Graphical Displays for Subgroup Analysis in Clinical Trials

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Joint work with: Chiu YD[2], König F[1], Posch M[1] and Jaki T[2]

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September 25th, 2018

Motivation

In a clinical trial, enrolling patients that have rather diverse **baseline** characteristics for considerations, such as age, gender, race, disease severity or biomarker profiles may create a large number of subgroups.

Subgroup analyses are a routine part of clinical trials:

- to ensure no groups of patients for whom the treatment is harmful despite being effective in the majority of patients
- to identify groups of patients that may benefit from a treatment when the overall effect is small or zero.


EUROPEAN MEDICINES AGENCY
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23 January 2014
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

Motivation

Graphical approaches may help to understand and communicate the results to a wider audience

Objective:

- Assess existing approaches based on a set of sensible criteria.
- Develop an effective visualization approach for subgroup analysis.

Example: The prostate cancer dataset

We use a prostate carcinoma dataset from a randomized clinical trial (Byar and Green , 1980). The data has been analyzed several times in the literature before[1].

The dataset consists of 475 subjects randomized to a control group or diethylstilbestrol.

Six variables to consider:

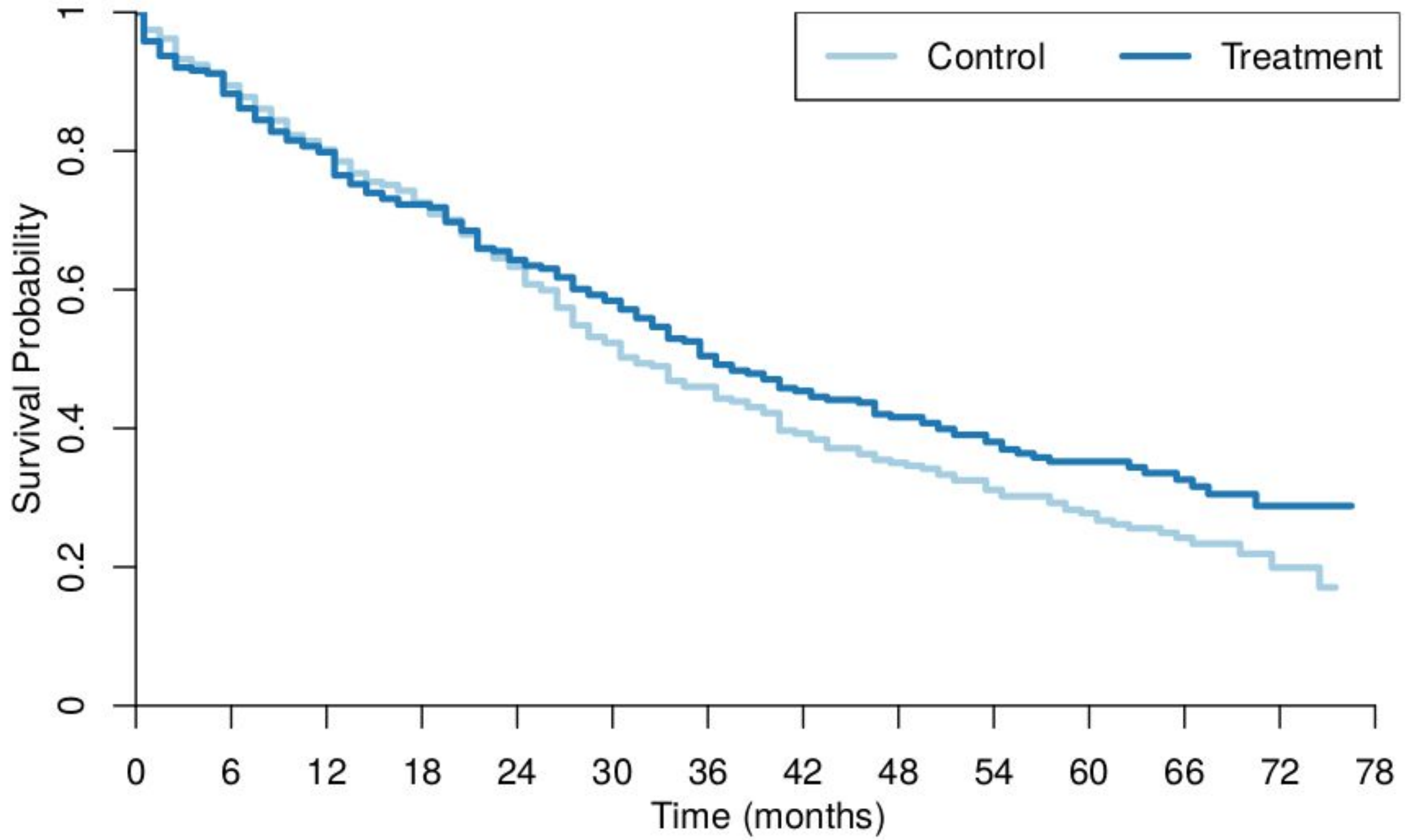
- existence of bone metastasis (yes/no),
- disease stage (3 or 4),
- performance rating (0: normal 1: limited activity),
- history of cardiovascular events (yes/no),
- age (years)
- weight (kg.)

