

Controlled variables

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Introduction

```
source("Survival/utils.R")

# Setup analysis environment
analysis_setup <- setup_analysis()
paths <- analysis_setup$paths
demo <- analysis_setup$demo
```

```

flare.df <- readRDS(paste0(paths$outdir, "flares-overview.RDS"))
flare.cd.df <- subset(flare.df, diagnosis2 == "CD")

flare.cd.df$Treatment <- factor(flare.cd.df$Treatment,
                                   levels = c("Mono immunotherapy",
                                             "Mono biologic",
                                             "Combo therapy",
                                             "5-ASA",
                                             "None reported"))

flare.uc.df <- subset(flare.df, diagnosis2 == "UC/IBDU")
flare.uc.df$Treatment <- factor(flare.uc.df$Treatment,
                                   levels = c("Mono immunotherapy",
                                             "Mono biologic",
                                             "Combo therapy",
                                             "5-ASA",
                                             "None reported"))

```

The variables being controlled for in later cox models analyses are first investigated.

Although smoking status was originally planned to be controlled for, the [high degree of missingness](#) for these data and the [lack of significant associations with time to flare](#) has resulted in smoking status not being controlled for in later analyses.

Of the variables considered here, only sex is associated with disease flare.

Sex

Crohn's disease

Patient-reported flare

```

p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(softflare_time, softflare) ~ Sex,
  legend_title = "Sex",
  legend_labs = c("Male", "Female"),
  palette = c("#00A6ED", "#F6511D"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,

```

```

  plot_path = "plots/cd/soft-flare/controlled/sex"
)
saveRDS(p, paste0(paths$outdir, "sex-cd-soft.RDS"))
p

```

Objective flare

```

p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(hardflare_time, hardflare) ~ Sex,
  legend_title = "Sex",
  legend_labs = c("Male", "Female"),
  palette = c("#00A6ED", "#F6511D"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,
  plot_path = "plots/cd/hard-flare/controlled/sex"
)
saveRDS(p, paste0(paths$outdir, "sex-cd-hard.RDS"))
p

```

Ulcerative colitis

Patient-reported flare

```

p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(softflare_time, softflare) ~ Sex,
  legend_title = "Sex",
  legend_labs = c("Male", "Female"),
  palette = c("#00A6ED", "#F6511D"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/uc/soft-flare/controlled/sex"
)
saveRDS(p, paste0(paths$outdir, "sex-uc-soft.RDS"))
p

```

Objective flare

```
p <- generate_survival_plot(  
  data = flare.uc.df,  
  formula = Surv(hardflare_time, hardflare) ~ Sex,  
  legend_title = "Sex",  
  legend_labs = c("Male", "Female"),  
  palette = c("#00A6ED", "#F6511D"),  
  xlab = "Time from study recruitment (days)",  
  title = "Time to objective flare",  
  break_time_by = 500,  
  plot_path = "plots/uc/hard-flare/controlled/sex"  
)  
saveRDS(p, paste0(paths$outdir, "sex-uc-hard.RDS"))  
p
```

Smoking status

Crohn's disease

Patient-reported flare

```
p <- generate_survival_plot(  
  data = flare.cd.df,  
  formula = Surv(softflare_time, softflare) ~ Smoke,  
  legend_title = "Smoking status",  
  legend_labs = c("Current", "Previous", "Never"),  
  palette = c("#00A6ED", "#FFB400", "#F6511D"),  
  xlab = "Time from study recruitment (days)",  
  title = "Time to patient-reported flare",  
  break_time_by = 200,  
  plot_path = "plots/cd/soft-flare/controlled/smoke"  
)  
saveRDS(p, paste0(paths$outdir, "smoke-cd-soft.RDS"))  
p
```

Objective flare

```

p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(hardflare_time, hardflare) ~ Smoke,
  legend_title = "Smoking status",
  legend_labs = c("Current", "Previous", "Never"),
  palette = c("#00A6ED", "#FFB400", "#F6511D"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,
  plot_path = "plots/cd/hard-flare/controlled/smoke"
)
saveRDS(p, paste0(paths$outdir, "smoke-cd-hard.RDS"))
p

```

Ulcerative colitis

Patient-reported flare

```

p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(softflare_time, softflare) ~ Smoke,
  legend_title = "Smoking status",
  legend_labs = c("Current", "Previous", "Never"),
  palette = c("#00A6ED", "#FFB400", "#F6511D"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/uc/soft-flare/controlled/smoke"
)
saveRDS(p, paste0(paths$outdir, "smoke-uc-soft.RDS"))
p

```

Objective flare

```

p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(hardflare_time, hardflare) ~ Smoke,
  legend_title = "Smoking status",
  legend_labs = c("Current", "Previous", "Never"),
  palette = c("#00A6ED", "#FFB400", "#F6511D"),

```

```

xlab = "Time from study recruitment (days)",
title = "Time to objective flare",
break_time_by = 500,
plot_path = "plots/uc/hard-flare/controlled/smoke"
)

saveRDS(p, paste0(paths$outdir, "smoke-uc-hard.RDS"))
p

```

Social deprivation

Crohn's disease

Patient-reported flare

```

p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(softflare_time, softflare) ~ IMD,
  legend_title = "IMD",
  legend_labs = c("1 (least deprived)", "2", "3", "4", "5 (most deprived)"),
  palette = c("#F05D5E", "#00C2D1", "#FFBA49", "#EDC9FF", "#034C3C"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/cd/soft-flare/controlled/imd"
)
saveRDS(p, paste0(paths$outdir, "imd-cd-soft.RDS"))
p

```

Objective flare

```

p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(hardflare_time, hardflare) ~ IMD,
  legend_title = "IMD",
  legend_labs = c("1 (least deprived)", "2", "3", "4", "5 (most deprived)"),
  palette = c("#F05D5E", "#00C2D1", "#FFBA49", "#EDC9FF", "#034C3C"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,

```

```

  plot_path = "plots/cd/hard-flare/controlled/imd"
)
saveRDS(p, paste0(paths$outdir, "imd-cd-hard.RDS"))
p

```

Ulcerative colitis

Patient-reported flare

```

p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(softflare_time, softflare) ~ IMD,
  legend_title = "IMD",
  legend_labs = c("1 (least deprived)", "2", "3", "4", "5 (most deprived)"),
  palette = c("#F05D5E", "#00C2D1", "#FFBA49", "#EDC9FF", "#034C3C"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/uc/soft-flare/controlled/imd"
)
saveRDS(p, paste0(paths$outdir, "imd-uc-soft.RDS"))
p

```

Objective flare

```

p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(hardflare_time, hardflare) ~ IMD,
  legend_title = "IMD",
  legend_labs = c("1 (least deprived)", "2", "3", "4", "5 (most deprived)"),
  palette = c("#F05D5E", "#00C2D1", "#FFBA49", "#EDC9FF", "#034C3C"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,
  plot_path = "plots/uc/hard-flare/controlled/imd"
)
saveRDS(p, paste0(paths$outdir, "imd-uc-hard.RDS"))
p

```

Faecal calprotectin

Crohn's disease

Patient-reported flare

```
p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(softflare_time, softflare) ~ cat,
  legend_title = "Faecal calprotectin",
  legend_labs = c("FC < 50", "50 FC 250", "FC > 250"),
  palette = c("#2AAACE", "#FFBF1C", "#FF6726"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/cd/soft-flare/controlled/fc"
)

saveRDS(p, paste0(paths$outdir, "fc-cd-soft.RDS"))

print(p, newpage = FALSE)
```

Objective flare

```
p <- generate_survival_plot(
  data = flare.cd.df,
  formula = Surv(hardflare_time, hardflare) ~ cat,
  legend_title = "Faecal calprotectin",
  legend_labs = c("FC < 50", "50 FC 250", "FC > 250"),
  palette = c("#2AAACE", "#FFBF1C", "#FF6726"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,
  plot_path = "plots/cd/hard-flare/controlled/fc"
)

saveRDS(p, paste0(paths$outdir, "fc-cd-hard.RDS"))

print(p, newpage = FALSE)
```

Ulcerative colitis

Patient-reported flare

```
p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(softflare_time, softflare) ~ cat,
  legend_title = "Faecal calprotectin",
  legend_labs = c("FC < 50", "50 < FC < 250", "FC > 250"),
  palette = c("#2AAACE", "#FFBF1C", "#FF6726"),
  xlab = "Time from study recruitment (days)",
  title = "Time to patient-reported flare",
  break_time_by = 200,
  plot_path = "plots/uc/soft-flare/controlled/fc"
)

saveRDS(p, paste0(paths$outdir, "fc-uc-soft.RDS"))

print(p, newpage = FALSE)
```

Objective flare

```
p <- generate_survival_plot(
  data = flare.uc.df,
  formula = Surv(hardflare_time, hardflare) ~ cat,
  legend_title = "Faecal calprotectin",
  legend_labs = c("FC < 50", "50 < FC < 250", "FC > 250"),
  palette = c("#2AAACE", "#FFBF1C", "#FF6726"),
  xlab = "Time from study recruitment (days)",
  title = "Time to objective flare",
  break_time_by = 500,
  plot_path = "plots/uc/hard-flare/controlled/fc"
)

saveRDS(p, paste0(paths$outdir, "fc-uc-hard.RDS"))

print(p, newpage = FALSE)
```

Cox models

Crohn's disease

Patient-reported flare

```
fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex + IMD + cat + Smoke + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.cd.df,
  model = TRUE
)

cd.clin.forest <- get_HR(
  fit.me,
  c("SmokePrevious", "SmokeNever")
)

fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex + IMD + cat + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.cd.df,
  model = TRUE
)

cd.clin.forest <- rbind(
  cd.clin.forest,
  get_HR(
    fit.me,
    c(
      "SexFemale",
      paste0("IMD", seq(2, 5)),
      "catFC 50-250",
      "catFC > 250"
    )
  )
)
```

```
invisible(cox_summary(fit.me))
```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.9989	1.5753	2.5364	0.0000
IMD2	0.9364	0.5970	1.4686	0.7746
IMD3	0.8868	0.5609	1.4021	0.6074
IMD4	0.9417	0.6062	1.4631	0.7894
IMD5	0.9857	0.6443	1.5078	0.9469
catFC 50-250	1.5844	1.2278	2.0445	0.0004
catFC > 250	2.4138	1.8192	3.2028	0.0000

Diagnostics:

