiCCt required subjects to be able to flare, this effectively excluded UC subjects who had undergone a proctocolectomy. As such, previous surgery is not considered. Montreal severity was not collected by PREdiCCt.

#### Montreal extent

```
mapping <- data.frame(
  code = seq(1, 6),
  definition = c(
    "Rectum",
    "Recto-sigmoid",
    "< Splenic",
    "< Hepatic",
    "Total",
    "Unknown"
  ),
  mont = c(1, 2, 2, 3, 3, NA)
)

demo.uc <- subset(demo, diagnosis2 == "UC/IBDU")
redcap.uc <- subset(redcap, participantno %in% demo.uc$ParticipantNo)
names(redcap.uc)[names(redcap.uc) == "participantno"] <- "ParticipantNo"
redcap.uc <- redcap.uc[, c("ParticipantNo", "max_extent")]
redcap.uc$Extent <- mapvalues(redcap.uc$max_extent,
  from = mapping$code,
  to = mapping$mont
)
```

```r
demo.uc <- merge(demo.uc,
  redcap.uc[, c("ParticipantNo", "Extent")],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)
demo.uc$Extent <- factor(demo.uc$Extent,
  levels = seq(1, 3),
  labels = c("E1", "E2", "E3")
)
```

Montreal extent has been obtained from REDCap. Similar to Montreal location, the extent of inflammation has been reported in more granular detail than is required for the Montreal classification. The below table shows how these definitions have been mapped to Montreal extent.

```r
kable(mapping,
  col.names = c("Coding", "Definition", "Montreal extent"),
  align = c("l", "c", "c")
)
```

| Coding | Definition | Montreal extent |
|---|---|---|
| 1 | Rectum | 1 |
| 2 | Recto-sigmoid | 2 |
| 3 | < Splenic | 2 |
| 4 | < Hepatic | 3 |
| 5 | Total | 3 |
| 6 | Unknown | NA |

As can be seen in Figure 19 E2 is the most common Montreal extent classification.

```r
demo.uc %>%
  drop_na(cat) %>%
  ggplot(aes(x = Extent, fill = Extent, color = Extent)) +
  geom_bar() +
  xlab("Montreal extent") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#7AE7C7", "#440381", "#D64045"),
```

```
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#07A282", "#340165", "#942E31"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Montreal extent"),
    color = guide_legend(title = "Montreal extent")
  )
```

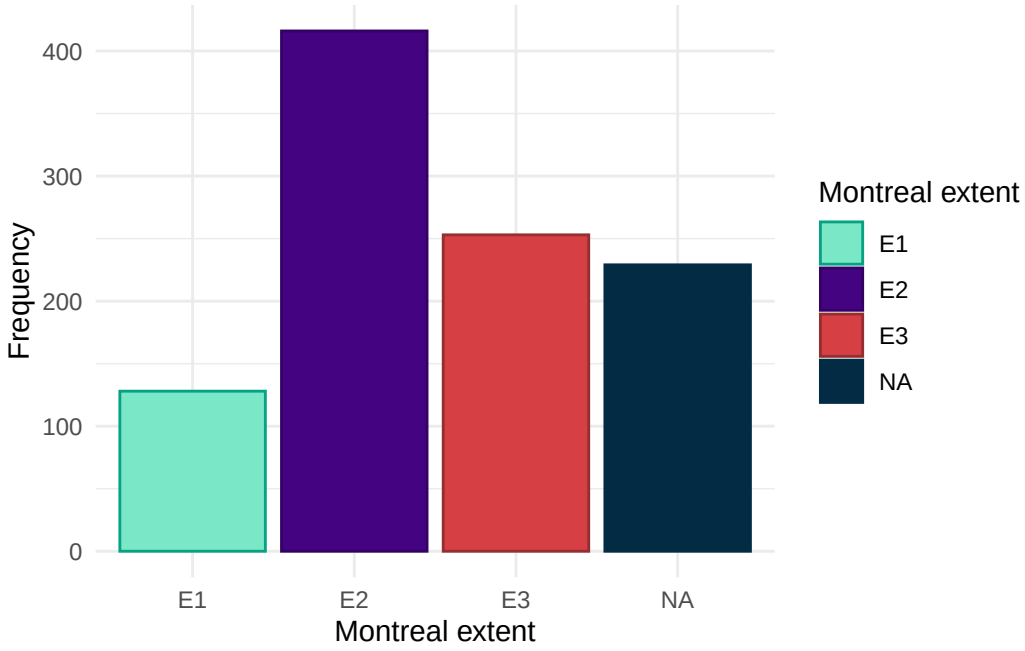



Figure 19: Montreal extent for UC/IBDU subjects in the FC cohort.

