Fragility of evidence for anti-fracture efficacy

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Data management

Libraries needed:

```
library(tidyverse)
```

```
## Warning: package 'ggplot2' was built under R version 4.4.3
```

```
## -- Attaching core tidyverse packages ------------------------ tidyverse 2.0.0 --
## v dplyr     1.1.4     v readr     2.1.5
## v forcats   1.0.0     v stringr   1.5.1
## v ggplot2   3.5.1     v tibble    3.2.1
## v lubridate 1.9.3     v tidyr     1.3.1
## v purrr     1.0.2
## -- Conflicts ---------------------------------------- tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
## i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become errors
```

```
library(dplyr)
library(fragility)
```

```
## Warning: package 'fragility' was built under R version 4.4.2
```

```
## Registered S3 method overwritten by 'netmeta':
##   method          from
##   subset.pairwise meta
```

```
library(expss)
```

```
## Warning: package 'expss' was built under R version 4.4.2
```

```
## Loading required package: maditr
```

```
## Warning: package 'maditr' was built under R version 4.4.2
```

```
##
## To modify variables or add new variables:
##              let(mtcars, new_var = 42, new_var2 = new_var*hp) %>% head()
##
##
## Attaching package: 'maditr'
##
## The following objects are masked from 'package:dplyr':
##
##     between, coalesce, first, last
##
## The following object is masked from 'package:purrr':
##
##     transpose
##
## The following object is masked from 'package:readr':
##
##     cols
##
##
## Attaching package: 'expss'
##
## The following objects are masked from 'package:stringr':
##
##     fixed, regex
##
## The following objects are masked from 'package:dplyr':
##
##     compute, contains, na_if, recode, vars, where
##
## The following objects are masked from 'package:purrr':
##
##     keep, modify, modify_if, when
##
## The following objects are masked from 'package:tidyr':
##
##     contains, nest
##
## The following object is masked from 'package:ggplot2':
##
##     vars
```

```
library(ggplot2)
library(gridExtra)
```

```
## Warning: package 'gridExtra' was built under R version 4.4.2
```

```
##
## Attaching package: 'gridExtra'
##
## The following object is masked from 'package:dplyr':
##
##     combine
```

```r
library(grid)
library(table1)
```

```
##
## Attaching package: 'table1'
##
## The following objects are masked from 'package:base':
##
##     units, units<-
```

```r
library(compareGroups)
```

```
## Warning: package 'compareGroups' was built under R version 4.4.2
```

Set-up data:

```r
fi = read.csv("C:\\Users\\nickt\\OneDrive\\Documents\\Work Stuff\\Projects\\FI Paper Study\\MOST UP TO D
head(fi)
```

```
##    id study_ext study            author year           st_names journal
## 1 a_1        6b    NA Leder_ACTIVExtend 2020 Leder (2020)_exta1    JCEM
## 2 a_2        1b    NA         Body_VERO 2020     Body (2020)_a1      OI
## 3 a_3        1b    NA         Body_VERO 2020     Body (2020)_a2      OI
## 4 a_4        1b    NA         Body_VERO 2020     Body (2020)_a3      OI
## 5 a_5         1     1      Kendler_VERO 2018  Kendler (2018)_a1  Lancet
## 6 a_6         1    NA      Kendler_VERO 2018  Kendler (2018)_a2  Lancet
##         country blinding    intervention     control women_per timing fi
## 1 International   Double   Abaloparatide Alendronate         1      4  4
## 2 International   Double Teriparatide_20 Risedronate         1      2 NA
## 3 International   Double Teriparatide_20 Risedronate         1      4 NA
## 4 International   Double Teriparatide_20 Risedronate         1      2 NA
## 5 International   Double    Teriparatide Risedronate         1      4 15
## 6 International   Double    Teriparatide Risedronate         1      4 17
##          fq      pval         fx_site outcome   HR lower upper
## 1 0.0035971 0.0092162        Vert_24m       1 0.29  0.10  0.87
## 2        NA        NA         MOF_12m       2 0.38  0.20  0.72
## 3        NA        NA         MOF_24m       2 0.20  0.05  0.86
## 4        NA        NA      ClinFx_12m       2 0.49  0.31  0.78
## 5 0.0142993 0.0002691        Vert_24m       1 0.44  0.29  0.68
## 6 0.0162059 0.0002114 NworsenVert_24m       1 0.46  0.31  0.68
##                                          Notes e_con n_rand_con e_intv
## 1                                                   16        581      3
## 2                                                   24        680     10
## 3                                                   40        680     16
## 4 Did not report clinical fractures @ 24 months    34        680     18
## 5                                                   64        680     28
## 6                                                   69        680     31
##   n_rand_intv      x95_ci p_value pri_endpoint sen_analysis extended
## 1         558  0.10, 0.87  0.0270            0            1        1
## 2         680  0.20, 0.72  0.0030            0            0        0
## 3         680  0.05, 0.86  0.0310            0            0        0
## 4         690  0.31, 0.78  0.0030            0            0        0
```

```
## 5         680 [0.29,0.68]  0.0001            1            0        0
## 6         680 [0.31,0.68]  0.0001            0            0        0
##                             notes
## 1      post-hoc analysis/extended
## 2                VERO (2nd paper)
## 3                VERO (2nd paper)
## 4                VERO (2nd paper)
## 5 6 pt excluded from the analyses
## 6
##                                          st_cohort rep_loss rep_withdr
## 1                  postm osteoporotic women aged 49+        9         62
## 2                   Survival analysis: no loss to FU       NA         NA
## 3                   Survival analysis: no loss to FU       NA         NA
## 4                   Survival analysis: no loss to FU       NA         NA
## 5 postm women aged 45+: <=-1.5, 2+ mod/1+ sev vert fx       12        185
## 6 postm women aged 45+: <=-1.5, 2+ mod/1+ sev vert fx       12        185
##   rep_death rep_compt n_control n_interven
## 1        68      1861       568        544
## 2        NA        NA       680        680
## 3        NA        NA       680        680
## 4        NA        NA       680        680
## 5        20      1013       533        516
## 6        20      1013       533        516
```

```
fi$no_rand = fi$n_rand_con + fi$n_rand_intv
fi$active_sample = fi$n_control + fi$n_interven
fi$n_event = fi$e_con + fi$e_intv

fi$loghr = log(fi$HR)
```

Data management:

(1) Fracture sites:

```
table(fi$fx_site)
```

```
##
##                      ClinFx_12m                      ClinFx_18m
##                               3                               1
##                      ClinFx_24m                      ClinFx_36m
##                               5                               2
##                      ClinFx_72m                      ClinFx_72w
##                               1                               2
##                    ClinVert_12m                    ClinVert_24m
##                               1                               3
##                    ClinVert_36m                    ClinVert_48m
##                               6                               1
##                    ClinVert_72m                    ClinVert_72w
##                               1                               2
##                     Forearm_60m                 ForearmWrist_72m
##                               1                               1
##                         Fx_36m                          Fx_70m
```

```
##                               2                               1
##                         Hip_18m                         Hip_24m
##                               3                               2
##                         Hip_36m           Hip_Wrist_Forearm_70m
##                               5                               1
## Hip_Wrist_Forearm_Vertebrae_70m                MajorNonVert_12m
##                               1                               1
##                 MajorNonVert_24m                MajorNonVert_36m
##                               2                               1
##                      MajVert_24m                MNworsenVert_12m
##                               2                               1
##                 MNworsenVert_24m                         MOF_12m
##                               1                               2
##                         MOF_18m                         MOF_24m
##                               1                               3
##                      MultiFx_36m                   MultiVert_24m
##                               1                               2
##                     MultiVert_36m                       MVert_24m
##                               1                               1
##                         MVert_36m                    NmodVert_12m
##                               2                               1
##                      NmodVert_24m                     NonVert_12m
##                               1                               1
##                      Nonvert_18m                     NonVert_18m
##                               3                               1
##                      NonVert_24m                     NonVert_36m
##                               5                               6
##                      NonVert_72m                   NonVertOFx_24m
##                               1                               2
##                   NworsenVert_12m                 NworsenVert_18m
##                               2                               1
##                   NworsenVert_24m                         OFx_12m
##                               4                               1
##                          OFx_24m                         OFx_72m
##                               1                               1
##                   OtherClinFx_48m                        Vert_12m
##                               1                              12
##                         Vert_18m                        Vert_24m
##                               3                              15
##                         Vert_36m                        Vert_48m
##                              11                               3
##                         Vert_48w                        Vert_60m
##                               1                               1
##                          Vert_6m                        Vert_72m
##                               1                               1
##                         Vert_72w                       Wrist_24m
##                               2                               1
```

```
fi_final = fi %>%
  mutate(fx_code1 = case_when(fx_site == "Fx_36m" | fx_site == "Fx_70m" | fx_site == "Fx_72m" | fx_site
                              fx_site == "ClinFx_12m" | fx_site == "ClinFx_18m" | fx_site == "ClinFx_24m
                                fx_site == "ClinFx_36m" | fx_site == "ClinFx_72m" | fx_site == "ClinFx_7
                                fx_site == "OtherClinFx_48m" ~ 2,
                              fx_site == "OFx_12m" | fx_site == "OFx_24m" | fx_site == "Ofx_48m" | fx_si
```

```
                              fx_site == "MOF_12m" | fx_site == "MOF_18m" | fx_site == "MOF_24m"  ~ 4,
                              fx_site == "Hip_Wrist_Forearm_70m" | fx_site == "Hip_Wrist_Forearm_Vertebra
                              fx_site == "MajorNonVert_12m" | fx_site == "MajorNonVert_24m" | fx_site ==
                                fx_site == "MajorNonVert_60m"  | fx_site == "NonVert_12m" | fx_site == "
                                fx_site == "NonVert_24m" | fx_site == "NonVert_36m" | fx_site == "NonVer
                                fx_site == "NonVert_72m" | fx_site == "NonVertOFx_24m" ~ 6,
                              fx_site == "MajVert_24m" | fx_site == "MNworsenVert_12m" | fx_site == "MNw
                                fx_site == "MultiVert_24m" | fx_site == "MultiVert_36m" | fx_site == "MV
                                fx_site == "MVert_36m" | fx_site == "NmodVert_12m" | fx_site == "NmodVer
                                fx_site == "NworsenVert_12m" | fx_site == "NworsenVert_24m"  | fx_site =
                                fx_site == "Vert_18m"  | fx_site == "Vert_24m" | fx_site == "Vert_36m" |
                                fx_site == "Vert_48m" | fx_site == "Vert_48w" | fx_site == "Vert_60m" | f
                                fx_site == "Vert_72m" | fx_site == "Vert_72w" ~ 7,
                             fx_site == "ClinVert_12m" | fx_site == "ClinVert_24m" | fx_site == "ClinVer
                               fx_site == "ClinVert_48m" | fx_site == "ClinVert_72m" | fx_site == "ClinV
                             fx_site == "Hip_18m" | fx_site == "Hip_24m" | fx_site == "Hip_36m" | fx_site
                             fx_site == "Forearm_60m" | fx_site == "ForearmWrist_72m" | fx_site == "Wris
var_lab(fi_final$fx_code1) = "Fracture sites"
val_lab(fi_final$fx_code1) = num_lab("
                                     1 Any_fx
                                     2 Clin_fx
                                     3 OFx
                                     4 MOF
                                     5 Dif_comb
                                     6 NonVert_fx
                                     7 Vert_fx
                                     8 ClinVert_fx
                                     9 Hip
                                     10 Forearm")
table(fi_final$fx_code1)
```

```
##
##      Any_fx     Clin_fx         OFx         MOF    Dif_comb  NonVert_fx
##           4          15           3           6           2          23
##     Vert_fx ClinVert_fx         Hip     Forearm
##          69          14          10           3
```

```
fi_final = fi_final %>%
  mutate(fx_code2 = case_when(fx_code1 == "1" | fx_code1 == "2" ~ 1,
                              fx_code1 == "3" | fx_code1 == "4" | fx_code1 == "5" ~ 2,
                              fx_code1 == "6" ~ 3,
                              fx_code1 == "7" ~ 4,
                              fx_code1 == "8" ~ 5,
                              fx_code1 == "9" ~ 6,
                              fx_code1 == "10" ~ 7))
var_lab(fi_final$fx_code2) = "Fracture sites"
val_lab(fi_final$fx_code2) = num_lab("
                                     1 Any
                                     2 Osteoporotic
                                     3 Non-Vertebrae
                                     4 Vertebrae
                                     5 Clinical Vertebrae
                                     6 Hip
```

```
                                    7 Forearm")
table(fi_final$fx_code2)
```

```
##
##                 Any       Osteoporotic      Non-Vertebrae          Vertebrae
##                  19                 11                 23                 69
## Clinical Vertebrae                Hip            Forearm
##                  14                 10                  3
```

(2) Interventions:

```
table(fi$intervention)
```

```
##
##            Abaloparatide              Alendronate                  Calcium
##                        5                        8                        2
##          Calcium + vit D               Denosumab        Ibandronate daily
##                       11                        9                        3
## Ibandronate intermittent              Minodronate                      PTH
##                        3                        4                        1
##           Risedronate_25           Risedronate_50              Risendronate
##                        1                        2                        5
##              Romosozumab       Strontium Ranelate              Teriparatide
##                       28                       13                       13
##          Teriparatide_20          Teriparatide_40                   Vit D
##                        8                        5                        3
##              Zoledronate
##                       25
```

```
fi_final = fi_final %>%
  mutate(interv_code1 = case_when(intervention == "Alendronate"  ~ 1.1,
                                  intervention == "Ibandronate daily" | intervention == "Ibandronate int
                                  intervention == "Risendronate" | intervention == "Risedronate_25" | in
                                  intervention == "Minodronate" ~ 1.4,
                                  intervention == "Zoledronate" ~ 1.5,
                                  intervention == "Teriparatide" | intervention == "Teriparatide_20" |
                                    intervention == "Teriparatide_40"  | intervention == "PTH" ~ 2.1,
                                  intervention == "Abaloparatide" ~ 2.2,
                                  intervention == "Romosozumab" ~ 3,
                                  intervention == "Denosumab" ~ 4,
                                  intervention == "Strontium Ranelate" ~ 5,
                                  intervention == "Calcium" | intervention == "Calcium + vit D" | interve
var_lab(fi_final$interv_code1) = "Interventions"
val_lab(fi_final$interv_code1) = num_lab("
                                    1.1 Alendronate
                                    1.2 Ibandronate
                                    1.3 Risedronate
                                    1.4 Minodronate
                                    1.5 Zoledronate
                                    2.1 Teriparatide
                                    2.2 Abaloparatide
                                    3 Romosozumab
```

```
                                    4 Denosumab
                                    5 Strontium_ranelate
                                    6 Calcium_VitD")
table(fi_final$interv_code1)
```

```
##
##        Alendronate        Ibandronate        Risedronate        Minodronate
##                  8                  6                  8                  4
##        Zoledronate       Teriparatide      Abaloparatide        Romosozumab
##                 25                 27                  5                 28
##          Denosumab Strontium_ranelate       Calcium_VitD
##                  9                 13                 16
```

```
fi_final = fi_final %>%
  mutate(interv_code2 = case_when(intervention == "Alendronate" | intervention == "Ibandronate daily" |
                                    intervention == "Ibandronate intermittent" | intervention == "Risen
                                    intervention == "Minodronate" | intervention == "Zoledronate" ~ 1,
                                  intervention == "Teriparatide" | intervention == "Teriparatide_20" |
                                    intervention == "Teriparatide_40" | intervention == "Abaloparatide"
                                  intervention == "Romosozumab" ~ 3,
                                  intervention == "Denosumab" ~ 4,
                                  intervention == "Strontium Ranelate" ~ 5,
                                  intervention == "Calcium" | intervention == "Calcium + vit D" | interv
var_lab(fi_final$interv_code2) = "Interventions"
val_lab(fi_final$interv_code2) = num_lab("
                                    1 Bisphosphonates
                                    2 PTH analog
                                    3 Romosozumab
                                    4 Denosumab
                                    5 Strontium_ranelate
                                    6 Calcium_VitD")
table(fi_final$interv_code2)
```

```
##
##    Bisphosphonates         PTH analog        Romosozumab          Denosumab
##                 51                 32                 28                  9
## Strontium_ranelate       Calcium_VitD
##                 13                 16
```

(3) Journals:

```
table(fi$journal)
```

```
##
## Ann Intern Med            BMJ           JAMA           JBMR           JCEM
##              1              7             11              6              8
##           JECM         Lancet           NEJM             OI
##              5             10             81             20
```

```
fi_final = fi_final %>%
  mutate(journal_code1 = case_when(journal == "NEJM" ~ 1,
                                   journal == "Lancet" ~ 2,
                                   journal == "BMJ" ~ 3,
                                   journal == "JAMA" ~ 4,
                                   journal == "Ann Intern Med" ~ 5,
                                   journal == "JBMR" ~ 6,
                                   journal == "JCEM" | journal == "JECM" ~ 7,
                                   journal == "OI" ~ 8,
                                   journal == "Am J Clin Nutr" | journal == "Arth Rheu" ~ 9))
var_lab(fi_final$journal_code1) = "Journal"
val_lab(fi_final$journal_code1) = num_lab("
                                   1 NEJM
                                   2 Lancet
                                   3 BMJ
                                   4 JAMA
                                   5 Ann Intern Med
                                   6 JBMR
                                   7 JCEM
                                   8 OI
                                   9 Other")
table(fi_final$journal_code1)
```

```
##
##           NEJM         Lancet            BMJ           JAMA Ann Intern Med
##             81             10              7             11               1
##           JBMR           JCEM             OI
##              6             13             20
```

```
fi_final = fi_final %>%
  mutate(journal_code2 = case_when(journal == "NEJM" ~ 1,
                                   journal == "Lancet" ~ 2,
                                   journal == "BMJ" ~ 3,
                                   journal == "JAMA" ~ 4,
                                   journal == "Ann Intern Med" ~ 5,
                                   journal == "JBMR" ~ 6,
                                   journal == "JCEM" | journal == "JECM" ~ 7,
                                   journal == "OI" | journal == "Am J Clin Nutr" | journal == "Arth Rheu
var_lab(fi_final$journal_code2) = "Journal"
val_lab(fi_final$journal_code2) = num_lab("
                                   1 NEJM
                                   2 Lancet
                                   3 BMJ
                                   4 JAMA
                                   5 Ann Intern Med
                                   6 JBMR
                                   7 JCEM
                                   8 Other")
table(fi_final$journal_code2)
```

```
##
##           NEJM         Lancet            BMJ           JAMA Ann Intern Med
```

```
##             81             10              7             11              1
##           JBMR           JCEM          Other
##              6             13             20
```

(4) Others:

```
var_lab(fi_final$outcome) = "Types of fracture outcome"
val_lab(fi_final$outcome) = num_lab("
                                    1 Binary
                                    2 Time-to-event")

var_lab(fi_final$timing) = "Timing of outcome assessed"
val_lab(fi_final$outcome) = num_lab("
                                    1 0-6m
                                    2 >6-12m
                                    3 >12-18m
                                    4 >18-24m
                                    5 >24-36m
                                    6 >36-48m
                                    7 >48-60m
                                    8 >60-72m
                                    9 >72m")

fi_final = fi_final %>%
  mutate(sex = case_when(women_per == 0 ~ "Men",
                         women_per == 1 ~ "Women",
                         women_per > 0 & women_per < 1 ~ "Both"))
var_lab(fi_final$sex) = "Sex"
table(fi_final$sex)
```

```
##
##  Both   Men Women
##    18    10   121
```

```
fi_final = fi_final %>%
  mutate(placebo = case_when(control == "Placebo" ~ "Placebo",
                             control == "Alendronate" | control == "Risedronate" ~ "Active"))
var_lab(fi_final$placebo) = "Placebo"
table(fi_final$placebo)
```

```
##
##  Active Placebo
##      30     119
```

Calculate Fragility index (FI)

All documented analyses (some with significant results from Cox PH might turn out to be statistically non-significant using logistic regression) n= 9 analyses with P>0.05 from logistic regression will be excluded (NO studies are excluded)

```r
fi_screen = frag.studies(e_con, n_control, e_intv, n_interven, data = fi_final, methods = "RR")
fi_screen
```

```
## The input dataset contains 149 studies
## Significance level = 0.05
## Null hypothesis: RR = 1
## p-value (two-sided) is based on:
##   relative risk
##
## Fragility index (FI) and fragility quotient (FQ):
## Based on relative risk,
##   141 studies yield significance with
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%;
##   8 studies yield non-significance with
##     median FI = 1, range 1-6, IQR 1-4 and
##     median FQ = 0.1%, range 0.0%-1.0%, IQR 0.0%-0.1%;
##   overall, among all studies,
##     median FI = 8, range 1-171, IQR 3-18 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%
```

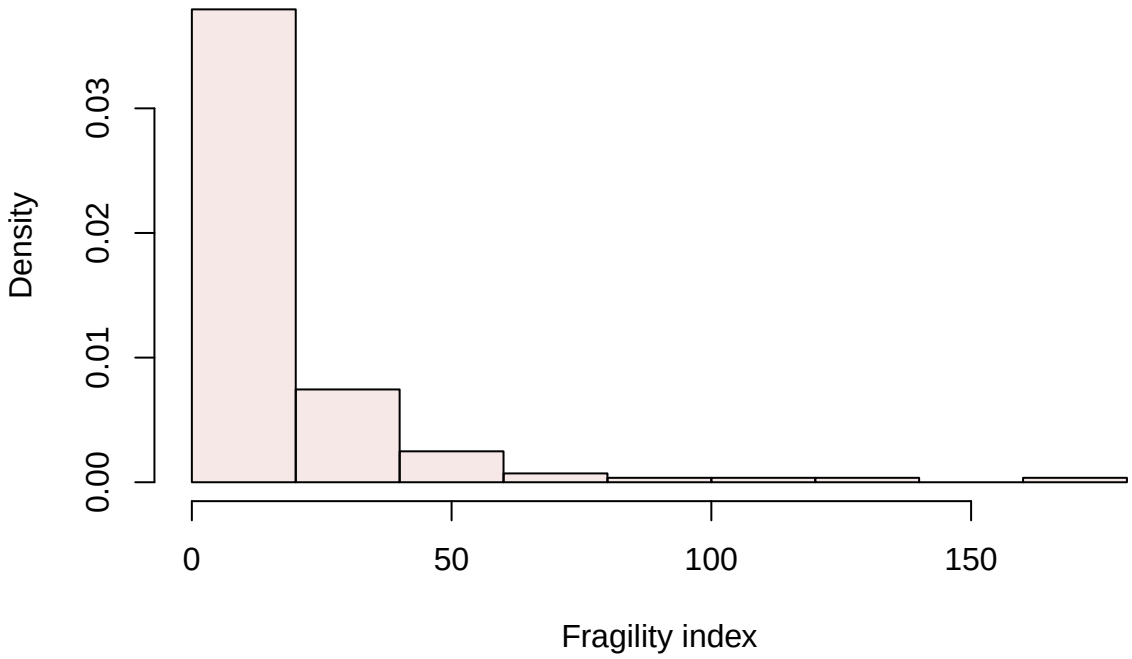
```r
fi_final$Pval_screen = fi_screen$pval
```