Endpoint: Survival time

Treatment effect measure: Hazard ratios (HR)

[1] *https://onlinelibrary.wiley.com/doi/full/10.1002/bimj.201500147*

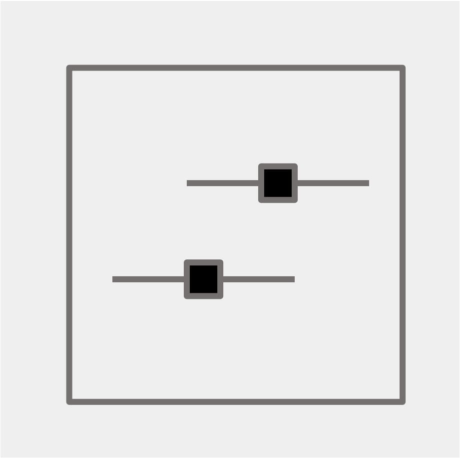
Example: The prostate cancer dataset



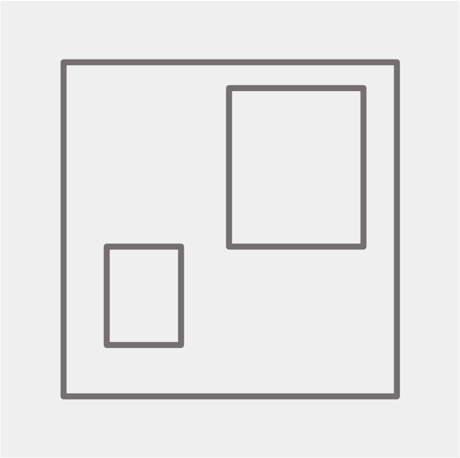
	coef	exp(coef)	se(coef)	Pr(>|z|)
Treatment	-0.1774	0.8375	0.1091	0.104

A Recipe for Graphics in Subgroup Analysis

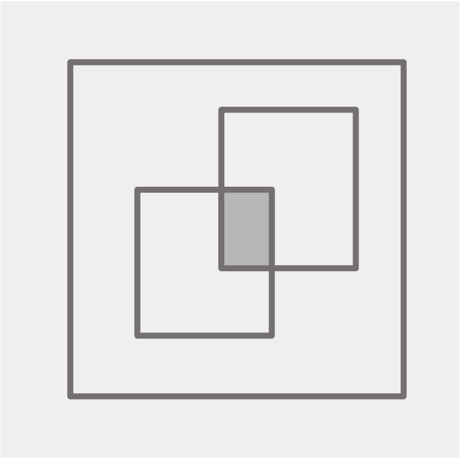
1 Show effect sizes AND confidence intervals for subgroups