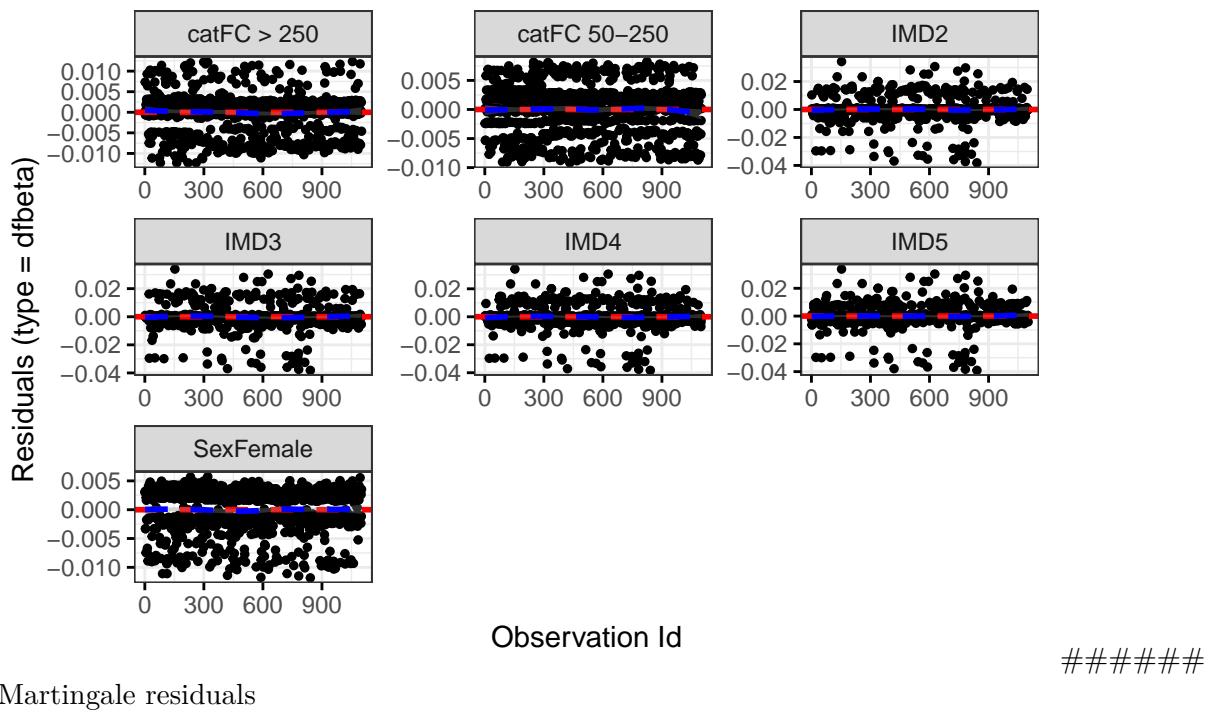
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	0.3091	0.9923	0.5750
IMD	5.8397	3.9497	0.2063
cat	2.3232	1.9815	0.3093
GLOBAL	8.4076	13.9400	0.8643

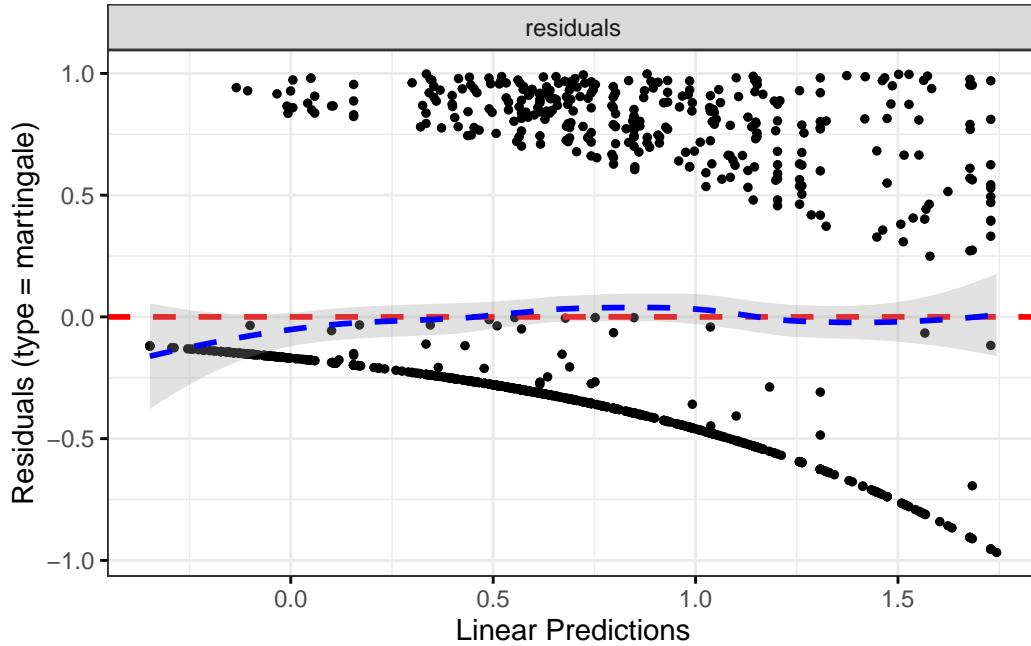
DF betas

```
Warning: `gather_()` was deprecated in tidyr 1.2.0.  
i Please use `gather()` instead.  
i The deprecated feature was likely used in the survminer package.  
Please report the issue at <https://github.com/kassambara/survminer/issues>.
```

```
`geom_smooth()` using formula = 'y ~ x'
```



```
`geom_smooth()` using formula = 'y ~ x'
```



Objective flare

```
fit.me <- coxph(  
  Surv(hardflare_time, hardflare) ~  
    Sex + IMD + cat + Smoke + frailty(SiteNo),  
  control = coxph.control(outer.max = 20),  
  data = flare.cd.df  
)  
  
cd.hard.forest <- get_HR(  
  fit.me,  
  c("SmokePrevious", "SmokeNever")  
)  
  
fit.me <- coxph(  
  Surv(hardflare_time, hardflare) ~  
    Sex + IMD + cat + frailty(SiteNo),  
  control = coxph.control(outer.max = 20),  
  data = flare.cd.df  
)  
  
cd.hard.forest <- rbind(  
  cd.hard.forest,  
  get_HR(  
    fit.me,  
    c(  
      "SexFemale",  
      paste0("IMD", seq(2, 5)),  
      "catFC > 250"  
    )  
  )  
)  
  
invisible(cox_summary(fit.me))
```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.3887	1.0579	1.8227	0.0180
IMD2	0.9220	0.5365	1.5844	0.7688

Variable	HR	Lower 95%	Upper 95%	P-value
IMD3	0.9675	0.5566	1.6817	0.9068
IMD4	0.8950	0.5222	1.5338	0.6864
IMD5	0.9035	0.5370	1.5199	0.7021
catFC 50-250	2.0217	1.4730	2.7750	0.0000
catFC > 250	3.3366	2.3693	4.6989	0.0000

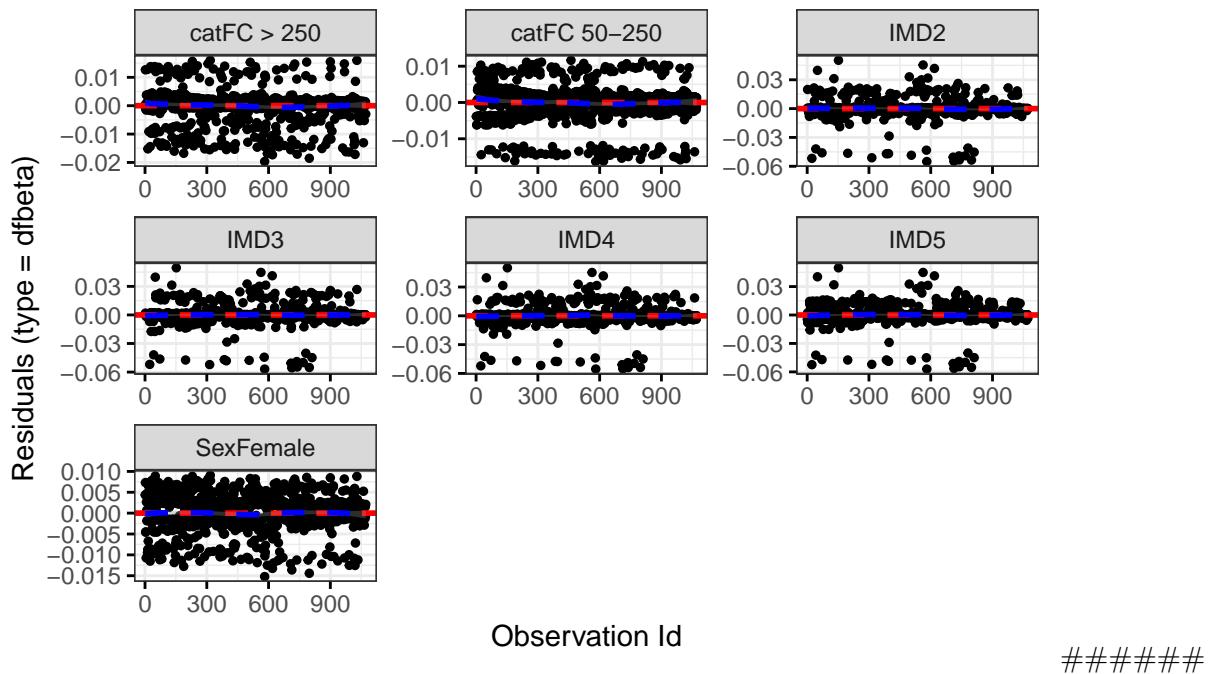
Diagnostics:

Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	0.2571	0.9863	0.6064
IMD	4.2174	3.9407	0.3689
cat	8.8712	1.9847	0.0116
GLOBAL	13.9394	19.6668	0.8190

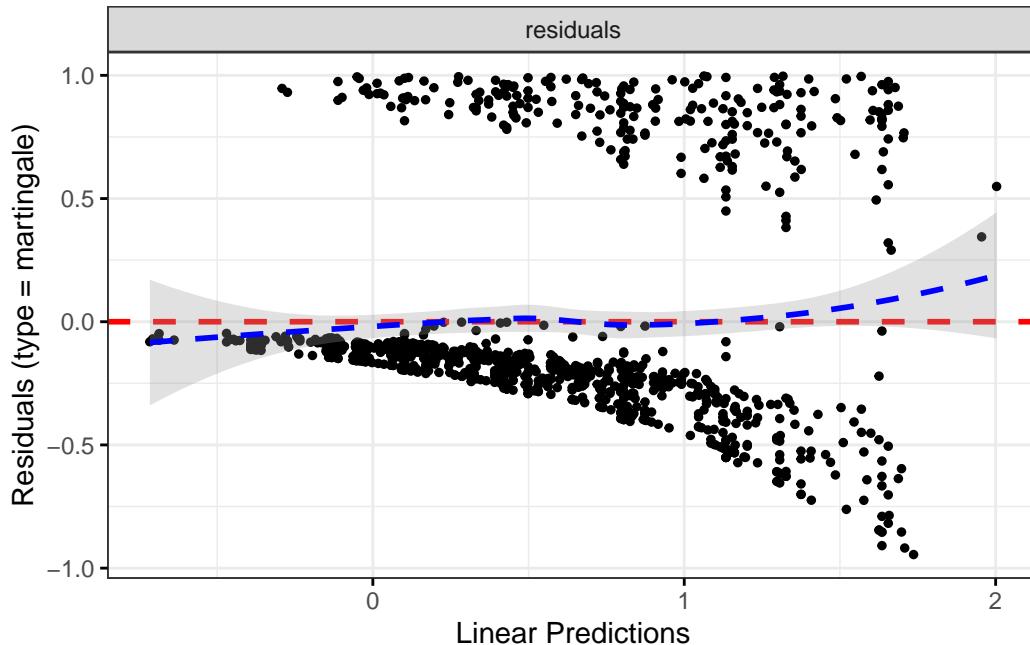
DF betas

`geom_smooth()` using formula = 'y ~ x'



Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Ulcerative colitis

Patient-reported flare

```
fit.me <- coxph(  
  Surv(softflare_time, softflare) ~  
    Sex + IMD + cat + Smoke + frailty(SiteNo),  
  control = coxph.control(outer.max = 20),  
  data = flare.uc.df  
)  
  
uc.clin.forest <- get_HR(  
  fit.me,  
  c("SmokePrevious", "SmokeNever")  
)
```

```

fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex + IMD + cat + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.uc.df
)

uc.clin.forest <- rbind(
  uc.clin.forest,
  get_HR(
    fit.me,
    c(
      "SexFemale",
      paste0("IMD", seq(2, 5)),
      "catFC > 250"
    )
  )
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.5438	1.2475	1.9104	0.0001
IMD2	1.2433	0.7856	1.9678	0.3525
IMD3	1.1010	0.7025	1.7255	0.6748
IMD4	1.4420	0.9388	2.2151	0.0946
IMD5	1.1988	0.7858	1.8290	0.4002
catFC 50-250	1.5688	1.2269	2.0058	0.0003
catFC > 250	2.1447	1.6433	2.7991	0.0000

Diagnostics:

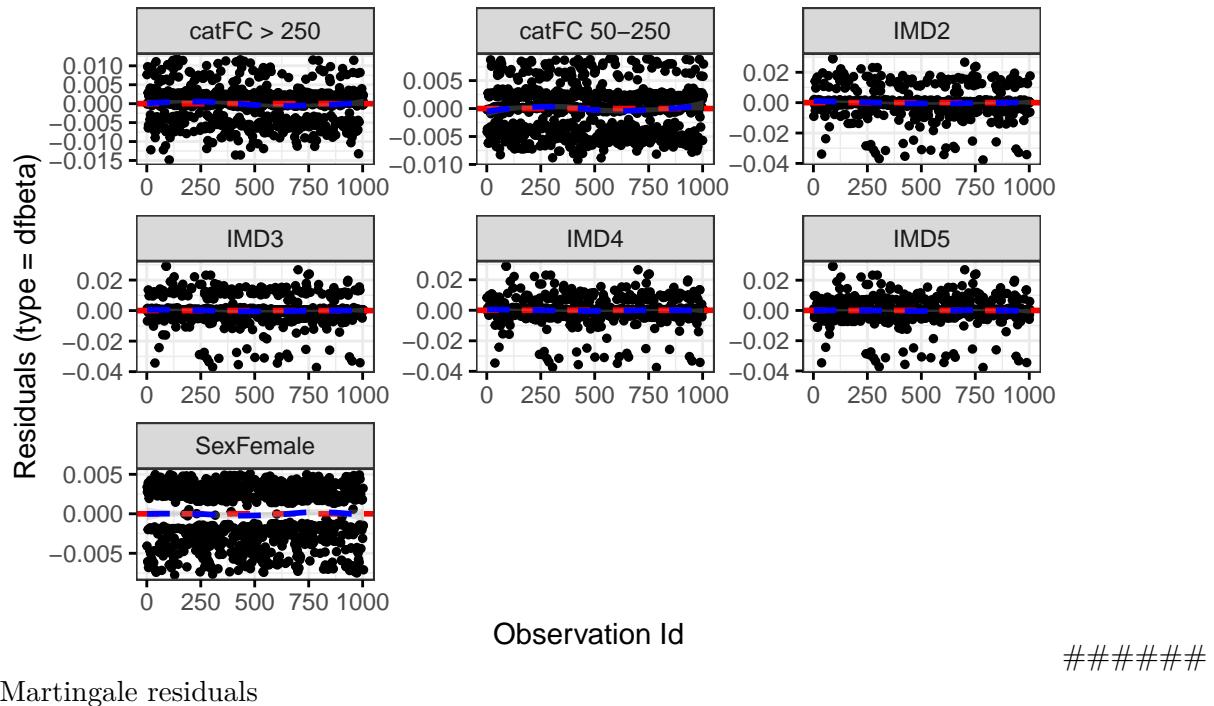
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	1.3013	0.9907	0.2514
IMD	4.0189	3.9418	0.3949

	Chi-squared statistic	DF	P-value
cat	5.7453	1.9706	0.0550
GLOBAL	11.3236	18.7016	0.9037

DF betas

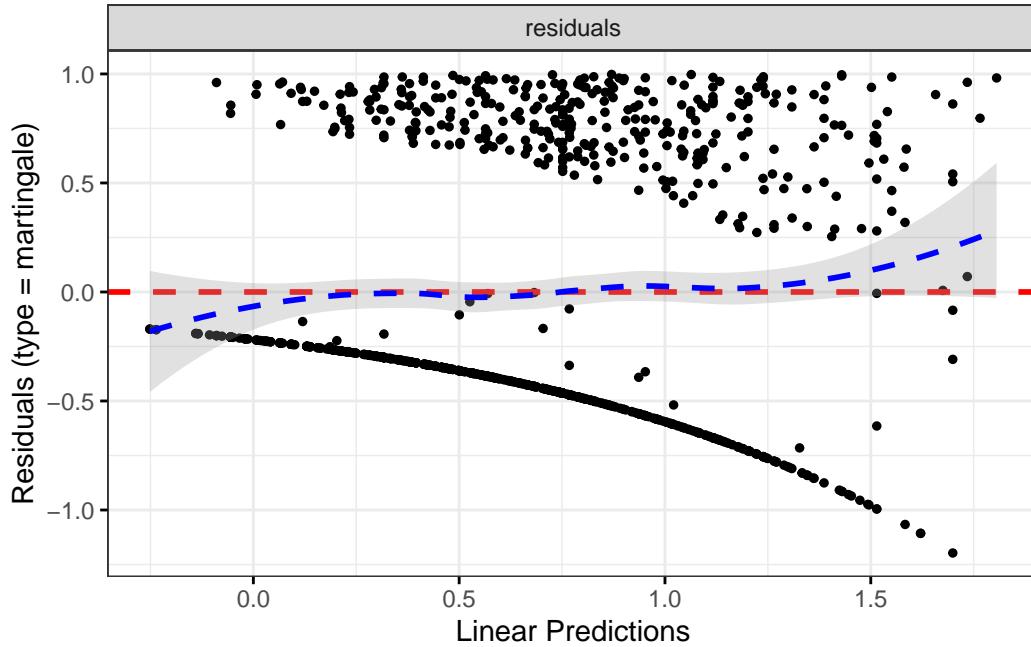
```
`geom_smooth()` using formula = 'y ~ x'
```



#####

Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Objective flare

```

fit.me <- coxph(
  Surv(hardflare_time, hardflare) ~
    Sex + IMD + cat + Smoke + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.uc.df
)

uc.hard.forest <- get_HR(
  fit.me,
  c("SmokePrevious", "SmokeNever")
)

fit.me <- coxph(
  Surv(hardflare_time, hardflare) ~
    Sex + IMD + cat + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.uc.df
)

```

```

uc.hard.forest <- rbind(
  uc.hard.forest,
  get_HR(
    fit.me,
    c(
      "SexFemale",
      paste0("IMD", seq(2, 5)),
      "catFC 50-250",
      "catFC > 250"
    )
  )
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.3259	1.0208	1.7221	0.0345
IMD2	1.4092	0.7861	2.5260	0.2494
IMD3	1.3774	0.7835	2.4213	0.2659
IMD4	1.7484	1.0130	3.0174	0.0448
IMD5	1.2989	0.7566	2.2298	0.3430
catFC 50-250	2.0322	1.4885	2.7744	0.0000
catFC > 250	3.2203	2.3245	4.4614	0.0000

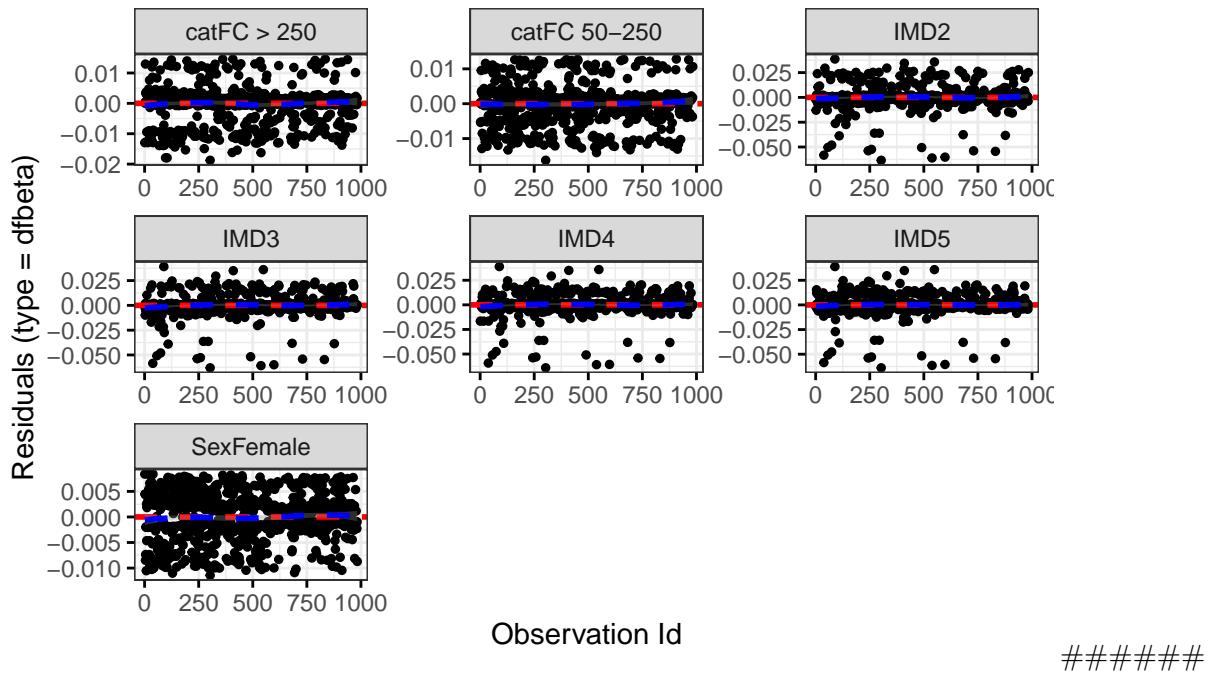
Diagnostics:

Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	0.1461	0.9849	0.6962
IMD	2.6145	3.9368	0.6145
cat	4.3647	1.9671	0.1096
GLOBAL	7.4355	23.5846	0.9994