Only analyses with statistically significant results from logistic regression/Fisher exact test (binary outcome) are included

```r
fi_sig = subset(fi_final, Pval_screen<= 0.05)
fi_only_sig = frag.studies(e_con, n_control, e_intv, n_interven, data = fi_sig, methods = "RR")
fi_only_sig
```

```
## The input dataset contains 141 studies
## Significance level = 0.05
## Null hypothesis: RR = 1
## p-value (two-sided) is based on:
##   relative risk
##
## Fragility index (FI) and fragility quotient (FQ):
## Based on relative risk,
##   141 studies yield significance with
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%;
##   0 study yields non-significance
##   overall, among all studies,
##     median FI = 9, range 1-171, IQR 4-19 and
##     median FQ = 0.5%, range 0.0%-9.7%, IQR 0.2%-1.0%
```

```r
plot(fi_only_sig, bar = FALSE, freq = FALSE)
```




```
fi_sig$FI_final = fi_only_sig$FI
fi_sig$FQ_final = fi_only_sig$FQ
fi_sig$Pval_final = fi_only_sig$pval
```

The final dataset is saved

```
write.csv(fi_sig, "C:\\Users\\nickt\\OneDrive\\Documents\\Work Stuff\\Projects\\FI Paper Study\\MOST UP
```

(1) Primary analysis: all analyses with statistically significant results

n= 141 analyses from all 27 studies (26 original + 1 extended studies) + another 5 extended studies

Data management - No. of participants lost to FU

```
fi_sig$missing_fi[fi_sig$rep_loss > fi_sig$FI_final] = 1
fi_sig$missing_fi[fi_sig$rep_loss <= fi_sig$FI_final] = 0
is.na(fi_sig$rep_loss)
```

```
##   [1] FALSE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [13] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [25] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [37] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
```

```
##  [49] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE
##  [61]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE
##  [73] FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE
##  [85] FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE  TRUE
##  [97]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE  TRUE  TRUE
## [109]  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE
## [121] FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE FALSE FALSE FALSE FALSE FALSE
## [133] FALSE FALSE FALSE FALSE FALSE  TRUE  TRUE  TRUE  TRUE
```

```
fi_sig$missing_fi[fi_sig$rep_loss == NA] = NA
fi_sig$fi4[fi_sig$FI_final>4] = "FI > 4"
  fi_sig$fi4[fi_sig$FI_final<=4] = "FI <= 4"
```

(1.1) Table 1. Characteristics of studies and analyses

```
fi_sig_st = subset(fi_sig, study >= 1)

table1(~ as.factor(interv_code2) + as.factor(journal_code1) + as.factor(placebo) + sex + no_rand, data =
```

By studies:

	Overall
	(N=27)
as.factor(interv_code2)	
Bisphosphonates	12 (44.4%)
PTH analog	5 (18.5%)
Romosozumab	2 (7.4%)
Denosumab	2 (7.4%)
Strontium_ranelate	2 (7.4%)
Calcium_VitD	4 (14.8%)
as.factor(journal_code1)	
NEJM	12 (44.4%)
Lancet	2 (7.4%)
BMJ	1 (3.7%)
JAMA	3 (11.1%)
Ann Intern Med	1 (3.7%)
JBMR	1 (3.7%)
JCEM	2 (7.4%)
OI	5 (18.5%)
as.factor(placebo)	
Active	3 (11.1%)
Placebo	24 (88.9%)
Sex	
Both	5 (18.5%)
Men	2 (7.4%)
Women	20 (74.1%)
no_rand	
Mean (SD)	2580 (2140)
Median [Q1, Q3]	1910 [1280, 2980]
Median [min, max]	1910 [450, 7870]

```
table1(~ as.factor(fx_code2) + as.factor(interv_code2) + as.factor(journal_code1) + as.factor(placebo) +
```

By analyses:

	Overall
	(N=141)
as.factor(fx__code2)	
Any	18 (12.8%)
Osteoporotic	10 (7.1%)
Non-Vertebrae	19 (13.5%)
Vertebrae	68 (48.2%)
Clinical Vertebrae	14 (9.9%)
Hip	9 (6.4%)
Forearm	3 (2.1%)
as.factor(interv__code2)	
Bisphosphonates	48 (34.0%)
PTH analog	30 (21.3%)
Romosozumab	28 (19.9%)
Denosumab	9 (6.4%)
Strontium_ranelate	12 (8.5%)
Calcium_VitD	14 (9.9%)
as.factor(journal__code1)	
NEJM	79 (56.0%)
Lancet	9 (6.4%)
BMJ	5 (3.5%)
JAMA	10 (7.1%)
Ann Intern Med	1 (0.7%)
JBMR	6 (4.3%)
JCEM	12 (8.5%)
OI	19 (13.5%)
as.factor(placebo)	
Active	29 (20.6%)
Placebo	112 (79.4%)
Sex	
Both	15 (10.6%)
Men	10 (7.1%)
Women	116 (82.3%)
HR	
Mean (SD)	0.487 (0.185)
Median [Q1, Q3]	0.510 [0.350, 0.640]
Median [min, max]	0.510 [0.0600, 0.810]
loghr	
Mean (SD)	-0.820 (0.497)
Median [Q1, Q3]	-0.673 [-1.05, -0.446]
Median [min, max]	-0.673 [-2.81, -0.211]
no__rand	
Mean (SD)	2870 (2300)
Median [Q1, Q3]	1960 [1220, 4090]
Median [min, max]	1960 [450, 7870]
active__sample	
Mean (SD)	2510 (2080)
Median [Q1, Q3]	1770 [1060, 3610]
Median [min, max]	1770 [339, 7810]
n__event	
Mean (SD)	155 (157)
Median [Q1, Q3]	86.0 [52.0, 210]
Median [min, max]	86.0 [10.0, 764]
FI__final	
Mean (SD)	16.8 (24.0)
Median [Q1, Q3]	9.00 [4.00, 19.0]

(1.2) Table 2. Fragility of evidence for anti-fracture efficacy

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

(1.2.1) By pharmacological interventions

	Bisphosphonates	PTH analog
	(N=48)	(N=30)
n_event		
Mean (SD)	139 (159)	49.4 (24.5)
Median [Q1, Q3]	72.5 [58.8, 141]	44.0 [34.0, 59.0]
Median [min, max]	72.5 [13.0, 764]	44.0 [14.0, 100]
FI_final		
Mean (SD)	15.9 (27.7)	8.53 (6.90)
Median [Q1, Q3]	8.50 [4.00, 14.0]	6.50 [3.00, 12.5]
Median [min, max]	8.50 [1.00, 171]	6.50 [1.00, 25.0]
FQ_final		
Mean (SD)	0.00767 (0.00754)	0.0101 (0.00876)
Median [Q1, Q3]	0.00535 [0.00272, 0.00859]	0.00741 [0.00325, 0.01
Median [min, max]	0.00535 [0.000615, 0.0368]	0.00741 [0.00114, 0.02
as.factor(missing_fi)		
0	5 (10.4%)	2 (6.7%)
1	34 (70.8%)	9 (30.0%)
Missing	9 (18.8%)	19 (63.3%)
as.factor(fi4)		
FI <= 4	16 (33.3%)	13 (43.3%)
FI > 4	32 (66.7%)	17 (56.7%)

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), c
```

(1.2.2) By fracture sites

	Any	Osteoporotic	Non-Vertebra
	(N=18)	(N=10)	(N=19)
n_event			
Mean (SD)	254 (216)	221 (195)	237 (190)
Median [Q1, Q3]	210 [76.0, 401]	163 [67.3, 320]	168 [71.0, 365
Median [min, max]	210 [23.0, 764]	163 [34.0, 658]	168 [37.0, 680
FI_final			
Mean (SD)	16.3 (20.5)	19.9 (19.3)	10.8 (11.6)
Median [Q1, Q3]	9.00 [5.00, 20.3]	12.0 [6.00, 29.0]	5.00 [2.00, 17.
Median [min, max]	9.00 [2.00, 89.0]	12.0 [3.00, 65.0]	5.00 [1.00, 43.
FQ_final			
Mean (SD)	0.00753 (0.00504)	0.00694 (0.00588)	0.00364 (0.00
Median [Q1, Q3]	0.00731 [0.00235, 0.0115]	0.00686 [0.00227, 0.00750]	0.00315 [0.001
Median [min, max]	0.00731 [0.00124, 0.0166]	0.00686 [0.000783, 0.0169]	0.00315 [0.000
as.factor(missing_fi)			
0	1 (5.6%)	2 (20.0%)	1 (5.3%)
1	11 (61.1%)	6 (60.0%)	13 (68.4%)
Missing	6 (33.3%)	2 (20.0%)	5 (26.3%)
as.factor(fi4)			
FI <= 4	4 (22.2%)	2 (20.0%)	9 (47.4%)
FI > 4	14 (77.8%)	8 (80.0%)	10 (52.6%)

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

(1.2.3) By timing of fracture assessment

	2	3
	(N=26)	(N=18)
n_event		
Mean (SD)	91.3 (72.9)	102 (109)
Median [Q1, Q3]	65.5 [52.3, 137]	53.0 [34.5, 142]
Median [min, max]	65.5 [10.0, 323]	53.0 [19.0, 375]
FI_final		
Mean (SD)	8.31 (8.32)	8.28 (6.09)
Median [Q1, Q3]	5.00 [3.00, 9.75]	7.50 [4.00, 11.0]
Median [min, max]	5.00 [1.00, 30.0]	7.50 [1.00, 25.0]
FQ_final		
Mean (SD)	0.00403 (0.00387)	0.00858 (0.00772)
Median [Q1, Q3]	0.00240 [0.00149, 0.00489]	0.00660 [0.00358, 0.010
Median [min, max]	0.00240 [0.000151, 0.0150]	0.00660 [0.000567, 0.02
as.factor(missing_fi)		
0	1 (3.8%)	0 (0%)
1	20 (76.9%)	12 (66.7%)
Missing	5 (19.2%)	6 (33.3%)
as.factor(fi4)		
FI <= 4	11 (42.3%)	6 (33.3%)
FI > 4	15 (57.7%)	12 (66.7%)

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

(1.2.4) By journal

	NEJM	Lancet	BMJ
	(N=79)	(N=9)	(N=5)
n_event			
Mean (SD)	177 (165)	115 (96.4)	352 (167)
Median [Q1, Q3]	117 [54.5, 248]	91.0 [63.0, 100]	315 [262, 475]
Median [min, max]	117 [10.0, 764]	91.0 [14.0, 322]	315 [147, 563]
FI_final			
Mean (SD)	21.3 (28.3)	12.9 (11.5)	15.6 (8.44)
Median [Q1, Q3]	12.0 [4.50, 26.0]	11.0 [4.00, 15.0]	16.0 [11.0, 22.0]
Median [min, max]	12.0 [1.00, 171]	11.0 [2.00, 40.0]	16.0 [4.00, 25.0]
FQ_final			
Mean (SD)	0.00727 (0.00800)	0.00877 (0.00681)	0.00760 (0.00430)
Median [Q1, Q3]	0.00393 [0.00226, 0.00831]	0.00691 [0.00259, 0.0143]	0.00695 [0.00623, 0.0
Median [min, max]	0.00393 [0.000151, 0.0361]	0.00691 [0.00191, 0.0206]	0.00695 [0.00149, 0.0
as.factor(missing_fi)			
0	7 (8.9%)	2 (22.2%)	0 (0%)
1	51 (64.6%)	7 (77.8%)	1 (20.0%)
Missing	21 (26.6%)	0 (0%)	4 (80.0%)
as.factor(fi4)			
FI <= 4	20 (25.3%)	3 (33.3%)	1 (20.0%)
FI > 4	59 (74.7%)	6 (66.7%)	4 (80.0%)

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

(1.2.5) By sex

	Both	Men	Women
	(N=15)	(N=10)	(N=116)
n_event			
Mean (SD)	59.9 (56.9)	26.5 (9.06)	179 (162)
Median [Q1, Q3]	39.0 [32.5, 58.5]	26.0 [21.5, 34.3]	107 [65.8, 251]
Median [min, max]	39.0 [19.0, 231]	26.0 [13.0, 39.0]	107 [10.0, 764]
FI_final			
Mean (SD)	5.27 (3.75)	2.90 (1.66)	19.4 (25.6)
Median [Q1, Q3]	4.00 [2.50, 7.00]	3.00 [1.25, 4.00]	11.0 [5.00, 23.0]
Median [min, max]	4.00 [1.00, 13.0]	3.00 [1.00, 6.00]	11.0 [1.00, 171]
FQ_final			
Mean (SD)	0.0102 (0.00820)	0.00236 (0.00140)	0.00857 (0.0113)
Median [Q1, Q3]	0.00840 [0.00454, 0.0132]	0.00216 [0.00115, 0.00296]	0.00538 [0.00244, 0.0105
Median [min, max]	0.00840 [0.00149, 0.0288]	0.00216 [0.000887, 0.00532]	0.00538 [0.000151, 0.096
as.factor(missing_fi)			
0	0 (0%)	0 (0%)	10 (8.6%)
1	7 (46.7%)	10 (100%)	68 (58.6%)
Missing	8 (53.3%)	0 (0%)	38 (32.8%)
as.factor(fi4)			
FI <= 4	9 (60.0%)	9 (90.0%)	27 (23.3%)
FI > 4	6 (40.0%)	1 (10.0%)	89 (76.7%)

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

(1.2.6) By placebo status

	Active	Placebo	Overall
	(N=29)	(N=112)	(N=141)
n_event			
Mean (SD)	176 (160)	150 (156)	155 (157)
Median [Q1, Q3]	107 [53.0, 255]	82.5 [50.3, 194]	86.0 [52.0,
Median [min, max]	107 [14.0, 658]	82.5 [10.0, 764]	86.0 [10.0,
FI_final			
Mean (SD)	16.9 (19.0)	16.7 (25.2)	16.8 (24.0)
Median [Q1, Q3]	10.0 [5.00, 18.0]	8.50 [4.00, 19.3]	9.00 [4.00,
Median [min, max]	10.0 [2.00, 77.0]	8.50 [1.00, 171]	9.00 [1.00,
FQ_final			
Mean (SD)	0.00650 (0.00525)	0.00878 (0.0117)	0.00831 (0.
Median [Q1, Q3]	0.00440 [0.00221, 0.00908]	0.00516 [0.00244, 0.0106]	0.00514 [0.
Median [min, max]	0.00440 [0.000554, 0.0188]	0.00516 [0.000151, 0.0966]	0.00514 [0.
as.factor(missing_fi)			
0	4 (13.8%)	6 (5.4%)	10 (7.1%)
1	22 (75.9%)	63 (56.3%)	85 (60.3%)
Missing	3 (10.3%)	43 (38.4%)	46 (32.6%)
as.factor(fi4)			
FI <= 4	7 (24.1%)	38 (33.9%)	45 (31.9%)
FI > 4	22 (75.9%)	74 (66.1%)	96 (68.1%)

(1.3) Table 3. Fragility of evidence for anti-fracture efficacy - Subgroup analyses

(1.3.1) Subgroup 1: fracture predefined as the primary endpoint Subgroup

```
fx_prim = subset(fi_sig, pri_endpoint == 1)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = fx_prim, render
```

	Overall
	(N=33)
n_event	
Mean (SD)	162 (126)
Median [Q1, Q3]	112 [60.0, 223]
Median [min, max]	112 [29.0, 464]
FI_final	
Mean (SD)	28.4 (36.7)
Median [Q1, Q3]	14.0 [11.0, 33.0]
Median [min, max]	14.0 [1.00, 171]
FQ_final	
Mean (SD)	0.0141 (0.0110)
Median [Q1, Q3]	0.0107 [0.00532, 0.0206]
Median [min, max]	0.0107 [0.000567, 0.0368]
as.factor(missing_fi)	
0	3 (9.1%)
1	20 (60.6%)
Missing	10 (30.3%)
as.factor(fi4)	
FI <= 4	3 (9.1%)
FI > 4	30 (90.9%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=14)	(N=8)	(N=5)	(N=1)
n_event				
Mean (SD)	154 (107)	60.0 (23.9)	247 (168)	NA
Median [Q1, Q3]	131 [103, 206]	54.0 [39.8, 83.8]	221 [105, 370]	350 [350, 350]
Median [min, max]	131 [29.0, 402]	54.0 [34.0, 92.0]	221 [75.0, 464]	350 [350, 350]
FI_final				
Mean (SD)	25.9 (43.0)	14.8 (6.18)	41.8 (21.3)	NA
Median [Q1, Q3]	13.0 [8.00, 18.8]	13.0 [11.0, 17.0]	40.0 [26.0, 42.0]	137 [137, 137]
Median [min, max]	13.0 [1.00, 171]	13.0 [7.00, 25.0]	40.0 [24.0, 77.0]	137 [137, 137]
FQ_final				
Mean (SD)	0.0131 (0.0108)	0.0180 (0.0102)	0.00941 (0.00598)	NA
Median [Q1, Q3]	0.00933 [0.00566, 0.0195]	0.0200 [0.00889, 0.0265]	0.00714 [0.00601, 0.0115]	0.0185 [0.0185, 0
Median [min, max]	0.00933 [0.000946, 0.0368]	0.0200 [0.00412, 0.0288]	0.00714 [0.00361, 0.0188]	0.0185 [0.0185, 0
as.factor(missing_fi)				
0	1 (7.1%)	1 (12.5%)	1 (20.0%)	0 (0%)
1	10 (71.4%)	3 (37.5%)	4 (80.0%)	0 (0%)
Missing	3 (21.4%)	4 (50.0%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI <= 4	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	13 (92.9%)	8 (100%)	5 (100%)	1 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), d
```

	Any	Osteoporotic	Vertebrae	Hip
	(N=2)	(N=1)	(N=26)	(N=4)
n_event				
Mean (SD)	348 (165)	NA	146 (122)	141 (59.2)
Median [Q1, Q3]	348 [289, 406]	312 [312, 312]	103 [51.0, 204]	158 [120, 180]
Median [min, max]	348 [231, 464]	312 [312, 312]	103 [29.0, 402]	158 [58.0, 190]
FI_final				
Mean (SD)	16.5 (13.4)	NA	32.5 (40.0)	6.00 (4.97)
Median [Q1, Q3]	16.5 [11.8, 21.3]	33.0 [33.0, 33.0]	15.0 [11.5, 40.0]	5.50 [2.50, 9.00]
Median [min, max]	16.5 [7.00, 26.0]	33.0 [33.0, 33.0]	15.0 [1.00, 171]	5.50 [1.00, 12.0]
FQ_final				
Mean (SD)	0.0109 (0.00529)	NA	0.0162 (0.0112)	0.00172 (0.00122)
Median [Q1, Q3]	0.0109 [0.00901, 0.0127]	0.0169 [0.0169, 0.0169]	0.0129 [0.00692, 0.0258]	0.00147 [0.000948, 0
Median [min, max]	0.0109 [0.00714, 0.0146]	0.0169 [0.0169, 0.0169]	0.0129 [0.000946, 0.0368]	0.00147 [0.000567, 0
as.factor(missing_fi)				
0	0 (0%)	1 (100%)	2 (7.7%)	0 (0%)
1	2 (100%)	0 (0%)	14 (53.8%)	4 (100%)
Missing	0 (0%)	0 (0%)	10 (38.5%)	0 (0%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	1 (3.8%)	2 (50.0%)
FI > 4	2 (100%)	1 (100%)	25 (96.2%)	2 (50.0%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=1)	(N=8)	(N=12)	(N=10)
n_event				
Mean (SD)	NA	80.4 (64.1)	154 (139)	236 (120)
Median [Q1, Q3]	75.0 [75.0, 75.0]	53.0 [39.8, 89.0]	96.0 [72.0, 222]	193 [141, 346]
Median [min, max]	75.0 [75.0, 75.0]	53.0 [34.0, 190]	96.0 [29.0, 464]	193 [110, 402]
FI_final				
Mean (SD)	NA	8.38 (4.50)	26.8 (20.9)	47.7 (58.6)
Median [Q1, Q3]	24.0 [24.0, 24.0]	9.50 [6.00, 11.5]	24.0 [13.0, 40.0]	14.5 [12.3, 50.
Median [min, max]	24.0 [24.0, 24.0]	9.50 [1.00, 13.0]	24.0 [1.00, 77.0]	14.5 [7.00, 171
FQ_final				
Mean (SD)	NA	0.0101 (0.0111)	0.0155 (0.0108)	0.0175 (0.0118
Median [Q1, Q3]	0.00361 [0.00361, 0.00361]	0.00591 [0.00279, 0.0134]	0.0129 [0.00686, 0.0219]	0.0166 [0.0077
Median [min, max]	0.00361 [0.00361, 0.00361]	0.00591 [0.000567, 0.0288]	0.0129 [0.000946, 0.0368]	0.0166 [0.0018
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)
1	1 (100%)	6 (75.0%)	8 (66.7%)	5 (50.0%)
Missing	0 (0%)	2 (25.0%)	2 (16.7%)	5 (50.0%)
as.factor(fi4)				
FI <= 4	0 (0%)	2 (25.0%)	1 (8.3%)	0 (0%)
FI > 4	1 (100%)	6 (75.0%)	11 (91.7%)	10 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	Ann Intern Med
	(N=19)	(N=2)	(N=4)	(N=1)
n_event				
Mean (SD)	213 (141)	158 (92.6)	86.3 (60.7)	NA
Median [Q1, Q3]	190 [84.5, 341]	158 [125, 190]	78.5 [35.5, 129]	60.0 [60.0, 60.0]
Median [min, max]	190 [29.0, 464]	158 [92.0, 223]	78.5 [34.0, 154]	60.0 [60.0, 60.0]
FI_final				
Mean (SD)	38.6 (45.7)	27.5 (17.7)	12.0 (1.15)	NA
Median [Q1, Q3]	25.0 [7.50, 43.5]	27.5 [21.3, 33.8]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
Median [min, max]	25.0 [1.00, 171]	27.5 [15.0, 40.0]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
FQ_final				
Mean (SD)	0.0138 (0.0118)	0.0174 (0.00442)	0.00703 (0.00268)	NA
Median [Q1, Q3]	0.0115 [0.00349, 0.0223]	0.0174 [0.0159, 0.0190]	0.00785 [0.00656, 0.00832]	0.00412 [0.00412,
Median [min, max]	0.0115 [0.000567, 0.0361]	0.0174 [0.0143, 0.0206]	0.00785 [0.00314, 0.00928]	0.00412 [0.00412,
as.factor(missing_fi)				
0	2 (10.5%)	1 (50.0%)	0 (0%)	0 (0%)
1	12 (63.2%)	1 (50.0%)	3 (75.0%)	1 (100%)
Missing	5 (26.3%)	0 (0%)	1 (25.0%)	0 (0%)
as.factor(fi4)				
FI <= 4	3 (15.8%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	16 (84.2%)	2 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(sex), data = fx_prim, render
```

	Both	Men	Women	Overall
	(N=4)	(N=2)	(N=27)	(N=33)
n_event				
Mean (SD)	89.8 (94.2)	33.0 (5.66)	183 (127)	162 (126)
Median [Q1, Q3]	44.5 [40.5, 93.8]	33.0 [31.0, 35.0]	140 [89.0, 268]	112 [60.0, 223]
Median [min, max]	44.5 [39.0, 231]	33.0 [29.0, 37.0]	140 [34.0, 464]	112 [29.0, 464]
FI_final				
Mean (SD)	9.50 (3.00)	3.50 (3.54)	33.0 (39.1)	28.4 (36.7)
Median [Q1, Q3]	9.00 [7.00, 11.5]	3.50 [2.25, 4.75]	20.0 [12.5, 40.0]	14.0 [11.0, 33.0
Median [min, max]	9.00 [7.00, 13.0]	3.50 [1.00, 6.00]	20.0 [1.00, 171]	14.0 [1.00, 171]
FQ_final				
Mean (SD)	0.0200 (0.00872)	0.00313 (0.00310)	0.0141 (0.0112)	0.0141 (0.0110)
Median [Q1, Q3]	0.0202 [0.0136, 0.0266]	0.00313 [0.00204, 0.00423]	0.00928 [0.00506, 0.0204]	0.0107 [0.00532
Median [min, max]	0.0202 [0.0107, 0.0288]	0.00313 [0.000946, 0.00532]	0.00928 [0.000567, 0.0368]	0.0107 [0.00056
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	3 (11.1%)	3 (9.1%)
1	2 (50.0%)	2 (100%)	16 (59.3%)	20 (60.6%)
Missing	2 (50.0%)	0 (0%)	8 (29.6%)	10 (30.3%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) | as.factor(placebo), data = fx_prim, re
```