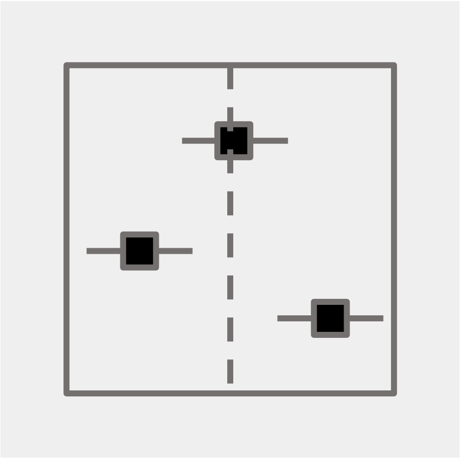
2 Show subgroup sample sizes



3 Show overlap information



4 Display Treatment effect in the overall population



(check for treatment effect heterogeneity)

5 Is it possible to show large number of subgroups?

Package 'SubgrPlots'

July 10, 2018

Type Package

Title Graphical Displays for Subgroup Analysis in Clinical Trials

Version 0.1.0

Description Provides functions for obtaining a variety of graphical displays that may be useful in the subgroup analysis setting. An example with a prostate cancer dataset is provided. The graphical techniques considered include level plots, mosaic plots, contour plots, bar charts, Venn diagrams, tree plots, forest plots, Galbraith plots, L'Abbé plots, the subpopulation treatment effect pattern plot, alluvial plots, circle plots and UpSet plots.

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Encoding UTF-8

LazyData true

Depends R (>= 2.10), graphics

Imports alluvial, circlize, colorspace, diagram, dplyr, ggplot2 (>= 2.1.1), geoR, grid, gridBase, gridExtra, methods, plyr, polyclip, scales, shape, sp, survRM2, survival, UpSetR, VennDiagram

Suggests rgeos

RoxygenNote 5.0.1

NeedsCompilation no

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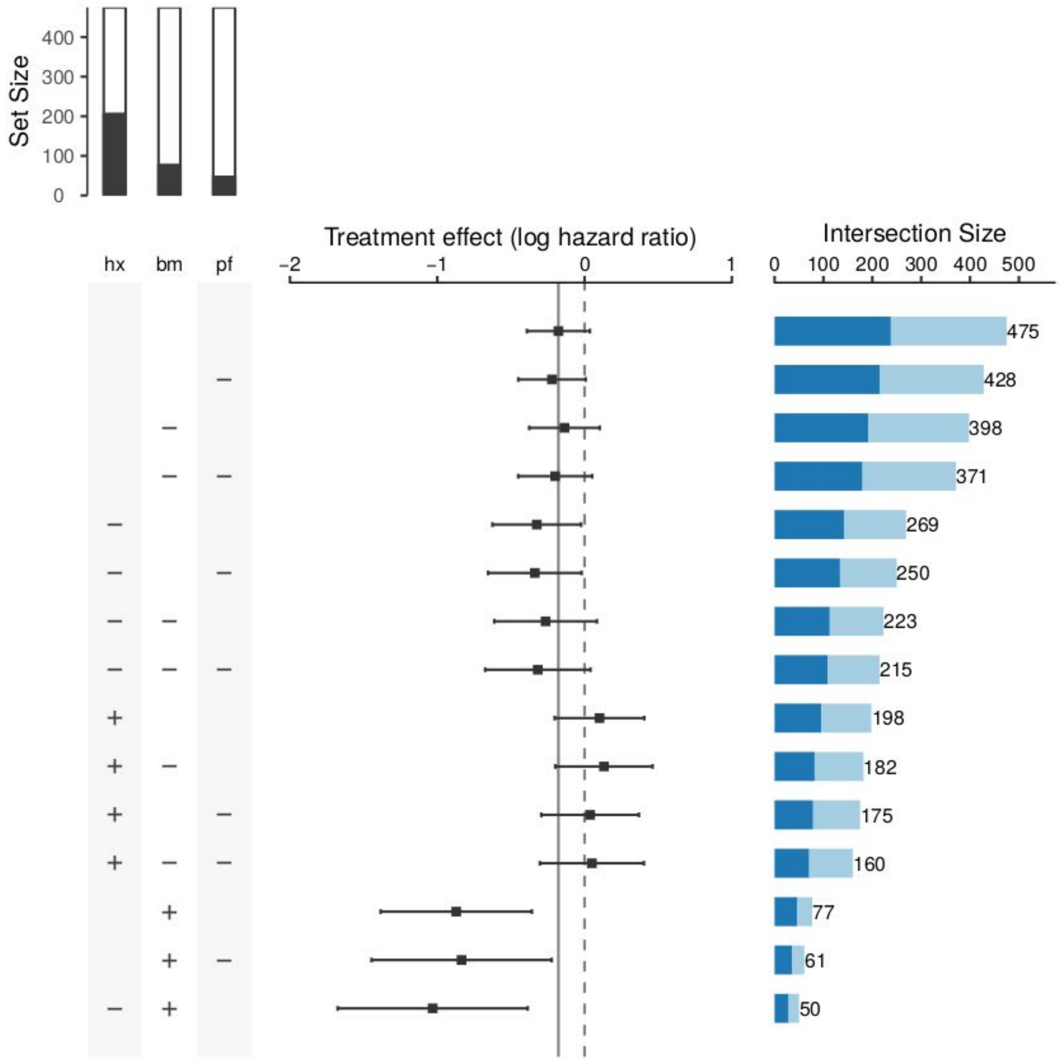
Nils Gehlenborg [ctb],
Michal Bojanowski [ctb],
Robin Edwards [ctb]

