

# Profil\_4cer\_Statistical\_analysis

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```
#Import and set cv death and cv complications to factors
data <- vroom::vroom(here::here("data/0033_profil_4cer_data_preprocessed.csv"))

## Rows: 721 Columns: 74
## -- Column specification -----
## Delimiter: "\t"
## dbl   (72): Sample_ID, Target_16, Target_18, Target_20, Target_22, Target_24...
## date   (2): pro_date_index, pro_date_end
##
## i Use `spec()` to retrieve the full column specification for this data.
## i Specify the column types or set `show_col_types = FALSE` to quiet this message.

#Convert factors
data <- data %>%
  mutate(across(which(
    apply(., 2, function(x) {
      tmp <- unique(x)
      length(tmp) - sum(is.na(tmp)) == 2L})),
    ~ factor(.))) %>%
  mutate_at(c("Sample_ID", "Albuminuri_3_groups", "Retinopathy"), ~ factor(.))

#Split curated (Complete data with 662 observations) and
#full data set (721 observations but many missing values)
data_full <- data
data_curated <- data %>%
  filter(Curated == 1)

#Scaled ceramides
data_scale <- data_curated %>%
  mutate(across(starts_with("Target")|starts_with("Ratio"), ~scale(.)))

#Go with curated
data <- data_curated

#Vector of all variables between "Age" and "Spiron" used for clinical characteristics table
CCTable_vars <- colnames(data)[which(colnames(data) == "Age"):
  which(colnames(data) == "Spiron")]

#Clinical characteristics table, stratified by previous CV complications
```

```

CCtable <- data %>%
  mutate(Gender = factor(Gender, levels = c(1, 0), labels = c("Man", "Woman"))) %>%
  mutate(RAAS = factor(RAAS, levels = c(2, 1))) %>%
  mutate(across(starts_with("Cer_"), ~.*1000)) %>%
  CreateTableOne(vars = CCtable_vars,
    strata = "cv_komb_profil",
    #strata = "ESRD_profil",
    #strata = "doed_profil",
    addOverall = TRUE)

CCtable

```

		Stratified by cv_komb_profil		
		Overall	0	1
##	n	662	568	94
##	Age (mean (SD))	54.61 (12.66)	53.61 (12.85)	60.70 (9.49)
##	Duration_DM (mean (SD))	32.74 (15.85)	31.31 (15.83)	41.33 (13.05)
##	Gender = Woman (%)	296 (44.8)	264 (46.6)	32 (34.4)
##	Smoking = 1 (%)	137 (20.7)	116 (20.4)	21 (22.3)
##	Weight (mean (SD))	76.37 (15.05)	76.22 (14.90)	77.29 (15.94)
##	Height (mean (SD))	173.40 (9.99)	173.48 (10.08)	172.94 (9.51)
##	BMI (mean (SD))	25.42 (5.79)	25.37 (6.02)	25.70 (4.15)
##	Previous_CVD = 1 (%)	139 (21.0)	85 (15.0)	54 (57.4)
##	Retinopathy (%)			
##	0	140 (21.1)	133 (23.4)	7 ( 7.4)
##	1	90 (13.6)	82 (14.4)	8 ( 8.5)
##	2	185 (27.9)	164 (28.9)	21 (22.3)
##	3	120 (18.1)	98 (17.3)	22 (23.4)
##	4	105 (15.9)	78 (13.7)	27 (28.7)
##	5	3 ( 0.5)	3 ( 0.5)	0 ( 0.0)
##	6	19 ( 2.9)	10 ( 1.8)	9 ( 9.6)
##	logUAER (mean (SD))	1.43 (0.70)	1.37 (0.68)	1.77 (0.71)
##	HbA1C_mmol_mol (mean (SD))	64.31 (12.65)	63.76 (12.60)	67.65 (12.49)
##	Blood_HgB (mean (SD))	8.45 (0.86)	8.49 (0.83)	8.21 (0.99)
##	Total_cholesterol (mean (SD))	4.68 (0.86)	4.66 (0.83)	4.80 (1.04)
##	Blood_HDL (mean (SD))	1.70 (0.54)	1.71 (0.54)	1.61 (0.55)
##	Blood_LDL (mean (SD))	2.47 (0.75)	2.44 (0.71)	2.60 (0.94)
##	Blood_VLDL (mean (SD))	0.51 (0.27)	0.50 (0.27)	0.57 (0.30)
##	Blood_CREAE (mean (SD))	90.78 (45.59)	87.06 (40.43)	112.88 (64.69)
##	Blood_TGA (mean (SD))	1.13 (0.66)	1.09 (0.58)	1.35 (1.01)
##	GFRepi (mean (SD))	81.53 (25.51)	83.95 (24.69)	67.00 (25.68)
##	hsCRP (mean (SD))	3.41 (7.02)	3.36 (7.20)	3.70 (5.83)
##	CALSBP (mean (SD))	131.77 (17.41)	130.89 (16.90)	137.10 (19.48)
##	Cal_DIA (mean (SD))	74.25 (9.31)	74.52 (9.15)	72.62 (10.08)
##	Albuminuri_3_groups (%)			
##	1	308 (46.5)	290 (51.1)	18 (19.1)
##	3	165 (24.9)	133 (23.4)	32 (34.0)
##	4	189 (28.5)	145 (25.5)	44 (46.8)
##	RAAS = 1 (%)	445 (67.3)	358 (63.1)	87 (92.6)
##	AHT = 1 (%)	475 (71.9)	382 (67.4)	93 (98.9)
##	BB = 1 (%)	85 (12.8)	58 (10.2)	27 (28.7)
##	CB (mean (SD))	0.32 (0.65)	0.29 (0.66)	0.50 (0.50)
##	Pump = 1 (%)	57 ( 8.6)	52 ( 9.2)	5 ( 5.3)

##	Insulin_day_dose (mean (SD))	48.66 (34.97)	48.78 (36.22)	47.91 (26.29)
##	Statin = 1 (%)	397 (60.1)	321 (56.6)	76 (80.9)
##	ASA_plavix = 1 (%)	349 (52.9)	273 (48.2)	76 (80.9)
##	Diuretics = 1 (%)	334 (50.5)	260 (45.8)	74 (78.7)
##	Thiazide = 1 (%)	186 (28.1)	159 (28.0)	27 (28.7)
##	Furosemide = 1 (%)	149 (22.5)	105 (18.5)	44 (46.8)
##	Spiron = 1 (%)	28 ( 4.2)	17 ( 3.0)	11 (11.7)
##		Stratified by cv_komb_profil		
##		p	test	
##	n			
##	Age (mean (SD))	<0.001		
##	Duration_DM (mean (SD))	<0.001		
##	Gender = Woman (%)	0.038		
##	Smoking = 1 (%)	0.774		
##	Weight (mean (SD))	0.524		
##	Height (mean (SD))	0.627		
##	BMI (mean (SD))	0.619		
##	Previous_CVD = 1 (%)	<0.001		
##	Retinopathy (%)	<0.001		
##	0			
##	1			
##	2			
##	3			
##	4			
##	5			
##	6			
##	logUAER (mean (SD))	<0.001		
##	HbA1C_mmol_mol (mean (SD))	0.006		
##	Blood_HgB (mean (SD))	0.004		
##	Total_cholesterol (mean (SD))	0.126		
##	Blood_HDL (mean (SD))	0.083		
##	Blood_LDL (mean (SD))	0.069		
##	Blood_VLDL (mean (SD))	0.017		
##	Blood_CREAE (mean (SD))	<0.001		
##	Blood_TGA (mean (SD))	<0.001		
##	GFRepi (mean (SD))	<0.001		
##	hsCRP (mean (SD))	0.666		
##	CALSBP (mean (SD))	0.001		
##	Cal_DIA (mean (SD))	0.067		
##	Albuminuri_3_groups (%)	<0.001		
##	1			
##	3			
##	4			
##	RAAS = 1 (%)	<0.001		
##	AHT = 1 (%)	<0.001		
##	BB = 1 (%)	<0.001		
##	CB (mean (SD))	0.004		
##	Pump = 1 (%)	0.303		
##	Insulin_day_dose (mean (SD))	0.824		
##	Statin = 1 (%)	<0.001		
##	ASA_plavix = 1 (%)	<0.001		
##	Diuretics = 1 (%)	<0.001		
##	Thiazide = 1 (%)	0.982		
##	Furosemide = 1 (%)	<0.001		

```

## Spiron = 1 (%) <0.001

#write.csv(print(CCtable, printToggle = FALSE), here("data/CCtable.csv"))

#Median days followed
data %>%
  mutate(followed = pro_date_end - pro_date_index) %>%
  summarise(
    Median = median(followed),
    IQR = IQR(followed),
    Median_year = (median(followed)) / 365,
    IQR_year = (IQR(followed)) / 365)

## # A tibble: 1 x 4
##   Median      IQR Median_year  IQR_year
##   <drtn>    <dbl> <drtn>      <dbl>
## 1 2312 days    293 6.334247 days  0.803

rm(CCtable, CCtable_vars)

#Note: measures are changed from ug/mol to ng/mol
#Table of mean, stratified by CVE
CerTable_CVE <- data %>%
  select(c(starts_with("Target"), starts_with("Ratio"), cv_komb_profil)) %>%
  mutate(across(starts_with("Target"), ~.*1000)) %>%
  rename_with( ~gsub("Target_", "Cer", .)) %>%
  rename_with( ~gsub("Ratio ", "Ratio Cer", .)) %>%
  rename_with( ~gsub("24_", "24:", .)) %>%
  rename_with( ~gsub("/24", "/Cer24", .)) %>%
  CreateTableOne(data = .,
    strata = "cv_komb_profil",
    #strata = "ESRD_profil",
    #strata = "doed_profil",
    addOverall = TRUE)

#Table of quartiles
CerTable_quartiles <- data %>%
  select(c(starts_with("Target"), starts_with("Ratio"))) %>%
  mutate(across(starts_with("Target"), ~.*1000)) %>%
  rename_with( ~gsub("Target_", "Cer", .)) %>%
  rename_with( ~gsub("Ratio ", "Ratio Cer", .)) %>%
  rename_with( ~gsub("24_", "24:", .)) %>%
  rename_with( ~gsub("/24", "/Cer24", .)) %>%
  summarise(across(everything(), ~quantile(.))) %>%
  t() %>%
  round(., digits = 2) %>%
  as.data.frame()

colnames(CerTable_quartiles) <- c("Min", "Q1", "Median", "Q3", "Max")