Montreal extent is not associated with FC

```
pander(chisq.test(demo.uc$Extent, demo.uc$cat))
```

Table 30: Chi-squared test between Montreal extent and FC groups.

Table 30: Pearson's Chi-squared test: `demo.uc$Extent` and `demo.uc$cat`

| Test statistic | df | P value |
|---|---|---|
| 2.281 | 4 | 0.6842 |

### Mayo score

Mayo score was collected via REDCap and is more complete than HBI.

```
mayo.df <- redcap[, c("participantid", "current_mayo")]
colnames(mayo.df) <- c("ParticipantId", "Mayo")
mayo.df <- subset(mayo.df, ParticipantId %in% demo.uc$ParticipantId)

demo.uc <- merge(demo.uc, mayo.df, by = "ParticipantId", all.x = TRUE)
demo.uc %>%
  drop_na(cat) %>%
  ggplot(aes(x = as.factor(Mayo))) +
  geom_bar(fill = "#284B63", color = "#153243") +
  theme_minimal() +
  ylab("Frequency") +
  xlab("Mayo score at time of recruitment")
```

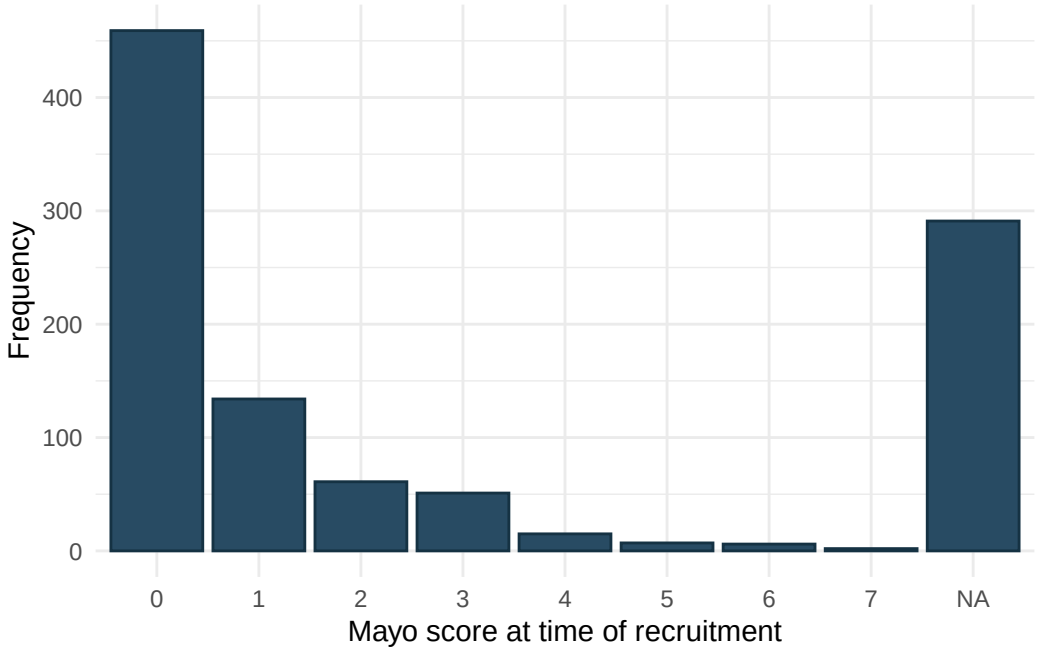



Figure 20

Mayo score is highly significantly associated with FC.

```
pander(summary(aov(Mayo ~ cat, data = demo.uc)))
```

Table 31: ANOVA between between Mayo score and FC groups.