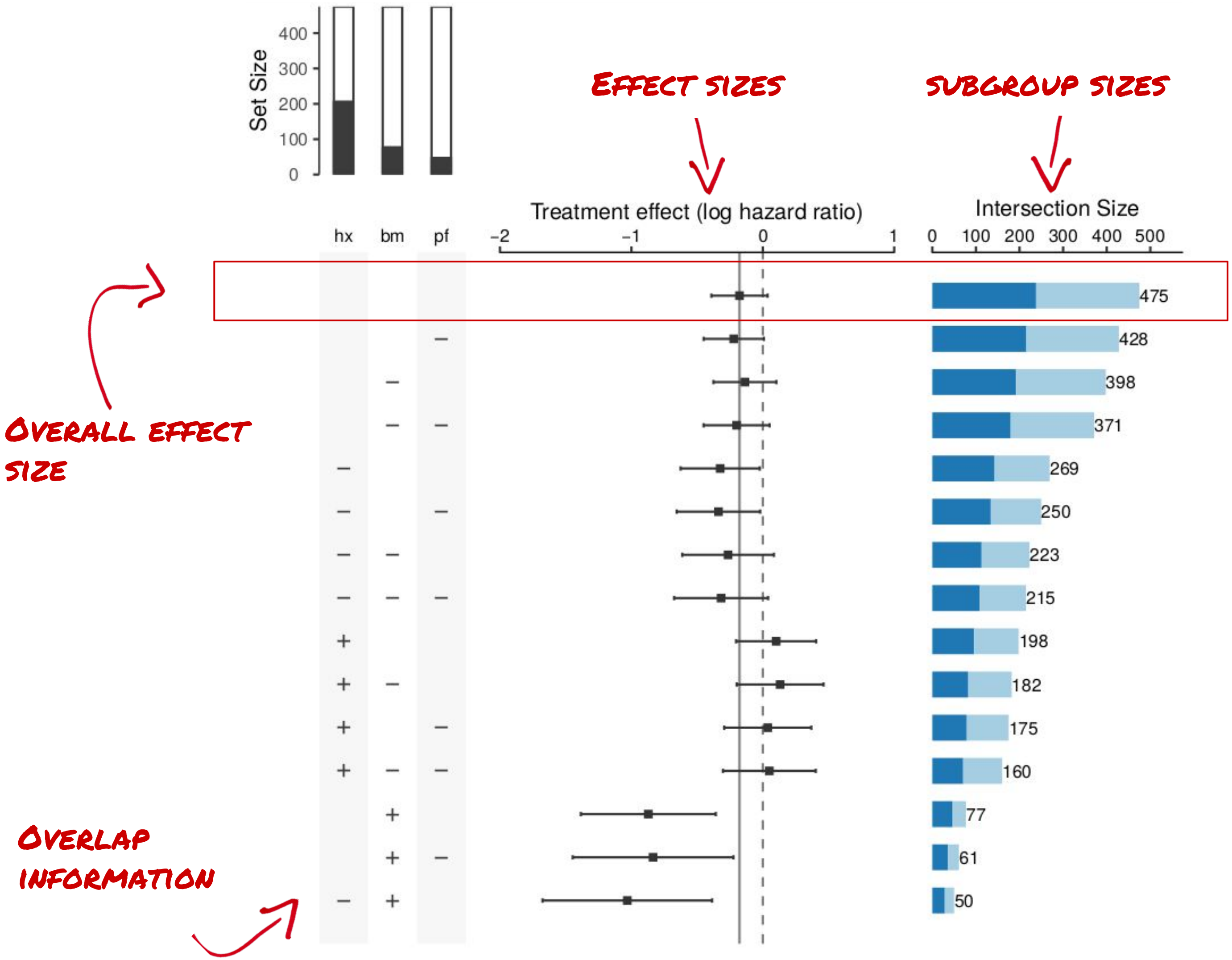
Maintainer Nicolas Ballarini <nicolas.ballarini@meduniwien.ac.at>