CerTable_CVE

## Stratified by cv_komb_profil

```

```
##                                Overall      0      1
##      n                        662      568      94
##      Cer16 (mean (SD))        2.21 (0.44)  2.19 (0.45)  2.32 (0.41)
##      Cer18 (mean (SD))        1.26 (0.36)  1.24 (0.35)  1.36 (0.41)
##      Cer20 (mean (SD))        1.78 (0.66)  1.78 (0.66)  1.83 (0.71)
##      Cer22 (mean (SD))       10.26 (4.28)  10.24 (4.22)  10.43 (4.65)
##      Cer24:0 (mean (SD))     39.99 (16.29) 39.94 (16.00) 40.30 (18.06)
##      Cer24:1 (mean (SD))     19.55 (7.44)  19.32 (7.20)  20.93 (8.66)
##      Ratio Cer16/Cer24:0 (mean (SD))  0.06 (0.02)  0.06 (0.02)  0.07 (0.03)
##      Ratio Cer18/Cer24:0 (mean (SD))  0.03 (0.01)  0.03 (0.01)  0.04 (0.01)
##      Ratio Cer20/Cer24:0 (mean (SD))  0.05 (0.01)  0.05 (0.01)  0.05 (0.01)
##      Ratio Cer22/Cer24:0 (mean (SD))  0.26 (0.04)  0.26 (0.04)  0.26 (0.04)
##      Ratio Cer24:1/Cer24:0 (mean (SD)) 0.51 (0.11)  0.50 (0.11)  0.54 (0.12)
##      cv_komb_profil = 1 (%)      94 (14.2)    0 (0.0)    94 (100.0)
##                                Stratified by cv_komb_profil
##                                p      test
##      n
##      Cer16 (mean (SD))        0.010
##      Cer18 (mean (SD))        0.002
##      Cer20 (mean (SD))        0.496
##      Cer22 (mean (SD))        0.686
##      Cer24:0 (mean (SD))      0.842
##      Cer24:1 (mean (SD))      0.052
##      Ratio Cer16/Cer24:0 (mean (SD))  0.102
##      Ratio Cer18/Cer24:0 (mean (SD))  0.009
##      Ratio Cer20/Cer24:0 (mean (SD))  0.218
##      Ratio Cer22/Cer24:0 (mean (SD))  0.437
##      Ratio Cer24:1/Cer24:0 (mean (SD)) 0.002
##      cv_komb_profil = 1 (%)    <0.001
```

#### CerTable\_quartiles

```
##      Min    Q1  Median    Q3    Max
## Cer16      0.86  1.91   2.18   2.48   3.58
## Cer18      0.45  0.99   1.20   1.45   2.38
## Cer20      0.42  1.31   1.69   2.14   3.75
## Cer22      2.17  7.10   9.60  12.57  23.10
## Cer24:0     7.78 28.00  37.75  48.93  89.78
## Cer24:1     5.38 14.08  18.50  23.20  41.82
## Ratio Cer16/Cer24:0  0.01  0.05   0.06   0.07   0.14
## Ratio Cer18/Cer24:0  0.01  0.03   0.03   0.04   0.07
## Ratio Cer20/Cer24:0  0.02  0.04   0.05   0.05   0.08
## Ratio Cer22/Cer24:0  0.15  0.23   0.26   0.28   0.37
## Ratio Cer24:1/Cer24:0 0.27  0.43   0.49   0.57   0.83
```

```
# write.csv(print(CerTable_CVE, printToggle = FALSE), here("data/CerTable_CVE.csv"))
# write.csv(print(CerTable_quartiles, printToggle = FALSE), here("data/CerTable_quartiles.csv"))

rm(CerTable_CVE, CerTable_quartiles)
```

```
#Function for extracting Coefficient, upper and lower confidence interval and p-value
Cox_extract <- function(Data, Formula){
```

```

#Extract explanatory variable
expl_var <- word(as.character(c(Formula)), 3)
#strsplit(as.character(Formula)[3], split = " ")[[1]][1]

#Fit Cox regression model
tmp_cox <- coxph(formula = as.formula(Formula), data = Data)

#Summary object
tmp_cox_sum <- summary(tmp_cox)

#Vector to output
out_df <- data.frame(expl_var = word(as.character(c(Formula)), 3),
  coeff = tmp_cox_sum$conf.int[expl_var, "exp(coef)"],
  conf_low = tmp_cox_sum$conf.int[expl_var, "lower .95"],
  conf_up = tmp_cox_sum$conf.int[expl_var, "upper .95"],
  pval = tmp_cox_sum$coefficients[expl_var, "Pr(>|z|)"])

return(out_df)
}

#Survival object
surv_object <- Surv(data_scale$t_cv_komb_profil, as.numeric(as.character(data_scale$cv_komb_profil)))

## 1) CVE - Crude model
#Use Cox_extract function across data that starts with Target or Ratio, pivot into a table
Cox_overview_1 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(Data = data_scale, Formula = surv_object ~ .))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Crude")

Cox_overview_1

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_low conf_up    pval    fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16      1.29    1.06    1.56 0.0101 0.0277 Crude
## 2 Target_18     Target_18      1.32    1.10    1.59 0.00263 0.0145 Crude
## 3 Target_20     Target_20      1.06    0.871   1.29 0.553   0.676 Crude
## 4 Target_22     Target_22      1.03    0.843   1.26 0.768   0.845 Crude
## 5 Target_24_0   Target_24_0     1.01    0.826   1.24 0.904   0.904 Crude
## 6 Target_24_1   Target_24_1     1.20    0.991   1.45 0.0619 0.124 Crude
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.19    0.987   1.44 0.0678 0.124 Crude
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.29    1.08    1.55 0.00588 0.0215 Crude
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.14    0.935   1.39 0.197   0.310 Crude
## 10 Ratio_22/24:0 `Ratio_22/24:0` 1.08    0.880   1.32 0.473   0.650 Crude
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.34    1.11    1.61 0.00188 0.0145 Crude

```

### ## 2) CVE - Adjusted model

```
Cox_overview_2 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(data_scale, Formula = surv_object ~ .
      + Age
      + BMI
      + Blood_LDL
      + Blood_TGA
      + CALSBP
      + Gender
      + GFRapi
      + HbA1C_mmol_mol
      + logUAER
      + Previous_CVD
      + Smoking
      + Statin))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Adjusted")
```

Cox\_overview\_2

## # A tibble: 11 x 8

	name	expl_var	coeff	conf_low	conf_up	pval	fdr	model
	<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<chr>
## 1	Target_16	Target_16	1.04	0.832	1.30	0.738	0.777	Adjust~
## 2	Target_18	Target_18	1.03	0.819	1.31	0.777	0.777	Adjust~
## 3	Target_20	Target_20	0.769	0.584	1.01	0.0614	0.135	Adjust~
## 4	Target_22	Target_22	0.722	0.537	0.971	0.0310	0.114	Adjust~
## 5	Target_24_0	Target_24_0	0.761	0.572	1.01	0.0606	0.135	Adjust~
## 6	Target_24_1	Target_24_1	0.832	0.630	1.10	0.195	0.357	Adjust~
## 7	Ratio_16/24:0	`Ratio_16/24:0`	1.32	1.04	1.67	0.0220	0.114	Adjust~
## 8	Ratio_18/24:0	`Ratio_18/24:0`	1.33	1.06	1.68	0.0140	0.114	Adjust~
## 9	Ratio_20/24:0	`Ratio_20/24:0`	1.08	0.862	1.36	0.491	0.675	Adjust~
## 10	Ratio_22/24:0	`Ratio_22/24:0`	0.963	0.767	1.21	0.743	0.777	Adjust~
## 11	Ratio_24:1/24:0	`Ratio_24:1/24:0`	1.10	0.886	1.36	0.391	0.614	Adjust~

### ## 3) CVE - Adjusted light model

```
Cox_overview_3 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(data_scale, Formula = surv_object ~ .
      + Age
      + BMI
      + Blood_LDL
      + Blood_TGA
      + CALSBP
      + Gender
      + HbA1C_mmol_mol
      + Previous_CVD
      + Smoking
```

```

+ Statin))) %>%
pivot_longer(cols = everything()) %>%
unnest(cols = everything()) %>%
mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
mutate("model" = "Adj. light")

```

Cox\_overview\_3

```

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_low conf_up    pval    fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16     1.06    0.850    1.31  0.621   0.760 Adj.~
## 2 Target_18     Target_18     1.04    0.825    1.31  0.743   0.817 Adj.~
## 3 Target_20     Target_20     0.776    0.596    1.01  0.0602  0.133 Adj.~
## 4 Target_22     Target_22     0.734    0.553    0.975 0.0330  0.121 Adj.~
## 5 Target_24_0   Target_24_0    0.755    0.573    0.994 0.0451  0.124 Adj.~
## 6 Target_24_1   Target_24_1    0.835    0.639    1.09  0.186   0.340 Adj.~
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.37     1.09     1.73  0.00787 0.0433 Adj.~
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.37     1.10     1.72  0.00580 0.0433 Adj.~
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.12     0.894    1.40  0.327   0.449 Adj.~
## 10 Ratio_22/24:0 `Ratio_22/24:0` 1.02     0.818    1.27  0.869   0.869 Adj.~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.14     0.923    1.40  0.228   0.358 Adj.~

```

*#Combine the 3 CVE models into a single table*

```

Cox_overview_CVE <- Cox_overview_1 %>%
  rbind(., Cox_overview_2, Cox_overview_3) %>%
  mutate("outcome" = "CVE")

```

```
rm(Cox_overview_1, Cox_overview_2, Cox_overview_3, surv_object)
```

*#Survival object*

```

surv_object <- Surv(data_scale$t_ESRD_profil, as.numeric(as.character(data_scale$ESRD_profil)))
# surv_object <- Surv(data_scale$t_komb_nyre_endepunkt_p, as.numeric(as.character(data_scale$komb_nyre_

```

*## 4) ESKD - Crude model*

*#Use Cox\_extract function across data that starts with Target or Ratio, pivot into a table*

```

Cox_overview_4 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(Data = data_scale, Formula = surv_object ~ .))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Crude")

```

Cox\_overview\_4

```

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_~1 conf_up    pval    fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16     1.52    1.04     2.21  0.0299  0.0821 Crude
## 2 Target_18     Target_18     1.20    0.823    1.75  0.344   0.472 Crude

```



```
## 3 Target_20      Target_20      1.16    0.794    1.70 0.439    0.536 Crude
## 4 Target_22      Target_22      1.13    0.773    1.67 0.519    0.571 Crude
## 5 Target_24_0    Target_24_0    0.914    0.599    1.40 0.677    0.677 Crude
## 6 Target_24_1    Target_24_1    1.31    0.911    1.88 0.145    0.228 Crude
## 7 Ratio_16/24:0  `Ratio_16/24:0`  1.42    0.998    2.02 0.0513    0.113 Crude
## 8 Ratio_18/24:0  `Ratio_18/24:0`  1.34    0.929    1.92 0.118    0.216 Crude
## 9 Ratio_20/24:0  `Ratio_20/24:0`  1.51    1.04     2.20 0.0289    0.0821 Crude
## 10 Ratio_22/24:0 `Ratio_22/24:0`  1.87    1.27     2.76 0.00145   0.00796 Crude
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.79    1.26     2.53 0.00106   0.00796 Crude
## # ... with abbreviated variable name 1: conf_low
```

#### ## 5) ESKD - Adjusted model

```
Cox_overview_5 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(data_scale, Formula = surv_object ~ .
      + Age
      + BMI
      + Blood_LDL
      + Blood_TGA
      + CALSBP
      + Gender
      + GFRapi
      + HbA1C_mmol_mol
      + logUAER
      + Previous_CVD
      + Smoking
      + Statin))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Adjusted")
```

Cox\_overview\_5

```
## # A tibble: 11 x 8
##   name      expl_var      coeff conf_low conf_up  pval   fdr model
##   <chr>      <chr>      <dbl>   <dbl>   <dbl> <dbl> <dbl> <chr>
## 1 Target_16  Target_16    0.786   0.426   1.45 0.440 0.726 Adjusted
## 2 Target_18  Target_18    0.764   0.415   1.41 0.387 0.726 Adjusted
## 3 Target_20  Target_20    0.783   0.412   1.49 0.456 0.726 Adjusted
## 4 Target_22  Target_22    0.882   0.442   1.76 0.722 0.795 Adjusted
## 5 Target_24_0 Target_24_0  0.747   0.392   1.42 0.374 0.726 Adjusted
## 6 Target_24_1 Target_24_1  1.31    0.605   2.85 0.490 0.726 Adjusted
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.23    0.640   2.37 0.533 0.726 Adjusted
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.03    0.590   1.79 0.923 0.923 Adjusted
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.18    0.647   2.14 0.594 0.726 Adjusted
## 10 Ratio_22/24:0 `Ratio_22/24:0` 1.52    0.841   2.74 0.166 0.726 Adjusted
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.52    0.902   2.55 0.116 0.726 Adjusted
```

#### ## 6) ESKD - Adjusted light model