	Active	Placebo	Overall
	(N=6)	(N=27)	(N=33)
n_event			
Mean (SD)	203 (182)	153 (113)	162 (126)
Median [Q1, Q3]	157 [50.0, 333]	112 [67.5, 207]	112 [60.0, 223]
Median [min, max]	157 [34.0, 464]	112 [29.0, 402]	112 [29.0, 464]
FI_final			
Mean (SD)	30.7 (25.5)	27.9 (39.1)	28.4 (36.7)
Median [Q1, Q3]	20.5 [13.5, 38.0]	13.0 [7.50, 29.0]	14.0 [11.0, 33.0]
Median [min, max]	20.5 [11.0, 77.0]	13.0 [1.00, 171]	14.0 [1.00, 171]
FQ_final			
Mean (SD)	0.0115 (0.00447)	0.0147 (0.0120)	0.0141 (0.0110)
Median [Q1, Q3]	0.0104 [0.00810, 0.0136]	0.0107 [0.00386, 0.0258]	0.0107 [0.00532, 0.0206]
Median [min, max]	0.0104 [0.00714, 0.0188]	0.0107 [0.000567, 0.0368]	0.0107 [0.000567, 0.0368]
as.factor(missing_fi)			
0	2 (33.3%)	1 (3.7%)	3 (9.1%)
1	4 (66.7%)	16 (59.3%)	20 (60.6%)
Missing	0 (0%)	10 (37.0%)	10 (30.3%)

(1.3.2) Subgroup 2: analyses with highly significant results (P< 0.001) Subgroup of analyses with P-values< 0.001

```
p_sig = subset(fi_sig, Pval_screen<= 0.001)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = p_sig, render.c
```

	Overall
	(N=45)
n_event	
Mean (SD)	220 (190)
Median [Q1, Q3]	128 [82.0, 330]
Median [min, max]	128 [34.0, 764]
FI_final	
Mean (SD)	37.9 (33.0)
Median [Q1, Q3]	26.0 [18.0, 42.0]
Median [min, max]	26.0 [9.00, 171]
FQ_final	
Mean (SD)	0.0163 (0.0154)
Median [Q1, Q3]	0.0131 [0.00670, 0.0193]
Median [min, max]	0.0131 [0.00230, 0.0966]
as.factor(missing_fi)	
0	6 (13.3%)
1	24 (53.3%)
Missing	15 (33.3%)
as.factor(fi4)	
FI > 4	45 (100%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=10)	(N=11)	(N=13)	(N=3)
n_event				
Mean (SD)	283 (258)	60.1 (24.7)	245 (160)	184 (145)
Median [Q1, Q3]	167 [101, 380]	48.0 [42.5, 84.5]	225 [106, 323]	121 [102, 236]
Median [min, max]	167 [58.0, 764]	48.0 [34.0, 100]	225 [75.0, 658]	121 [82.0, 350]
FI_final				
Mean (SD)	50.2 (47.7)	16.0 (5.35)	38.3 (16.9)	64.3 (63.9)
Median [Q1, Q3]	39.0 [23.3, 42.8]	15.0 [12.0, 19.5]	36.0 [26.0, 42.0]	39.0 [28.0, 88.0]
Median [min, max]	39.0 [11.0, 171]	15.0 [9.00, 25.0]	36.0 [21.0, 77.0]	39.0 [17.0, 137]
FQ_final				
Mean (SD)	0.0154 (0.0108)	0.0188 (0.00838)	0.00820 (0.00525)	0.00861 (0.00870)
Median [Q1, Q3]	0.0109 [0.00694, 0.0197]	0.0193 [0.0118, 0.0258]	0.00601 [0.00391, 0.0115]	0.00499 [0.00365, 0
Median [min, max]	0.0109 [0.00653, 0.0368]	0.0193 [0.00711, 0.0288]	0.00601 [0.00315, 0.0188]	0.00499 [0.00230, 0
as.factor(missing_fi)				
0	1 (10.0%)	2 (18.2%)	2 (15.4%)	0 (0%)
1	8 (80.0%)	3 (27.3%)	11 (84.6%)	0 (0%)
Missing	1 (10.0%)	6 (54.5%)	0 (0%)	3 (100%)
as.factor(fi4)				
FI > 4	10 (100%)	11 (100%)	13 (100%)	3 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), c
```

	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=2)	(N=5)	(N=4)	(N=31)
n_event				
Mean (SD)	505 (366)	338 (218)	357 (229)	173 (154)
Median [Q1, Q3]	505 [376, 635]	323 [312, 355]	290 [211, 436]	100 [74.0, 258]
Median [min, max]	505 [246, 764]	323 [44.0, 658]	290 [168, 680]	100 [34.0, 696]
FI_final				
Mean (SD)	62.5 (37.5)	32.6 (20.4)	28.0 (10.1)	39.0 (37.6)
Median [Q1, Q3]	62.5 [49.3, 75.8]	30.0 [26.0, 33.0]	24.0 [22.5, 29.5]	24.0 [17.0, 43.5
Median [min, max]	62.5 [36.0, 89.0]	30.0 [9.00, 65.0]	24.0 [21.0, 43.0]	24.0 [11.0, 171]
FQ_final				
Mean (SD)	0.00949 (0.00580)	0.0112 (0.00526)	0.00593 (0.00343)	0.0196 (0.0174)
Median [Q1, Q3]	0.00949 [0.00743, 0.0115]	0.00754 [0.00736, 0.0169]	0.00502 [0.00338, 0.00757]	0.0185 [0.00799
Median [min, max]	0.00949 [0.00538, 0.0136]	0.00754 [0.00711, 0.0169]	0.00502 [0.00315, 0.0105]	0.0185 [0.00230
as.factor(missing_fi)				
0	0 (0%)	2 (40.0%)	0 (0%)	4 (12.9%)
1	2 (100%)	3 (60.0%)	4 (100%)	14 (45.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	13 (41.9%)
as.factor(fi4)				
FI > 4	2 (100%)	5 (100%)	4 (100%)	31 (100%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=5)	(N=6)	(N=18)	(N=14)
n_event				
Mean (SD)	132 (110)	93.0 (128)	194 (152)	300 (215)
Median [Q1, Q3]	76.0 [75.0, 128]	42.5 [37.3, 47.0]	137 [94.0, 241]	296 [113, 378]
Median [min, max]	76.0 [58.0, 323]	42.5 [34.0, 355]	137 [46.0, 658]	296 [73.0, 764]
FI_final				
Mean (SD)	22.2 (7.46)	13.7 (5.75)	33.1 (17.1)	55.3 (46.3)
Median [Q1, Q3]	24.0 [19.0, 27.0]	12.0 [11.0, 13.0]	25.5 [21.3, 40.0]	42.5 [26.8, 50.3]
Median [min, max]	24.0 [11.0, 30.0]	12.0 [9.00, 25.0]	25.5 [15.0, 77.0]	42.5 [15.0, 171]
FQ_final				
Mean (SD)	0.00741 (0.00410)	0.0149 (0.00976)	0.0154 (0.00949)	0.0153 (0.0108)
Median [Q1, Q3]	0.00754 [0.00391, 0.00828]	0.00990 [0.00810, 0.0220]	0.0153 [0.00635, 0.0202]	0.0130 [0.00661,
Median [min, max]	0.00754 [0.00361, 0.0137]	0.00990 [0.00711, 0.0288]	0.0153 [0.00315, 0.0368]	0.0130 [0.00230,
as.factor(missing_fi)				
0	1 (20.0%)	0 (0%)	3 (16.7%)	1 (7.1%)
1	3 (60.0%)	4 (66.7%)	11 (61.1%)	6 (42.9%)
Missing	1 (20.0%)	2 (33.3%)	4 (22.2%)	7 (50.0%)
as.factor(fi4)				
FI > 4	5 (100%)	6 (100%)	18 (100%)	14 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	JBMR
	(N=31)	(N=3)	(N=4)	(N=1)
n_event				
Mean (SD)	250 (190)	138 (73.4)	43.0 (10.9)	NA
Median [Q1, Q3]	221 [94.5, 353]	100 [96.0, 162]	40.0 [35.5, 47.5]	110 [110, 110]
Median [min, max]	221 [46.0, 764]	100 [92.0, 223]	40.0 [34.0, 58.0]	110 [110, 110]
FI_final				
Mean (SD)	43.6 (34.3)	24.0 (13.9)	11.0 (1.63)	NA
Median [Q1, Q3]	36.0 [23.5, 44.0]	17.0 [16.0, 28.5]	11.0 [10.5, 11.5]	15.0 [15.0, 15.0]
Median [min, max]	36.0 [17.0, 171]	17.0 [15.0, 40.0]	11.0 [9.00, 13.0]	15.0 [15.0, 15.0]
FQ_final				
Mean (SD)	0.0134 (0.00951)	0.0170 (0.00321)	0.00809 (0.000924)	NA
Median [Q1, Q3]	0.0115 [0.00594, 0.0187]	0.0162 [0.0153, 0.0184]	0.00799 [0.00755, 0.00853]	0.00768 [0.00768, 0
Median [min, max]	0.0115 [0.00230, 0.0361]	0.0162 [0.0143, 0.0206]	0.00799 [0.00711, 0.00928]	0.00768 [0.00768, 0
as.factor(missing_fi)				
0	3 (9.7%)	2 (66.7%)	0 (0%)	0 (0%)
1	17 (54.8%)	1 (33.3%)	4 (100%)	0 (0%)
Missing	11 (35.5%)	0 (0%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI > 4	31 (100%)	3 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Women	Overall
	(N=2)	(N=43)	(N=45)
n_event			
Mean (SD)	44.5 (4.95)	229 (191)	220 (190)
Median [Q1, Q3]	44.5 [42.8, 46.3]	168 [84.5, 331]	128 [82.0, 330]
Median [min, max]	44.5 [41.0, 48.0]	168 [34.0, 764]	128 [34.0, 764]
FI_final			
Mean (SD)	12.0 (1.41)	39.1 (33.3)	37.9 (33.0)
Median [Q1, Q3]	12.0 [11.5, 12.5]	27.0 [19.5, 42.5]	26.0 [18.0, 42.0]
Median [min, max]	12.0 [11.0, 13.0]	27.0 [9.00, 171]	26.0 [9.00, 171]
FQ_final			
Mean (SD)	0.0273 (0.00212)	0.0157 (0.0156)	0.0163 (0.0154)
Median [Q1, Q3]	0.0273 [0.0266, 0.0281]	0.0125 [0.00664, 0.0188]	0.0131 [0.00670, 0.0193]
Median [min, max]	0.0273 [0.0258, 0.0288]	0.0125 [0.00230, 0.0966]	0.0131 [0.00230, 0.0966]
as.factor(missing_fi)			
0	0 (0%)	6 (14.0%)	6 (13.3%)
1	0 (0%)	24 (55.8%)	24 (53.3%)
Missing	2 (100%)	13 (30.2%)	15 (33.3%)
as.factor(fi4)			
FI > 4	2 (100%)	43 (100%)	45 (100%)

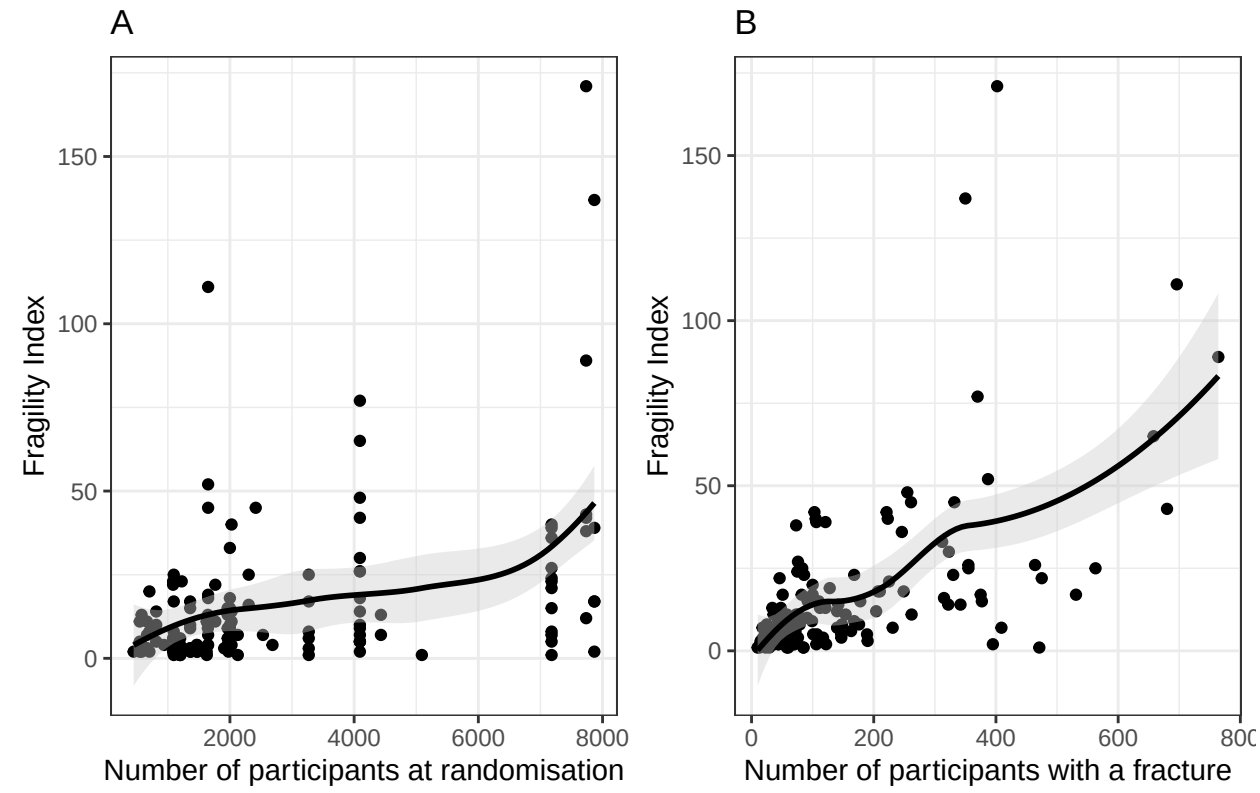
```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=11)	(N=34)	(N=45)
n_event			
Mean (SD)	226 (193)	219 (192)	220 (190)
Median [Q1, Q3]	221 [68.0, 339]	125 [82.3, 326]	128 [82.0, 330]
Median [min, max]	221 [34.0, 658]	125 [41.0, 764]	128 [34.0, 764]
FI_final			
Mean (SD)	32.1 (23.1)	39.8 (35.7)	37.9 (33.0)
Median [Q1, Q3]	26.0 [14.0, 45.0]	26.0 [20.3, 41.5]	26.0 [18.0, 42.0]
Median [min, max]	26.0 [9.00, 77.0]	26.0 [11.0, 171]	26.0 [9.00, 171]
FQ_final			
Mean (SD)	0.0118 (0.00431)	0.0177 (0.0174)	0.0163 (0.0154)
Median [Q1, Q3]	0.0115 [0.00762, 0.0153]	0.0137 [0.00614, 0.0255]	0.0131 [0.00670, 0.0193]
Median [min, max]	0.0115 [0.00711, 0.0188]	0.0137 [0.00230, 0.0966]	0.0131 [0.00230, 0.0966]
as.factor(missing_fi)			
0	4 (36.4%)	2 (5.9%)	6 (13.3%)
1	7 (63.6%)	17 (50.0%)	24 (53.3%)
Missing	0 (0%)	15 (44.1%)	15 (33.3%)
as.factor(fi4)			
FI > 4	11 (100%)	34 (100%)	45 (100%)

(1.4) Fig 3. Correlation between Fragility Index and number of participants at randomisation (A) or number of participants with a fracture (B)

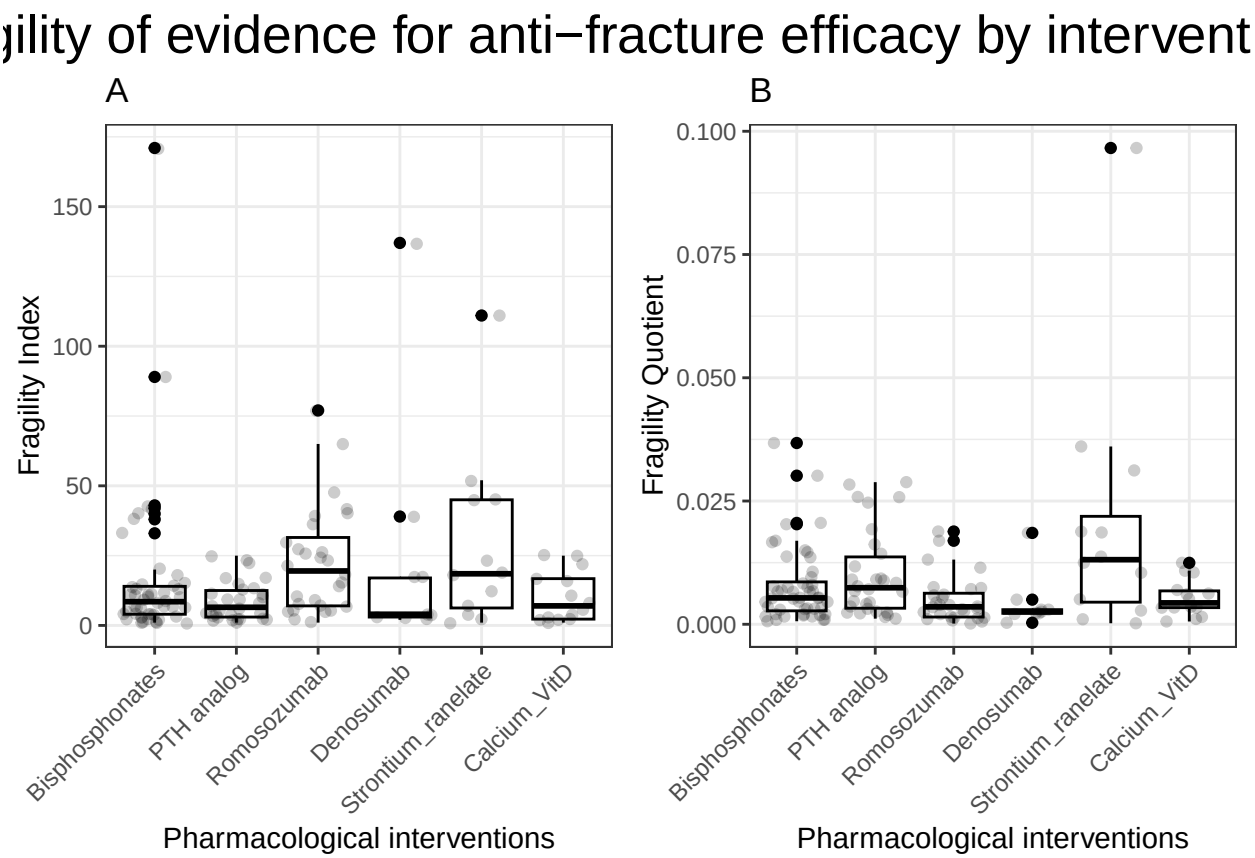
```
p = ggplot(data = fi_sig, aes(x = no_rand, y = FI_final))
p1 = p + geom_point() + geom_smooth(color = "black", fill = "grey80") + labs(title = "A", x = "Number o

p.0 = ggplot(data = fi_sig, aes(x = n_event, y = FI_final))
p2 = p.0 + geom_point() + geom_smooth(color = "black", fill = "grey80") + labs(title = "B", x = "Number

grid.arrange(p1, p2, nrow = 1, top = textGrob("Relationship between Fragility Index and sample size", g
```

```
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
## `geom_smooth()` using method = 'loess' and formula = 'y ~ x'
```