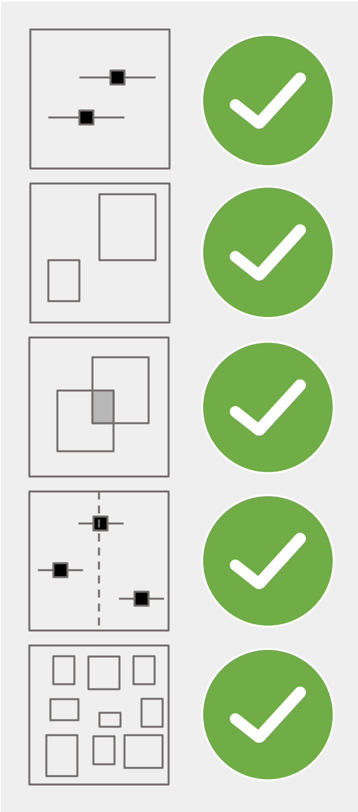
Repository CRAN

UpSet plot with treatment effects



UpSet plot with treatment effects



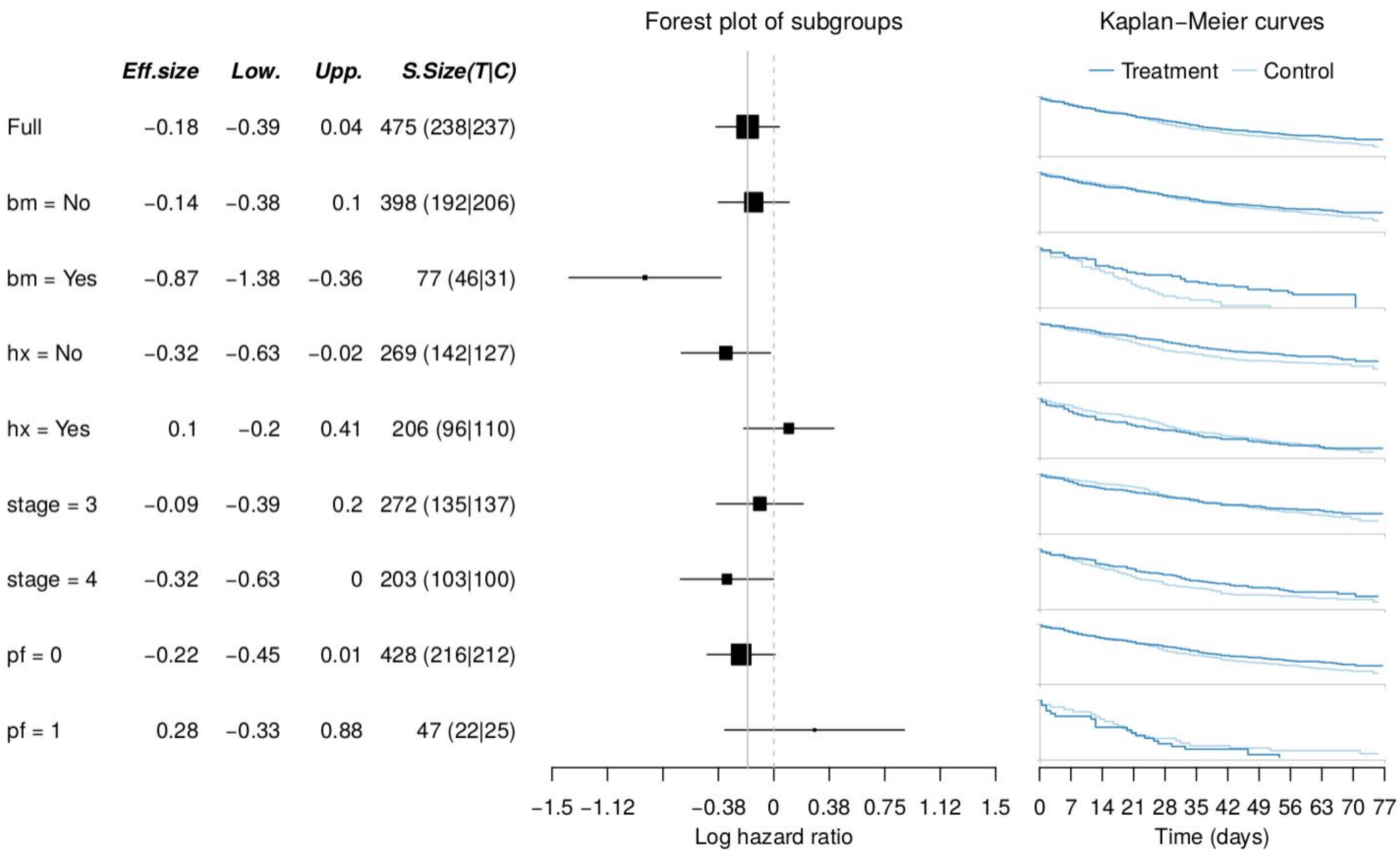


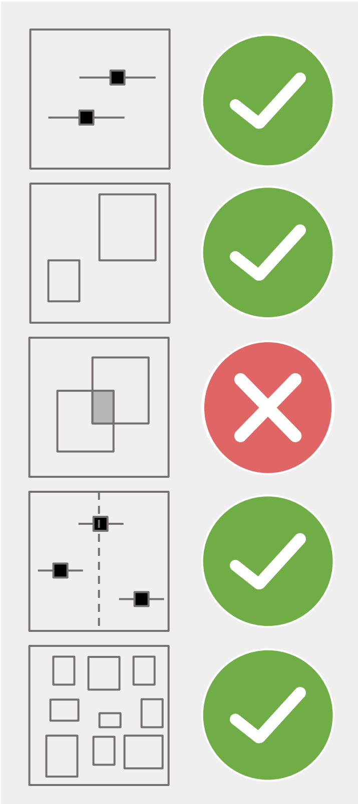
UpSet plot with treatment effects

SubgrPlots implementation

```
subgroupset(data = prca,
            outcome.type = "survival",
            effects.summary = c("survtime", "cens"),
            treatment.var = "trt",
            sets = c("bm", "pf", "hx"),
            order.by = "freq",
            empty.intersections = "on",
            mb.ratio = c(0.25, 0.50, 0.20),
            icon = "pm",
            transpose = TRUE)
```