```
Cox_overview_6 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
```

```

summarise(across(starts_with("Target") | starts_with("Ratio"),
  ~ Cox_extract(data_scale, Formula = surv_object ~ .
    + Age
    + BMI
    + Blood_LDL
    + Blood_TGA
    + CALSBP
    + Gender
    + HbA1C_mmol_mol
    + Previous_CVD
    + Smoking
    + Statin))) %>%
pivot_longer(cols = everything()) %>%
unnest(cols = everything()) %>%
mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
mutate("model" = "Adj. light")

```

Cox\_overview\_6

```

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_~1 conf_up    pval      fdr model
##   <chr>         <chr>         <dbl>  <dbl>  <dbl>  <dbl>  <dbl> <chr>
## 1 Target_16     Target_16         1.42   0.910   2.22 1.22e-1 0.191 Adj.~
## 2 Target_18     Target_18         1.01   0.634   1.60 9.78e-1 0.978 Adj.~
## 3 Target_20     Target_20         0.909  0.560   1.47 6.99e-1 0.854 Adj.~
## 4 Target_22     Target_22         0.806  0.475   1.37 4.25e-1 0.584 Adj.~
## 5 Target_24_0   Target_24_0       0.591  0.342   1.02 5.85e-2 0.107 Adj.~
## 6 Target_24_1   Target_24_1       1.04   0.643   1.68 8.77e-1 0.965 Adj.~
## 7 Ratio_16/24:0 `Ratio_16/24:0`  2.10   1.37    3.22 6.56e-4 0.00361 Adj.~
## 8 Ratio_18/24:0 `Ratio_18/24:0`  1.69   1.11    2.58 1.50e-2 0.0330 Adj.~
## 9 Ratio_20/24:0 `Ratio_20/24:0`  1.73   1.14    2.62 9.93e-3 0.0273 Adj.~
## 10 Ratio_22/24:0 `Ratio_22/24:0`  1.90   1.23    2.94 3.83e-3 0.0141 Adj.~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 2.06   1.38    3.07 4.14e-4 0.00361 Adj.~
## # ... with abbreviated variable name 1: conf_low

```

*#Combine the 3 ESKD models into a single table*

```

Cox_overview_ESKD <- Cox_overview_4 %>%
  rbind(., Cox_overview_5, Cox_overview_6) %>%
  mutate("outcome" = "ESKD")

rm(Cox_overview_4, Cox_overview_5, Cox_overview_6, surv_object)

```

*#Survival object*

```

surv_object <- Surv(data_scale$t_doe_d_profil , as.numeric(as.character(data_scale$doed_profil)))

```

**## 7) Mortality - Crude model**

*#Use Cox\_extract function across data that starts with Target or Ratio, pivot into a table*

```

Cox_overview_7 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(Data = data_scale, Formula = surv_object ~ .))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%

```

```
mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
mutate("model" = "Crude")
```

Cox\_overview\_7

```
## # A tibble: 11 x 8
##   name          expl_var      coeff conf_~1 conf_up    pval      fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16      1.07    0.830    1.38   6.00e-1 6.60e-1 Crude
## 2 Target_18     Target_18      0.925    0.710    1.21   5.65e-1 6.60e-1 Crude
## 3 Target_20     Target_20      0.728    0.544    0.974  3.23e-2 5.08e-2 Crude
## 4 Target_22     Target_22      0.545    0.392    0.758  3.16e-4 6.95e-4 Crude
## 5 Target_24_0   Target_24_0     0.584    0.425    0.801  8.67e-4 1.59e-3 Crude
## 6 Target_24_1   Target_24_1     0.734    0.547    0.986  4.00e-2 5.50e-2 Crude
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.77     1.43     2.17   9.21e-8 1.01e-6 Crude
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.71     1.39     2.11   6.04e-7 3.32e-6 Crude
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.58     1.25     2.00   1.29e-4 3.54e-4 Crude
## 10 Ratio_22/24:0 `Ratio_22/24:0` 1.02     0.789    1.32   8.70e-1 8.70e-1 Crude
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.65     1.31     2.06   1.46e-5 5.36e-5 Crude
## # ... with abbreviated variable name 1: conf_low
```

## 8) ESKD - Adjusted model

```
Cox_overview_8 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(data_scale, Formula = surv_object ~ .
      + Age
      + BMI
      + Blood_LDL
      + Blood_TGA
      + CALSBP
      + Gender
      + GFRapi
      + HbA1C_mmol_mol
      + logUAER
      + Previous_CVD
      + Smoking
      + Statin))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Adjusted")
```

Cox\_overview\_8

```
## # A tibble: 11 x 8
##   name          expl_var      coeff conf_~1 conf_up    pval      fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16      0.809    0.587    1.11   1.93e-1 2.12e-1 Adju~
## 2 Target_18     Target_18      0.711    0.509    0.994  4.59e-2 7.22e-2 Adju~
## 3 Target_20     Target_20      0.554    0.379    0.811  2.36e-3 5.20e-3 Adju~
## 4 Target_22     Target_22      0.376    0.237    0.597  3.26e-5 3.58e-4 Adju~
## 5 Target_24_0   Target_24_0     0.473    0.307    0.727  6.61e-4 2.42e-3 Adju~
```

```
## 6 Target_24_1      Target_24_1      0.480  0.310  0.743 9.99e-4 2.75e-3 Adju-
## 7 Ratio_16/24:0    `Ratio_16/24:0`    1.69   1.27   2.23  2.78e-4 1.53e-3 Adju-
## 8 Ratio_18/24:0    `Ratio_18/24:0`    1.48   1.12   1.94  5.03e-3 9.22e-3 Adju-
## 9 Ratio_20/24:0    `Ratio_20/24:0`    1.31   0.992  1.72  5.71e-2 7.86e-2 Adju-
## 10 Ratio_22/24:0   `Ratio_22/24:0`    0.899  0.669  1.21  4.83e-1 4.83e-1 Adju-
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0`  1.21   0.935  1.57  1.46e-1 1.78e-1 Adju-
## # ... with abbreviated variable name 1: conf_low
```

#### ## 9) ESKD - Adjusted light model

```
Cox_overview_9 <- data_scale %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(data_scale, Formula = surv_object ~ .
      + Age
      + BMI
      + Blood_LDL
      + Blood_TGA
      + CALSBP
      + Gender
      + HbA1C_mmol_mol
      + Previous_CVD
      + Smoking
      + Statin))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Adj. light")
```

Cox\_overview\_9

```
## # A tibble: 11 x 8
##   name      expl_var      coeff conf_~1 conf_up    pval    fdr model
##   <chr>      <chr>      <dbl> <dbl> <dbl> <dbl> <dbl> <chr>
## 1 Target_16    Target_16    0.876  0.639  1.20  4.13e-1 4.55e-1 Adj.~
## 2 Target_18    Target_18    0.746  0.533  1.04  8.68e-2 1.06e-1 Adj.~
## 3 Target_20    Target_20    0.570  0.390  0.835 3.85e-3 7.06e-3 Adj.~
## 4 Target_22    Target_22    0.382  0.242  0.603 3.62e-5 2.34e-4 Adj.~
## 5 Target_24_0  Target_24_0    0.459  0.299  0.704 3.56e-4 1.31e-3 Adj.~
## 6 Target_24_1  Target_24_1    0.521  0.344  0.790 2.15e-3 4.73e-3 Adj.~
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.76   1.34   2.31  4.25e-5 2.34e-4 Adj.~
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.58   1.21   2.05  7.04e-4 1.93e-3 Adj.~
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.41   1.08   1.84  1.13e-2 1.77e-2 Adj.~
## 10 Ratio_22/24:0 `Ratio_22/24:0` 0.983  0.737  1.31  9.05e-1 9.05e-1 Adj.~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.33   1.03   1.72  3.00e-2 4.12e-2 Adj.~
## # ... with abbreviated variable name 1: conf_low
```

#### #Combine the 3 mortality models into a single table

```
Cox_overview_Mortality <- Cox_overview_7 %>%
  rbind(., Cox_overview_8, Cox_overview_9) %>%
  mutate("outcome" = "Mortality")

rm(Cox_overview_7, Cox_overview_8, Cox_overview_9, surv_object)
```

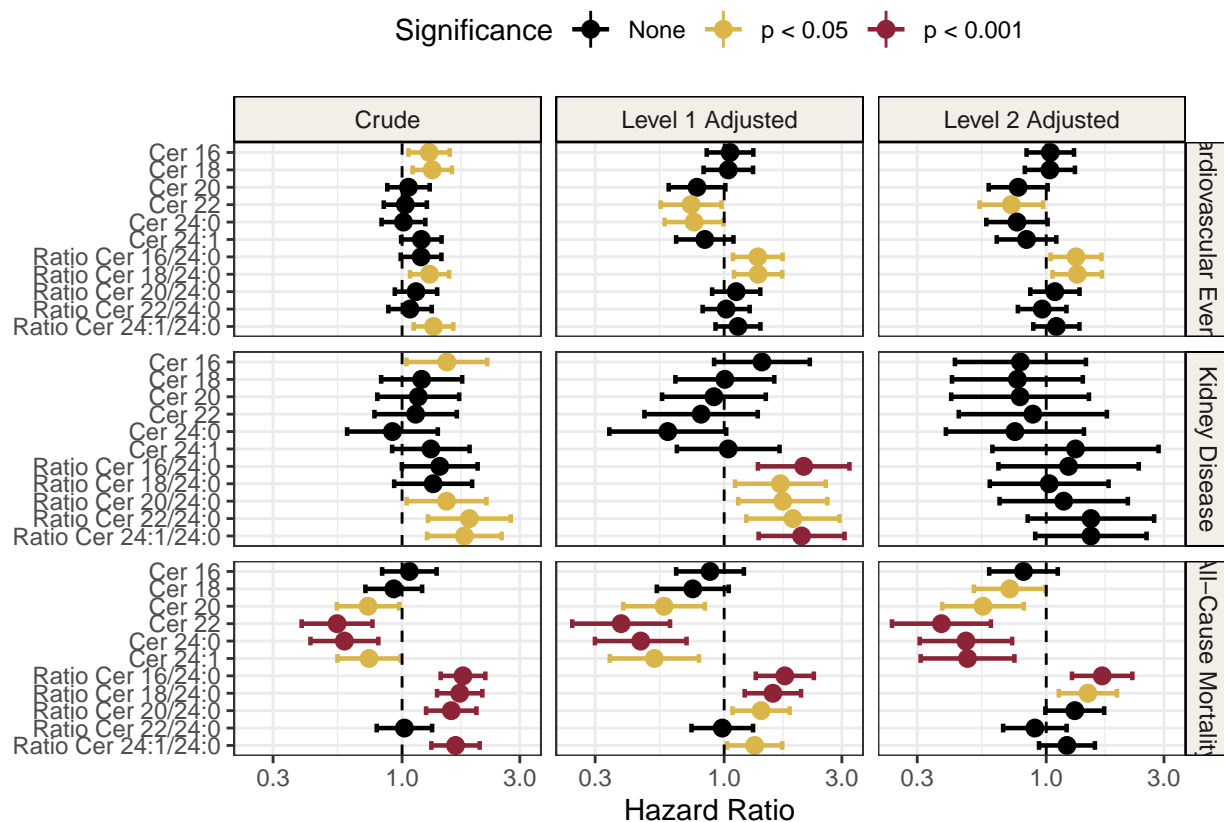
```