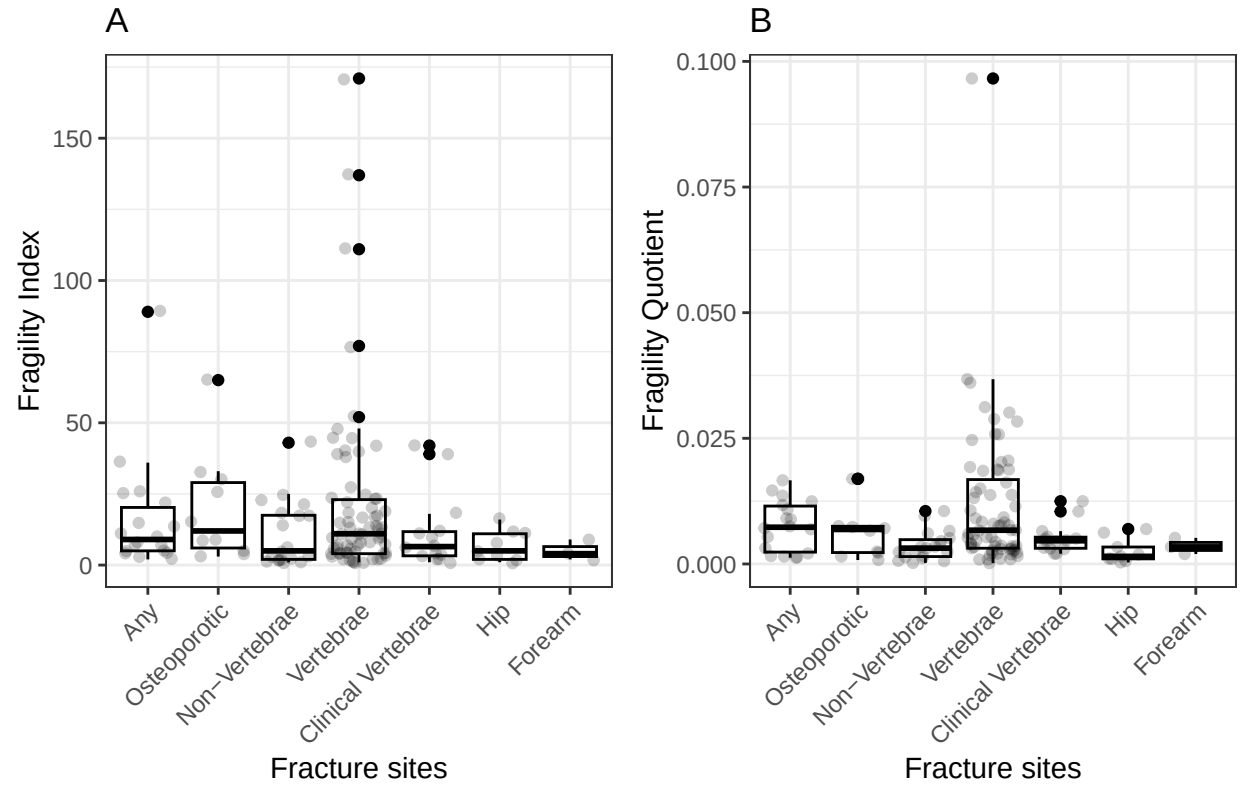
(1.5) Fig 4. Fragility of evidence for anti-fracture efficacy by pharmacological interventions: Fragility Index (A) and Fragility Quotient (B)

```
p1 = ggplot(data = fi_sig, aes(y = FI_final, x = as.factor(interv_code2), fill = as.factor(interv_code2)
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "A", x = "Pharmacological interventions", y = "Fragility Index") + theme(axis.text.x = el

p2 = ggplot(data = fi_sig, aes(y = FQ_final, x = as.factor(interv_code2), fill = as.factor(interv_code2)
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "B", x = "Pharmacological interventions", y = "Fragility Quotient") + theme(axis.text.x =

grid.arrange(p1, p2, nrow = 1, top = textGrob("Fragility of evidence for anti-fracture efficacy by inte
```



(1.6) Fig 5. Fragility of evidence for anti-fracture efficacy by fracture sites: Fragility Index (A) and Fragility Quotient (B)

```
p1 = ggplot(data = fi_sig, aes(y = FI_final, x = as.factor(fx_code2), fill = as.factor(fx_code2))) + ge
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "A", x = "Fracture sites", y = "Fragility Index") + theme(axis.text.x = element_text(ang
p2 = ggplot(data = fi_sig, aes(y = FQ_final, x = as.factor(fx_code2), fill = as.factor(fx_code2))) + ge
  geom_jitter(alpha=0.2) + theme_bw() + theme(legend.position="none") +
  labs(title = "B", x = "Fracture sites", y = "Fragility Quotient") + theme(axis.text.x = element_text(

grid.arrange(p1, p2, nrow = 1, top = textGrob("Fragility of evidence for anti-fracture efficacy by frac
```

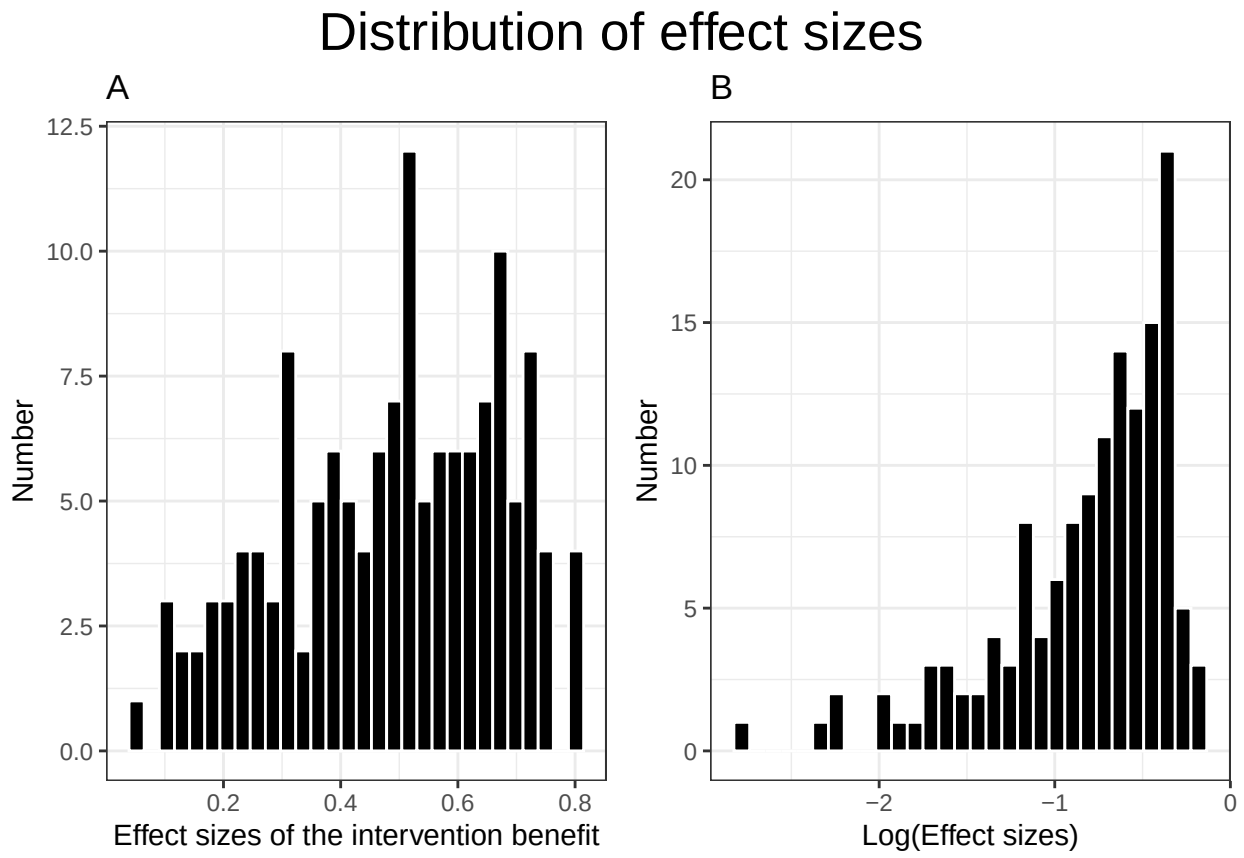


(1.7) Supplementary Figures:

```
p = ggplot(data = fi_sig, aes(x = HR))
p1 = p + geom_histogram(color = "white", fill = "black") + labs(title = "A", x = "Effect sizes of the i

p = ggplot(data = fi_sig, aes(x = loghr))
p2 = p + geom_histogram(color = "white", fill = "black") + labs(title = "B", x = "Log(Effect sizes)", y

grid.arrange(p1, p2, nrow = 1, top = textGrob("Distribution of effect sizes", gp = gpar(fontsize = 20,
```

Fig S1. Distribution of effect sizes for intervention benefits: Effect size (A) or Logarithm of effect size (B)

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```



(1.8) Supplementary Tables - Sensitivity analysis, excluding the analyses from the extended studies or sensitivity/subgroup analyses

Set-up data

```
ori_st = subset(fi_sig, sen_analysis == 0)
ori_st_st = subset(ori_st, study == 1)
```

Cohort characteristics

```
# Studies:
table1(~ as.factor(interv_code2) + as.factor(journal_code1) + as.factor(placebo) + sex + no_rand, data =
```

	Overall
	(N=26)
as.factor(interv_code2)	
Bisphosphonates	12 (46.2%)
PTH analog	5 (19.2%)
Romosozumab	2 (7.7%)
Denosumab	2 (7.7%)
Strontium_ranelate	2 (7.7%)
Calcium_VitD	3 (11.5%)
as.factor(journal_code1)	
NEJM	12 (46.2%)
Lancet	2 (7.7%)
BMJ	1 (3.8%)
JAMA	3 (11.5%)
Ann Intern Med	1 (3.8%)
JBMR	1 (3.8%)
JCEM	2 (7.7%)
OI	4 (15.4%)
as.factor(placebo)	
Active	3 (11.5%)
Placebo	23 (88.5%)
Sex	
Both	5 (19.2%)
Men	2 (7.7%)
Women	19 (73.1%)
no_rand	
Mean (SD)	2620 (2170)
Median [Q1, Q3]	1940 [1240, 3120]
Median [min, max]	1940 [450, 7870]

```
# Analyses:
table1(~ as.factor(fx_code2) + as.factor(interv_code2) + as.factor(journal_code1) + as.factor(placebo) +
```

	Overall
	(N=124)
as.factor(fx_code2)	
Any	17 (13.7%)
Osteoporotic	10 (8.1%)
Non-Vertebrae	17 (13.7%)
Vertebrae	59 (47.6%)
Clinical Vertebrae	12 (9.7%)
Hip	6 (4.8%)
Forearm	3 (2.4%)
as.factor(interv_code2)	
Bisphosphonates	47 (37.9%)
PTH analog	26 (21.0%)
Romosozumab	26 (21.0%)
Denosumab	9 (7.3%)
Strontium_ranelate	6 (4.8%)
Calcium_VitD	10 (8.1%)
as.factor(journal_code1)	
NEJM	69 (55.6%)
Lancet	9 (7.3%)
BMJ	5 (4.0%)
JAMA	10 (8.1%)
Ann Intern Med	1 (0.8%)
JBMR	6 (4.8%)
JCEM	5 (4.0%)
OI	19 (15.3%)
as.factor(placebo)	
Active	26 (21.0%)
Placebo	98 (79.0%)
Sex	
Both	12 (9.7%)
Men	9 (7.3%)
Women	103 (83.1%)
HR	
Mean (SD)	0.479 (0.185)
Median [Q1, Q3]	0.500 [0.338, 0.633]
Median [min, max]	0.500 [0.0600, 0.810]
loghr	
Mean (SD)	-0.839 (0.504)
Median [Q1, Q3]	-0.693 [-1.09, -0.458]
Median [min, max]	-0.693 [-2.81, -0.211]
no_rand	
Mean (SD)	2970 (2400)
Median [Q1, Q3]	1960 [1360, 4090]
Median [min, max]	1960 [450, 7870]
active_sample	
Mean (SD)	2600 (2160)
Median [Q1, Q3]	1770 [1050, 3660]
Median [min, max]	1770 [339, 7810]
n_event	
Mean (SD)	151 (160)
Median [Q1, Q3]	82.5 [52.8, 181]
Median [min, max]	82.5 [10.0, 764]
FI_final	
Mean (SD)	16.6 (24.5)
Median [Q1, Q3]	9.00 [4.00, 18.3]

```
# Pharmacological intervention
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code
```

(1.8.1) Table S3. Predefined sensitivity analysis - Fragility of evidence for anti-fracture efficacy

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=47)	(N=26)	(N=26)	(N=9)
n_event				
Mean (SD)	141 (160)	52.7 (24.3)	203 (148)	140 (180)
Median [Q1, Q3]	73.0 [59.5, 141]	47.0 [34.3, 72.0]	168 [105, 253]	69.0 [29.0, 121
Median [min, max]	73.0 [13.0, 764]	47.0 [14.0, 100]	168 [10.0, 658]	69.0 [15.0, 531
FI_final				
Mean (SD)	16.2 (27.9)	9.00 (7.19)	20.8 (16.6)	25.1 (43.7)
Median [Q1, Q3]	9.00 [4.00, 14.0]	7.50 [3.00, 13.0]	18.0 [7.00, 29.3]	4.00 [3.00, 17.
Median [min, max]	9.00 [1.00, 171]	7.50 [1.00, 25.0]	18.0 [1.00, 65.0]	4.00 [2.00, 137
FQ_final				
Mean (SD)	0.00781 (0.00756)	0.00985 (0.00872)	0.00451 (0.00413)	0.00432 (0.005
Median [Q1, Q3]	0.00537 [0.00301, 0.00891]	0.00741 [0.00273, 0.0130]	0.00330 [0.00140, 0.00598]	0.00255 [0.002
Median [min, max]	0.00537 [0.000615, 0.0368]	0.00741 [0.00114, 0.0288]	0.00330 [0.000151, 0.0169]	0.00255 [0.000
as.factor(missing_fi)				
0	5 (10.6%)	2 (7.7%)	1 (3.8%)	0 (0%)
1	33 (70.2%)	8 (30.8%)	25 (96.2%)	4 (44.4%)
Missing	9 (19.1%)	16 (61.5%)	0 (0%)	5 (55.6%)
as.factor(fi4)				
FI <= 4	15 (31.9%)	11 (42.3%)	2 (7.7%)	5 (55.6%)
FI > 4	32 (68.1%)	15 (57.7%)	24 (92.3%)	4 (44.4%)

```
# Fracture site
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), 
```

	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=17)	(N=10)	(N=17)	(N=59)
n_event				
Mean (SD)	267 (215)	221 (195)	222 (196)	102 (116)
Median [Q1, Q3]	231 [76.0, 409]	163 [67.3, 320]	163 [57.0, 342]	70.0 [38.0, 10
Median [min, max]	231 [23.0, 764]	163 [34.0, 658]	163 [37.0, 680]	70.0 [10.0, 69
FI_final				
Mean (SD)	16.9 (20.9)	19.9 (19.3)	9.65 (11.6)	20.4 (31.1)
Median [Q1, Q3]	10.0 [5.00, 22.0]	12.0 [6.00, 29.0]	3.00 [2.00, 17.0]	11.0 [4.50, 21
Median [min, max]	10.0 [2.00, 89.0]	12.0 [3.00, 65.0]	3.00 [1.00, 43.0]	11.0 [1.00, 17
FQ_final				
Mean (SD)	0.00729 (0.00508)	0.00694 (0.00588)	0.00309 (0.00240)	0.0113 (0.014
Median [Q1, Q3]	0.00714 [0.00209, 0.0109]	0.00686 [0.00227, 0.00750]	0.00255 [0.00136, 0.00393]	0.00670 [0.00
Median [min, max]	0.00714 [0.00124, 0.0166]	0.00686 [0.000783, 0.0169]	0.00255 [0.000203, 0.00955]	0.00670 [0.00
as.factor(missing_fi)				
0	1 (5.9%)	2 (20.0%)	1 (5.9%)	3 (5.1%)
1	11 (64.7%)	6 (60.0%)	11 (64.7%)	37 (62.7%)
Missing	5 (29.4%)	2 (20.0%)	5 (29.4%)	19 (32.2%)
as.factor(fi4)				
FI <= 4	4 (23.5%)	2 (20.0%)	9 (52.9%)	15 (25.4%)
FI > 4	13 (76.5%)	8 (80.0%)	8 (47.1%)	44 (74.6%)

```
# Timing of fracture assessment
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=25)	(N=11)	(N=45)	(N=29)
n_event				
Mean (SD)	86.6 (70.2)	59.4 (38.8)	133 (137)	238 (212)
Median [Q1, Q3]	65.0 [52.0, 128]	48.0 [35.0, 68.0]	83.0 [44.0, 178]	140 [73.0, 38
Median [min, max]	65.0 [10.0, 323]	48.0 [21.0, 163]	83.0 [14.0, 658]	140 [23.0, 76
FI_final				
Mean (SD)	7.92 (8.25)	7.09 (4.16)	16.0 (14.7)	28.0 (40.3)
Median [Q1, Q3]	5.00 [3.00, 9.00]	7.00 [4.00, 10.0]	11.0 [5.00, 23.0]	14.0 [4.00, 38
Median [min, max]	5.00 [1.00, 30.0]	7.00 [1.00, 13.0]	11.0 [1.00, 65.0]	14.0 [1.00, 17
FQ_final				
Mean (SD)	0.00401 (0.00394)	0.00829 (0.00773)	0.00864 (0.00832)	0.00834 (0.00
Median [Q1, Q3]	0.00222 [0.00147, 0.00505]	0.00711 [0.00376, 0.00907]	0.00543 [0.00307, 0.0115]	0.00653 [0.00
Median [min, max]	0.00222 [0.000151, 0.0150]	0.00711 [0.000567, 0.0288]	0.00543 [0.000554, 0.0368]	0.00653 [0.00
as.factor(missing_fi)				
0	1 (4.0%)	0 (0%)	2 (4.4%)	0 (0%)
1	19 (76.0%)	8 (72.7%)	31 (68.9%)	14 (48.3%)
Missing	5 (20.0%)	3 (27.3%)	12 (26.7%)	15 (51.7%)
as.factor(fi4)				
FI <= 4	11 (44.0%)	4 (36.4%)	11 (24.4%)	9 (31.0%)
FI > 4	14 (56.0%)	7 (63.6%)	34 (75.6%)	20 (69.0%)

```
# Journal
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	BMJ	JAMA
	(N=69)	(N=9)	(N=5)	(N=10)
n_event				
Mean (SD)	168 (170)	115 (96.4)	352 (167)	108 (112)
Median [Q1, Q3]	103 [48.0, 231]	91.0 [63.0, 100]	315 [262, 475]	70.5 [47.5, 112]
Median [min, max]	103 [10.0, 764]	91.0 [14.0, 322]	315 [147, 563]	70.5 [34.0, 409]
FI_final				
Mean (SD)	21.3 (29.0)	12.9 (11.5)	15.6 (8.44)	8.20 (4.47)
Median [Q1, Q3]	10.0 [5.00, 26.0]	11.0 [4.00, 15.0]	16.0 [11.0, 22.0]	10.0 [4.75, 11.0
Median [min, max]	10.0 [1.00, 171]	11.0 [2.00, 40.0]	16.0 [4.00, 25.0]	10.0 [1.00, 13.0
FQ_final				
Mean (SD)	0.00700 (0.00778)	0.00877 (0.00681)	0.00760 (0.00430)	0.00504 (0.0033
Median [Q1, Q3]	0.00391 [0.00222, 0.00748]	0.00691 [0.00259, 0.0143]	0.00695 [0.00623, 0.0109]	0.00513 [0.0019
Median [min, max]	0.00391 [0.000151, 0.0361]	0.00691 [0.00191, 0.0206]	0.00695 [0.00149, 0.0125]	0.00513 [0.0006
as.factor(missing_fi)				
0	6 (8.7%)	2 (22.2%)	0 (0%)	0 (0%)
1	45 (65.2%)	7 (77.8%)	1 (20.0%)	8 (80.0%)
Missing	18 (26.1%)	0 (0%)	4 (80.0%)	2 (20.0%)
as.factor(fi4)				
FI <= 4	17 (24.6%)	3 (33.3%)	1 (20.0%)	3 (30.0%)
FI > 4	52 (75.4%)	6 (66.7%)	4 (80.0%)	7 (70.0%)

```
# Sex
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Men	Women	Overall
	(N=12)	(N=9)	(N=103)	(N=124)
n_event				
Mean (SD)	67.3 (61.7)	26.2 (9.56)	172 (167)	151 (160)
Median [Q1, Q3]	43.5 [34.8, 64.0]	23.0 [21.0, 36.0]	100 [63.5, 224]	82.5 [52.8, 18
Median [min, max]	43.5 [21.0, 231]	23.0 [13.0, 39.0]	100 [10.0, 764]	82.5 [10.0, 76
FI_final				
Mean (SD)	5.08 (3.73)	3.11 (1.62)	19.1 (26.1)	16.6 (24.5)
Median [Q1, Q3]	4.00 [2.75, 7.00]	3.00 [2.00, 4.00]	11.0 [5.00, 22.5]	9.00 [4.00, 18
Median [min, max]	4.00 [1.00, 13.0]	3.00 [1.00, 6.00]	11.0 [1.00, 171]	9.00 [1.00, 17
FQ_final				
Mean (SD)	0.00926 (0.00771)	0.00252 (0.00139)	0.00837 (0.0116)	0.00803 (0.01
Median [Q1, Q3]	0.00677 [0.00451, 0.0116]	0.00222 [0.00177, 0.00296]	0.00537 [0.00237, 0.00918]	0.00510 [0.00
Median [min, max]	0.00677 [0.00149, 0.0288]	0.00222 [0.000887, 0.00532]	0.00537 [0.000151, 0.0966]	0.00510 [0.00
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	8 (7.8%)	8 (6.5%)
1	7 (58.3%)	9 (100%)	60 (58.3%)	76 (61.3%)
Missing	5 (41.7%)	0 (0%)	35 (34.0%)	40 (32.3%)
as.factor(fi4)				
FI <= 4	8 (66.7%)	8 (88.9%)	23 (22.3%)	39 (31.5%)
FI > 4	4 (33.3%)	1 (11.1%)	80 (77.7%)	85 (68.5%)