Table 31: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 25.2 | 12.6 | 8.212 | 0.0002973 |
| **Residuals** | 732 | 1123 | 1.534 | NA | NA |

### PRO-2 in ulcerative colitis

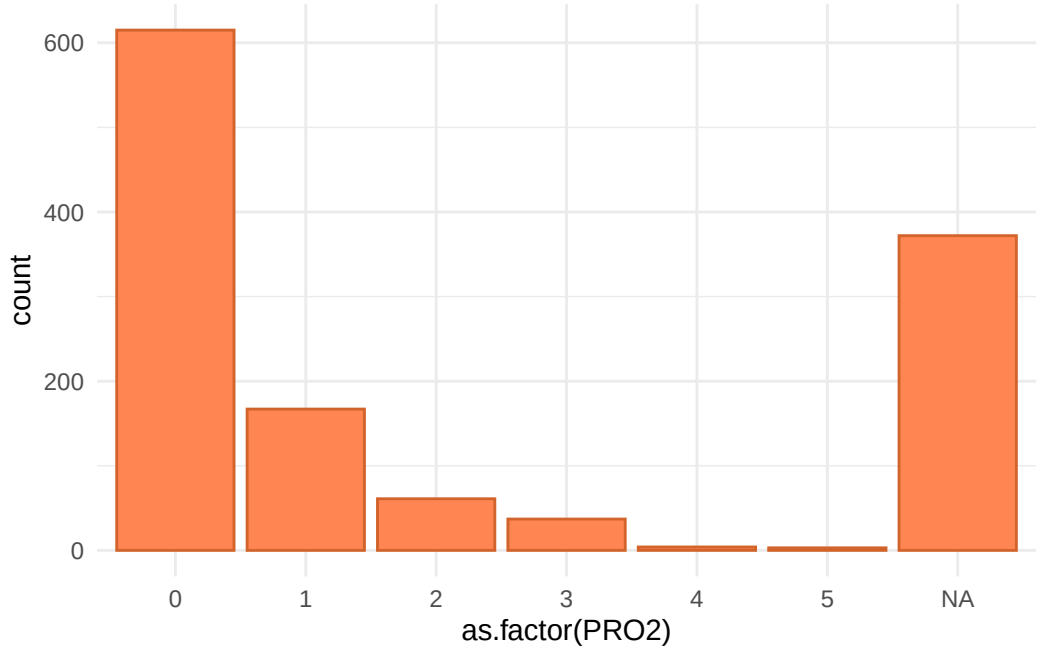
Sum of stool frequency and rectal bleeding categories.

```
PRO2 <- redcap[, c("participantno", "stool_freq", "rectal_bleed")]

PRO2$PRO2 <- with(PRO2, stool_freq + rectal_bleed)
```

```r
PRO2$ParticipantNo <- PRO2$participantno
demo.uc <- merge(demo.uc,
  PRO2[, c("ParticipantNo", "PRO2")],
  by = "ParticipantNo",
  all.x = TRUE,
  all.y = FALSE
)

demo.uc %>%
  ggplot(aes(x = as.factor(PRO2), fill = diagnosis2, color = diagnosis2)) +
  geom_bar() +
  scale_fill_manual(values = "#FF8552", na.value = "#032B43") +
  scale_color_manual(values = "#D2632A", na.value = "#032B43") +
  theme_minimal() +
  theme(legend.position = "none")
```




```r
pander(summary(aov(PRO2 ~ cat, data = demo.uc)))
```

Table 32: ANOVA between between PRO2 and FC groups in ulcerative colitis/IBDU.