#Combine the 3 outcome tables into a single table
Cox_overview <- Cox_overview_CVE %>%
  rbind(., Cox_overview_ESKD, Cox_overview_Mortality)

rm(Cox_overview_CVE, Cox_overview_ESKD, Cox_overview_Mortality)

#Plot overview table as a Forest Plot
Cox_overview %>%
  mutate(name = gsub("Target_", "Cer ", name)) %>%
  mutate(name = gsub("Ratio_", "Ratio Cer ", name)) %>%
  mutate(name = gsub("_", ":", name)) %>%
  mutate(name = factor(name, levels = rev(unique(name)))) %>%
  mutate(model = factor(model, levels = c("Crude", "Adj. light", "Adjusted"),
    labels = c("Crude",
      "Level 1 Adjusted",
      "Level 2 Adjusted"))) %>%
  mutate(outcome = factor(outcome, levels = c("CVE", "ESKD", "Mortality"),
    labels = c("Cardiovascular Events",
      "Kidney Disease",
      "All-Cause Mortality"))) %>%
  mutate(Significance = if_else(pval < 0.05, "p < 0.05", "None")) %>%
  mutate(Significance = if_else(pval < 0.001, "p < 0.001", Significance)) %>%
  mutate(Significance = factor(Significance, levels = c("None", "p < 0.05", "p < 0.001"))) %>%
  ggplot(aes(x = coeff, y = name, color = Significance)) +
    geom_errorbar(aes(xmin = conf_low, xmax = conf_up), width = 0.5, size = 0.8) +
    geom_pointrange(aes(xmin = conf_low, xmax = conf_up)) +
    geom_vline(xintercept = 1, linetype = "dashed") +
    scale_x_log10() +
    scale_color_manual(values = c("black", "#D9B54A", "#8C2336")) +
    facet_grid(outcome ~ model) +
    xlab(label = "Hazard Ratio") +
    theme_bw() +
    theme(axis.title.y = element_blank(),
      legend.position = "top",
      strip.background = element_rect(colour="black",
        fill="#F2EFE9"))

```



```
#export at 8x8
```

```
#Correct naming in Cox_overview
# #Cox_overview <- Cox_overview %>%
#   mutate(model = gsub("Adjusted", "Level 2 Adjusted", model)) %>%
#   mutate(model = gsub("Adj. light", "Level 1 Adjusted", model)) %>%
#   mutate(name = gsub("Target_", "Cer", name)) %>%
#   mutate(name = gsub("Ratio_", "Ratio Cer", name)) %>%
#   mutate(name = gsub("/24", "/Cer24", name)) %>%
#   mutate(name = gsub("_", ":", name)) %>%
#   select(-"expl_var")
#write supplementary table
#write.csv(Cox_overview, here("data/Cox_overview.csv"))

# #Plot single model as a Forest Plot
# Cox_overview %>%
#   mutate(name = gsub("Target_", "Cer ", name)) %>%
#   mutate(name = gsub("Ratio_", "Ratio Cer ", name)) %>%
#   mutate(name = gsub("_", ":", name)) %>%
#   #arrange(value$pval) %>%
#   mutate(name = factor(name, levels = rev(unique(name)))) %>%
#   filter(model == "Adj. light") %>%
#   filter(outcome == "ESKD") %>%
#   ggplot(aes(x = coeff, y = name)) +
#     geom_errorbar(aes(xmin = conf_low, xmax = conf_up), width = 0.5, size = 0.8) +
```

```

#       geom_pointrange(aes(xmin = conf_low, xmax = conf_up)) +
#       geom_vline(xintercept = 1, linetype = "dashed") +
#       scale_x_log10() +
#       xlab(label = "Hazard Ratio") +
#       theme_bw() +
#       theme(axis.title.y = element_blank())

#Survival object - Cardiovascular events
surv_object <- Surv(data$t_cv_komb_profil, as.numeric(as.character(data$cv_komb_profil)))

#Vector of clinical factors to investigate
clin_num <- c("Age", "BMI", "Blood_LDL", "Blood_TGA", "CALSBP", "GFRapi", "HbA1C_mmol_mol", "logUAER")

clin_fac <- c("Gender", "Previous_CVD", "Smoking", "Statin")

## 10) CVE - Clinical Crude model
#Create an empty dataframe to populate
Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                   "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data, Formula = paste0("surv_object ~ ", clin_num[i]))

}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_tmp <-
    summary(coxph(formula = as.formula(paste0("surv_object ~ ", clin_fac[j])), data = data))

  Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
    rownames(Cox_clinical_tmp$conf.int)
  Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
    Cox_clinical_tmp$conf.int[1, "exp(coef)"]
  Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
    Cox_clinical_tmp$conf.int[1, "lower .95"]
  Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
    Cox_clinical_tmp$conf.int[1, "upper .95"]
  Cox_clinical_overview[length(clin_num)+j, "pval"] <-
    Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]

}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

```

```

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model
Cox_clinical_overview$model <- "Crude"

#Rename data frame
Cox_clinical_overview_10 <- Cox_clinical_overview

## 11) CVE - Clinical adjusted model
#Create an empty dataframe to populate
Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                     "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #String of adjustments
  clin_tmp <- c(clin_num, clin_fac)
  clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_num[i])]
  clin_tmp <- paste(clin_tmp, collapse = " + ")

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data,
                Formula = paste0("surv_object ~ ", clin_num[i], " + ", clin_tmp))
}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

  #String of adjustments
  clin_tmp <- c(clin_num, clin_fac)
  clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_fac[j])]
  clin_tmp <- paste(clin_tmp, collapse = " + ")

  #Run Cox model
  Cox_clinical_tmp <-
    summary(coxph(data = data,
                  formula = as.formula(paste0("surv_object ~ ", clin_fac[j], " + ", clin_tmp)), ))

  #Extract the results and save into data frame
  Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
    rownames(Cox_clinical_tmp$conf.int)[1]
  Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
    Cox_clinical_tmp$conf.int[1, "exp(coef)"]
  Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
    Cox_clinical_tmp$conf.int[1, "lower .95"]
  Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
    Cox_clinical_tmp$conf.int[1, "upper .95"]
  Cox_clinical_overview[length(clin_num)+j, "pval"] <-

```



```

    Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]
}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model
Cox_clinical_overview$model <- "Adjusted"

#Rename data frame
Cox_clinical_overview_11 <- Cox_clinical_overview

#Combine the 2 CVE models into a single table
Cox_clinical_overview_CVE <- Cox_clinical_overview_10 %>%
  rbind(., Cox_clinical_overview_11) %>%
  mutate("outcome" = "CVE")

#Remove temporary objects
rm(Cox_clinical_overview, Cox_clinical_overview_10, Cox_clinical_overview_11,
    Cox_clinical_tmp, clin_fac, clin_num, clin_tmp, i, j, surv_object)

#Survival object - kidney disease
surv_object <- Surv(data$t_ESRD_profil, as.numeric(as.character(data$ESRD_profil)))

#Vector of clinical factors to investigate
clin_num <- c("Age", "BMI", "Blood_LDL", "Blood_TGA", "CALSBP", "GFRepi", "HbA1C_mmol_mol", "logUAER")

clin_fac <- c("Gender", "Previous_CVD", "Smoking", "Statin")

## 12) ESKD - Clinical Crude model
#Create an empty dataframe to populate
Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                     "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data, Formula = paste0("surv_object ~ ", clin_num[i]))
}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

```

```

#Run Cox model, extract the results, save into data frame
Cox_clinical_tmp <-
  summary(coxph(formula = as.formula(paste0("surv_object ~ ", clin_fac[j])), data = data))

Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
  rownames(Cox_clinical_tmp$conf.int)
Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
  Cox_clinical_tmp$conf.int[1, "exp(coef)"]
Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
  Cox_clinical_tmp$conf.int[1, "lower .95"]
Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
  Cox_clinical_tmp$conf.int[1, "upper .95"]
Cox_clinical_overview[length(clin_num)+j, "pval"] <-
  Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]
}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model
Cox_clinical_overview$model <- "Crude"

#Rename data frame
Cox_clinical_overview_12 <- Cox_clinical_overview

## 13) ESKD - Clinical adjusted model
#Create an empty dataframe to populate
Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                     "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #String of adjustments
  clin_tmp <- c(clin_num, clin_fac)
  clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_num[i])]
  clin_tmp <- paste(clin_tmp, collapse = " + ")

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data,
               Formula = paste0("surv_object ~ ", clin_num[i], " + ", clin_tmp))
}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

```

```

#String of adjustments
clin_tmp <- c(clin_num, clin_fac)
clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_fac[j])]
clin_tmp <- paste(clin_tmp, collapse = " + ")

#Run Cox model
Cox_clinical_tmp <-
  summary(coxph(data = data,
    formula = as.formula(paste0("surv_object ~ ", clin_fac[j], " + ", clin_tmp)), ))

#Extract the results and save into data frame
Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
  rownames(Cox_clinical_tmp$conf.int)[1]
Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
  Cox_clinical_tmp$conf.int[1, "exp(coef)"]
Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
  Cox_clinical_tmp$conf.int[1, "lower .95"]
Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
  Cox_clinical_tmp$conf.int[1, "upper .95"]
Cox_clinical_overview[length(clin_num)+j, "pval"] <-
  Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]
}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model
Cox_clinical_overview$model <- "Adjusted"

#Rename data frame
Cox_clinical_overview_13 <- Cox_clinical_overview

#Combine the 2 kidney models into a single table
Cox_clinical_overview_ESKD <- Cox_clinical_overview_12 %>%
  rbind(., Cox_clinical_overview_13) %>%
  mutate("outcome" = "ESKD")

#Remove temporary objects
rm(Cox_clinical_overview, Cox_clinical_overview_12, Cox_clinical_overview_13,
  Cox_clinical_tmp, clin_fac, clin_num, clin_tmp, i, j, surv_object)

#Survival object - kidney disease
surv_object <- Surv(data$t_doe_d_profil, as.numeric(as.character(data$doed_profil)))

#Vector of clinical factors to investigate
clin_num <- c("Age", "BMI", "Blood_LDL", "Blood_TGA", "CALSBP", "GFRapi", "HbA1C_mmol_mol", "logUAER")

```

```

clin_fac <- c("Gender", "Previous_CVD", "Smoking", "Statin")

## 14) Mortality - Clinical Crude model
#Create an empty dataframe to populate
Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                   "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data, Formula = paste0("surv_object ~ ", clin_num[i]))
}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_tmp <-
    summary(coxph(formula = as.formula(paste0("surv_object ~ ", clin_fac[j])), data = data))

  Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
    rownames(Cox_clinical_tmp$conf.int)
  Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
    Cox_clinical_tmp$conf.int[1, "exp(coef)"]
  Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
    Cox_clinical_tmp$conf.int[1, "lower .95"]
  Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
    Cox_clinical_tmp$conf.int[1, "upper .95"]
  Cox_clinical_overview[length(clin_num)+j, "pval"] <-
    Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]
}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model
Cox_clinical_overview$model <- "Crude"

#Rename data frame
Cox_clinical_overview_14 <- Cox_clinical_overview

## 15) Mortality - Clinical adjusted model
#Create an empty dataframe to populate

```

```

Cox_clinical_overview <- data.frame("expl_var" = NA, "coeff" = NA,
                                   "conf_low" = NA, "conf_up" = NA, "pval" = NA)