Forest plot with treatment effects



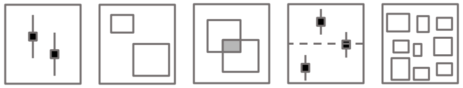


Forest plot with treatment effects

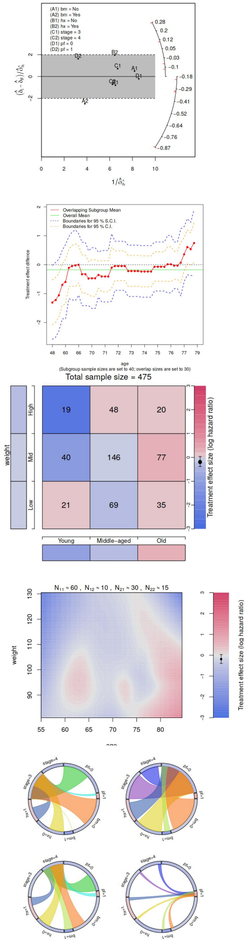
SubgrPlots implementation

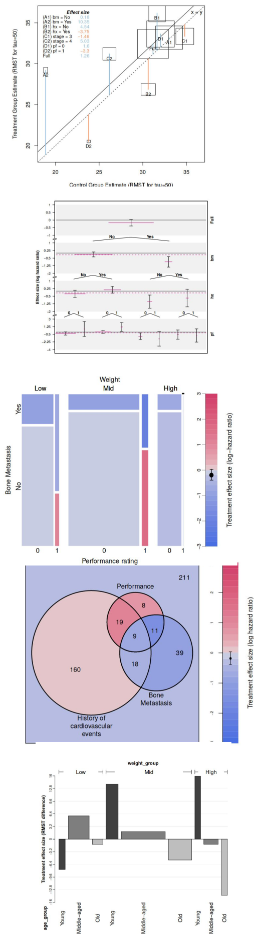
```
plot_forest(dat = prca,
            covari.sel = c(4, 5, 6, 7),
            trt.sel = 3,
            resp.sel = c(1, 2),
            outcome.type = "survival",
            time = 50,
            KM   = TRUE,
            show.km.axis = 2,
            n.brk    = 12,
            max.time = 77,
            widths   = c(1, 1, 0.6))
```