```
# Placebo status
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=26)	(N=98)	(N=124)
n_event			
Mean (SD)	173 (161)	145 (160)	151 (160)
Median [Q1, Q3]	104 [53.8, 247]	76.0 [52.3, 161]	82.5 [52.8, 181]
Median [min, max]	104 [14.0, 658]	76.0 [10.0, 764]	82.5 [10.0, 764]
FI_final			
Mean (SD)	15.1 (15.8)	17.0 (26.4)	16.6 (24.5)
Median [Q1, Q3]	9.50 [5.00, 16.5]	8.50 [4.00, 18.8]	9.00 [4.00, 18.3]
Median [min, max]	9.50 [2.00, 65.0]	8.50 [1.00, 171]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.00622 (0.00493)	0.00851 (0.0120)	0.00803 (0.0109)
Median [Q1, Q3]	0.00528 [0.00210, 0.00874]	0.00510 [0.00240, 0.00902]	0.00510 [0.00234, 0.00907]
Median [min, max]	0.00528 [0.000554, 0.0169]	0.00510 [0.000151, 0.0966]	0.00510 [0.000151, 0.0966]
as.factor(missing_fi)			
0	3 (11.5%)	5 (5.1%)	8 (6.5%)
1	20 (76.9%)	56 (57.1%)	76 (61.3%)
Missing	3 (11.5%)	37 (37.8%)	40 (32.3%)
as.factor(fi4)			
FI <= 4	6 (23.1%)	33 (33.7%)	39 (31.5%)
FI > 4	20 (76.9%)	65 (66.3%)	85 (68.5%)

(1.8.2) Table S4. Predefined sensitivity analysis - Fragility of evidence for anti-fracture efficacy in subgroup analyses

Subgroup 1. Fracture predefined as the primary endpoint Subgroup

```
fx_prim2 = subset(ori_st, pri_endpoint == 1)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = fx_prim2, rende
```

	Overall
	(N=27)
n_event	
Mean (SD)	156 (125)
Median [Q1, Q3]	110 [67.5, 222]
Median [min, max]	110 [34.0, 464]
FI_final	
Mean (SD)	29.3 (38.4)
Median [Q1, Q3]	15.0 [11.5, 29.5]
Median [min, max]	15.0 [1.00, 171]
FQ_final	
Mean (SD)	0.0142 (0.0107)
Median [Q1, Q3]	0.0107 [0.00634, 0.0204]
Median [min, max]	0.0107 [0.000567, 0.0368]
as.factor(missing_fi)	
0	2 (7.4%)
1	17 (63.0%)
Missing	8 (29.6%)
as.factor(fi4)	
FI <= 4	1 (3.7%)
FI > 4	26 (96.3%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=13)	(N=7)	(N=4)	(N=1)
n_event				
Mean (SD)	163 (104)	62.7 (24.4)	216 (177)	NA
Median [Q1, Q3]	140 [110, 223]	60.0 [42.0, 84.5]	163 [97.5, 282]	350 [350, 350]
Median [min, max]	140 [37.0, 402]	60.0 [34.0, 92.0]	163 [75.0, 464]	350 [350, 350]
FI_final				
Mean (SD)	27.8 (44.2)	15.3 (6.47)	33.0 (9.31)	NA
Median [Q1, Q3]	13.0 [11.0, 20.0]	13.0 [12.0, 19.0]	33.0 [25.5, 40.5]	137 [137, 137]
Median [min, max]	13.0 [6.00, 171]	13.0 [7.00, 25.0]	33.0 [24.0, 42.0]	137 [137, 137]
FQ_final				
Mean (SD)	0.0140 (0.0106)	0.0169 (0.0105)	0.00706 (0.00329)	NA
Median [Q1, Q3]	0.0107 [0.00666, 0.0203]	0.0143 [0.00849, 0.0271]	0.00658 [0.00541, 0.00822]	0.0185 [0.0185, 0.
Median [min, max]	0.0107 [0.00186, 0.0368]	0.0143 [0.00412, 0.0288]	0.00658 [0.00361, 0.0115]	0.0185 [0.0185, 0.
as.factor(missing_fi)				
0	1 (7.7%)	1 (14.3%)	0 (0%)	0 (0%)
1	9 (69.2%)	3 (42.9%)	4 (100%)	0 (0%)
Missing	3 (23.1%)	3 (42.9%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	13 (100%)	7 (100%)	4 (100%)	1 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), c
```

	Any	Osteoporotic	Vertebrae	Hip
	(N=2)	(N=1)	(N=22)	(N=2)
n_event				
Mean (SD)	348 (165)	NA	137 (112)	99.0 (58.0)
Median [Q1, Q3]	348 [289, 406]	312 [312, 312]	103 [63.8, 151]	99.0 [78.5, 120]
Median [min, max]	348 [231, 464]	312 [312, 312]	103 [34.0, 402]	99.0 [58.0, 140]
FI_final				
Mean (SD)	16.5 (13.4)	NA	32.4 (41.7)	6.50 (7.78)
Median [Q1, Q3]	16.5 [11.8, 21.3]	33.0 [33.0, 33.0]	15.0 [13.0, 36.3]	6.50 [3.75, 9.25]
Median [min, max]	16.5 [7.00, 26.0]	33.0 [33.0, 33.0]	15.0 [6.00, 171]	6.50 [1.00, 12.0]
FQ_final				
Mean (SD)	0.0109 (0.00529)	NA	0.0156 (0.0110)	0.00121 (0.000916)
Median [Q1, Q3]	0.0109 [0.00901, 0.0127]	0.0169 [0.0169, 0.0169]	0.0111 [0.00692, 0.0245]	0.00121 [0.000890, 0.
Median [min, max]	0.0109 [0.00714, 0.0146]	0.0169 [0.0169, 0.0169]	0.0111 [0.00314, 0.0368]	0.00121 [0.000567, 0.
as.factor(missing_fi)				
0	0 (0%)	1 (100%)	1 (4.5%)	0 (0%)
1	2 (100%)	0 (0%)	13 (59.1%)	2 (100%)
Missing	0 (0%)	0 (0%)	8 (36.4%)	0 (0%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)
FI > 4	2 (100%)	1 (100%)	22 (100%)	1 (50.0%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=1)	(N=5)	(N=10)	(N=9)
n_event				
Mean (SD)	NA	47.2 (12.0)	145 (129)	225 (122)
Median [Q1, Q3]	75.0 [75.0, 75.0]	48.0 [36.0, 58.0]	96.0 [83.8, 192]	154 [140, 350]
Median [min, max]	75.0 [75.0, 75.0]	48.0 [34.0, 60.0]	96.0 [37.0, 464]	154 [110, 402]
FI_final				
Mean (SD)	NA	9.00 (5.10)	24.4 (13.1)	48.0 (62.1)
Median [Q1, Q3]	24.0 [24.0, 24.0]	11.0 [7.00, 13.0]	24.0 [16.3, 36.5]	14.0 [12.0, 52.0
Median [min, max]	24.0 [24.0, 24.0]	11.0 [1.00, 13.0]	24.0 [6.00, 42.0]	14.0 [7.00, 171]
FQ_final				
Mean (SD)	NA	0.0101 (0.0110)	0.0166 (0.0108)	0.0160 (0.0115)
Median [Q1, Q3]	0.00361 [0.00361, 0.00361]	0.00770 [0.00412, 0.00928]	0.0129 [0.00802, 0.0245]	0.0146 [0.00768
Median [min, max]	0.00361 [0.00361, 0.00361]	0.00770 [0.000567, 0.0288]	0.0129 [0.00532, 0.0368]	0.0146 [0.00186
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	1 (10.0%)	0 (0%)
1	1 (100%)	4 (80.0%)	7 (70.0%)	5 (55.6%)
Missing	0 (0%)	1 (20.0%)	2 (20.0%)	4 (44.4%)
as.factor(fi4)				
FI <= 4	0 (0%)	1 (20.0%)	0 (0%)	0 (0%)
FI > 4	1 (100%)	4 (80.0%)	10 (100%)	9 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	Ann Intern Med
	(N=14)	(N=2)	(N=4)	(N=1)
n_event				
Mean (SD)	211 (147)	158 (92.6)	86.3 (60.7)	NA
Median [Q1, Q3]	181 [83.8, 341]	158 [125, 190]	78.5 [35.5, 129]	60.0 [60.0, 60.0]
Median [min, max]	181 [37.0, 464]	158 [92.0, 223]	78.5 [34.0, 154]	60.0 [60.0, 60.0]
FI_final				
Mean (SD)	42.8 (49.7)	27.5 (17.7)	12.0 (1.15)	NA
Median [Q1, Q3]	25.5 [14.8, 41.5]	27.5 [21.3, 33.8]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
Median [min, max]	25.5 [1.00, 171]	27.5 [15.0, 40.0]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
FQ_final				
Mean (SD)	0.0147 (0.0116)	0.0174 (0.00442)	0.00703 (0.00268)	NA
Median [Q1, Q3]	0.0130 [0.00550, 0.0240]	0.0174 [0.0159, 0.0190]	0.00785 [0.00656, 0.00832]	0.00412 [0.00412,
Median [min, max]	0.0130 [0.000567, 0.0361]	0.0174 [0.0143, 0.0206]	0.00785 [0.00314, 0.00928]	0.00412 [0.00412,
as.factor(missing_fi)				
0	1 (7.1%)	1 (50.0%)	0 (0%)	0 (0%)
1	9 (64.3%)	1 (50.0%)	3 (75.0%)	1 (100%)
Missing	4 (28.6%)	0 (0%)	1 (25.0%)	0 (0%)
as.factor(fi4)				
FI <= 4	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	13 (92.9%)	2 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Men	Women	Overall
	(N=3)	(N=1)	(N=23)	(N=27)
n_event				
Mean (SD)	106 (108)	NA	168 (127)	156 (125)
Median [Q1, Q3]	48.0 [43.5, 140]	37.0 [37.0, 37.0]	112 [84.5, 222]	110 [67.5, 222]
Median [min, max]	48.0 [39.0, 231]	37.0 [37.0, 37.0]	112 [34.0, 464]	110 [34.0, 464]
FI_final				
Mean (SD)	9.00 (3.46)	NA	33.0 (40.6)	29.3 (38.4)
Median [Q1, Q3]	7.00 [7.00, 10.0]	6.00 [6.00, 6.00]	20.0 [13.0, 36.5]	15.0 [11.5, 29.5]
Median [min, max]	7.00 [7.00, 13.0]	6.00 [6.00, 6.00]	20.0 [1.00, 171]	15.0 [1.00, 171]
FQ_final				
Mean (SD)	0.0180 (0.00956)	NA	0.0141 (0.0110)	0.0142 (0.0107)
Median [Q1, Q3]	0.0146 [0.0126, 0.0217]	0.00532 [0.00532, 0.00532]	0.00928 [0.00634, 0.0204]	0.0107 [0.00634,
Median [min, max]	0.0146 [0.0107, 0.0288]	0.00532 [0.00532, 0.00532]	0.00928 [0.000567, 0.0368]	0.0107 [0.000567
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	2 (8.7%)	2 (7.4%)
1	2 (66.7%)	1 (100%)	14 (60.9%)	17 (63.0%)
Missing	1 (33.3%)	0 (0%)	7 (30.4%)	8 (29.6%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	1 (4.3%)	1 (3.7%)
FI > 4	3 (100%)	1 (100%)	22 (95.7%)	26 (96.3%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=5)	(N=22)	(N=27)
n_event			
Mean (SD)	169 (181)	153 (114)	156 (125)
Median [Q1, Q3]	92.0 [36.0, 221]	111 [77.0, 206]	110 [67.5, 222]
Median [min, max]	92.0 [34.0, 464]	111 [37.0, 402]	110 [34.0, 464]
FI_final			
Mean (SD)	21.4 (12.9)	31.1 (42.1)	29.3 (38.4)
Median [Q1, Q3]	15.0 [13.0, 26.0]	14.5 [11.3, 31.0]	15.0 [11.5, 29.5]
Median [min, max]	15.0 [11.0, 42.0]	14.5 [1.00, 171]	15.0 [1.00, 171]
FQ_final			
Mean (SD)	0.00998 (0.00294)	0.0152 (0.0116)	0.0142 (0.0107)
Median [Q1, Q3]	0.00928 [0.00770, 0.0115]	0.0126 [0.00550, 0.0245]	0.0107 [0.00634, 0.0204]
Median [min, max]	0.00928 [0.00714, 0.0143]	0.0126 [0.000567, 0.0368]	0.0107 [0.000567, 0.0368]
as.factor(missing_fi)			
0	1 (20.0%)	1 (4.5%)	2 (7.4%)
1	4 (80.0%)	13 (59.1%)	17 (63.0%)
Missing	0 (0%)	8 (36.4%)	8 (29.6%)
as.factor(fi4)			
FI <= 4	0 (0%)	1 (4.5%)	1 (3.7%)
FI > 4	5 (100%)	21 (95.5%)	26 (96.3%)

Subgroup 2. Analyses with P< 0.001 Subgroup

```
p_sig2 = subset(ori_st, Pval_screen<= 0.001)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = p_sig2, render.
```

	Overall
	(N=38)
n_event	
Mean (SD)	211 (201)
Median [Q1, Q3]	108 [77.5, 298]
Median [min, max]	108 [34.0, 764]
FI_final	
Mean (SD)	38.5 (34.8)
Median [Q1, Q3]	26.5 [17.5, 41.5]
Median [min, max]	26.5 [9.00, 171]
FQ_final	
Mean (SD)	0.0157 (0.0165)
Median [Q1, Q3]	0.0104 [0.00655, 0.0191]
Median [min, max]	0.0104 [0.00230, 0.0966]
as.factor(missing_fi)	
0	4 (10.5%)
1	22 (57.9%)
Missing	12 (31.6%)
as.factor(fi4)	
FI > 4	38 (100%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=10)	(N=10)	(N=12)	(N=3)
n_event				
Mean (SD)	283 (258)	62.0 (25.2)	234 (163)	184 (145)
Median [Q1, Q3]	167 [101, 380]	49.5 [44.5, 85.3]	223 [106, 272]	121 [102, 236]
Median [min, max]	167 [58.0, 764]	49.5 [34.0, 100]	223 [75.0, 658]	121 [82.0, 350]
FI_final				
Mean (SD)	50.2 (47.7)	16.5 (5.36)	35.1 (12.8)	64.3 (63.9)
Median [Q1, Q3]	39.0 [23.3, 42.8]	16.0 [13.0, 20.8]	33.0 [25.5, 40.5]	39.0 [28.0, 88.0]
Median [min, max]	39.0 [11.0, 171]	16.0 [9.00, 25.0]	33.0 [21.0, 65.0]	39.0 [17.0, 137]
FQ_final				
Mean (SD)	0.0154 (0.0108)	0.0181 (0.00849)	0.00732 (0.00436)	0.00861 (0.00870)
Median [Q1, Q3]	0.0109 [0.00694, 0.0197]	0.0177 [0.0105, 0.0255]	0.00594 [0.00383, 0.00853]	0.00499 [0.00365,
Median [min, max]	0.0109 [0.00653, 0.0368]	0.0177 [0.00711, 0.0288]	0.00594 [0.00315, 0.0169]	0.00499 [0.00230,
as.factor(missing_fi)				
0	1 (10.0%)	2 (20.0%)	1 (8.3%)	0 (0%)
1	8 (80.0%)	3 (30.0%)	11 (91.7%)	0 (0%)
Missing	1 (10.0%)	5 (50.0%)	0 (0%)	3 (100%)
as.factor(fi4)				
FI > 4	10 (100%)	10 (100%)	12 (100%)	3 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), c
```

	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=2)	(N=5)	(N=3)	(N=26)
n_event				
Mean (SD)	505 (366)	338 (218)	358 (281)	155 (154)
Median [Q1, Q3]	505 [376, 635]	323 [312, 355]	225 [197, 453]	96.0 [73.5, 198]
Median [min, max]	505 [246, 764]	323 [44.0, 658]	225 [168, 680]	96.0 [34.0, 696]
FI_final				
Mean (SD)	62.5 (37.5)	32.6 (20.4)	29.0 (12.2)	38.7 (39.9)
Median [Q1, Q3]	62.5 [49.3, 75.8]	30.0 [26.0, 33.0]	23.0 [22.0, 33.0]	23.5 [17.0, 40.0
Median [min, max]	62.5 [36.0, 89.0]	30.0 [9.00, 65.0]	23.0 [21.0, 43.0]	23.5 [11.0, 171]
FQ_final				
Mean (SD)	0.00949 (0.00580)	0.0112 (0.00526)	0.00440 (0.00190)	0.0191 (0.0188)
Median [Q1, Q3]	0.00949 [0.00743, 0.0115]	0.00754 [0.00736, 0.0169]	0.00346 [0.00330, 0.00502]	0.0140 [0.00769
Median [min, max]	0.00949 [0.00538, 0.0136]	0.00754 [0.00711, 0.0169]	0.00346 [0.00315, 0.00659]	0.0140 [0.00230
as.factor(missing_fi)				
0	0 (0%)	2 (40.0%)	0 (0%)	2 (7.7%)
1	2 (100%)	3 (60.0%)	3 (100%)	13 (50.0%)
Missing	0 (0%)	0 (0%)	0 (0%)	11 (42.3%)
as.factor(fi4)				
FI > 4	2 (100%)	5 (100%)	3 (100%)	26 (100%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=5)	(N=4)	(N=17)	(N=10)
n_event				
Mean (SD)	132 (110)	40.5 (6.61)	184 (150)	307 (255)
Median [Q1, Q3]	76.0 [75.0, 128]	40.0 [35.5, 45.0]	106 [92.0, 225]	236 [105, 398]
Median [min, max]	76.0 [58.0, 323]	40.0 [34.0, 48.0]	106 [46.0, 658]	236 [73.0, 764]
FI_final				
Mean (SD)	22.2 (7.46)	11.5 (1.91)	30.5 (13.6)	64.3 (52.0)
Median [Q1, Q3]	24.0 [19.0, 27.0]	12.0 [10.5, 13.0]	25.0 [21.0, 40.0]	42.5 [38.3, 79.8]
Median [min, max]	24.0 [11.0, 30.0]	12.0 [9.00, 13.0]	25.0 [15.0, 65.0]	42.5 [15.0, 171]
FQ_final				
Mean (SD)	0.00741 (0.00410)	0.0132 (0.0104)	0.0152 (0.00975)	0.0133 (0.0115)
Median [Q1, Q3]	0.00754 [0.00391, 0.00828]	0.00849 [0.00755, 0.0142]	0.0143 [0.00601, 0.0206]	0.00719 [0.00655
Median [min, max]	0.00754 [0.00361, 0.0137]	0.00849 [0.00711, 0.0288]	0.0143 [0.00315, 0.0368]	0.00719 [0.00230
as.factor(missing_fi)				
0	1 (20.0%)	0 (0%)	2 (11.8%)	0 (0%)
1	3 (60.0%)	3 (75.0%)	11 (64.7%)	5 (50.0%)
Missing	1 (20.0%)	1 (25.0%)	4 (23.5%)	5 (50.0%)
as.factor(fi4)				
FI > 4	5 (100%)	4 (100%)	17 (100%)	10 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	JBMR
	(N=27)	(N=3)	(N=4)	(N=1)
n_event				
Mean (SD)	240 (200)	138 (73.4)	43.0 (10.9)	NA
Median [Q1, Q3]	168 [84.5, 337]	100 [96.0, 162]	40.0 [35.5, 47.5]	110 [110, 110]
Median [min, max]	168 [46.0, 764]	100 [92.0, 223]	40.0 [34.0, 58.0]	110 [110, 110]
FI_final				
Mean (SD)	44.0 (35.7)	24.0 (13.9)	11.0 (1.63)	NA
Median [Q1, Q3]	36.0 [23.5, 42.5]	17.0 [16.0, 28.5]	11.0 [10.5, 11.5]	15.0 [15.0, 15.0]
Median [min, max]	36.0 [17.0, 171]	17.0 [15.0, 40.0]	11.0 [9.00, 13.0]	15.0 [15.0, 15.0]
FQ_final				
Mean (SD)	0.0127 (0.00949)	0.0170 (0.00321)	0.00809 (0.000924)	NA
Median [Q1, Q3]	0.00754 [0.00562, 0.0177]	0.0162 [0.0153, 0.0184]	0.00799 [0.00755, 0.00853]	0.00768 [0.00768,
Median [min, max]	0.00754 [0.00230, 0.0361]	0.0162 [0.0143, 0.0206]	0.00799 [0.00711, 0.00928]	0.00768 [0.00768,
as.factor(missing_fi)				
0	2 (7.4%)	2 (66.7%)	0 (0%)	0 (0%)
1	16 (59.3%)	1 (33.3%)	4 (100%)	0 (0%)
Missing	9 (33.3%)	0 (0%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI > 4	27 (100%)	3 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Women	Overall
	(N=1)	(N=37)	(N=38)
n_event			
Mean (SD)	NA	216 (202)	211 (201)
Median [Q1, Q3]	48.0 [48.0, 48.0]	110 [82.0, 312]	108 [77.5, 298]
Median [min, max]	48.0 [48.0, 48.0]	110 [34.0, 764]	108 [34.0, 764]
FI_final			
Mean (SD)	NA	39.2 (35.0)	38.5 (34.8)
Median [Q1, Q3]	13.0 [13.0, 13.0]	27.0 [19.0, 42.0]	26.5 [17.5, 41.5]
Median [min, max]	13.0 [13.0, 13.0]	27.0 [9.00, 171]	26.5 [9.00, 171]
FQ_final			
Mean (SD)	NA	0.0153 (0.0166)	0.0157 (0.0165)
Median [Q1, Q3]	0.0288 [0.0288, 0.0288]	0.00928 [0.00653, 0.0185]	0.0104 [0.00655, 0.0191]
Median [min, max]	0.0288 [0.0288, 0.0288]	0.00928 [0.00230, 0.0966]	0.0104 [0.00230, 0.0966]
as.factor(missing_fi)			
0	0 (0%)	4 (10.8%)	4 (10.5%)
1	0 (0%)	22 (59.5%)	22 (57.9%)
Missing	1 (100%)	11 (29.7%)	12 (31.6%)
as.factor(fi4)			
FI > 4	1 (100%)	37 (100%)	38 (100%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=10)	(N=28)	(N=38)
n_event			
Mean (SD)	212 (198)	211 (205)	211 (201)
Median [Q1, Q3]	161 [56.0, 306]	108 [80.5, 263]	108 [77.5, 298]
Median [min, max]	161 [34.0, 658]	108 [46.0, 764]	108 [34.0, 764]
FI_final			
Mean (SD)	27.6 (18.7)	42.4 (38.5)	38.5 (34.8)
Median [Q1, Q3]	21.5 [13.5, 39.0]	30.0 [20.8, 40.5]	26.5 [17.5, 41.5]
Median [min, max]	21.5 [9.00, 65.0]	30.0 [11.0, 171]	26.5 [9.00, 171]
FQ_final			
Mean (SD)	0.0111 (0.00383)	0.0173 (0.0189)	0.0157 (0.0165)
Median [Q1, Q3]	0.0104 [0.00758, 0.0140]	0.0109 [0.00574, 0.0249]	0.0104 [0.00655, 0.0191]
Median [min, max]	0.0104 [0.00711, 0.0169]	0.0109 [0.00230, 0.0966]	0.0104 [0.00230, 0.0966]
as.factor(missing_fi)			
0	3 (30.0%)	1 (3.6%)	4 (10.5%)
1	7 (70.0%)	15 (53.6%)	22 (57.9%)
Missing	0 (0%)	12 (42.9%)	12 (31.6%)
as.factor(fi4)			
FI > 4	10 (100%)	28 (100%)	38 (100%)