#Iterate over numeric clinical variables
for(i in 1:length(clin_num)){

  #String of adjustments
  clin_tmp <- c(clin_num, clin_fac)
  clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_num[i])]
  clin_tmp <- paste(clin_tmp, collapse = " + ")

  #Run Cox model, extract the results, save into data frame
  Cox_clinical_overview[i,] <-
    Cox_extract(Data = data,
                Formula = paste0("surv_object ~ ", clin_num[i], " + ", clin_tmp))
}

#Iterate over factorized clinical variables
for(j in 1:length(clin_fac)){

  #String of adjustments
  clin_tmp <- c(clin_num, clin_fac)
  clin_tmp <- clin_tmp[!clin_tmp %in% c(clin_fac[j])]
  clin_tmp <- paste(clin_tmp, collapse = " + ")

  #Run Cox model
  Cox_clinical_tmp <-
    summary(coxph(data = data,
                  formula = as.formula(paste0("surv_object ~ ", clin_fac[j], " + ", clin_tmp)), ))

  #Extract the results and save into data frame
  Cox_clinical_overview[length(clin_num)+j, "expl_var"] <-
    rownames(Cox_clinical_tmp$conf.int)[1]
  Cox_clinical_overview[length(clin_num)+j, "coeff"] <-
    Cox_clinical_tmp$conf.int[1, "exp(coef)"]
  Cox_clinical_overview[length(clin_num)+j, "conf_low"] <-
    Cox_clinical_tmp$conf.int[1, "lower .95"]
  Cox_clinical_overview[length(clin_num)+j, "conf_up"] <-
    Cox_clinical_tmp$conf.int[1, "upper .95"]
  Cox_clinical_overview[length(clin_num)+j, "pval"] <-
    Cox_clinical_tmp$coefficients[1, "Pr(>|z|)"]
}

#Insert names of clinical variables
Cox_clinical_overview$name <- c(clin_num, clin_fac)
Cox_clinical_overview <- Cox_clinical_overview[, c(6, 1:5)]

#FDR
Cox_clinical_overview$fdr <- p.adjust(Cox_clinical_overview$pval, method = "fdr")

#Model

```

```

Cox_clinical_overview$model <- "Adjusted"

#Rename data frame
Cox_clinical_overview_15 <- Cox_clinical_overview

#Combine the 2 mortality models into a single table
Cox_clinical_overview_Mortality <- Cox_clinical_overview_14 %>%
  rbind(., Cox_clinical_overview_15) %>%
  mutate("outcome" = "Mortality")

#Remove temporary objects
rm(Cox_clinical_overview, Cox_clinical_overview_14, Cox_clinical_overview_15,
    Cox_clinical_tmp, clin_fac, clin_num, clin_tmp, i, j, surv_object)

#Combine the 3 outcome tables into a single table
Cox_clinical_overview <- Cox_clinical_overview_CVE %>%
  rbind(., Cox_clinical_overview_ESKD, Cox_clinical_overview_Mortality)

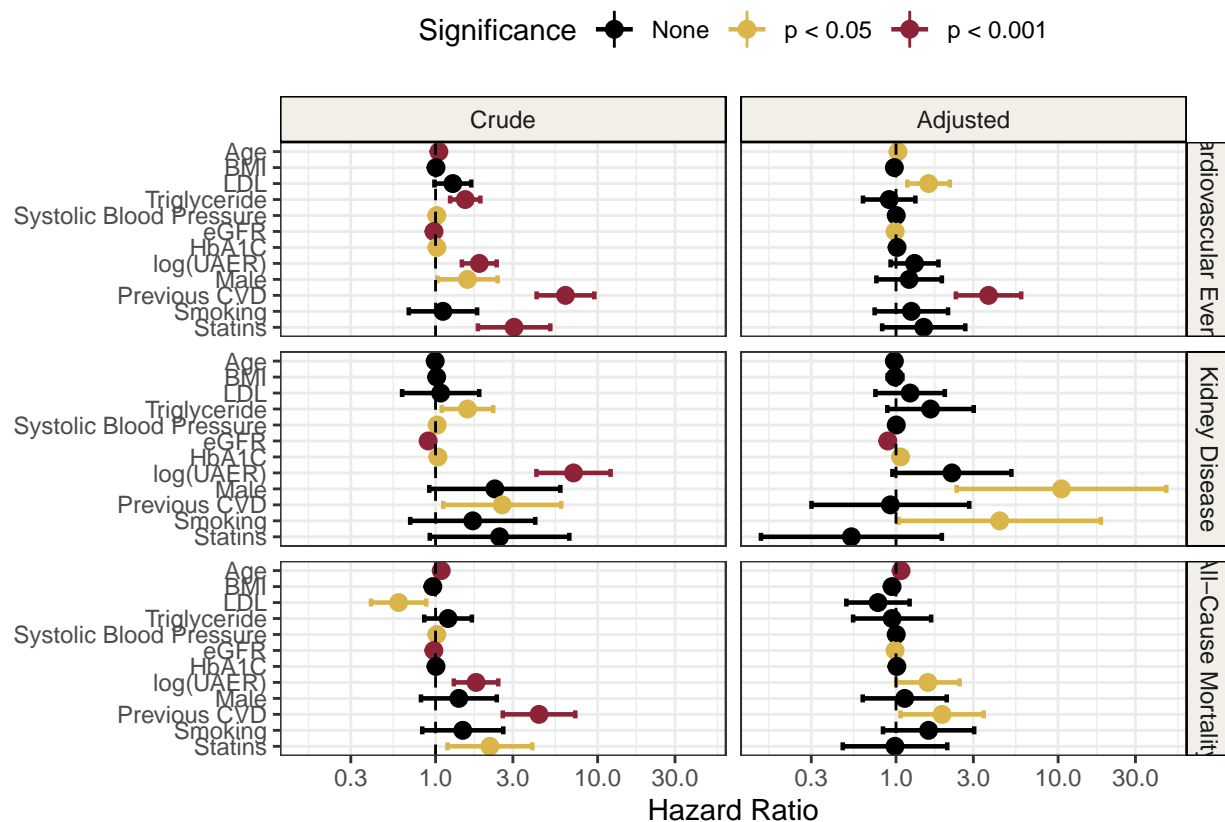
rm(Cox_clinical_overview_CVE, Cox_clinical_overview_ESKD, Cox_clinical_overview_Mortality)

#Clean names, !!NOTE VULNERABLE TO CHANGES!!
tmp_names <- c("Age", "BMI", "LDL", "Triglyceride", "Systolic Blood Pressure",
               "eGFR", "HbA1C", "log(UAER)", "Male", "Previous CVD", "Smoking", "Statins")

Cox_clinical_overview$name <- tmp_names

#Plot cox clinical overview table as a Forest Plot
Cox_clinical_overview %>%
  mutate(name = factor(name, levels = rev(unique(name)))) %>%
  mutate(model = factor(model, levels = c("Crude", "Adjusted"))) %>%
  mutate(outcome = factor(outcome, levels = c("CVE", "ESKD", "Mortality"),
    labels = c("Cardiovascular Events",
               "Kidney Disease",
               "All-Cause Mortality"))) %>%
  mutate(Significance = if_else(pval < 0.05, "p < 0.05", "None")) %>%
  mutate(Significance = if_else(pval < 0.001, "p < 0.001", Significance)) %>%
  mutate(Significance = factor(Significance, levels = c("None", "p < 0.05", "p < 0.001"))) %>%
  ggplot(aes(x = coeff, y = name, color = Significance)) +
    geom_errorbar(aes(xmin = conf_low, xmax = conf_up), width = 0.5, size = 0.8) +
    geom_pointrange(aes(xmin = conf_low, xmax = conf_up)) +
    geom_vline(xintercept = 1, linetype = "dashed") +
    scale_x_log10() +
    scale_color_manual(values = c("black", "#D9B54A", "#8C2336")) +
    facet_grid(outcome ~ model) +
    xlab(label = "Hazard Ratio") +
    theme_bw() +
    theme(axis.title.y = element_blank(),
          legend.position = "top",
          strip.background = element_rect(colour="black",
            fill="#F2EFE9"))

```



```
#export at 8x8
```

```
#write supplementary table
```

```
#write.csv(Cox_clinical_overview, here("data/Cox_clinical_overview.csv"))
```

```
rm(tmp_names)
```

```
#Ceramide Ratio and CVE
```

```
#Survival object
```

```
surv_object <- Surv(data$cv_komb_profil, as.numeric(as.character(data$cv_komb_profil)))
```

```
#Create binary variable for targets and ratios
```

```
data_bin <- data %>%
```

```
  #rename(Ratio241_240 = `Ratio 24:1/24:0`) %>%
```

```
  rename(Ratio18_240 = `Ratio 18/24:0`) %>%
```

```
  mutate(across(starts_with("Target") | starts_with("Ratio"),
```

```
    ~ ifelse(. >= quantile(.)[["75%"]], "Q3-Q4", "Q1-Q3"))
```

```
#FitKaplan-Meier model
```

```
KM_fit <- survfit(formula = surv_object ~ data_bin$Ratio18_240, data = data_bin)
```

```
#Plot Model
```

```
p1 <- ggsurvplot(
```

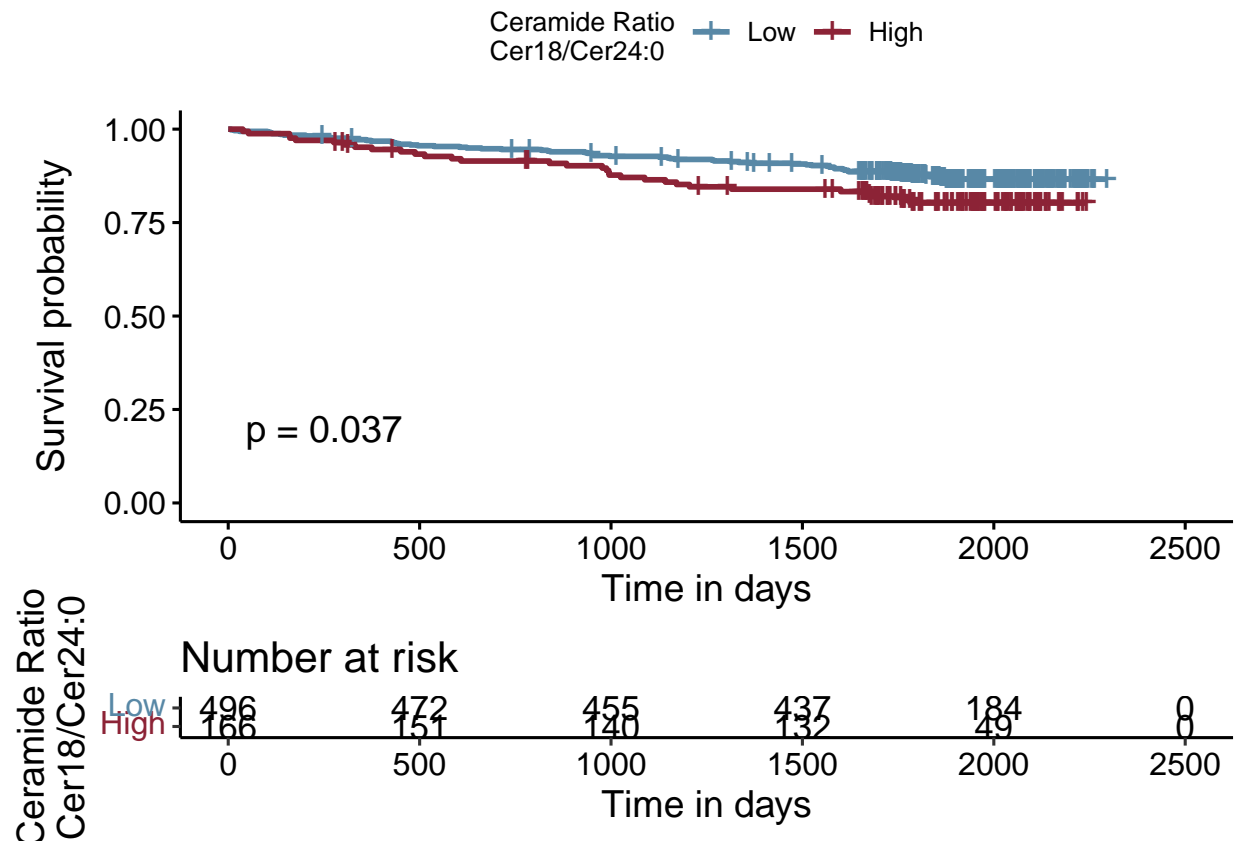
```
  KM_fit,
```