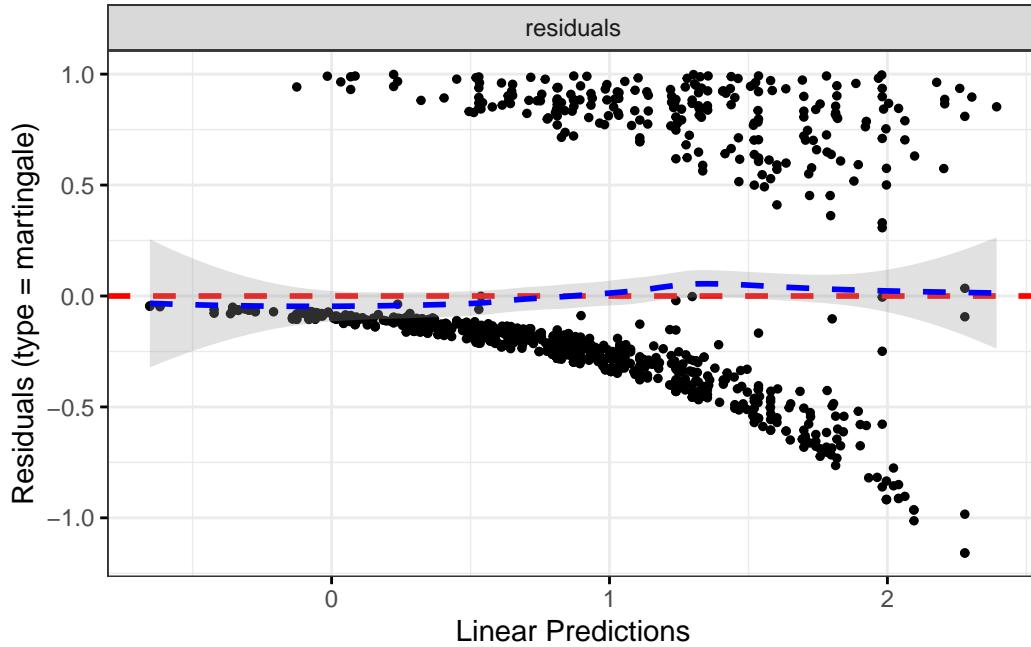
DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Across IBD

Patient-reported flare

```

fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex + IMD + cat + frailty(SiteNo),
  control = coxph.control(outer.max = 20),
  data = flare.df
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.7183	1.4676	2.0119	0.0000
IMD2	1.0417	0.7555	1.4364	0.8032
IMD3	0.9689	0.7027	1.3360	0.8474
IMD4	1.1549	0.8490	1.5712	0.3590
IMD5	1.0554	0.7814	1.4255	0.7252

Variable	HR	Lower 95%	Upper 95%	P-value
catFC 50-250	1.5194	1.2743	1.8117	0.0000
catFC > 250	2.2203	1.8303	2.6934	0.0000

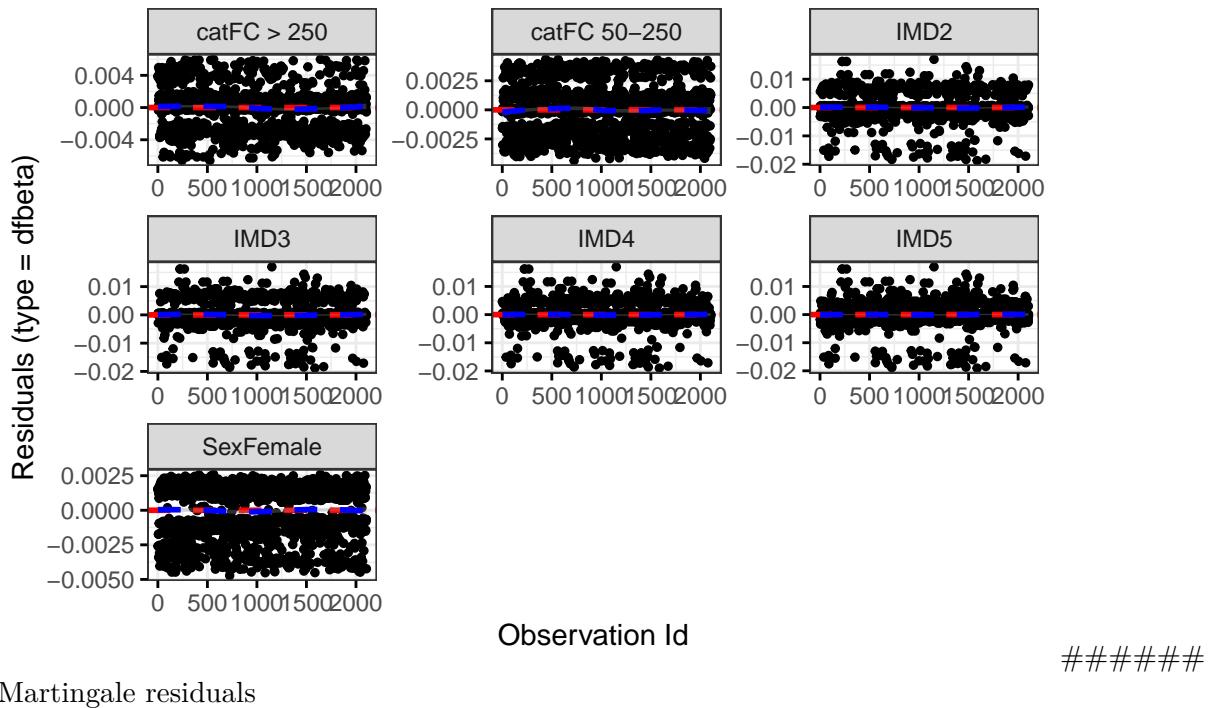
Diagnostics:

Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	1.9368	0.9936	0.1627
IMD	8.9273	3.9484	0.0609
cat	1.1234	1.9824	0.5659
GLOBAL	12.1742	22.3691	0.9594

DF betas

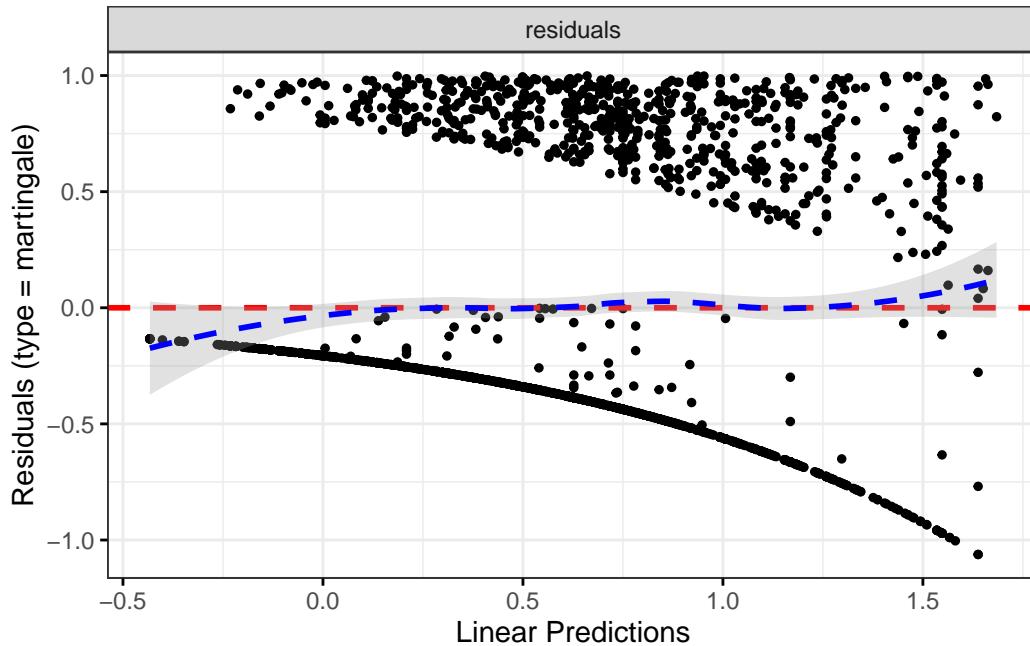
```
`geom_smooth()` using formula = 'y ~ x'
```



Martingale residuals

#####

```
`geom_smooth()` using formula = 'y ~ x'
```



Objective flare

```
fit.me <- coxph(  
  Surv(hardflare_time, hardflare) ~  
    Sex + IMD + cat + frailty(SiteNo),  
  control = coxph.control(outer.max = 20),  
  data = flare.df  
)  
  
invisible(cox_summary(fit.me))
```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.3310	1.1037	1.6051	0.0028
IMD2	1.1029	0.7416	1.6402	0.6286
IMD3	1.1157	0.7525	1.6542	0.5858
IMD4	1.2392	0.8452	1.8169	0.2720
IMD5	1.0508	0.7220	1.5293	0.7959

Variable	HR	Lower 95%	Upper 95%	P-value
catFC 50-250	1.9760	1.5846	2.4641	0.0000
catFC > 250	3.2506	2.5702	4.1112	0.0000

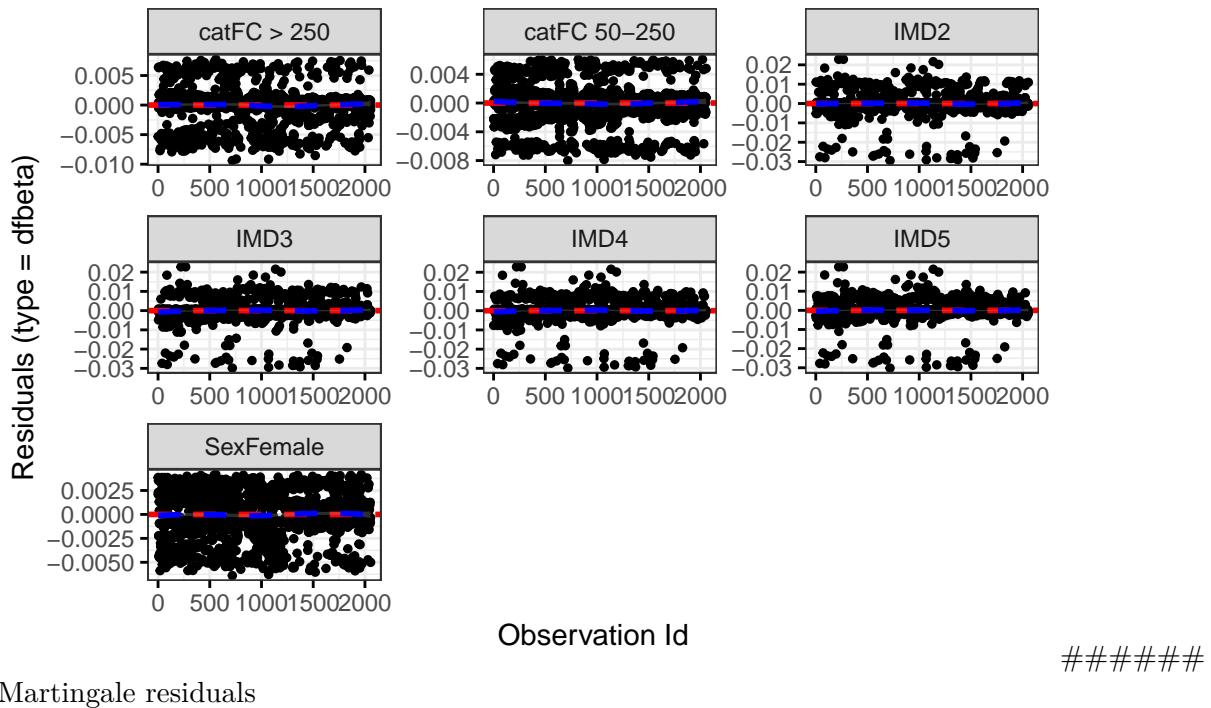
Diagnostics:

Proportional hazards assumption test

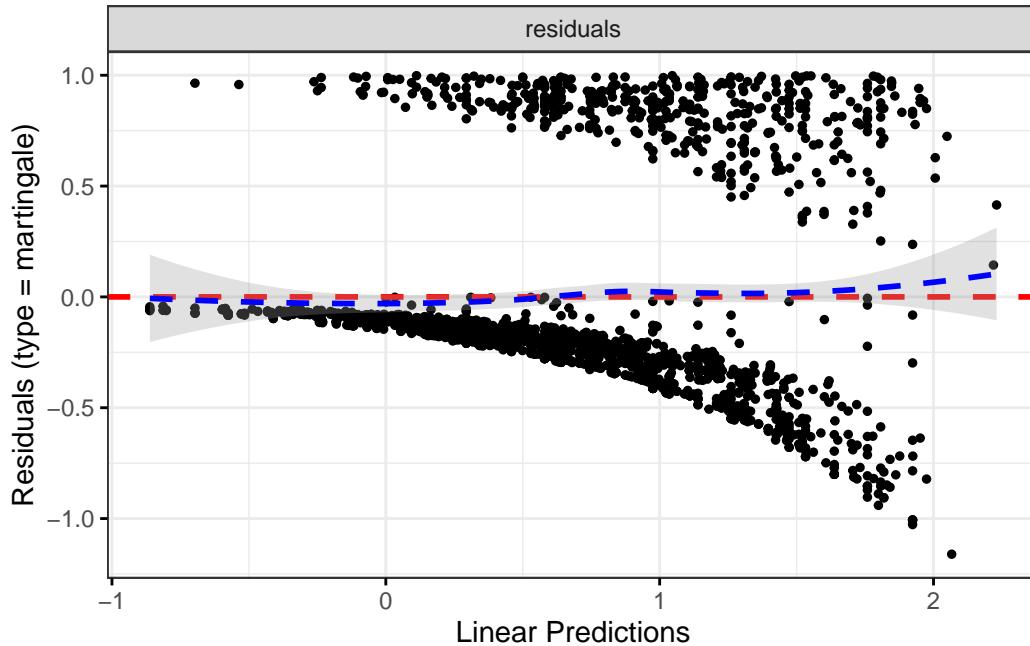
	Chi-squared statistic	DF	P-value
Sex	0.2285	0.9928	0.6297
IMD	0.8488	3.9546	0.9289
cat	8.4343	1.9867	0.0145
GLOBAL	9.9289	29.8504	0.9998

DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