Respond the reviewer's inqueries

(1) Reviewer 2:

(1.1) Q4. Fracture site-specific FI/FQ for each of the pharmacological interventions Set-up

```
fi_sig$interv_f = as.factor(fi_sig$interv_code2)
fi_sig$fx_f = as.factor(fi_sig$fx_code2)
fi_sig$timing_f = as.factor(fi_sig$timing)
fi_sig$journal_f = as.factor(fi_sig$journal_code2)
fi_sig$sex_f = as.factor(fi_sig$sex)
fi_sig$placebo_f = as.factor(fi_sig$placebo)
```

```
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | interv_f*fx_f, data =
```

Table S2. Pharmacological intervention by fracture sites

```
## Warning in .table1.internal(x = x, labels = labels, groupspan = groupspan, :
## Table has 40 columns. Are you sure this is what you want?
```

				Bisphosph
	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=6)	(N=1)	(N=5)	(N=26)
n_event				
Mean (SD)	363 (230)	NA	225 (266)	89.0 (79.1)
Median [Q1, Q3]	350 [254, 401]	312 [312, 312]	85.0 [57.0, 249]	69.0 [43.8, 108]
Median [min, max]	350 [76.0, 764]	312 [312, 312]	85.0 [56.0, 680]	69.0 [13.0, 402]
FI_final				
Mean (SD)	23.8 (32.1)	NA	13.6 (17.8)	16.3 (33.1)
Median [Q1, Q3]	12.5 [8.00, 14.8]	33.0 [33.0, 33.0]	3.00 [3.00, 18.0]	8.50 [4.00, 13.0]
Median [min, max]	12.5 [7.00, 89.0]	33.0 [33.0, 33.0]	3.00 [1.00, 43.0]	8.50 [1.00, 171]
FQ_final				
Mean (SD)	0.0101 (0.00574)	NA	0.00457 (0.00366)	0.00891 (0.00906)
Median [Q1, Q3]	0.0105 [0.00705, 0.0144]	0.0169 [0.0169, 0.0169]	0.00454 [0.00157, 0.00659]	0.00602 [0.00319,
Median [min, max]	0.0105 [0.00158, 0.0166]	0.0169 [0.0169, 0.0169]	0.00454 [0.000615, 0.00955]	0.00602 [0.000887
as.factor(missing_fi)				
0	1 (16.7%)	1 (100%)	1 (20.0%)	1 (3.8%)
1	4 (66.7%)	0 (0%)	4 (80.0%)	19 (73.1%)
Missing	1 (16.7%)	0 (0%)	0 (0%)	6 (23.1%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	3 (60.0%)	8 (30.8%)
FI > 4	6 (100%)	1 (100%)	2 (40.0%)	18 (69.2%)

```
# Timing
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi)  + as.factor(fi4) | interv_f*timing_f, da
```

Pharmacological intervention by other factors (optional)

```
## Warning in .table1.internal(x = x, labels = labels, groupspan = groupspan, :
## Table has 28 columns. Are you sure this is what you want?
```

	Bisphosphonates			
	2	3	4	5
	(N=8)	(N=1)	(N=15)	(N=15)
n_event				
Mean (SD)	50.6 (21.3)	NA	82.9 (82.3)	212 (225)
Median [Q1, Q3]	58.5 [47.3, 64.3]	79.0 [79.0, 79.0]	63.0 [38.0, 74.5]	112 [79.0, 193]
Median [min, max]	58.5 [13.0, 69.0]	79.0 [79.0, 79.0]	63.0 [22.0, 322]	112 [60.0, 764]
FI_final				
Mean (SD)	4.50 (3.89)	NA	9.33 (9.95)	31.0 (45.3)
Median [Q1, Q3]	2.50 [2.00, 6.25]	8.00 [8.00, 8.00]	6.00 [3.50, 11.0]	13.0 [5.50, 40.0]
Median [min, max]	2.50 [1.00, 11.0]	8.00 [8.00, 8.00]	6.00 [1.00, 40.0]	13.0 [1.00, 171]
FQ_final				
Mean (SD)	0.00499 (0.00494)	NA	0.00843 (0.00962)	0.00869 (0.0080
Median [Q1, Q3]	0.00256 [0.00157, 0.00773]	0.0137 [0.0137, 0.0137]	0.00461 [0.00331, 0.00878]	0.00666 [0.00250
Median [min, max]	0.00256 [0.000887, 0.0150]	0.0137 [0.0137, 0.0137]	0.00461 [0.000887, 0.0368]	0.00666 [0.00061
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1	8 (100%)	1 (100%)	13 (86.7%)	11 (73.3%)
Missing	0 (0%)	0 (0%)	2 (13.3%)	4 (26.7%)
as.factor(fi4)				
FI <= 4	5 (62.5%)	0 (0%)	6 (40.0%)	4 (26.7%)
FI > 4	3 (37.5%)	1 (100%)	9 (60.0%)	11 (73.3%)

```
# Journal
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi)  + as.factor(fi4) | interv_f*journal_f, c
```

```
## Warning in .table1.internal(x = x, labels = labels, groupspan = groupspan, :
## Table has 27 columns. Are you sure this is what you want?
```

			Bisphosphonates	
	NEJM	Lancet	JAMA	JBMR
	(N=20)	(N=4)	(N=6)	(N=6)
n_event				
Mean (SD)	189 (219)	170 (125)	149 (133)	81.5 (23.1)
Median [Q1, Q3]	86.0 [38.5, 265]	148 [70.5, 248]	103 [70.0, 146]	70.5 [64.5, 10
Median [min, max]	86.0 [13.0, 764]	148 [63.0, 322]	103 [58.0, 409]	70.5 [63.0, 11
FI_final				
Mean (SD)	25.5 (40.6)	17.3 (15.7)	7.50 (5.05)	8.50 (4.68)
Median [Q1, Q3]	9.50 [3.50, 34.3]	12.5 [9.25, 20.5]	9.00 [3.25, 11.0]	7.50 [4.50, 12
Median [min, max]	9.50 [1.00, 171]	12.5 [4.00, 40.0]	9.00 [1.00, 13.0]	7.50 [4.00, 15
FQ_final				
Mean (SD)	0.00720 (0.00710)	0.00872 (0.00816)	0.00386 (0.00341)	0.00435 (0.00
Median [Q1, Q3]	0.00535 [0.00268, 0.00800]	0.00617 [0.00456, 0.0103]	0.00236 [0.00157, 0.00679]	0.00384 [0.00
Median [min, max]	0.00535 [0.000887, 0.0301]	0.00617 [0.00197, 0.0206]	0.00236 [0.000615, 0.00828]	0.00384 [0.00
as.factor(missing_fi)				
0	5 (25.0%)	0 (0%)	0 (0%)	0 (0%)
1	15 (75.0%)	4 (100%)	4 (66.7%)	0 (0%)
Missing	0 (0%)	0 (0%)	2 (33.3%)	6 (100%)
as.factor(fi4)				
FI <= 4	6 (30.0%)	1 (25.0%)	2 (33.3%)	2 (33.3%)
FI > 4	14 (70.0%)	3 (75.0%)	4 (66.7%)	4 (66.7%)

```
# Sex
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi)  + as.factor(fi4) | interv_f*sex_f, data
```

```
## Warning in .table1.internal(x = x, labels = labels, groupspan = groupspan, :
## Table has 14 columns. Are you sure this is what you want?
```

	Bisphosphonates			
	Both	Men	Women	Both
	(N=6)	(N=6)	(N=36)	(N=7)
n_event				
Mean (SD)	80.8 (75.9)	27.0 (9.96)	167 (172)	32.7 (10.3)
Median [Q1, Q3]	58.5 [43.5, 72.0]	26.0 [21.5, 35.0]	92.0 [67.3, 171]	34.0 [26.0, 38
Median [min, max]	58.5 [22.0, 231]	26.0 [13.0, 39.0]	92.0 [48.0, 764]	34.0 [19.0, 48
FI_final				
Mean (SD)	5.33 (3.67)	2.50 (2.07)	19.9 (31.0)	5.86 (4.38)
Median [Q1, Q3]	5.00 [3.00, 7.00]	1.50 [1.00, 3.50]	11.0 [5.75, 15.8]	4.00 [3.00, 8.
Median [min, max]	5.00 [1.00, 11.0]	1.50 [1.00, 6.00]	11.0 [1.00, 171]	4.00 [2.00, 13
FQ_final				
Mean (SD)	0.00899 (0.00581)	0.00223 (0.00183)	0.00836 (0.00808)	0.0133 (0.009
Median [Q1, Q3]	0.00760 [0.00454, 0.0136]	0.00136 [0.000902, 0.00311]	0.00656 [0.00313, 0.00859]	0.00887 [0.00
Median [min, max]	0.00760 [0.00295, 0.0166]	0.00136 [0.000887, 0.00532]	0.00656 [0.000615, 0.0368]	0.00887 [0.00
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	5 (13.9%)	0 (0%)
1	6 (100%)	6 (100%)	22 (61.1%)	0 (0%)
Missing	0 (0%)	0 (0%)	9 (25.0%)	7 (100%)
as.factor(fi4)				
FI <= 4	3 (50.0%)	5 (83.3%)	8 (22.2%)	4 (57.1%)
FI > 4	3 (50.0%)	1 (16.7%)	28 (77.8%)	3 (42.9%)

```
# Placebo
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi)  + as.factor(fi4) | interv_f*placebo_f, c
```

	Bisphosphonates		PTH analog	
	Placebo	Active	Placebo	Active
	(N=48)	(N=13)	(N=17)	(N=16)
n_event				
Mean (SD)	139 (159)	53.9 (28.1)	45.9 (21.5)	275 (154)
Median [Q1, Q3]	72.5 [58.8, 141]	52.0 [34.0, 76.0]	44.0 [31.0, 51.0]	238 [163, 359]
Median [min, max]	72.5 [13.0, 764]	52.0 [14.0, 100]	44.0 [19.0, 86.0]	238 [62.0, 658
FI_final				
Mean (SD)	15.9 (27.7)	7.85 (5.19)	9.06 (8.08)	24.3 (22.9)
Median [Q1, Q3]	8.50 [4.00, 14.0]	9.00 [3.00, 11.0]	6.00 [2.00, 13.0]	16.0 [6.50, 33.
Median [min, max]	8.50 [1.00, 171]	9.00 [2.00, 17.0]	6.00 [1.00, 25.0]	16.0 [2.00, 77.
FQ_final				
Mean (SD)	0.00767 (0.00754)	0.00655 (0.00475)	0.0127 (0.0102)	0.00645 (0.005
Median [Q1, Q3]	0.00535 [0.00272, 0.00859]	0.00662 [0.00259, 0.00908]	0.00887 [0.00443, 0.0247]	0.00417 [0.001
Median [min, max]	0.00535 [0.000615, 0.0368]	0.00662 [0.00147, 0.0162]	0.00887 [0.00114, 0.0288]	0.00417 [0.000
as.factor(missing_fi)				
0	5 (10.4%)	2 (15.4%)	0 (0%)	2 (12.5%)
1	34 (70.8%)	8 (61.5%)	1 (5.9%)	14 (87.5%)
Missing	9 (18.8%)	3 (23.1%)	16 (94.1%)	0 (0%)
as.factor(fi4)				
FI <= 4	16 (33.3%)	6 (46.2%)	7 (41.2%)	1 (6.3%)
FI > 4	32 (66.7%)	7 (53.8%)	10 (58.8%)	15 (93.8%)

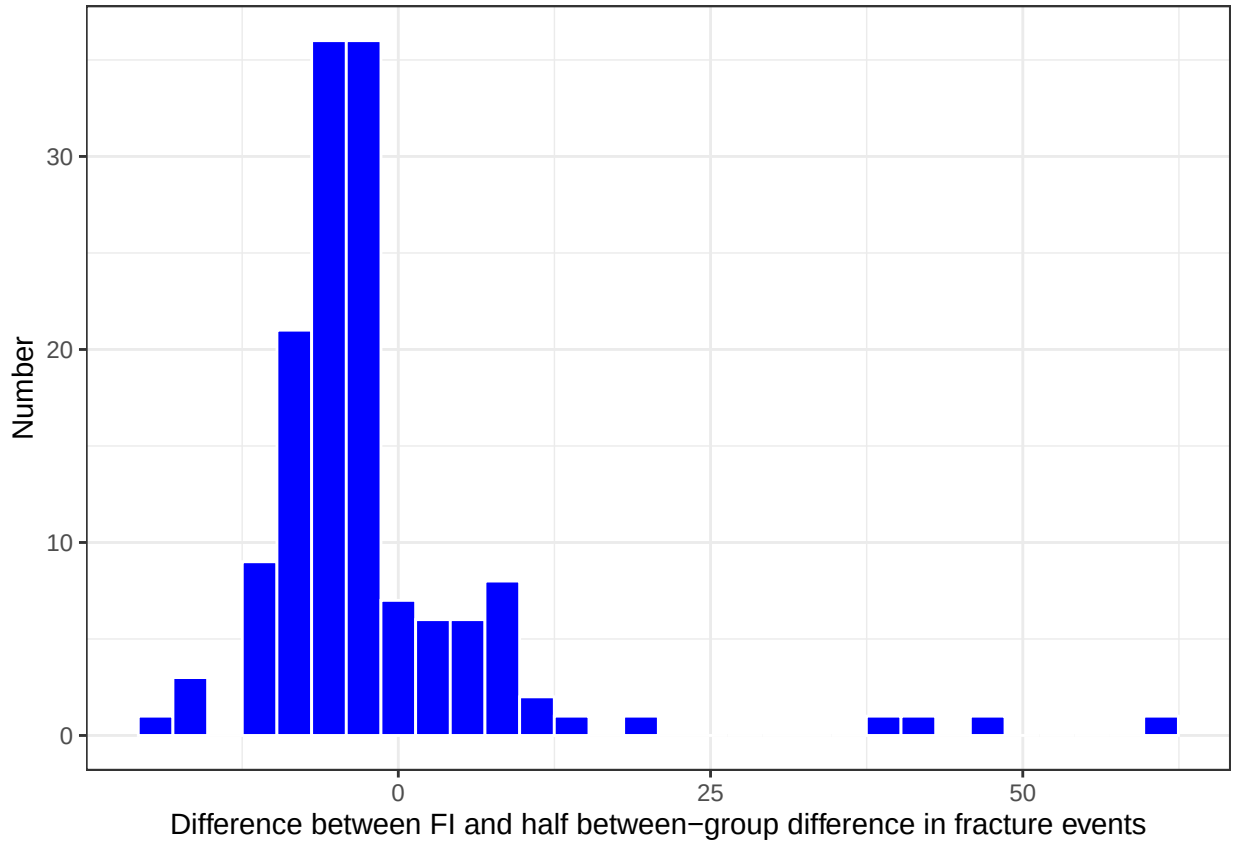
```
fi_sig$fi_fx = fi_sig$FI_final - (fi_sig$e_con - fi_sig$e_intv)/2

quantile(fi_sig$fi_fx, c(.01, .05, .1, .25, .5, .75, .79, .8, .9, .95, .99))
```

(1.2) Q9. Relationship between FI and between-group differences in number of fracture events

```
##    1%    5%   10%   25%   50%   75%   79%   80%   90%   95%   99%
## -17.1 -11.0  -9.5  -6.5  -4.0  -1.5   0.3   1.0   7.5  11.5  46.0
```

```
p = ggplot(data = fi_sig, aes(x = fi_fx))
p + geom_histogram(color = "white", fill = "blue") + labs(x = "Difference between FI and half between-gr
```

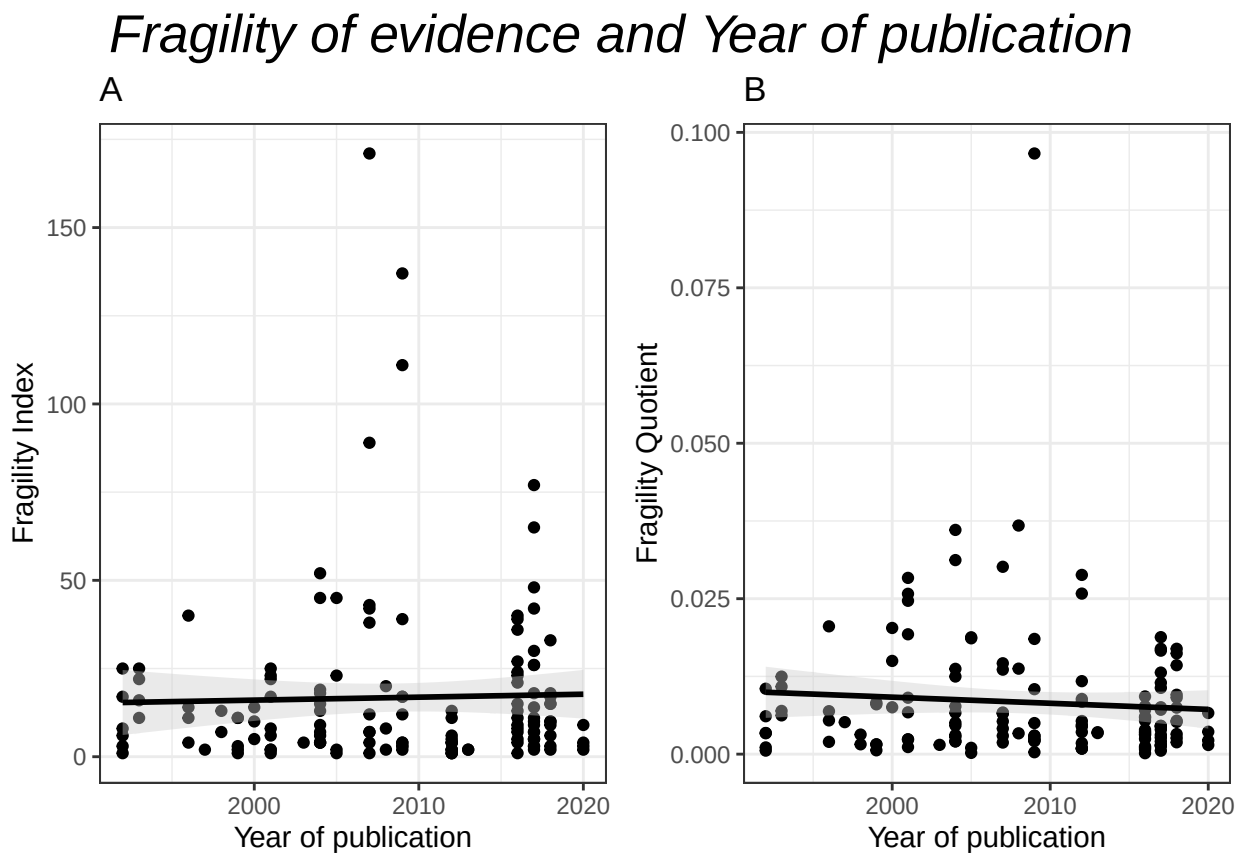
```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```