```

data = data_bin,
conf.int = FALSE,
pval = TRUE,
xlab = "Time in days",
palette = c("#5888A6", "#8C2336"),
#legend = "bottom",
legend.title = "Ceramide Ratio\nCer18/Cer24:0",
legend.labs = c("Low", "High"),
risk.table = TRUE)
#ggtheme = theme_bw())

```

p1



```

p1t <- p1$table + labs(x = "", y = "")

```

```

## LDL and CVE

```

```

#Create binary variable for targets and ratios

```

```

data_bin <- data %>%
  mutate(across(starts_with("Target") | starts_with("Ratio"),
    ~ ifelse(. >= quantile(.)["75%"], "Q3-Q4", "Q1-Q3"))) %>%
  filter(!is.na(Blood_LDL)) %>%
  mutate(Blood_LDL = ifelse(Blood_LDL >= quantile(Blood_LDL)["75%"], "Q3-Q4", "Q1-Q3"))

```



```

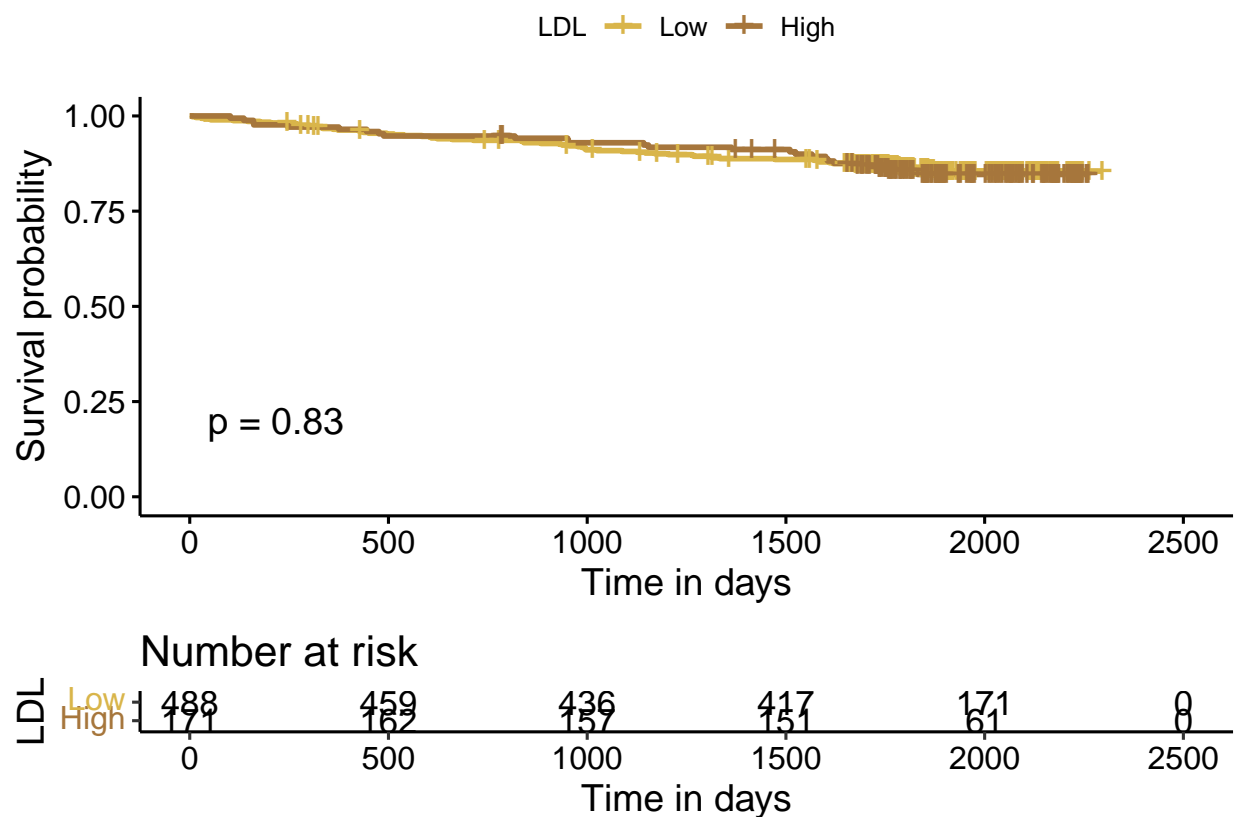
#Survival object
surv_object <- Surv(data_bin$t_cv_komb_profil, as.numeric(as.character(data_bin$cv_komb_profil)))

#FitKaplan-Meier model
KM_fit <- survfit(formula = surv_object ~ data_bin$Blood_LDL, data = data_bin)

#Plot Model
p2 <- ggsurvplot(
  KM_fit,
  data = data_bin,
  conf.int = FALSE,
  pval = TRUE,
  xlab = "Time in days",
  palette = c("#D9B54A", "#A6763C"),
  #legend = "bottom",
  legend.title = "LDL",
  legend.labs = c("Low", "High"),
  risk.table = TRUE)
#ggtheme = theme_bw()

```

p2

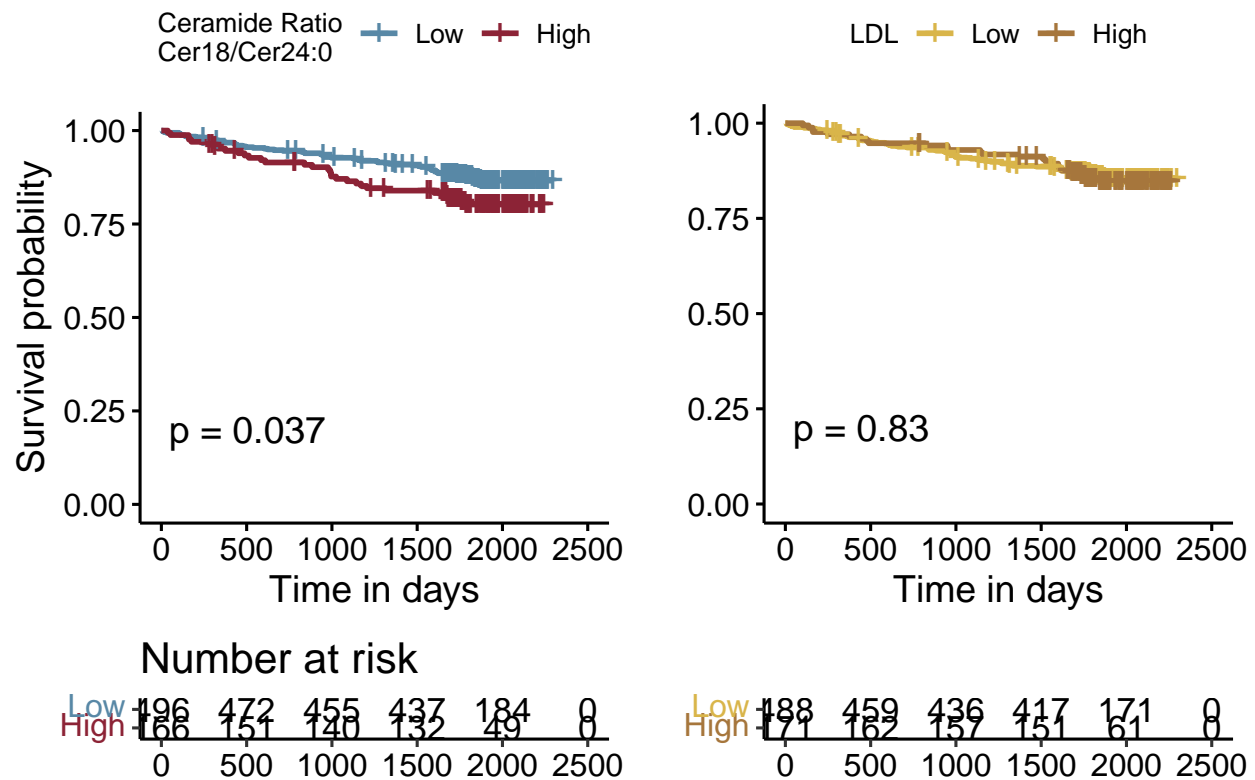


```

p2$plot <- p2$plot + labs(y = "")
p2t <- p2$table + labs(x = "", y = "", title = "")

```

```
## Join plots together
ggarrange(p1$plot, p2$plot, p1t, p2t,
  #labels = c("A", "B"),
  heights = c(1.5, 0.5),
  align = "v",
  ncol = 2, nrow = 2)
```



```
#Export ratio 5x10
```

```
rm(surv_object, data_bin, KM_fit, p1, p1t, p2, p2t)
```

```
library(ggcorrplot)
library(Hmisc)
```

```
## Warning: package 'Hmisc' was built under R version 4.2.1
```

```
## Loading required package: lattice
```

```
## Loading required package: Formula
```

```
##
```

```
## Attaching package: 'Hmisc'
```

```

## The following objects are masked from 'package:dplyr':
##
##     src, summarize

## The following objects are masked from 'package:base':
##
##     format.pval, units

#prepare data frame
tmp_cor <- data %>%
  select_if(., is.numeric) %>%
  select(!contains("censor")) %>%
  select(!contains("retino")) %>%
  select(-c(Height, Weight, t_komb_nyre_endepunkt_p, t_alb_prog, t_gfrfald30_p, CB)) %>%
  #select(-c(hsCRP, Cal_DIA, CB,)) %>%
  #select(-c(Target_20, Target_22, Target_24_1,
  #          `Ratio 16/24:0`, `Ratio 18/24:0`, `Ratio 20/24:0`, `Ratio 22/24:0`)) %>%
  rename_with( ~gsub("Target_", "Cer_", .)) %>%
  rename_with( ~gsub(" ", "_", .)) %>%
  rename_with( ~gsub(":", "_", .)) %>%
  rename_with( ~gsub("/", "_", .)) %>%
  mutate(across(everything(), ~ if_else(is.na(.x), median(., na.rm = TRUE), .)))