```
`geom_smooth()` using formula = 'y ~ x'
```



```
saveRDS(flare.df, paste0(paths$outdir, "flares-controlled.RDS"))
saveRDS(flare.cd.df, paste0(paths$outdir, "flares-controlled-cd.RDS"))
saveRDS(flare.uc.df, paste0(paths$outdir, "flares-controlled-uc.RDS"))

saveRDS(cd.clin.forest, paste0(paths$outdir, "cd-clin-controlled.RDS"))
saveRDS(cd.hard.forest, paste0(paths$outdir, "cd-hard-controlled.RDS"))
saveRDS(uc.clin.forest, paste0(paths$outdir, "uc-clin-controlled.RDS"))
saveRDS(uc.hard.forest, paste0(paths$outdir, "uc-hard-controlled.RDS"))
```

Control for additional covariates

Crohn's disease

Patient-reported flare

```
fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex +
    IMD +
    cat +
    `IBD Duration` +
```

```

    BMI +
    Treatment +
    Age +
    Smoke +
    frailty(SiteNo),
control = coxph.control(outer.max = 20),
data = flare.cd.df
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	2.3665	1.7880	3.1321	0.0000
IMD2	0.8606	0.5236	1.4145	0.5538
IMD3	0.9000	0.5432	1.4909	0.6824
IMD4	0.9740	0.6039	1.5710	0.9141
IMD5	0.9757	0.6125	1.5544	0.9175
catFC 50-250	1.4066	1.0607	1.8653	0.0178
catFC > 250	2.2945	1.6660	3.1602	0.0000
IBD Duration	0.9880	0.9764	0.9998	0.0460
BMI	1.0025	0.9799	1.0255	0.8320
TreatmentMono biologic	1.0530	0.7278	1.5236	0.7840
TreatmentCombo therapy	0.7668	0.4787	1.2281	0.2692
Treatment5-ASA	1.4407	0.7997	2.5952	0.2241
TreatmentNone reported	0.9300	0.6568	1.3166	0.6823
Age	1.0083	0.9989	1.0179	0.0851
SmokePrevious	1.5225	0.9006	2.5740	0.1166
SmokeNever	1.2868	0.7664	2.1606	0.3402

Diagnostics:

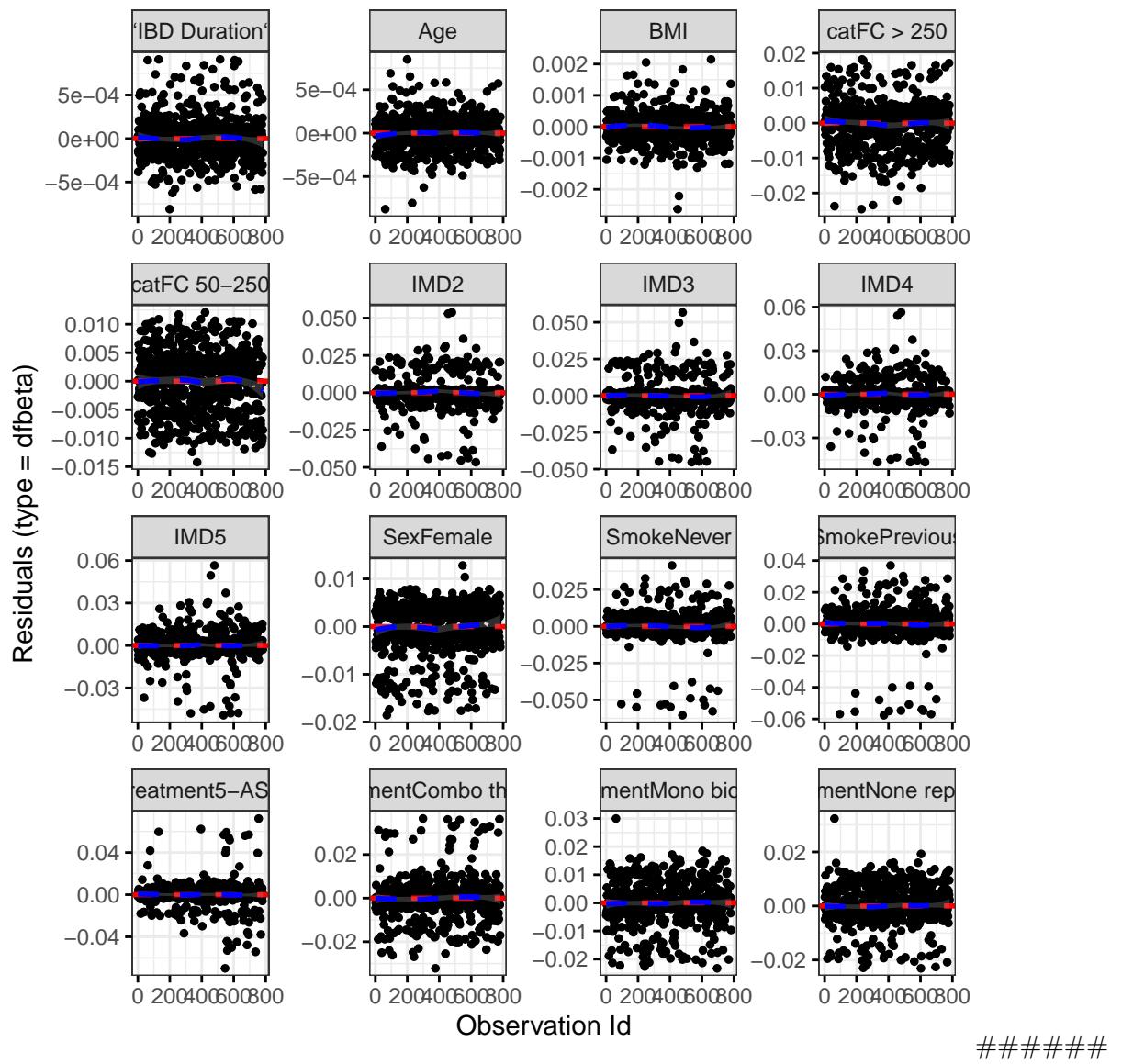
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	0.0372	1.0000	0.8470
IMD	5.7872	4.0000	0.2156
cat	1.2874	2.0000	0.5254

	Chi-squared statistic	DF	P-value
IBD Duration	3.3065	1.0000	0.0690
BMI	2.2687	1.0000	0.1320
Treatment	6.5956	4.0000	0.1589
Age	0.6126	1.0000	0.4338
Smoke	0.4805	2.0000	0.7864
GLOBAL	20.7752	16.0001	0.1873