Table 32: Analysis of Variance Model

| | Df | Sum Sq | Mean Sq | F value | Pr(>F) |
|---|---|---|---|---|---|
| **cat** | 2 | 7.752 | 3.876 | 5.049 | 0.006645 |
| **Residuals** | 728 | 558.9 | 0.7678 | NA | NA |

### Smoking

As with CD subjects, smoking status for UC/IBDU subjects is self-reported.

```
demo.uc %>%
  drop_na(cat) %>%
  ggplot(aes(x = Smoke, fill = Smoke, color = Smoke)) +
  geom_bar() +
  xlab("Smoking status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "Smoking status"),
    color = guide_legend(title = "Smoking status")
  )
```

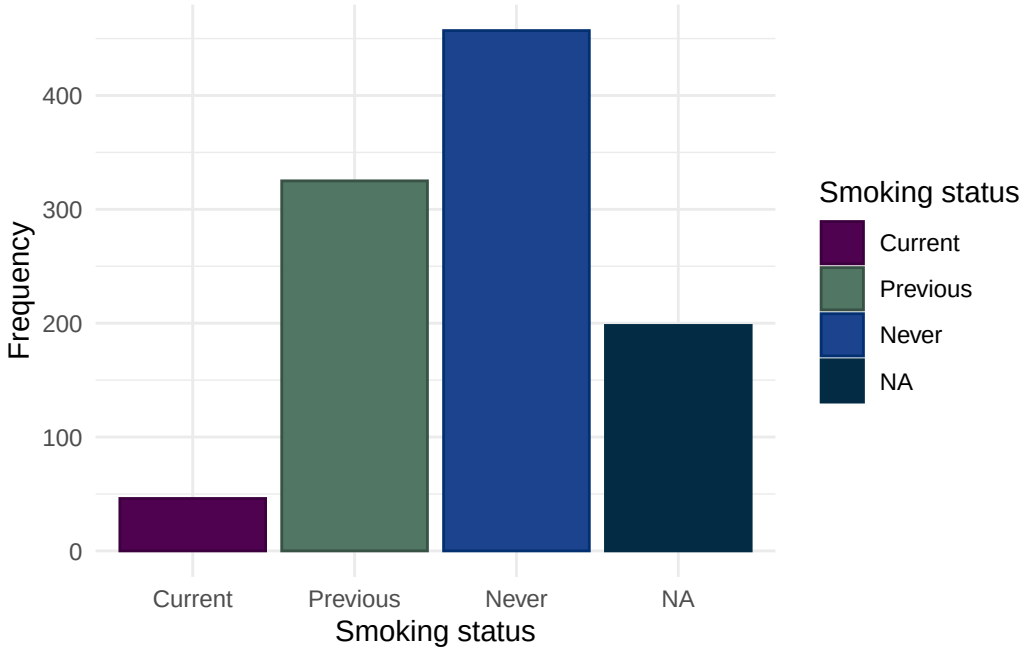



Figure 21: Smoking status for UC/IBDU subjects in the FC cohort.

As with CD, smoking status is significantly associated with FC.

```
pander(chisq.test(demo.uc$Smoke, demo.uc$cat))
```

Table 33: Chi-squared test between between smoking status and FC groups for UC subjects.

Table 33: Pearson's Chi-squared test: `demo.uc$Smoke` and `demo.uc$cat`

| Test statistic | df | P value |
|---|---|---|
| 9.781 | 4 | 0.04427 * |

### E-cigarette use

Similar to CD, very few subjects reported using E-cigarettes.

```
demo.uc %>%
  drop_na(cat) %>%
  ggplot(aes(x = ECigs, fill = ECigs, color = ECigs)) +
  geom_bar() +
```

```
  xlab("E-cigarette status") +
  ylab("Frequency") +
  theme_minimal() +
  scale_fill_manual(
    values = c("#4E0250", "#517664", "#1C448E"),
    na.value = "#032B43"
  ) +
  scale_color_manual(
    values = c("#3D003F", "#385245", "#033070"),
    na.value = "#032B43"
  ) +
  guides(
    fill = guide_legend(title = "E-cigarette status"),
    color = guide_legend(title = "E-cigarette status")
  )
```