#Calculate correlation matrix
tmp_cor <- rcorr(as.matrix(tmp_cor), type = "pearson")

#extract correlation coeffiecints and p-values
tmp1 <- tmp_cor$r

#set NA p-values to 0
tmp_cor$P[is.na(tmp_cor$P)] <- 0
tmp2 <- tmp_cor$P

#Clean names, !!NOTE VULNERABLE TO CHANGES!!
tmp_names <- c("Cer16", "Cer18", "Cer20", "Cer22", "Cer24:0", "Cer24:1",
  "Ratio Cer16/Cer24:0", "Ratio Cer18/Cer24:0", "Ratio Cer20/Cer24:0",
  "Ratio Cer22/Cer24:0", "Ratio Cer24:1/Cer24:0", "Age",
  "Diabetes Duration", "BMI", "log(UAER)",
  "HbA1C", "Hemoglobin", "Cholesterol", "HDL", "LDL", "VLDL", "Creatinine",
  "Triglyceride", "eGFR", "hsCRP", "Systolic Blood Pressure",
  "Diastolic Blood Pressure", "Insulin Dose", "Mortality",
  "CVE", "ESRD")

colnames(tmp1) <- rownames(tmp1) <- rownames(tmp2) <- colnames(tmp2) <- tmp_names

#plot
ggcorrplot(tmp1,
  hc.order = FALSE,
  outline.col = "#F2EFE9",
  p.mat = tmp2,
  sig.level = 0.05,
  insig = "blank",
  lab = TRUE,

```

```
ggtheme = ggplot2::theme_minimal,  
colors = c("#5888A6", "white", "#8C2336"))
```



```
#export size 15x15
```

```
#Subset plot for of Cer18/cer24:0 and CVD confounders only
```

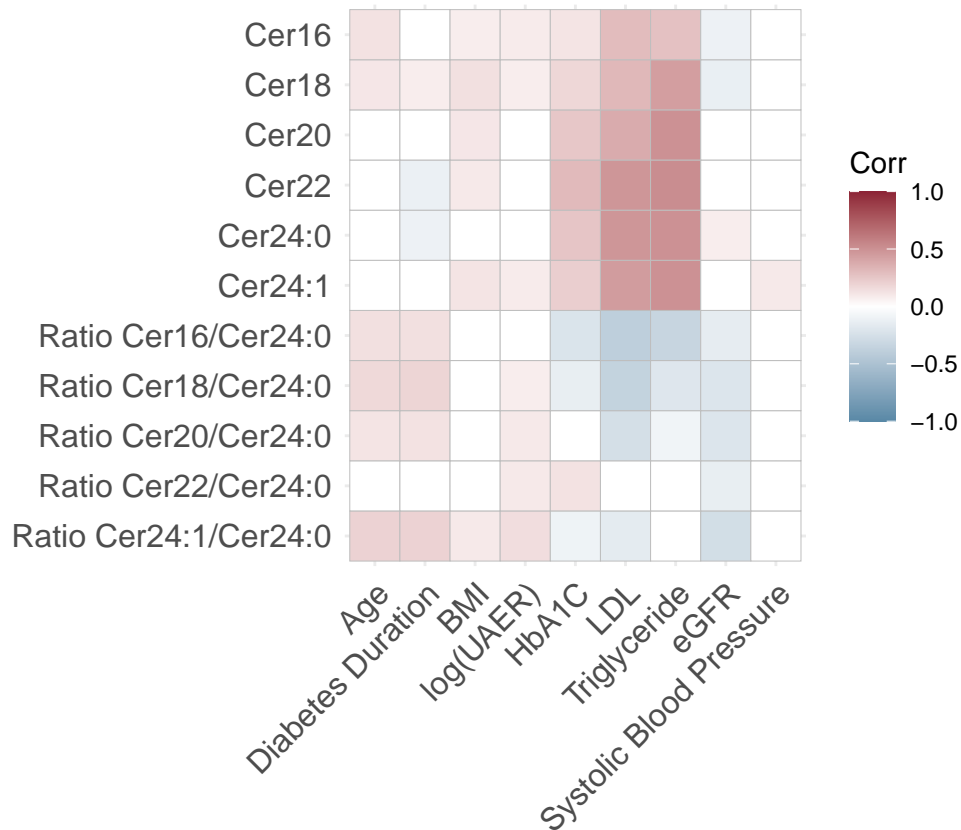
```
subset_vars <- c("Age",
  "Diabetes Duration", "BMI", "log(UAER)",
  "HbA1C", "LDL", "Triglyceride", "eGFR",
  "Systolic Blood Pressure")
```

```
tmp3 <- tmp1[subset_vars, grepl("Cer", colnames(tmp1))]  
tmp3 <- tmp3[,rev(colnames(tmp3))]
```

```
tmp4 <- tmp2[subset_vars, grepl("Cer", colnames(tmp2))]  
tmp4 <- tmp4[, rev(colnames(tmp4))]
```

## #Ceramides vs. CVD confounders

```
ggcorrplot(tmp3,
            p.mat = tmp4, insig = "blank",
            colors = c("#5888A6", "white", "#8C2336"))
```



```
# #export size 6x6
```

```
# #Ratio Cer18/Cer24:0 vs confounder
```

```
# tmp3 <- as.data.frame(tmp1[subset_vars, "Ratio Cer18/Cer24:0"])
```

```
# colnames(tmp3) <- "Ratio Cer18/Cer24:0"
```

```
#
```

```
# ggcorrplot(tmp3, method = "circle",
```

```
#           colors = c("#5888A6", "white", "#8C2336"))
```

```
#export size 6x6
```

```
rm(tmp_cor, tmp1, tmp2, tmp3, tmp4, subset_vars, tmp_names)
```

```
## Normoalbuminuria - n = 308
```

```
#Subset normoalbuminuria group
```

```
data_scale_norm <- data_scale %>%
```

```
  filter(Albuminuri_3_groups == 1)
```

```
#Survival object
```

```
surv_object <- Surv(data_scale_norm$t_cv_komb_profil, as.numeric(as.character(data_scale_norm$cv_komb_p
```

```
## 16) CVE - Crude model Normoalbuminuria
```

```
#Use Cox_extract function across data that starts with Target or Ratio, pivot into a table
```

```
Cox_overview_norm <- data_scale_norm %>%
```

```
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
```

```

summarise(across(starts_with("Target") | starts_with("Ratio"),
  ~ Cox_extract(Data = data_scale_norm, Formula = surv_object ~ .))) %>%
pivot_longer(cols = everything()) %>%
unnest(cols = everything()) %>%
mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
mutate("model" = "Normoalbuminuria")

```

Cox\_overview\_norm

```

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_low conf_up    pval    fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16     1.02    0.649    1.60 0.939   0.939 Norm~
## 2 Target_18     Target_18     1.27    0.825    1.96 0.276   0.439 Norm~
## 3 Target_20     Target_20     0.892   0.555    1.44 0.639   0.781 Norm~
## 4 Target_22     Target_22     0.872   0.539    1.41 0.577   0.781 Norm~
## 5 Target_24_0   Target_24_0   0.757   0.457    1.25 0.279   0.439 Norm~
## 6 Target_24_1   Target_24_1   0.950   0.591    1.53 0.831   0.914 Norm~
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.44    0.948    2.18 0.0874  0.192 Norm~
## 8 Ratio_18/24:0 `Ratio_18/24:0` 1.78    1.23     2.58 0.00230 0.0253 Norm~
## 9 Ratio_20/24:0 `Ratio_20/24:0` 1.50    0.979    2.31 0.0625  0.172 Norm~
## 10 Ratio_22/24:0 `Ratio_22/24:0` 1.61    1.03     2.51 0.0363  0.133 Norm~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.72    1.12     2.65 0.0138  0.0760 Norm~

```

```
rm(data_scale_norm)
```

```
## Microalbuminuria - n = 165
```

```
#Subset Microalbuminuria group
```

```
data_scale_micro <- data_scale %>%
  filter(Albuminuri_3_groups == 3)
```

```
#Survival object
```

```
surv_object <- Surv(data_scale_micro$t_cv_komb_profil, as.numeric(as.character(data_scale_micro$cv_komb)))
```

```
## 17) CVE - Crude model Microalbuminuria
```

```
#Use Cox_extract function across data that starts with Target or Ratio, pivot into a table
```

```

Cox_overview_micro <- data_scale_micro %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(Data = data_scale_micro, Formula = surv_object ~ .))) %>%
pivot_longer(cols = everything()) %>%
unnest(cols = everything()) %>%
mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
mutate("model" = "Microalbuminuria")

```

Cox\_overview\_micro

```

## # A tibble: 11 x 8
##   name          expl_var      coeff conf_~1 conf_up    pval    fdr model
##   <chr>         <chr>      <dbl>   <dbl>   <dbl>   <dbl>   <dbl> <chr>
## 1 Target_16     Target_16     1.54    1.08     2.21 1.82e-2 0.0667 Micr~
## 2 Target_18     Target_18     1.80    1.31     2.48 2.99e-4 0.00329 Micr~

```

```
## 3 Target_20      Target_20      1.30    0.923    1.84 1.33e-1 0.269 Micr~
## 4 Target_22      Target_22      1.26    0.887    1.79 1.97e-1 0.310 Micr~
## 5 Target_24_0    Target_24_0    1.30    0.928    1.82 1.27e-1 0.269 Micr~
## 6 Target_24_1    Target_24_1    1.54    1.14     2.08 4.73e-3 0.0260 Micr~
## 7 Ratio_16/24:0  `Ratio_16/24:0`    1.06    0.760    1.48 7.28e-1 0.801 Micr~
## 8 Ratio_18/24:0  `Ratio_18/24:0`    1.20    0.875    1.63 2.62e-1 0.360 Micr~
## 9 Ratio_20/24:0  `Ratio_20/24:0`    1.01    0.717    1.42 9.61e-1 0.961 Micr~
## 10 Ratio_22/24:0 `Ratio_22/24:0`    0.892    0.630    1.26 5.20e-1 0.635 Micr~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 1.25    0.926    1.68 1.47e-1 0.269 Micr~
## # ... with abbreviated variable name 1: conf_low
```

```
rm(data_scale_micro)
```

```
## Macroalbuminuria - n = 189
```

```
#Subset Microalbuminuria group
```

```
data_scale_macro <- data_scale %>%
  filter(Albuminuri_3_groups == 4)
```

```
#Survival object
```

```
surv_object <- Surv(data_scale_macro$t_cv_komb_profil, as.numeric(as.character(data_scale_macro$cv_komb)))
```

```
## 18) CVE - Crude model Macroalbuminuria
```

```
#Use Cox_extract function across data that starts with Target or Ratio, pivot into a table
```

```
Cox_overview_macro <- data_scale_macro %>%
  rename_with(~gsub("Ratio ", "Ratio_", .), starts_with("Ratio")) %>%
  summarise(across(starts_with("Target") | starts_with("Ratio"),
    ~ Cox_extract(Data = data_scale_macro, Formula = surv_object ~ .))) %>%
  pivot_longer(cols = everything()) %>%
  unnest(cols = everything()) %>%
  mutate("fdr" = p.adjust(pval, method = "fdr")) %>%
  mutate("model" = "Macroalbuminuria")
```