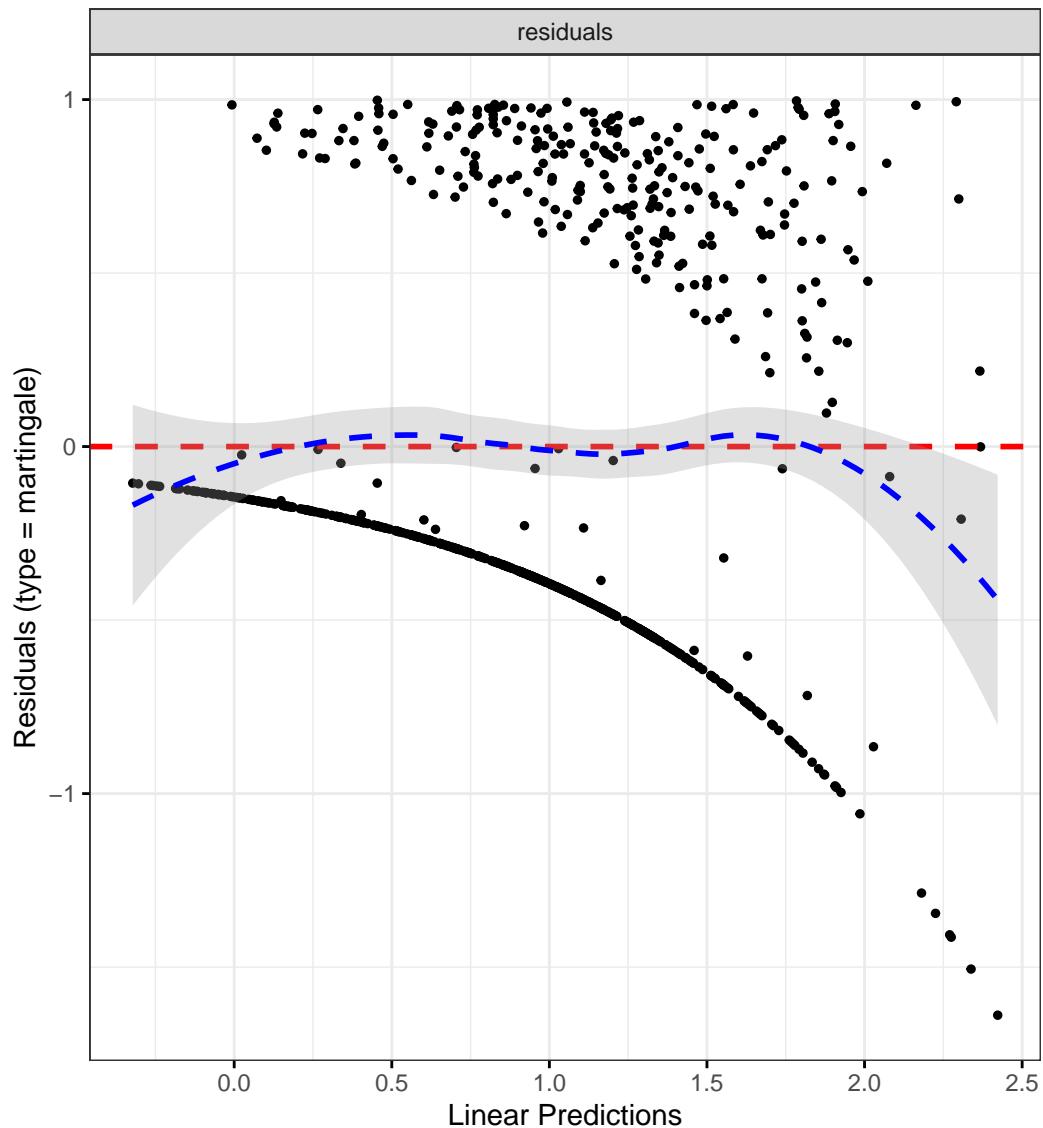
DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Objective flare

```
fit.me <- coxph(
  Surv(hardflare_time, hardflare) ~
    Sex +
    IMD +
    cat +
    `IBD Duration` +
    BMI +
    Treatment +
```

```

Age +
Smoke +
frailty(SiteNo),
control = coxph.control(outer.max = 20),
data = flare.cd.df
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.6591	1.1856	2.3216	0.0031
IMD2	0.8097	0.4303	1.5234	0.5126
IMD3	0.7955	0.4172	1.5170	0.4873
IMD4	0.9072	0.4914	1.6750	0.7557
IMD5	0.9736	0.5391	1.7582	0.9293
catFC 50-250	1.9761	1.3551	2.8815	0.0004
catFC > 250	3.6593	2.4321	5.5057	0.0000
IBD Duration	0.9833	0.9676	0.9993	0.0408
BMI	1.0190	0.9907	1.0481	0.1903
TreatmentMono biologic	0.9804	0.6278	1.5309	0.9306
TreatmentCombo therapy	0.7114	0.4007	1.2627	0.2447
Treatment5-ASA	1.3718	0.5994	3.1394	0.4542
TreatmentNone reported	0.7259	0.4741	1.1114	0.1405
Age	0.9922	0.9805	1.0041	0.1978
SmokePrevious	1.3309	0.6861	2.5820	0.3978
SmokeNever	1.2458	0.6572	2.3616	0.5007

Diagnostics:

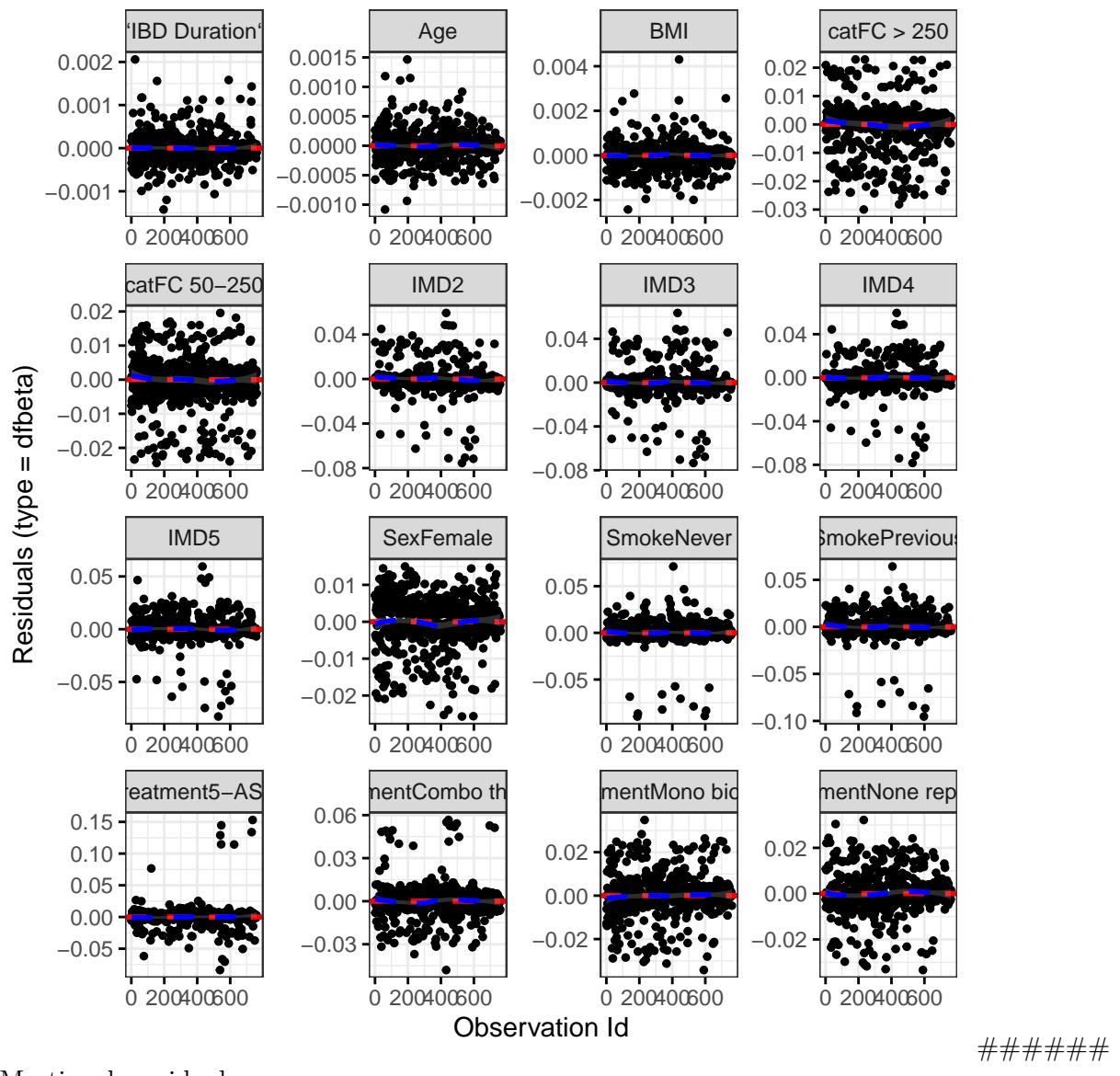
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	1.3707	0.9959	0.2406
IMD	4.6773	3.9847	0.3200
cat	8.8312	1.9978	0.0121
IBD Duration	0.0682	0.9984	0.7934
BMI	4.4479	0.9976	0.0348

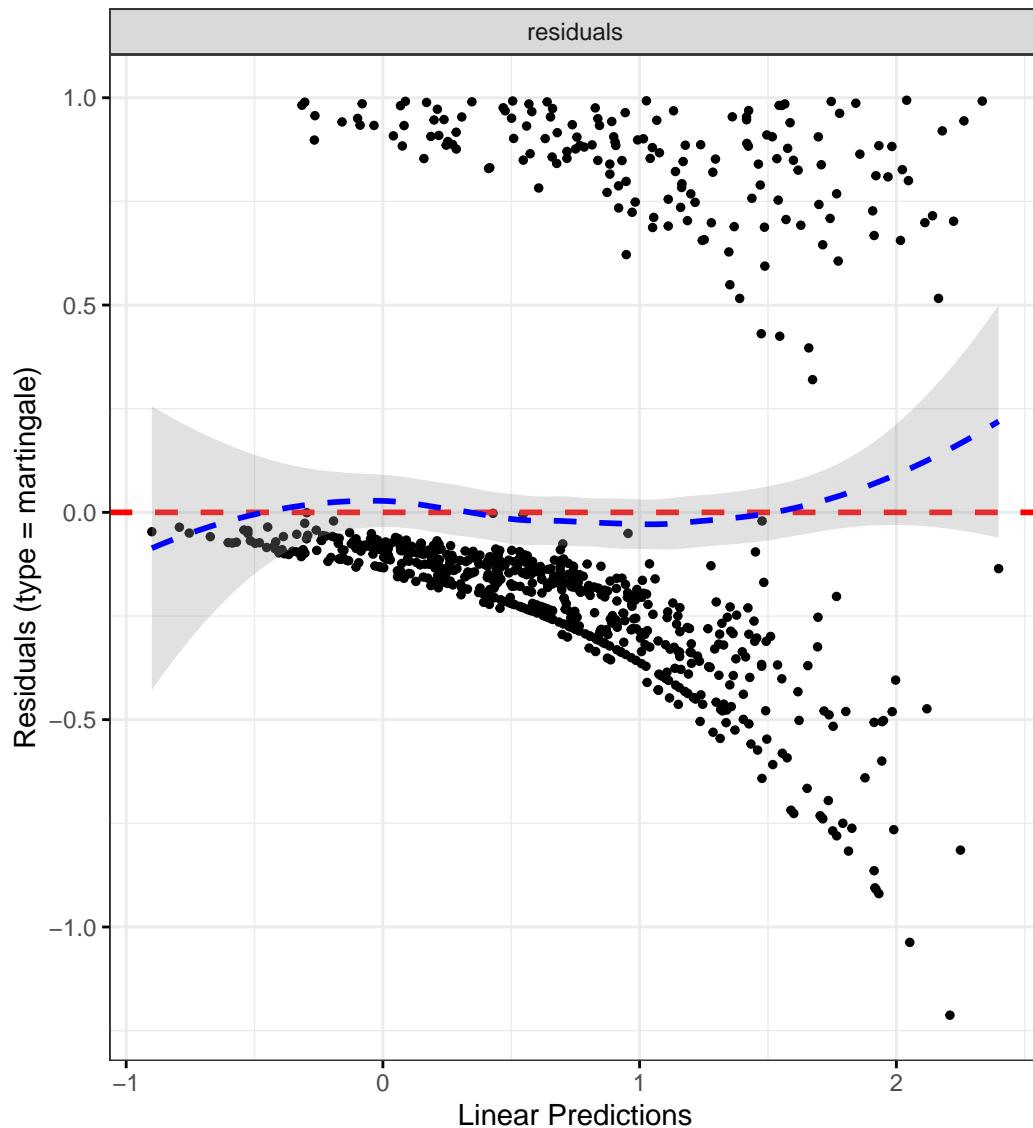
	Chi-squared statistic	DF	P-value
Treatment	3.7406	3.9729	0.4381
Age	2.9221	0.9978	0.0871
Smoke	0.4614	1.9966	0.7933
GLOBAL	26.7768	16.7962	0.0575

DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



```
`geom_smooth()` using formula = 'y ~ x'
```



Ulcerative colitis

Patient-reported flare

```
fit.me <- coxph(
  Surv(softflare_time, softflare) ~
    Sex +
    IMD +
    cat +
    `IBD Duration` +
```