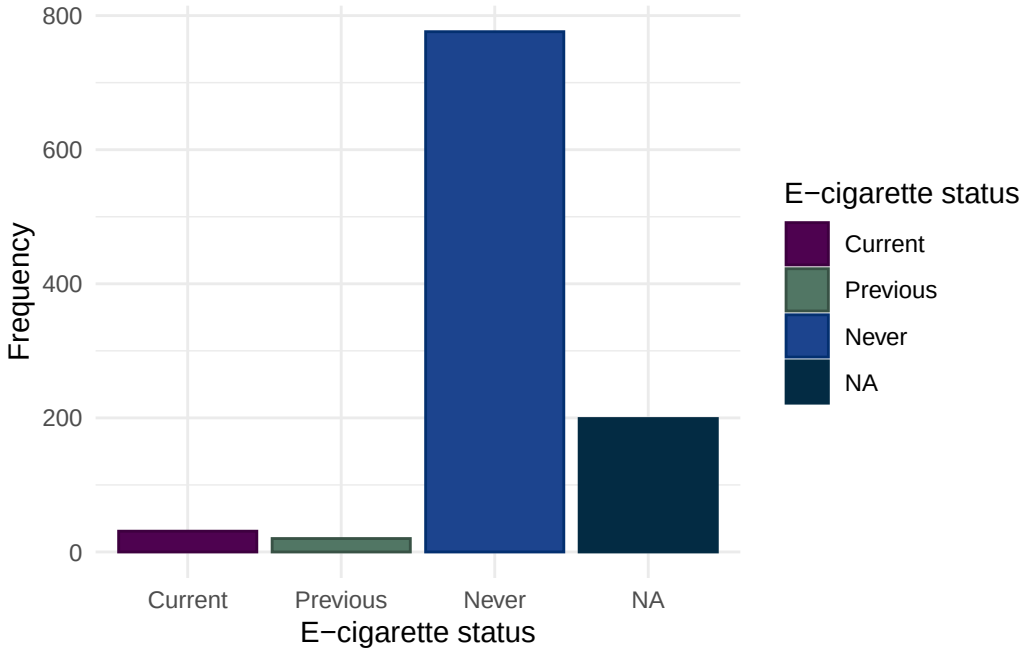



Figure 22: E-cigarette usage for UC subjects in the FC cohort.

E-cigarette use was found to significantly differ between FC groups in UC. However, the low number of subjects reported to use E-cigarettes (Figure 22) should be beared in mind when interpretting this finding.

```
pander(fisher.test(demo.uc$ECigs, demo.uc$cat))
```

Table 34: Chi-squared test between between E-cigarettte usage and FC groups for UC subjects.

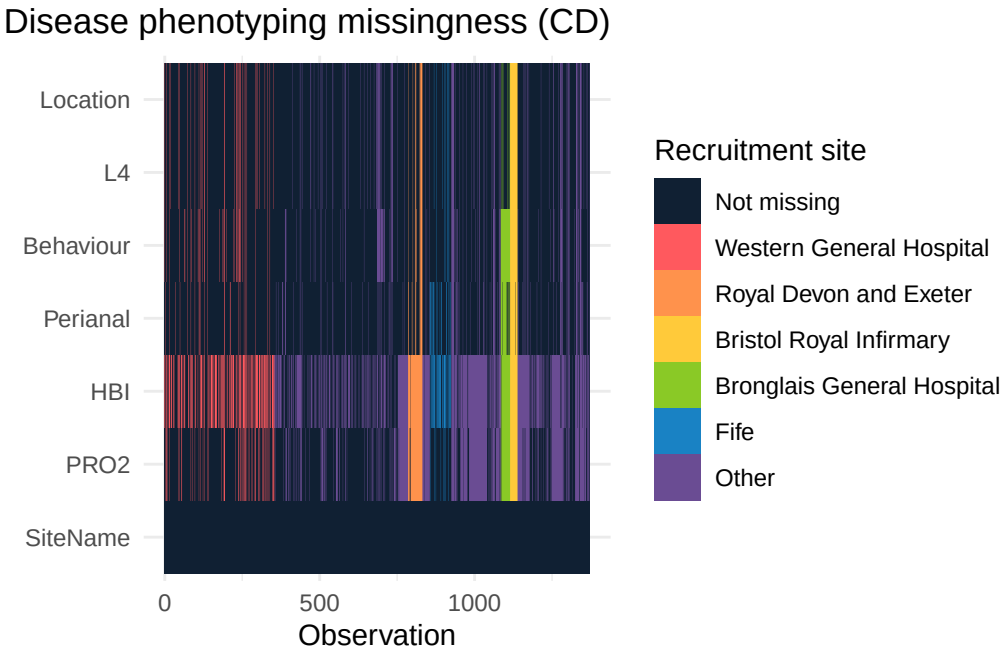
Table 34: Fisher's Exact Test for Count Data: `demo.uc$ECigs` and `demo.uc$cat`