```
Cox_overview_macro
```

```
## # A tibble: 11 x 8
```

```
##   name      expl_var      coeff conf_low conf_up   pval   fdr model
##   <chr>      <chr>      <dbl>   <dbl>   <dbl> <dbl> <dbl> <chr>
## 1 Target_16   Target_16   1.30    0.996    1.68 0.0536 0.590 Macroa~
## 2 Target_18   Target_18   1.11    0.851    1.44 0.451  0.879 Macroa~
## 3 Target_20   Target_20   1.03    0.781    1.37 0.812  0.879 Macroa~
## 4 Target_22   Target_22   1.07    0.809    1.42 0.629  0.879 Macroa~
## 5 Target_24_0 Target_24_0  1.11    0.832    1.48 0.477  0.879 Macroa~
## 6 Target_24_1 Target_24_1  1.09    0.823    1.44 0.549  0.879 Macroa~
## 7 Ratio_16/24:0 `Ratio_16/24:0` 1.02    0.767    1.36 0.879  0.879 Macroa~
## 8 Ratio_18/24:0 `Ratio_18/24:0` 0.956    0.710    1.29 0.769  0.879 Macroa~
## 9 Ratio_20/24:0 `Ratio_20/24:0` 0.897    0.669    1.20 0.467  0.879 Macroa~
## 10 Ratio_22/24:0 `Ratio_22/24:0` 0.908    0.681    1.21 0.509  0.879 Macroa~
## 11 Ratio_24:1/24:0 `Ratio_24:1/24:0` 0.971    0.715    1.32 0.848  0.879 Macroa~
```

```
rm(data_scale_macro)
```

```

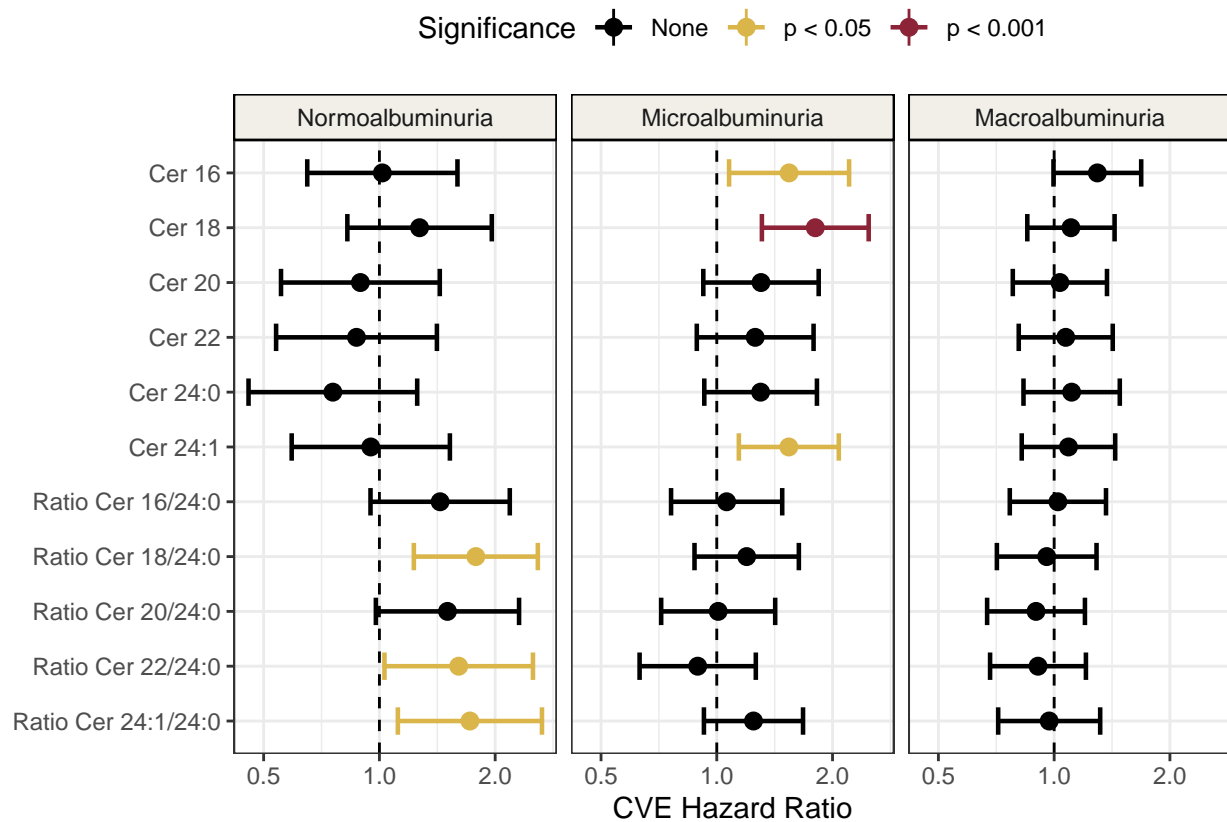
#Combine the 3 albuminuria groups into a single table
Cox_overview_albuminuria <- Cox_overview_norm %>%
  rbind(., Cox_overview_micro, Cox_overview_macro)

rm(Cox_overview_norm, Cox_overview_micro, Cox_overview_macro)

#Plot overview table as a Forest Plot
Cox_overview_albuminuria %>%
  mutate(name = gsub("Target_", "Cer ", name)) %>%
  mutate(name = gsub("Ratio_", "Ratio Cer ", name)) %>%
  mutate(name = gsub("_", ":", name)) %>%
  mutate(name = factor(name, levels = rev(unique(name)))) %>%
  mutate(model = factor(model, levels = c("Normoalbuminuria",
                                           "Microalbuminuria",
                                           "Macroalbuminuria"))) %>%
  # mutate(outcome = factor(outcome, levels = c("CVE", "ESKD", "Mortality"),
  #                           labels = c("Cardiovascular Events",
  #                                       "Kidney Disease",
  #                                       "All-Cause Mortality"))) %>%
  mutate(Significance = if_else(pval < 0.05, "p < 0.05", "None")) %>%
  mutate(Significance = if_else(pval < 0.001, "p < 0.001", Significance)) %>%
  mutate(Significance = factor(Significance, levels = c("None", "p < 0.05", "p < 0.001"))) %>%
  ggplot(aes(x = coeff, y = name, color = Significance)) +
    geom_errorbar(aes(xmin = conf_low, xmax = conf_up), width = 0.5, size = 0.8) +
    geom_pointrange(aes(xmin = conf_low, xmax = conf_up)) +
    geom_vline(xintercept = 1, linetype = "dashed") +
    scale_x_log10() +
    scale_color_manual(values = c("black", "#D9B54A", "#8C2336")) +
    facet_grid( ~ model) +
    xlab(label = "CVE Hazard Ratio") +
    theme_bw() +
    theme(axis.title.y = element_blank(),
          legend.position = "top",
          strip.background = element_rect(colour="black",
                                           fill="#F2EFE9"))

```





```
#export at 3x6
```

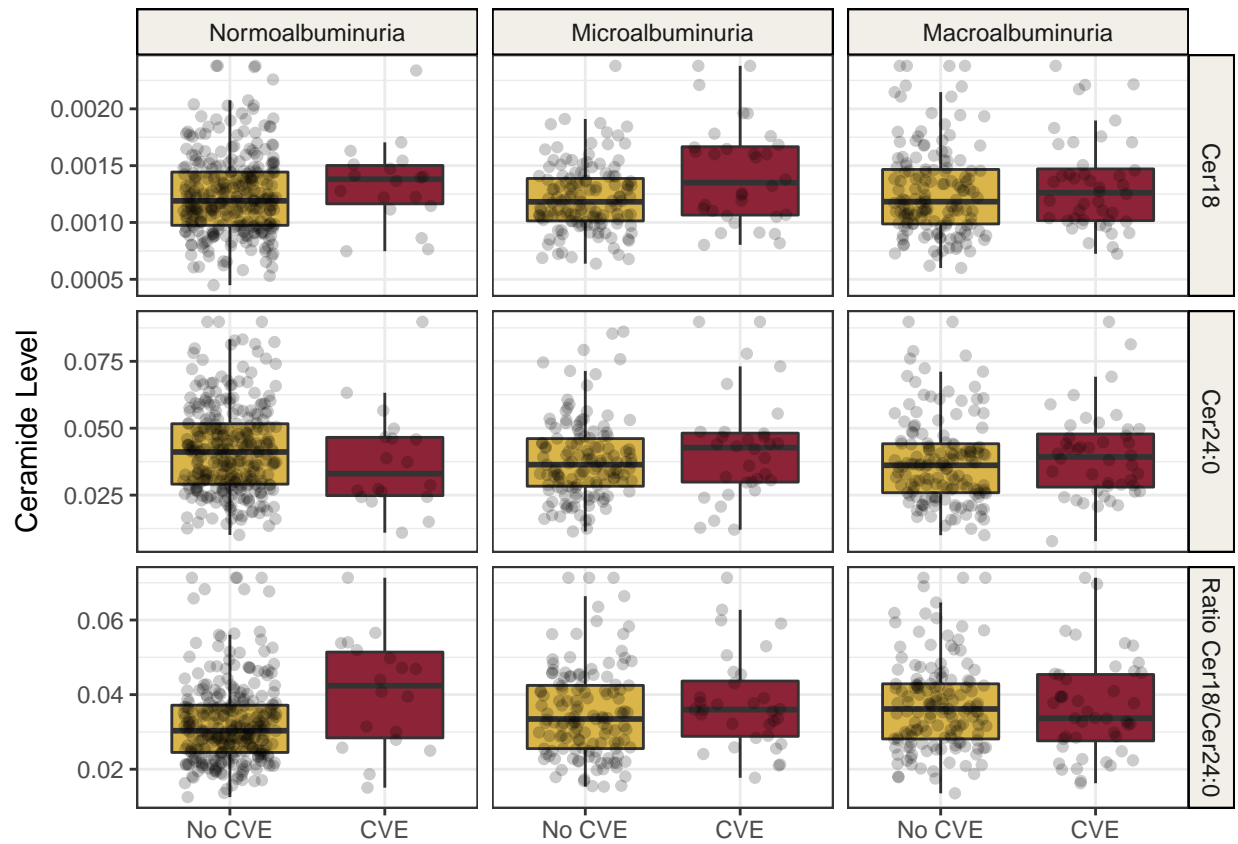
```
#write supplementary table
```

```
#write.csv(Cox_overview_albuminuria, here("data/Cox_overview_albuminuria.csv"))
```

```
#Scatterplot UAER and egfr
```

```
data %>%
  select(Target_18, Target_24_0, `Ratio 18/24:0`,
         Albuminuri_3_groups, cv_komb_profil) %>%
  mutate(Albuminuri_3_groups = factor(Albuminuri_3_groups,
                                       labels = c("Normoalbuminuria",
                                                  "Microalbuminuria",
                                                  "Macroalbuminuria"))) %>%
  mutate(cv_komb_profil = factor(cv_komb_profil,
                                 labels = c("No CVE", "CVE"))) %>%
  pivot_longer(cols = starts_with("Target") | starts_with("Ratio"),
               names_to = "Cer_Name", values_to = "Cer_val") %>%
  mutate(Cer_Name = gsub("Target_", "Cer", Cer_Name)) %>%
  mutate(Cer_Name = gsub("/24", "/Cer24", Cer_Name)) %>%
  mutate(Cer_Name = gsub("_", ":", Cer_Name)) %>%
  mutate(Cer_Name = gsub("Ratio ", "Ratio Cer", Cer_Name)) %>%
  ggplot(aes(x = cv_komb_profil, y = Cer_val, fill = cv_komb_profil)) +
  geom_boxplot(outlier.shape = NA) +
  geom_jitter(position = position_jitter(0.3),
             alpha = 0.2) +
  scale_fill_manual(values = c("#D9B54A", "#8C2336"))+
```

```
facet_grid(Cer_Name ~ Albuminuri_3_groups, scales = "free")+
ylab("Ceramide Level")+
theme_bw()+
theme(axis.title.x=element_blank(),
      legend.position="none",
      strip.background = element_rect(colour="black",
                                      fill="#F2EFE9"))
```



*#export as 7x7*