```
p = ggplot(data = fi_sig, aes(x = year, y = FI_final))
p1 = p + geom_point() + geom_smooth(method = "lm", color = "black", fill = "grey80") + labs(title = "A"

p.0 = ggplot(data = fi_sig, aes(x = year, y = FQ_final))
p2 = p.0 + geom_point() + geom_smooth(method = "lm", color = "black", fill = "grey80") + labs(title = "

grid.arrange(p1, p2, nrow = 1, top = textGrob("Fragility of evidence and Year of publication", gp = gpa
```

(1.3) Q11. Association between years of publication and FI/FQ (Fig S2)

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

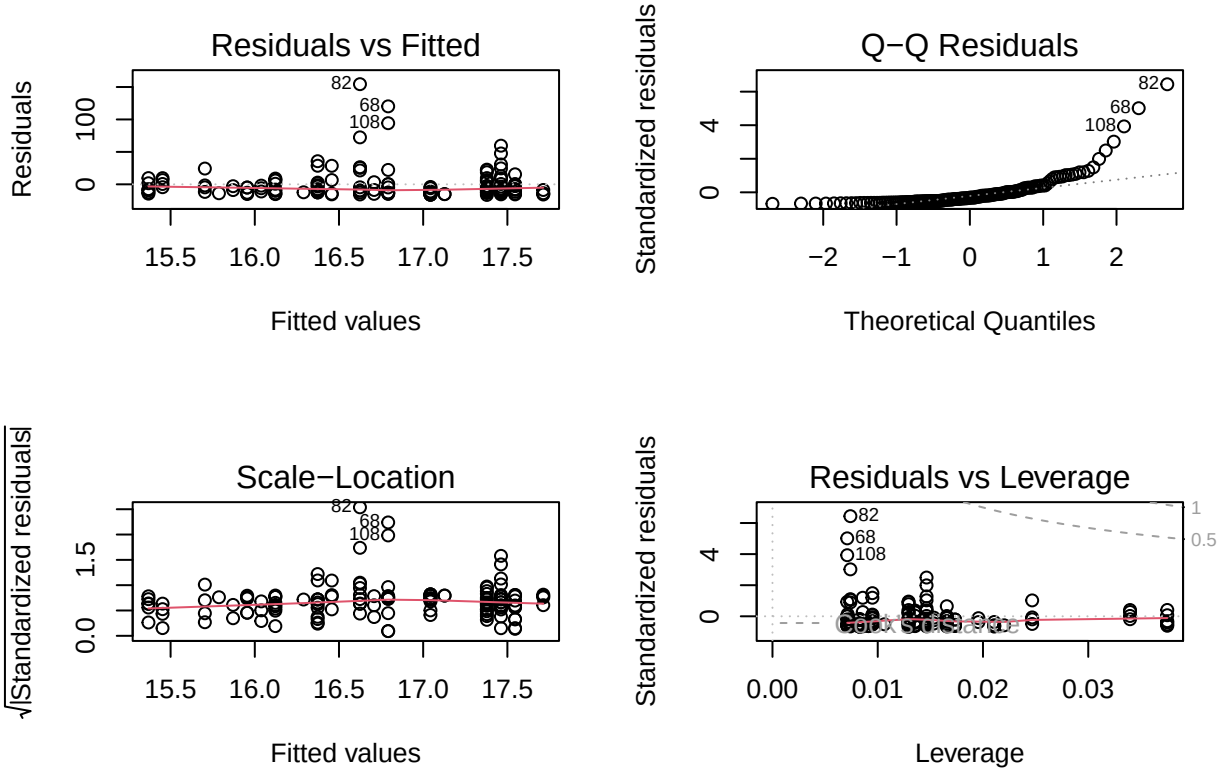


Linear model

```
m1 = lm(FI_final ~ year, data = fi_sig)
  summary(m1)
```

```
##
## Call:
## lm(formula = FI_final ~ year, data = fi_sig)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -16.378 -12.955  -7.546   2.627 154.375
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept) -151.43194  505.04655  -0.300    0.765
## year           0.08374    0.25143   0.333    0.740
##
## Residual standard error: 24.06 on 139 degrees of freedom
## Multiple R-squared:  0.0007973,  Adjusted R-squared:  -0.006391
## F-statistic: 0.1109 on 1 and 139 DF,  p-value: 0.7396
```

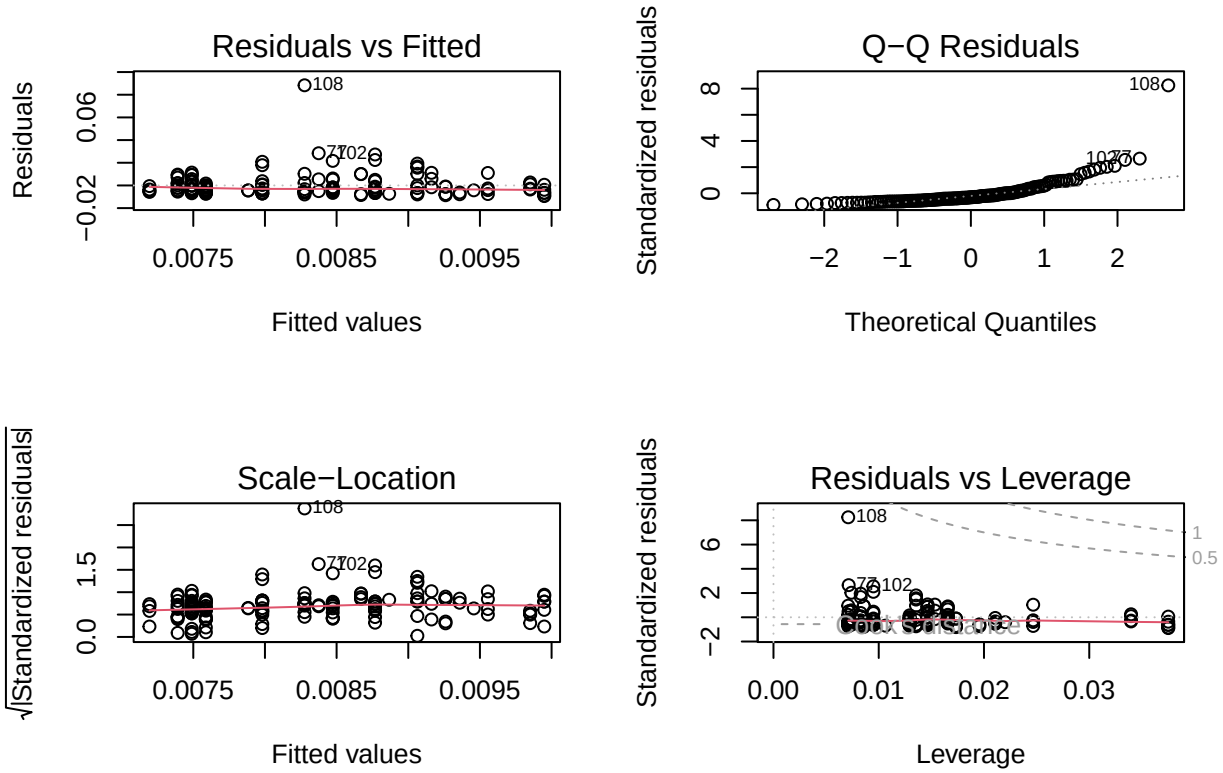
```r
par(mfrow = c(2,2))
plot(m1)
```




```r
m2 = lm(FQ_final ~ year, data = fi_sig)
  summary(m2)
```

```
##
## Call:
## lm(formula = FQ_final ~ year, data = fi_sig)
##
## Residuals:
##       Min        1Q    Median        3Q       Max
## -0.009382 -0.005977 -0.003282  0.001692  0.088329
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  2.059e-01  2.256e-01   0.913    0.363
## year        -9.839e-05  1.123e-04  -0.876    0.383
##
## Residual standard error: 0.01075 on 139 degrees of freedom
## Multiple R-squared:  0.005491,   Adjusted R-squared:  -0.001664
## F-statistic: 0.7674 on 1 and 139 DF,  p-value: 0.3825
```

```r
plot(m2)
```




```r
par(mfrow = c(1,1))
```

(2) Associate Editor:

(2.1) Q3. Calcium/VitD trials excluded Set-up dataset without Calcium/VitD trials

```r
trial_wocalvitd = subset(fi_sig, interv_code2 != "6")
table(trial_wocalvitd$interv_code2)
```

```
##
##    Bisphosphonates         PTH analog        Romosozumab          Denosumab
##                 48                 30                 28                  9
## Strontium_ranelate
##                 12
```

```r
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = trial_wocalvitd
```

(2.1.1) Table S5. Post-hoc exploratory analysis excluding trials with calcium and/or vitD supplementation - Fragility of evidence

	Overall
	(N=127)
n_event	
Mean (SD)	146 (154)
Median [Q1, Q3]	82.0 [48.0, 197]
Median [min, max]	82.0 [10.0, 764]
FI_final	
Mean (SD)	17.5 (25.0)
Median [Q1, Q3]	9.00 [4.00, 19.5]
Median [min, max]	9.00 [1.00, 171]
FQ_final	
Mean (SD)	0.00863 (0.0112)
Median [Q1, Q3]	0.00519 [0.00237, 0.0105]
Median [min, max]	0.00519 [0.000151, 0.0966]
as.factor(missing_fi)	
0	10 (7.9%)
1	76 (59.8%)
Missing	41 (32.3%)
as.factor(fi4)	
FI <= 4	39 (30.7%)
FI > 4	88 (69.3%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=48)	(N=30)	(N=28)	(N=9)
n_event				
Mean (SD)	139 (159)	49.4 (24.5)	209 (146)	140 (180)
Median [Q1, Q3]	72.5 [58.8, 141]	44.0 [34.0, 59.0]	173 [106, 272]	69.0 [29.0, 121
Median [min, max]	72.5 [13.0, 764]	44.0 [14.0, 100]	173 [10.0, 658]	69.0 [15.0, 531
FI_final				
Mean (SD)	15.9 (27.7)	8.53 (6.90)	22.7 (19.2)	25.1 (43.7)
Median [Q1, Q3]	8.50 [4.00, 14.0]	6.50 [3.00, 12.5]	19.5 [7.00, 31.5]	4.00 [3.00, 17.
Median [min, max]	8.50 [1.00, 171]	6.50 [1.00, 25.0]	19.5 [1.00, 77.0]	4.00 [2.00, 137
FQ_final				
Mean (SD)	0.00767 (0.00754)	0.0101 (0.00876)	0.00501 (0.00481)	0.00432 (0.005
Median [Q1, Q3]	0.00535 [0.00272, 0.00859]	0.00741 [0.00325, 0.0137]	0.00354 [0.00147, 0.00629]	0.00255 [0.002
Median [min, max]	0.00535 [0.000615, 0.0368]	0.00741 [0.00114, 0.0288]	0.00354 [0.000151, 0.0188]	0.00255 [0.000
as.factor(missing_fi)				
0	5 (10.4%)	2 (6.7%)	2 (7.1%)	0 (0%)
1	34 (70.8%)	9 (30.0%)	26 (92.9%)	4 (44.4%)
Missing	9 (18.8%)	19 (63.3%)	0 (0%)	5 (55.6%)
as.factor(fi4)				
FI <= 4	16 (33.3%)	13 (43.3%)	2 (7.1%)	5 (55.6%)
FI > 4	32 (66.7%)	17 (56.7%)	26 (92.9%)	4 (44.4%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), d
```

	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=16)	(N=9)	(N=15)	(N=67)
n_event				
Mean (SD)	221 (205)	229 (205)	239 (202)	115 (123)
Median [Q1, Q3]	169 [70.0, 336]	178 [56.0, 323]	168 [71.0, 369]	72.0 [38.0, 1
Median [min, max]	169 [23.0, 764]	178 [34.0, 658]	168 [44.0, 680]	72.0 [10.0, 6
FI_final				
Mean (SD)	15.4 (21.6)	21.7 (19.6)	10.4 (12.1)	21.3 (30.4)
Median [Q1, Q3]	7.50 [4.75, 14.3]	15.0 [9.00, 30.0]	3.00 [2.00, 17.5]	11.0 [4.50, 2
Median [min, max]	7.50 [2.00, 89.0]	15.0 [3.00, 65.0]	3.00 [1.00, 43.0]	11.0 [1.00, 1
FQ_final				
Mean (SD)	0.00702 (0.00511)	0.00755 (0.00589)	0.00293 (0.00250)	0.0118 (0.01
Median [Q1, Q3]	0.00702 [0.00196, 0.00975]	0.00711 [0.00246, 0.00754]	0.00239 [0.00125, 0.00370]	0.00673 [0.0
Median [min, max]	0.00702 [0.00124, 0.0166]	0.00711 [0.000783, 0.0169]	0.00239 [0.000203, 0.00955]	0.00673 [0.0
as.factor(missing_fi)				
0	1 (6.3%)	2 (22.2%)	1 (6.7%)	5 (7.5%)
1	11 (68.8%)	5 (55.6%)	10 (66.7%)	40 (59.7%)
Missing	4 (25.0%)	2 (22.2%)	4 (26.7%)	22 (32.8%)
as.factor(fi4)				
FI <= 4	4 (25.0%)	1 (11.1%)	8 (53.3%)	17 (25.4%)
FI > 4	12 (75.0%)	8 (88.9%)	7 (46.7%)	50 (74.6%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=26)	(N=12)	(N=48)	(N=30)
n_event				
Mean (SD)	91.3 (72.9)	43.6 (19.3)	134 (139)	220 (194)
Median [Q1, Q3]	65.5 [52.3, 137]	38.5 [33.3, 51.0]	79.5 [42.8, 189]	131 [82.8, 332
Median [min, max]	65.5 [10.0, 323]	38.5 [19.0, 79.0]	79.5 [14.0, 658]	131 [23.0, 764
FI_final				
Mean (SD)	8.31 (8.32)	7.42 (4.03)	16.7 (17.0)	29.1 (39.9)
Median [Q1, Q3]	5.00 [3.00, 9.75]	7.50 [4.00, 11.0]	10.5 [4.00, 23.0]	14.5 [4.00, 41.
Median [min, max]	5.00 [1.00, 30.0]	7.50 [2.00, 13.0]	10.5 [1.00, 77.0]	14.5 [1.00, 171
FQ_final				
Mean (SD)	0.00403 (0.00387)	0.0108 (0.00837)	0.00859 (0.00830)	0.00951 (0.009
Median [Q1, Q3]	0.00240 [0.00149, 0.00489]	0.00829 [0.00463, 0.0122]	0.00540 [0.00304, 0.0119]	0.00656 [0.002
Median [min, max]	0.00240 [0.000151, 0.0150]	0.00829 [0.00314, 0.0288]	0.00540 [0.000554, 0.0368]	0.00656 [0.000
as.factor(missing_fi)				
0	1 (3.8%)	0 (0%)	3 (6.3%)	1 (3.3%)
1	20 (76.9%)	6 (50.0%)	33 (68.8%)	16 (53.3%)
Missing	5 (19.2%)	6 (50.0%)	12 (25.0%)	13 (43.3%)
as.factor(fi4)				
FI <= 4	11 (42.3%)	4 (33.3%)	13 (27.1%)	10 (33.3%)
FI > 4	15 (57.7%)	8 (66.7%)	35 (72.9%)	20 (66.7%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	Ann Intern M
	(N=72)	(N=9)	(N=10)	(N=1)
n_event				
Mean (SD)	175 (169)	115 (96.4)	108 (112)	NA
Median [Q1, Q3]	107 [50.3, 247]	91.0 [63.0, 100]	70.5 [47.5, 112]	60.0 [60.0, 60
Median [min, max]	107 [10.0, 764]	91.0 [14.0, 322]	70.5 [34.0, 409]	60.0 [60.0, 60
FI_final				
Mean (SD)	22.5 (29.2)	12.9 (11.5)	8.20 (4.47)	NA
Median [Q1, Q3]	14.5 [5.00, 27.8]	11.0 [4.00, 15.0]	10.0 [4.75, 11.0]	7.00 [7.00, 7.
Median [min, max]	14.5 [1.00, 171]	11.0 [2.00, 40.0]	10.0 [1.00, 13.0]	7.00 [7.00, 7.
FQ_final				
Mean (SD)	0.00756 (0.00827)	0.00877 (0.00681)	0.00504 (0.00332)	NA
Median [Q1, Q3]	0.00417 [0.00228, 0.00919]	0.00691 [0.00259, 0.0143]	0.00513 [0.00197, 0.00793]	0.00412 [0.00
Median [min, max]	0.00417 [0.000151, 0.0361]	0.00691 [0.00191, 0.0206]	0.00513 [0.000615, 0.00928]	0.00412 [0.00
as.factor(missing_fi)				
0	7 (9.7%)	2 (22.2%)	0 (0%)	0 (0%)
1	45 (62.5%)	7 (77.8%)	8 (80.0%)	1 (100%)
Missing	20 (27.8%)	0 (0%)	2 (20.0%)	0 (0%)
as.factor(fi4)				
FI <= 4	17 (23.6%)	3 (33.3%)	3 (30.0%)	0 (0%)
FI > 4	55 (76.4%)	6 (66.7%)	7 (70.0%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Men	Women	Overall
	(N=13)	(N=10)	(N=104)	(N=127)
n_event				
Mean (SD)	54.9 (55.5)	26.5 (9.06)	169 (161)	146 (154)
Median [Q1, Q3]	39.0 [31.0, 57.0]	26.0 [21.5, 34.3]	102 [63.8, 224]	82.0 [48.0, 19
Median [min, max]	39.0 [19.0, 231]	26.0 [13.0, 39.0]	102 [10.0, 764]	82.0 [10.0, 76
FI_final				
Mean (SD)	5.62 (3.91)	2.90 (1.66)	20.4 (26.8)	17.5 (25.0)
Median [Q1, Q3]	4.00 [3.00, 7.00]	3.00 [1.25, 4.00]	11.5 [5.00, 23.3]	9.00 [4.00, 19
Median [min, max]	4.00 [1.00, 13.0]	3.00 [1.00, 6.00]	11.5 [1.00, 171]	9.00 [1.00, 17
FQ_final				
Mean (SD)	0.0113 (0.00829)	0.00236 (0.00140)	0.00890 (0.0119)	0.00863 (0.01
Median [Q1, Q3]	0.00887 [0.00454, 0.0146]	0.00216 [0.00115, 0.00296]	0.00538 [0.00238, 0.0107]	0.00519 [0.00
Median [min, max]	0.00887 [0.00295, 0.0288]	0.00216 [0.000887, 0.00532]	0.00538 [0.000151, 0.0966]	0.00519 [0.00
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	10 (9.6%)	10 (7.9%)
1	6 (46.2%)	10 (100%)	60 (57.7%)	76 (59.8%)
Missing	7 (53.8%)	0 (0%)	34 (32.7%)	41 (32.3%)
as.factor(fi4)				
FI <= 4	7 (53.8%)	9 (90.0%)	23 (22.1%)	39 (30.7%)
FI > 4	6 (46.2%)	1 (10.0%)	81 (77.9%)	88 (69.3%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=29)	(N=98)	(N=127)
n_event			
Mean (SD)	176 (160)	137 (152)	146 (154)
Median [Q1, Q3]	107 [53.0, 255]	75.5 [46.5, 153]	82.0 [48.0, 197]
Median [min, max]	107 [14.0, 658]	75.5 [10.0, 764]	82.0 [10.0, 764]
FI_final			
Mean (SD)	16.9 (19.0)	17.6 (26.6)	17.5 (25.0)
Median [Q1, Q3]	10.0 [5.00, 18.0]	9.00 [4.00, 19.8]	9.00 [4.00, 19.5]
Median [min, max]	10.0 [2.00, 77.0]	9.00 [1.00, 171]	9.00 [1.00, 171]
FQ_final			
Mean (SD)	0.00650 (0.00525)	0.00926 (0.0124)	0.00863 (0.0112)
Median [Q1, Q3]	0.00440 [0.00221, 0.00908]	0.00523 [0.00240, 0.0115]	0.00519 [0.00237, 0.0105]
Median [min, max]	0.00440 [0.000554, 0.0188]	0.00523 [0.000151, 0.0966]	0.00519 [0.000151, 0.0966]
as.factor(missing_fi)			
0	4 (13.8%)	6 (6.1%)	10 (7.9%)
1	22 (75.9%)	54 (55.1%)	76 (59.8%)
Missing	3 (10.3%)	38 (38.8%)	41 (32.3%)
as.factor(fi4)			
FI <= 4	7 (24.1%)	32 (32.7%)	39 (30.7%)
FI > 4	22 (75.9%)	66 (67.3%)	88 (69.3%)

(2.1.2) Table S6. Post-hoc exploratory analysis excluding trials with calcium and/or vitD supplementation - Fragility of evidence in subgroup analysis

Subgroup 1. Fracture predefined as the primary endpoint Subgroup

```
fx_prim3 = subset(trial_wocalvitd, pri_endpoint == 1)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = fx_prim3, rende
```