| P value | Alternative hypothesis |
|---|---|
| 0.0196 * | two.sided |

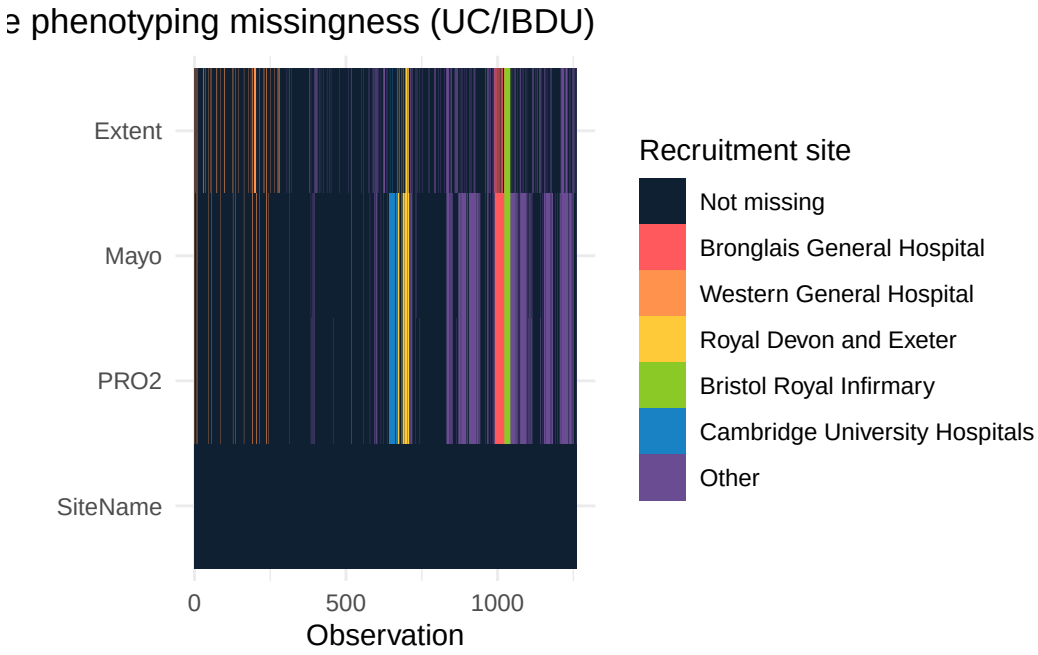
## Missingness

```
demo %>%
  select(
  `IBD Duration`,
  control_8,
  vas_control,
  Smoke,
  ECigs,
  SiteName
  ) %>%
missing_plot2(title = "Disease phenotyping missingness")
```


```
demo.cd %>%
  select(
  Location,
  L4,
  Behaviour,
  Perianal,
  HBI,
  PRO2,
  SiteName
  ) %>%
missing_plot2(title = "Disease phenotyping missingness (CD)")
```




```
demo.uc %>%
  select(
  Extent,
  Mayo,
  PRO2,
  SiteName
  ) %>%
missing_plot2(title = "Disease phenotyping missingness (UC/IBDU)")
```




```
saveRDS(demo, paste0(outdir, "demo-IBD.RDS"))
saveRDS(demo.cd, paste0(outdir, "demo-cd.RDS"))
saveRDS(demo.uc, paste0(outdir, "demo-uc.RDS"))
```