```

    BMI +
    Treatment +
    Age +
    Smoke +
    frailty(SiteNo),
control = coxph.control(outer.max = 20),
data = flare.uc.df
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.5639	1.2287	1.9906	0.0003
IMD2	1.2949	0.7603	2.2053	0.3415
IMD3	1.0556	0.6368	1.7498	0.8338
IMD4	1.4290	0.8815	2.3164	0.1475
IMD5	1.1729	0.7255	1.8963	0.5152
catFC 50-250	1.6777	1.2763	2.2053	0.0002
catFC > 250	2.0136	1.4864	2.7278	0.0000
IBD Duration	0.9960	0.9827	1.0095	0.5586
BMI	0.9860	0.9631	1.0095	0.2408
TreatmentMono biologic	0.7771	0.4934	1.2238	0.2764
TreatmentCombo therapy	0.3769	0.1836	0.7739	0.0079
Treatment5-ASA	1.2407	0.8814	1.7465	0.2163
TreatmentNone reported	1.0219	0.7218	1.4468	0.9028
Age	0.9872	0.9778	0.9967	0.0083
SmokePrevious	1.2613	0.6917	2.3000	0.4488
SmokeNever	1.0499	0.5771	1.9099	0.8733

Diagnostics:

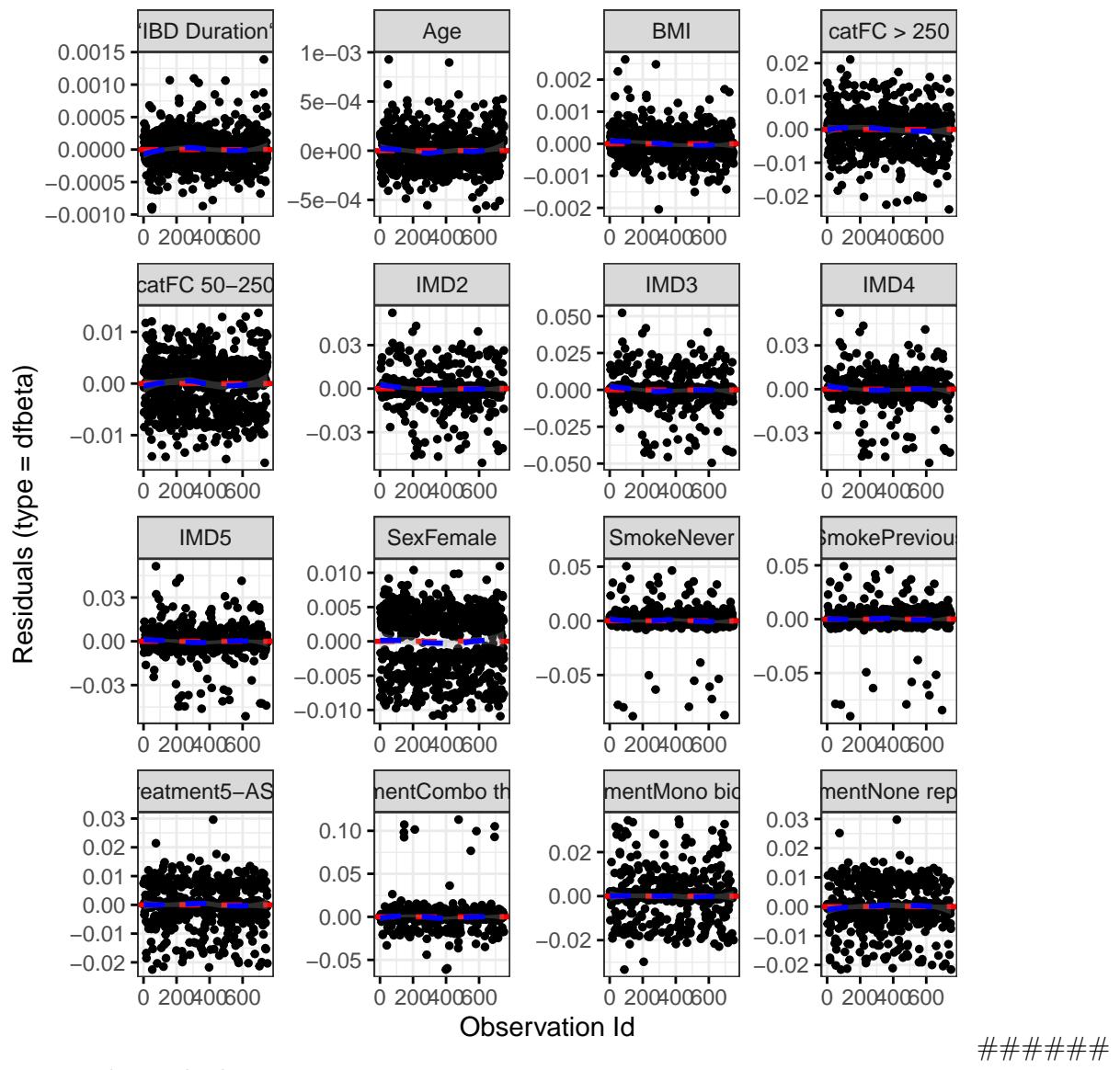
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	3.1159	0.9986	0.0774
IMD	3.9747	3.9903	0.4080
cat	3.2704	1.9961	0.1944

	Chi-squared statistic	DF	P-value
IBD Duration	1.5844	0.9987	0.2078
BMI	0.2759	0.9981	0.5986
Treatment	1.7348	3.9815	0.7820
Age	0.0232	0.9955	0.8776
Smoke	1.1879	1.9972	0.5515
GLOBAL	16.3694	16.8521	0.4875

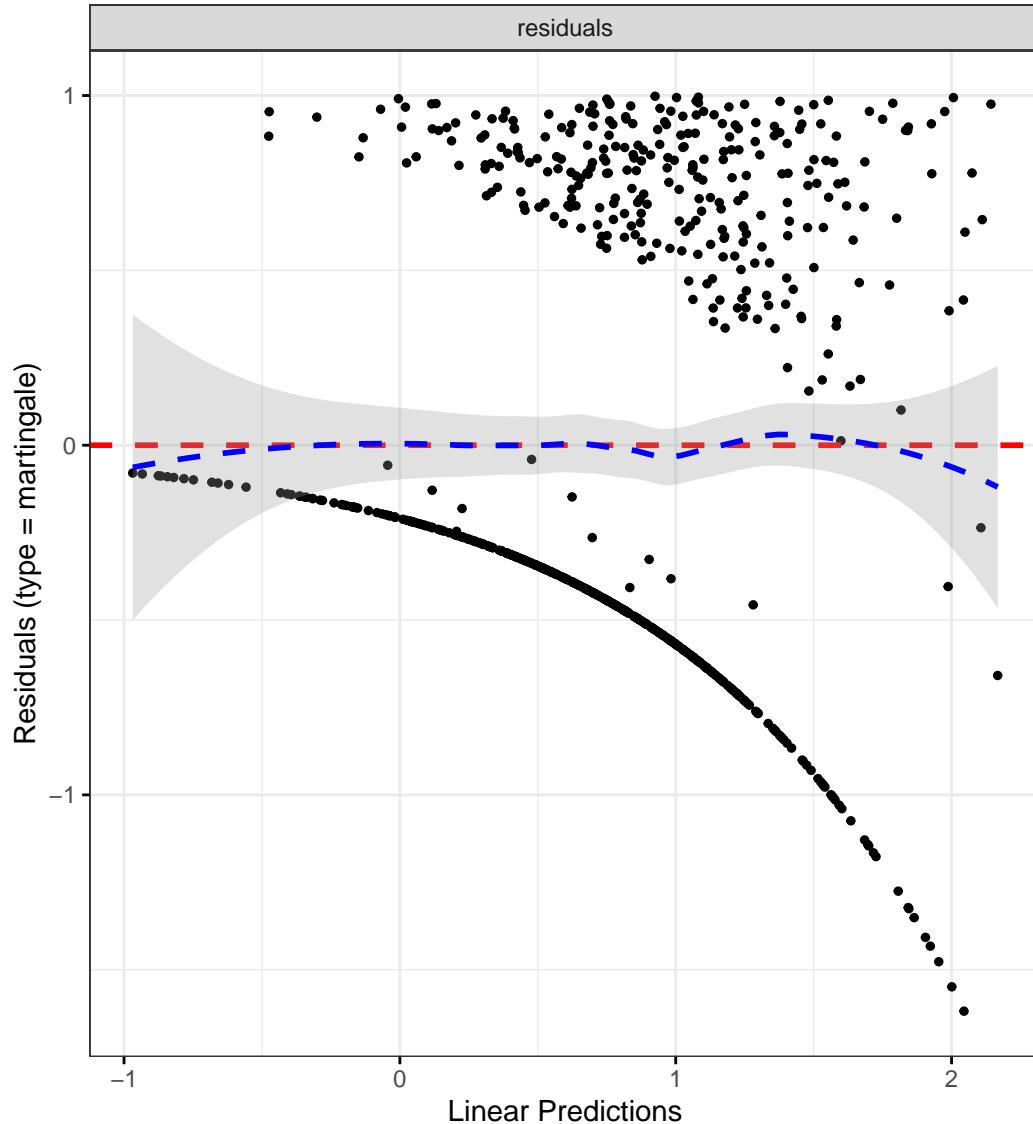
DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Objective flare

```
fit.me <- coxph(
  Surv(hardflare_time, hardflare) ~
    Sex +
    IMD +
    cat +
    `IBD Duration` +
    BMI +
    Treatment +
```

```

Age +
Smoke +
frailty(SiteNo),
control = coxph.control(outer.max = 20),
data = flare.uc.df
)

invisible(cox_summary(fit.me))

```

Cox model summary:

Variable	HR	Lower 95%	Upper 95%	P-value
SexFemale	1.4592	1.0646	2.0001	0.0188
IMD2	1.2474	0.5924	2.6266	0.5607
IMD3	1.3381	0.6647	2.6939	0.4146
IMD4	1.9784	1.0177	3.8458	0.0442
IMD5	1.4512	0.7400	2.8460	0.2785
catFC 50-250	2.1379	1.4800	3.0884	0.0001
catFC > 250	2.9624	2.0081	4.3702	0.0000
IBD Duration	0.9943	0.9762	1.0127	0.5398
BMI	0.9883	0.9574	1.0201	0.4652
TreatmentMono biologic	1.1294	0.6652	1.9176	0.6522
TreatmentCombo therapy	0.7832	0.3752	1.6348	0.5151
Treatment5-ASA	1.0290	0.6613	1.6011	0.8991
TreatmentNone reported	0.7403	0.4680	1.1710	0.1987
Age	0.9872	0.9746	0.9998	0.0471
SmokePrevious	1.7680	0.7079	4.4156	0.2224
SmokeNever	1.6201	0.6522	4.0246	0.2987

Diagnostics:

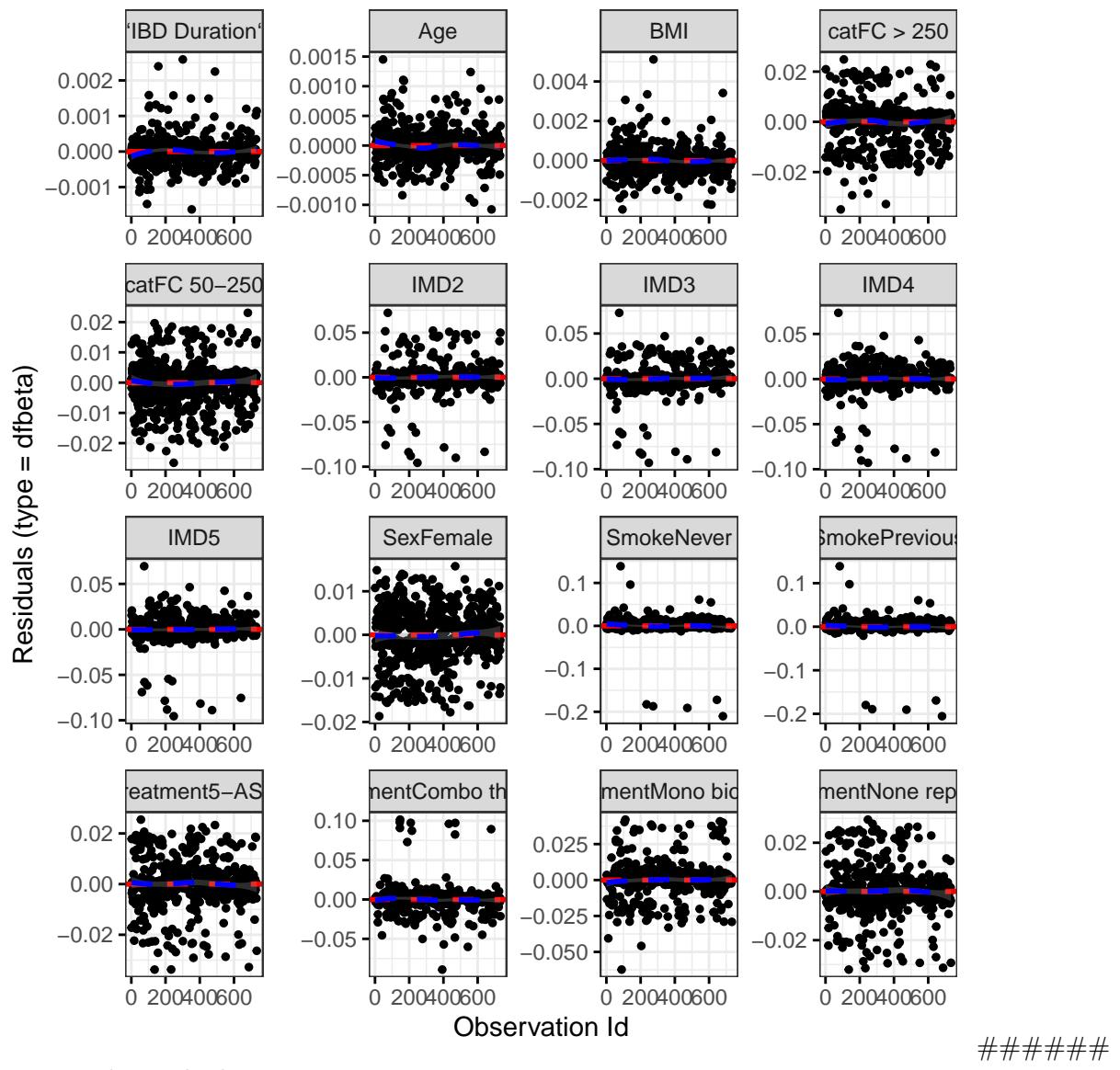
Proportional hazards assumption test

	Chi-squared statistic	DF	P-value
Sex	0.0956	0.9877	0.7526
IMD	1.9114	3.9373	0.7435
cat	3.3536	1.9695	0.1827
IBD Duration	0.6163	0.9842	0.4264
BMI	0.0101	0.9823	0.9162

	Chi-squared statistic	DF	P-value
Treatment	21.3704	3.8531	0.0002
Age	0.8918	0.9752	0.3365
Smoke	1.1111	1.9748	0.5675
GLOBAL	30.6267	26.5528	0.2665

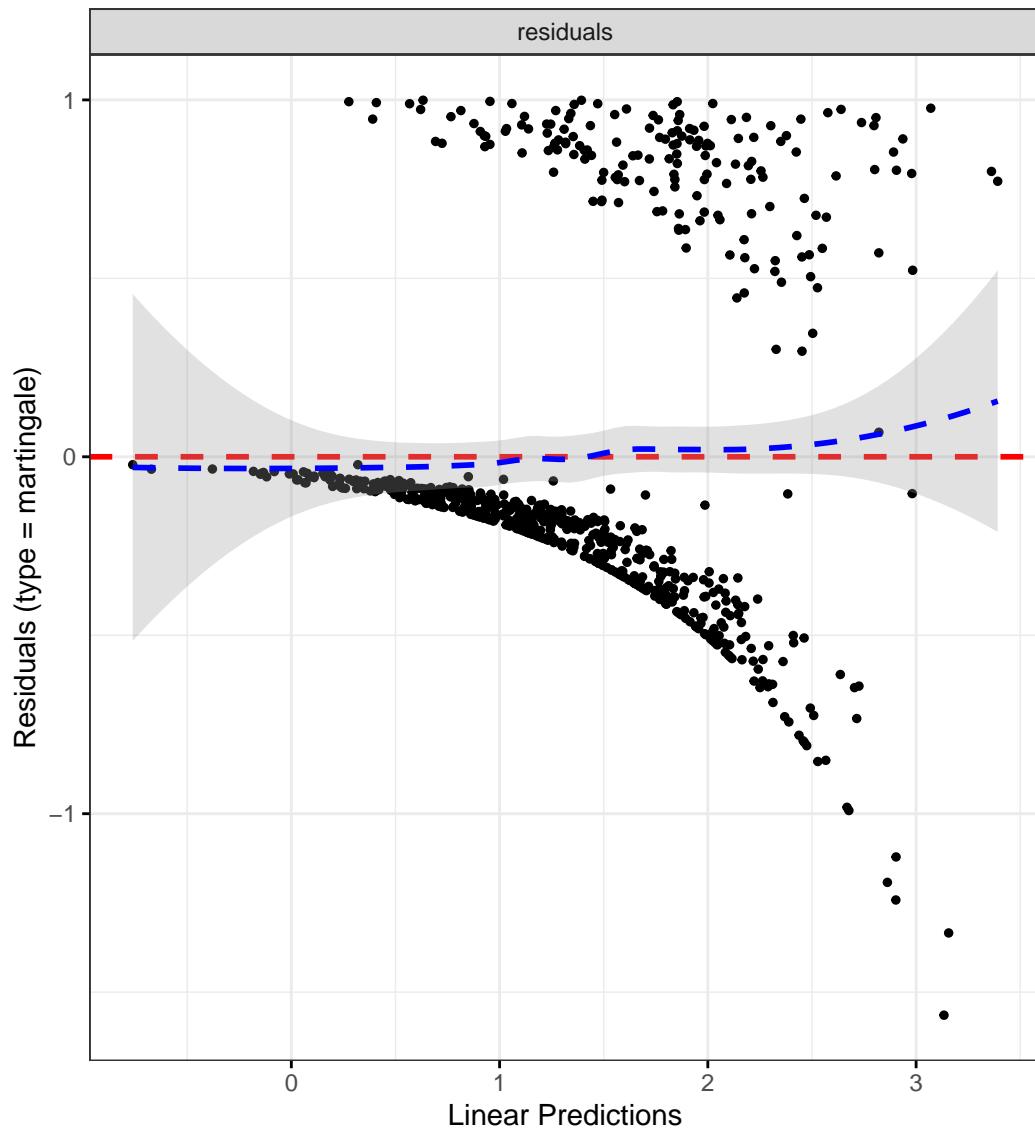
DF betas

```
`geom_smooth()` using formula = 'y ~ x'
```



Martingale residuals

```
`geom_smooth()` using formula = 'y ~ x'
```



Reproduction and reproducibility

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: *gtsummary(v.1.7.2)*, *DescTools(v.0.99.54)*, *finalfit(v.1.0.7)*,
coxme(v.2.2-20), *bdsmatrix(v.1.3-7)*, *pander(v.0.6.5)*, *survminer(v.0.4.9)*, *ggpubr(v.0.6.0)*,
survival(v.3.5-8), *datefixR(v.1.6.1)*, *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 *readxl(v.1.4.3)*

loaded via a namespace (and not attached): *gridExtra(v.2.3)*, *gld(v.2.6.6)*,
rlang(v.1.1.3), *magrittr(v.2.0.3)*, *e1071(v.1.7-14)*, *compiler(v.4.4.0)*, *mgcv(v.1.9-1)*, *vc-*
trs(v.0.6.5), *pkgconfig(v.2.0.3)*, *shape(v.1.4.6.1)*, *fastmap(v.1.2.0)*, *backports(v.1.5.0)*,
labeling(v.0.4.3), *KMsurv(v.0.1-5)*, *utf8(v.1.2.4)*, *rmarkdown(v.2.27)*, *markdown(v.1.12)*,
tzdb(v.0.4.0), *nloptr(v.2.0.3)*, *xfun(v.0.44)*, *glmnet(v.4.1-8)*, *jomo(v.2.7-6)*, *jsonlite(v.1.8.8)*,
pan(v.1.9), *broom(v.1.0.6)*, *R6(v.2.5.1)*, *stringi(v.1.8.4)*, *car(v.3.1-2)*, *boot(v.1.3-30)*,
rpart(v.4.1.23), *cellranger(v.1.1.0)*, *Rcpp(v.1.0.12)*, *iterators(v.1.0.14)*, *knitr(v.1.47)*,
zoo(v.1.8-12), *Matrix(v.1.7-0)*, *splines(v.4.4.0)*, *nnet(v.7.3-19)*, *timechange(v.0.3.0)*,
tidyselect(v.1.2.1), *rstudioapi(v.0.16.0)*, *abind(v.1.4-5)*, *yaml(v.2.3.8)*, *ggtext(v.0.1.2)*,
codetools(v.0.2-20), *lattice(v.0.22-6)*, *withr(v.3.0.0)*, *evaluate(v.0.23)*, *proxy(v.0.4-27)*,
xml2(v.1.3.6), *survMisc(v.0.5.6)*, *pillar(v.1.9.0)*, *carData(v.3.0-5)*, *mice(v.3.16.0)*, *fore-*
ach(v.1.5.2), *generics(v.0.1.3)*, *hms(v.1.1.3)*, *commonmark(v.1.9.1)*, *munsell(v.0.5.1)*,
scales(v.1.3.0), *rootSolve(v.1.8.2.4)*, *minqa(v.1.2.7)*, *xtable(v.1.8-4)*, *class(v.7.3-22)*,
glue(v.1.7.0), *lmom(v.3.0)*, *tools(v.4.4.0)*, *data.table(v.1.15.4)*, *lme4(v.1.1-35.3)*, *ggsig-*
nif(v.0.6.4), *Exact(v.3.2)*, *mvtnorm(v.1.2-5)*, *grid(v.4.4.0)*, *colorspace(v.2.1-0)*, *nlme(v.3.1-*
164), *cli(v.3.6.2)*, *km.ci(v.0.5-6)*, *fansi(v.1.0.6)*, *expm(v.0.999-9)*, *broom.helpers(v.1.15.0)*,
gt(v.0.10.1), *gtable(v.0.3.5)*, *rstatix(v.0.7.2)*, *digest(v.0.6.35)*, *farver(v.2.1.2)*, *html-*
tools(v.0.5.8.1), *lifecycle(v.1.0.4)*, *httr(v.1.4.7)*, *mitml(v.0.4-5)*, *gridtext(v.0.1.5)* and
MASS(v.7.3-60.2)

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