	Overall
	(N=30)
n_event	
Mean (SD)	165 (131)
Median [Q1, Q3]	111 [63.8, 229]
Median [min, max]	111 [29.0, 464]
FI_final	
Mean (SD)	30.8 (37.6)
Median [Q1, Q3]	15.0 [11.3, 38.3]
Median [min, max]	15.0 [1.00, 171]
FQ_final	
Mean (SD)	0.0154 (0.0108)
Median [Q1, Q3]	0.0129 [0.00678, 0.0245]
Median [min, max]	0.0129 [0.000946, 0.0368]
as.factor(missing_fi)	
0	3 (10.0%)
1	17 (56.7%)
Missing	10 (33.3%)
as.factor(fi4)	
FI <= 4	1 (3.3%)
FI > 4	29 (96.7%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=14)	(N=8)	(N=5)	(N=1)
n_event				
Mean (SD)	154 (107)	60.0 (23.9)	247 (168)	NA
Median [Q1, Q3]	131 [103, 206]	54.0 [39.8, 83.8]	221 [105, 370]	350 [350, 350]
Median [min, max]	131 [29.0, 402]	54.0 [34.0, 92.0]	221 [75.0, 464]	350 [350, 350]
FI_final				
Mean (SD)	25.9 (43.0)	14.8 (6.18)	41.8 (21.3)	NA
Median [Q1, Q3]	13.0 [8.00, 18.8]	13.0 [11.0, 17.0]	40.0 [26.0, 42.0]	137 [137, 137]
Median [min, max]	13.0 [1.00, 171]	13.0 [7.00, 25.0]	40.0 [24.0, 77.0]	137 [137, 137]
FQ_final				
Mean (SD)	0.0131 (0.0108)	0.0180 (0.0102)	0.00941 (0.00598)	NA
Median [Q1, Q3]	0.00933 [0.00566, 0.0195]	0.0200 [0.00889, 0.0265]	0.00714 [0.00601, 0.0115]	0.0185 [0.0185, 0
Median [min, max]	0.00933 [0.000946, 0.0368]	0.0200 [0.00412, 0.0288]	0.00714 [0.00361, 0.0188]	0.0185 [0.0185, 0
as.factor(missing_fi)				
0	1 (7.1%)	1 (12.5%)	1 (20.0%)	0 (0%)
1	10 (71.4%)	3 (37.5%)	4 (80.0%)	0 (0%)
Missing	3 (21.4%)	4 (50.0%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI <= 4	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	13 (92.9%)	8 (100%)	5 (100%)	1 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), d
```

	Any	Osteoporotic	Vertebrae	Hip
	(N=2)	(N=1)	(N=26)	(N=1)
n_event				
Mean (SD)	348 (165)	NA	146 (122)	NA
Median [Q1, Q3]	348 [289, 406]	312 [312, 312]	103 [51.0, 204]	140 [140, 140]
Median [min, max]	348 [231, 464]	312 [312, 312]	103 [29.0, 402]	140 [140, 140]
FI_final				
Mean (SD)	16.5 (13.4)	NA	32.5 (40.0)	NA
Median [Q1, Q3]	16.5 [11.8, 21.3]	33.0 [33.0, 33.0]	15.0 [11.5, 40.0]	12.0 [12.0, 12.0]
Median [min, max]	16.5 [7.00, 26.0]	33.0 [33.0, 33.0]	15.0 [1.00, 171]	12.0 [12.0, 12.0]
FQ_final				
Mean (SD)	0.0109 (0.00529)	NA	0.0162 (0.0112)	NA
Median [Q1, Q3]	0.0109 [0.00901, 0.0127]	0.0169 [0.0169, 0.0169]	0.0129 [0.00692, 0.0258]	0.00186 [0.00186, 0.
Median [min, max]	0.0109 [0.00714, 0.0146]	0.0169 [0.0169, 0.0169]	0.0129 [0.000946, 0.0368]	0.00186 [0.00186, 0.
as.factor(missing_fi)				
0	0 (0%)	1 (100%)	2 (7.7%)	0 (0%)
1	2 (100%)	0 (0%)	14 (53.8%)	1 (100%)
Missing	0 (0%)	0 (0%)	10 (38.5%)	0 (0%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	1 (3.8%)	0 (0%)
FI > 4	2 (100%)	1 (100%)	25 (96.2%)	1 (100%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=1)	(N=5)	(N=12)	(N=10)
n_event				
Mean (SD)	NA	43.8 (10.5)	154 (139)	236 (120)
Median [Q1, Q3]	75.0 [75.0, 75.0]	41.0 [36.0, 48.0]	96.0 [72.0, 222]	193 [141, 346]
Median [min, max]	75.0 [75.0, 75.0]	41.0 [34.0, 60.0]	96.0 [29.0, 464]	193 [110, 402]
FI_final				
Mean (SD)	NA	11.0 (2.45)	26.8 (20.9)	47.7 (58.6)
Median [Q1, Q3]	24.0 [24.0, 24.0]	11.0 [11.0, 13.0]	24.0 [13.0, 40.0]	14.5 [12.3, 50.3
Median [min, max]	24.0 [24.0, 24.0]	11.0 [7.00, 13.0]	24.0 [1.00, 77.0]	14.5 [7.00, 171]
FQ_final				
Mean (SD)	NA	0.0151 (0.0113)	0.0155 (0.0108)	0.0175 (0.0118)
Median [Q1, Q3]	0.00361 [0.00361, 0.00361]	0.00928 [0.00770, 0.0258]	0.0129 [0.00686, 0.0219]	0.0166 [0.00776
Median [min, max]	0.00361 [0.00361, 0.00361]	0.00928 [0.00412, 0.0288]	0.0129 [0.000946, 0.0368]	0.0166 [0.00186
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)
1	1 (100%)	3 (60.0%)	8 (66.7%)	5 (50.0%)
Missing	0 (0%)	2 (40.0%)	2 (16.7%)	5 (50.0%)
as.factor(fi4)				
FI <= 4	0 (0%)	0 (0%)	1 (8.3%)	0 (0%)
FI > 4	1 (100%)	5 (100%)	11 (91.7%)	10 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	Ann Intern Med
	(N=16)	(N=2)	(N=4)	(N=1)
n_event				
Mean (SD)	227 (148)	158 (92.6)	86.3 (60.7)	NA
Median [Q1, Q3]	226 [85.3, 355]	158 [125, 190]	78.5 [35.5, 129]	60.0 [60.0, 60.0]
Median [min, max]	226 [29.0, 464]	158 [92.0, 223]	78.5 [34.0, 154]	60.0 [60.0, 60.0]
FI_final				
Mean (SD)	45.1 (47.1)	27.5 (17.7)	12.0 (1.15)	NA
Median [Q1, Q3]	29.5 [20.3, 46.8]	27.5 [21.3, 33.8]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
Median [min, max]	29.5 [1.00, 171]	27.5 [15.0, 40.0]	12.0 [11.0, 13.0]	7.00 [7.00, 7.00]
FQ_final				
Mean (SD)	0.0161 (0.0115)	0.0174 (0.00442)	0.00703 (0.00268)	NA
Median [Q1, Q3]	0.0158 [0.00584, 0.0264]	0.0174 [0.0159, 0.0190]	0.00785 [0.00656, 0.00832]	0.00412 [0.00412,
Median [min, max]	0.0158 [0.000946, 0.0361]	0.0174 [0.0143, 0.0206]	0.00785 [0.00314, 0.00928]	0.00412 [0.00412,
as.factor(missing_fi)				
0	2 (12.5%)	1 (50.0%)	0 (0%)	0 (0%)
1	9 (56.3%)	1 (50.0%)	3 (75.0%)	1 (100%)
Missing	5 (31.3%)	0 (0%)	1 (25.0%)	0 (0%)
as.factor(fi4)				
FI <= 4	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)
FI > 4	15 (93.8%)	2 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Men	Women	Overall
	(N=4)	(N=2)	(N=24)	(N=30)
n_event				
Mean (SD)	89.8 (94.2)	33.0 (5.66)	188 (132)	165 (131)
Median [Q1, Q3]	44.5 [40.5, 93.8]	33.0 [31.0, 35.0]	131 [90.5, 317]	111 [63.8, 229]
Median [min, max]	44.5 [39.0, 231]	33.0 [29.0, 37.0]	131 [34.0, 464]	111 [29.0, 464]
FI_final				
Mean (SD)	9.50 (3.00)	3.50 (3.54)	36.6 (40.1)	30.8 (37.6)
Median [Q1, Q3]	9.00 [7.00, 11.5]	3.50 [2.25, 4.75]	23.5 [13.0, 40.5]	15.0 [11.3, 38.3]
Median [min, max]	9.00 [7.00, 13.0]	3.50 [1.00, 6.00]	23.5 [7.00, 171]	15.0 [1.00, 171]
FQ_final				
Mean (SD)	0.0200 (0.00872)	0.00313 (0.00310)	0.0156 (0.0110)	0.0154 (0.0108)
Median [Q1, Q3]	0.0202 [0.0136, 0.0266]	0.00313 [0.00204, 0.00423]	0.0129 [0.00702, 0.0219]	0.0129 [0.00678, 0
Median [min, max]	0.0202 [0.0107, 0.0288]	0.00313 [0.000946, 0.00532]	0.0129 [0.00186, 0.0368]	0.0129 [0.000946,
as.factor(missing_fi)				
0	0 (0%)	0 (0%)	3 (12.5%)	3 (10.0%)
1	2 (50.0%)	2 (100%)	13 (54.2%)	17 (56.7%)
Missing	2 (50.0%)	0 (0%)	8 (33.3%)	10 (33.3%)
as.factor(fi4)				
FI <= 4	0 (0%)	1 (50.0%)	0 (0%)	1 (3.3%)
FI > 4	4 (100%)	1 (50.0%)	24 (100%)	29 (96.7%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=6)	(N=24)	(N=30)
n_event			
Mean (SD)	203 (182)	155 (119)	165 (131)
Median [Q1, Q3]	157 [50.0, 333]	111 [71.3, 225]	111 [63.8, 229]
Median [min, max]	157 [34.0, 464]	111 [29.0, 402]	111 [29.0, 464]
FI_final			
Mean (SD)	30.7 (25.5)	30.8 (40.6)	30.8 (37.6)
Median [Q1, Q3]	20.5 [13.5, 38.0]	14.5 [11.0, 34.8]	15.0 [11.3, 38.3]
Median [min, max]	20.5 [11.0, 77.0]	14.5 [1.00, 171]	15.0 [1.00, 171]
FQ_final			
Mean (SD)	0.0115 (0.00447)	0.0163 (0.0117)	0.0154 (0.0108)
Median [Q1, Q3]	0.0104 [0.00810, 0.0136]	0.0158 [0.00584, 0.0265]	0.0129 [0.00678, 0.0245]
Median [min, max]	0.0104 [0.00714, 0.0188]	0.0158 [0.000946, 0.0368]	0.0129 [0.000946, 0.0368]
as.factor(missing_fi)			
0	2 (33.3%)	1 (4.2%)	3 (10.0%)
1	4 (66.7%)	13 (54.2%)	17 (56.7%)
Missing	0 (0%)	10 (41.7%)	10 (33.3%)
as.factor(fi4)			
FI <= 4	0 (0%)	1 (4.2%)	1 (3.3%)
FI > 4	6 (100%)	23 (95.8%)	29 (96.7%)

Subgroup 2. Analyses with P< 0.001 Subgroup

```
p_sig3 = subset(trial_wocalvitd, Pval_screen<= 0.001)
```

Results

```
# Overall:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4), data = p_sig3, render.
```

	Overall
	(N=44)
n_event	
Mean (SD)	217 (191)
Median [Q1, Q3]	125 [80.5, 325]
Median [min, max]	125 [34.0, 764]
FI_final	
Mean (SD)	38.2 (33.3)
Median [Q1, Q3]	26.5 [17.8, 42.3]
Median [min, max]	26.5 [9.00, 171]
FQ_final	
Mean (SD)	0.0164 (0.0156)
Median [Q1, Q3]	0.0134 [0.00667, 0.0196]
Median [min, max]	0.0134 [0.00230, 0.0966]
as.factor(missing_fi)	
0	6 (13.6%)
1	23 (52.3%)
Missing	15 (34.1%)
as.factor(fi4)	
FI > 4	44 (100%)

```
# Pharmacological intervention:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(interv_code1
```

	Bisphosphonates	PTH analog	Romosozumab	Denosumab
	(N=10)	(N=11)	(N=13)	(N=3)
n_event				
Mean (SD)	283 (258)	60.1 (24.7)	245 (160)	184 (145)
Median [Q1, Q3]	167 [101, 380]	48.0 [42.5, 84.5]	225 [106, 323]	121 [102, 236]
Median [min, max]	167 [58.0, 764]	48.0 [34.0, 100]	225 [75.0, 658]	121 [82.0, 350]
FI_final				
Mean (SD)	50.2 (47.7)	16.0 (5.35)	38.3 (16.9)	64.3 (63.9)
Median [Q1, Q3]	39.0 [23.3, 42.8]	15.0 [12.0, 19.5]	36.0 [26.0, 42.0]	39.0 [28.0, 88.0]
Median [min, max]	39.0 [11.0, 171]	15.0 [9.00, 25.0]	36.0 [21.0, 77.0]	39.0 [17.0, 137]
FQ_final				
Mean (SD)	0.0154 (0.0108)	0.0188 (0.00838)	0.00820 (0.00525)	0.00861 (0.00870)
Median [Q1, Q3]	0.0109 [0.00694, 0.0197]	0.0193 [0.0118, 0.0258]	0.00601 [0.00391, 0.0115]	0.00499 [0.00365, 0
Median [min, max]	0.0109 [0.00653, 0.0368]	0.0193 [0.00711, 0.0288]	0.00601 [0.00315, 0.0188]	0.00499 [0.00230, 0
as.factor(missing_fi)				
0	1 (10.0%)	2 (18.2%)	2 (15.4%)	0 (0%)
1	8 (80.0%)	3 (27.3%)	11 (84.6%)	0 (0%)
Missing	1 (10.0%)	6 (54.5%)	0 (0%)	3 (100%)
as.factor(fi4)				
FI > 4	10 (100%)	11 (100%)	13 (100%)	3 (100%)

```
# Fracture site:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(fx_code2), c
```

	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=2)	(N=5)	(N=3)	(N=31)
n_event				
Mean (SD)	505 (366)	338 (218)	358 (281)	173 (154)
Median [Q1, Q3]	505 [376, 635]	323 [312, 355]	225 [197, 453]	100 [74.0, 258]
Median [min, max]	505 [246, 764]	323 [44.0, 658]	225 [168, 680]	100 [34.0, 696]
FI_final				
Mean (SD)	62.5 (37.5)	32.6 (20.4)	29.0 (12.2)	39.0 (37.6)
Median [Q1, Q3]	62.5 [49.3, 75.8]	30.0 [26.0, 33.0]	23.0 [22.0, 33.0]	24.0 [17.0, 43.5
Median [min, max]	62.5 [36.0, 89.0]	30.0 [9.00, 65.0]	23.0 [21.0, 43.0]	24.0 [11.0, 171]
FQ_final				
Mean (SD)	0.00949 (0.00580)	0.0112 (0.00526)	0.00440 (0.00190)	0.0196 (0.0174)
Median [Q1, Q3]	0.00949 [0.00743, 0.0115]	0.00754 [0.00736, 0.0169]	0.00346 [0.00330, 0.00502]	0.0185 [0.00799
Median [min, max]	0.00949 [0.00538, 0.0136]	0.00754 [0.00711, 0.0169]	0.00346 [0.00315, 0.00659]	0.0185 [0.00230
as.factor(missing_fi)				
0	0 (0%)	2 (40.0%)	0 (0%)	4 (12.9%)
1	2 (100%)	3 (60.0%)	3 (100%)	14 (45.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	13 (41.9%)
as.factor(fi4)				
FI > 4	2 (100%)	5 (100%)	3 (100%)	31 (100%)

```
# Timing of fracture assessment:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(timing), da
```

	2	3	4	5
	(N=5)	(N=5)	(N=18)	(N=14)
n_event				
Mean (SD)	132 (110)	40.6 (5.73)	194 (152)	300 (215)
Median [Q1, Q3]	76.0 [75.0, 128]	41.0 [36.0, 44.0]	137 [94.0, 241]	296 [113, 378]
Median [min, max]	76.0 [58.0, 323]	41.0 [34.0, 48.0]	137 [46.0, 658]	296 [73.0, 764]
FI_final				
Mean (SD)	22.2 (7.46)	11.4 (1.67)	33.1 (17.1)	55.3 (46.3)
Median [Q1, Q3]	24.0 [19.0, 27.0]	11.0 [11.0, 13.0]	25.5 [21.3, 40.0]	42.5 [26.8, 50.3]
Median [min, max]	24.0 [11.0, 30.0]	11.0 [9.00, 13.0]	25.5 [15.0, 77.0]	42.5 [15.0, 171]
FQ_final				
Mean (SD)	0.00741 (0.00410)	0.0157 (0.0106)	0.0154 (0.00949)	0.0153 (0.0108)
Median [Q1, Q3]	0.00754 [0.00391, 0.00828]	0.00928 [0.00770, 0.0258]	0.0153 [0.00635, 0.0202]	0.0130 [0.00661,
Median [min, max]	0.00754 [0.00361, 0.0137]	0.00928 [0.00711, 0.0288]	0.0153 [0.00315, 0.0368]	0.0130 [0.00230,
as.factor(missing_fi)				
0	1 (20.0%)	0 (0%)	3 (16.7%)	1 (7.1%)
1	3 (60.0%)	3 (60.0%)	11 (61.1%)	6 (42.9%)
Missing	1 (20.0%)	2 (40.0%)	4 (22.2%)	7 (50.0%)
as.factor(fi4)				
FI > 4	5 (100%)	5 (100%)	18 (100%)	14 (100%)

```
# Journal:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(journal_cod
```

	NEJM	Lancet	JAMA	JBMR
	(N=30)	(N=3)	(N=4)	(N=1)
n_event				
Mean (SD)	246 (192)	138 (73.4)	43.0 (10.9)	NA
Median [Q1, Q3]	214 [90.3, 346]	100 [96.0, 162]	40.0 [35.5, 47.5]	110 [110, 110]
Median [min, max]	214 [46.0, 764]	100 [92.0, 223]	40.0 [34.0, 58.0]	110 [110, 110]
FI_final				
Mean (SD)	44.3 (34.7)	24.0 (13.9)	11.0 (1.63)	NA
Median [Q1, Q3]	37.0 [23.3, 44.5]	17.0 [16.0, 28.5]	11.0 [10.5, 11.5]	15.0 [15.0, 15.0]
Median [min, max]	37.0 [17.0, 171]	17.0 [15.0, 40.0]	11.0 [9.00, 13.0]	15.0 [15.0, 15.0]
FQ_final				
Mean (SD)	0.0135 (0.00965)	0.0170 (0.00321)	0.00809 (0.000924)	NA
Median [Q1, Q3]	0.0120 [0.00590, 0.0187]	0.0162 [0.0153, 0.0184]	0.00799 [0.00755, 0.00853]	0.00768 [0.00768, 0
Median [min, max]	0.0120 [0.00230, 0.0361]	0.0162 [0.0143, 0.0206]	0.00799 [0.00711, 0.00928]	0.00768 [0.00768, 0
as.factor(missing_fi)				
0	3 (10.0%)	2 (66.7%)	0 (0%)	0 (0%)
1	16 (53.3%)	1 (33.3%)	4 (100%)	0 (0%)
Missing	11 (36.7%)	0 (0%)	0 (0%)	1 (100%)
as.factor(fi4)				
FI > 4	30 (100%)	3 (100%)	4 (100%)	1 (100%)

```
# Sex:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(sex), data =
```

	Both	Women	Overall
	(N=2)	(N=42)	(N=44)
n_event			
Mean (SD)	44.5 (4.95)	226 (192)	217 (191)
Median [Q1, Q3]	44.5 [42.8, 46.3]	148 [83.8, 328]	125 [80.5, 325]
Median [min, max]	44.5 [41.0, 48.0]	148 [34.0, 764]	125 [34.0, 764]
FI_final			
Mean (SD)	12.0 (1.41)	39.5 (33.6)	38.2 (33.3)
Median [Q1, Q3]	12.0 [11.5, 12.5]	28.5 [19.3, 42.8]	26.5 [17.8, 42.3]
Median [min, max]	12.0 [11.0, 13.0]	28.5 [9.00, 171]	26.5 [9.00, 171]
FQ_final			
Mean (SD)	0.0273 (0.00212)	0.0159 (0.0158)	0.0164 (0.0156)
Median [Q1, Q3]	0.0273 [0.0266, 0.0281]	0.0128 [0.00661, 0.0188]	0.0134 [0.00667, 0.0196]
Median [min, max]	0.0273 [0.0258, 0.0288]	0.0128 [0.00230, 0.0966]	0.0134 [0.00230, 0.0966]
as.factor(missing_fi)			
0	0 (0%)	6 (14.3%)	6 (13.6%)
1	0 (0%)	23 (54.8%)	23 (52.3%)
Missing	2 (100%)	13 (31.0%)	15 (34.1%)
as.factor(fi4)			
FI > 4	2 (100%)	42 (100%)	44 (100%)

```
# Placebo status:
table1(~ n_event + FI_final + FQ_final + as.factor(missing_fi) + as.factor(fi4) | as.factor(placebo), da
```

	Active	Placebo	Overall
	(N=11)	(N=33)	(N=44)
n_event			
Mean (SD)	226 (193)	214 (194)	217 (191)
Median [Q1, Q3]	221 [68.0, 339]	121 [82.0, 312]	125 [80.5, 325]
Median [min, max]	221 [34.0, 658]	121 [41.0, 764]	125 [34.0, 764]
FI_final			
Mean (SD)	32.1 (23.1)	40.3 (36.2)	38.2 (33.3)
Median [Q1, Q3]	26.0 [14.0, 45.0]	27.0 [20.0, 42.0]	26.5 [17.8, 42.3]
Median [min, max]	26.0 [9.00, 77.0]	27.0 [11.0, 171]	26.5 [9.00, 171]
FQ_final			
Mean (SD)	0.0118 (0.00431)	0.0179 (0.0176)	0.0164 (0.0156)
Median [Q1, Q3]	0.0115 [0.00762, 0.0153]	0.0137 [0.00601, 0.0258]	0.0134 [0.00667, 0.0196]
Median [min, max]	0.0115 [0.00711, 0.0188]	0.0137 [0.00230, 0.0966]	0.0134 [0.00230, 0.0966]
as.factor(missing_fi)			
0	4 (36.4%)	2 (6.1%)	6 (13.6%)
1	7 (63.6%)	16 (48.5%)	23 (52.3%)
Missing	0 (0%)	15 (45.5%)	15 (34.1%)
as.factor(fi4)			
FI > 4	11 (100%)	33 (100%)	44 (100%)

```
# Proportion of fracture as No. fracture events/No. participants at randomisation
## It's not possible to calculate rate of fractures (per 100 person-years) as no individual data are av
fi_sig$fx_rate = fi_sig$n_event/fi_sig$no_rand

quantile(fi_sig$fx_rate, c(.05, .1, .25, .5, .75, .9, .95))
```

(2.2) Q5. Rate of fractures

```
##          5%         10%         25%         50%         75%         90%         95%
## 0.01044568 0.01514781 0.02614219 0.04758668 0.08380682 0.12553062 0.17444717
```

Results

```
table1(~ n_event + fx_rate | sex_f*fx_f, data = fi_sig, render.continuous = c(. = "Mean (SD)", . = "Medi
```

```
## Warning in .table1.internal(x = x, labels = labels, groupspan = groupspan, :
## Table has 21 columns. Are you sure this is what you want?
```

	Both			
	Any	Osteoporotic	Non-Vertebrae	Vertebrae
	(N=4)	(N=1)	(N=2)	(N=4)
n_event				
Mean (SD)	93.0 (94.3)	NA	47.0 (14.1)	40.8 (5.44)
Median [Q1, Q3]	55.0 [33.3, 115]	147 [147, 147]	47.0 [42.0, 52.0]	40.0 [38.0, 42.8]
Median [min, max]	55.0 [31.0, 231]	147 [147, 147]	47.0 [37.0, 57.0]	40.0 [35.0, 48.0]
fx_rate				
Mean (SD)	0.0845 (0.0312)	NA	0.0840 (0.00247)	0.0692 (0.0117)
Median [Q1, Q3]	0.0837 [0.0582, 0.110]	0.0547 [0.0547, 0.0547]	0.0840 [0.0831, 0.0848]	0.0676 [0.0601, 0.0768]
Median [min, max]	0.0837 [0.0565, 0.114]	0.0547 [0.0547, 0.0547]	0.0840 [0.0822, 0.0857]	0.0676 [0.0586, 0.0830]