## Reproducibility & reproduction

Session info

**R version 4.4.0 (2024-04-24)**

**Platform:** aarch64-unknown-linux-gnu

**locale:** *LC_CTYPE=en_US.UTF-8*, *LC_NUMERIC=C*, *LC_TIME=en_US.UTF-8*, *LC_COLLATE=en_US.UTF-8*, *LC_MONETARY=en_US.UTF-8*, *LC_MESSAGES=en_US.UTF-8*, *LC_PAPER=en_US.UTF-8*, *LC_NAME=C*, *LC_ADDRESS=C*, *LC_TELEPHONE=C*, *LC_MEASUREMENT=en_US.UTF-8* and *LC_IDENTIFICATION=C*

**attached base packages:** *stats*, *graphics*, *grDevices*, *utils*, *datasets*, *methods* and *base*

**other attached packages:** *DiagrammeRsvg(v.0.1)*, *DiagrammeR(v.1.0.11)*, *pander(v.0.6.5)*, *knitr(v.1.47)*, *table1(v.1.4.3)*, *patchwork(v.1.2.0)*, *datefixR(v.1.6.1)*, *readxl(v.1.4.3)*, *lubridate(v.1.9.3)*, *forcats(v.1.0.0)*, *stringr(v.1.5.1)*, *dplyr(v.1.1.4)*, *purrr(v.1.0.2)*, *readr(v.2.1.5)*, *tidyr(v.1.3.1)*, *tibble(v.3.2.1)*, *ggplot2(v.3.5.1)*, *tidyverse(v.2.0.0)* and *plyr(v.1.8.9)*

**loaded via a namespace (and not attached):** *tidyselect(v.1.2.1)*, *finalfit(v.1.0.7)*, *viridisLite(v.0.4.2)*, *farver(v.2.1.2)*, *viridis(v.0.6.5)*, *fastmap(v.1.2.0)*, *rpart(v.4.1.23)*, *digest(v.0.6.35)*, *timechange(v.0.3.0)*, *lifecycle(v.1.0.4)*, *survival(v.3.5-8)*, *magrittr(v.2.0.3)*, *compiler(v.4.4.0)*, *rlang(v.1.1.3)*, *tools(v.4.4.0)*, *utf8(v.1.2.4)*, *yaml(v.2.3.8)*, *labeling(v.0.4.3)*, *htmlwidgets(v.1.6.4)*, *curl(v.5.2.1)*, *RColorBrewer(v.1.1-3)*, *withr(v.3.0.0)*, *nnet(v.7.3-19)*, *grid(v.4.4.0)*, *fansi(v.1.0.6)*, *jomo(v.2.7-6)*, *colorspace(v.2.1-0)*, *mice(v.3.16.0)*, *scales(v.1.3.0)*, *iterators(v.1.0.14)*, *MASS(v.7.3-60.2)*, *cli(v.3.6.2)*, *rmarkdown(v.2.27)*, *ragg(v.1.3.2)*, *generics(v.0.1.3)*, *tzdb(v.0.4.0)*, *visNetwork(v.2.1.2)*, *minqa(v.1.2.7)*, *splines(v.4.4.0)*, *cellranger(v.1.1.0)*, *vctrs(v.0.6.5)*, *V8(v.4.4.2)*, *boot(v.1.3-30)*, *glmnet(v.4.1-8)*, *Matrix(v.1.7-0)*, *jsonlite(v.1.8.8)*, *hms(v.1.1.3)*, *mitml(v.0.4-5)*, *Formula(v.1.2-5)*, *systemfonts(v.1.3.1)*, *foreach(v.1.5.2)*, *glue(v.1.7.0)*, *pan(v.1.9)*, *nloptr(v.2.0.3)*, *codetools(v.0.2-20)*, *stringi(v.1.8.4)*, *gtable(v.0.3.5)*, *shape(v.1.4.6.1)*, *lme4(v.1.1-35.3)*, *munsell(v.0.5.1)*, *pillar(v.1.9.0)*, *htmltools(v.0.5.8.1)*, *R6(v.2.5.1)*, *textshaping(v.0.4.0)*, *evaluate(v.0.23)*, *lattice(v.0.22-6)*, *backports(v.1.5.0)*, *broom(v.1.0.6)*, *Rcpp(v.1.0.12)*, *gridExtra(v.2.3)*, *nlme(v.3.1-164)*, *xfun(v.0.44)* and *pkgconfig(v.2.0.3)*

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