Other approaches

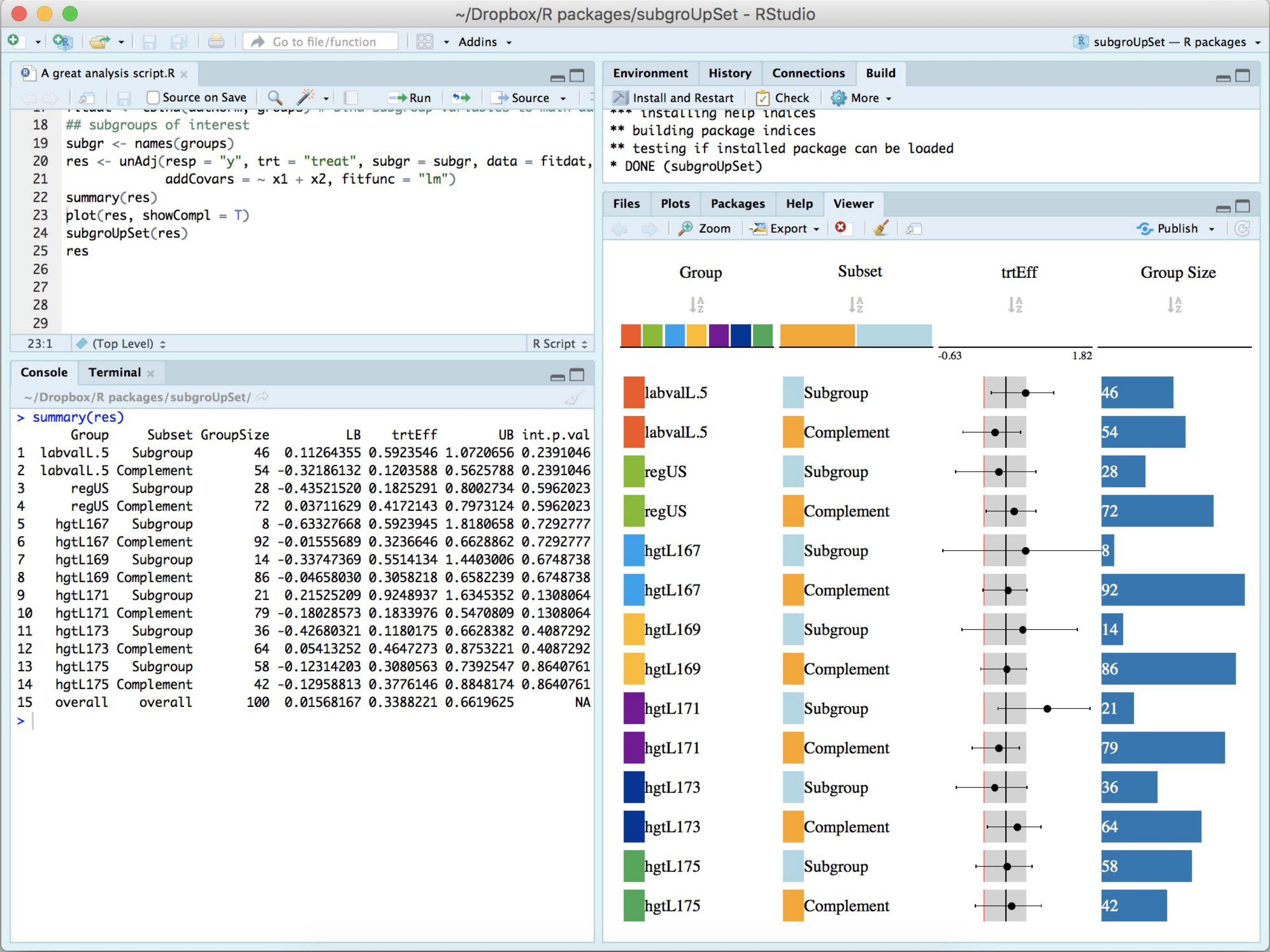


Forest plot	✓	✓	✗	✓	✓
Upset plot	✓	✓	✓	✓	✓
Galbraith plot	✓	✓	✗	✓	✓
L'Abbe plot	✓	✓	✗	✓	✓
STEPP	✓	✗	–	✓	✓
Tree plot	✓	✓	✓	✓	✓
Level plot	✓	–	✓	✗	✓
Mosaic plot	✓	✓	✓	✗	✓
Contour plot	✓	✗	✓	✗	✓
Venn diagram	✓	✓	✓	✗	✓
Circle plot	✓	✓	✓	✗	✓
Bar plot	✓	✓	✓	✗	✓





Interactive Plots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20 res <- unAdj(resp = "y", trt = "treat", subgr = subgr, data = fitdat,
21 addCovars = ~ x1 + x2, fitfunc = "lm")
22 summary(res)
23 plot(res, showCompl = T)
24 subgroUpSet(res)
25 res
23:1
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* DONE (subgroUpSet)
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Group Size
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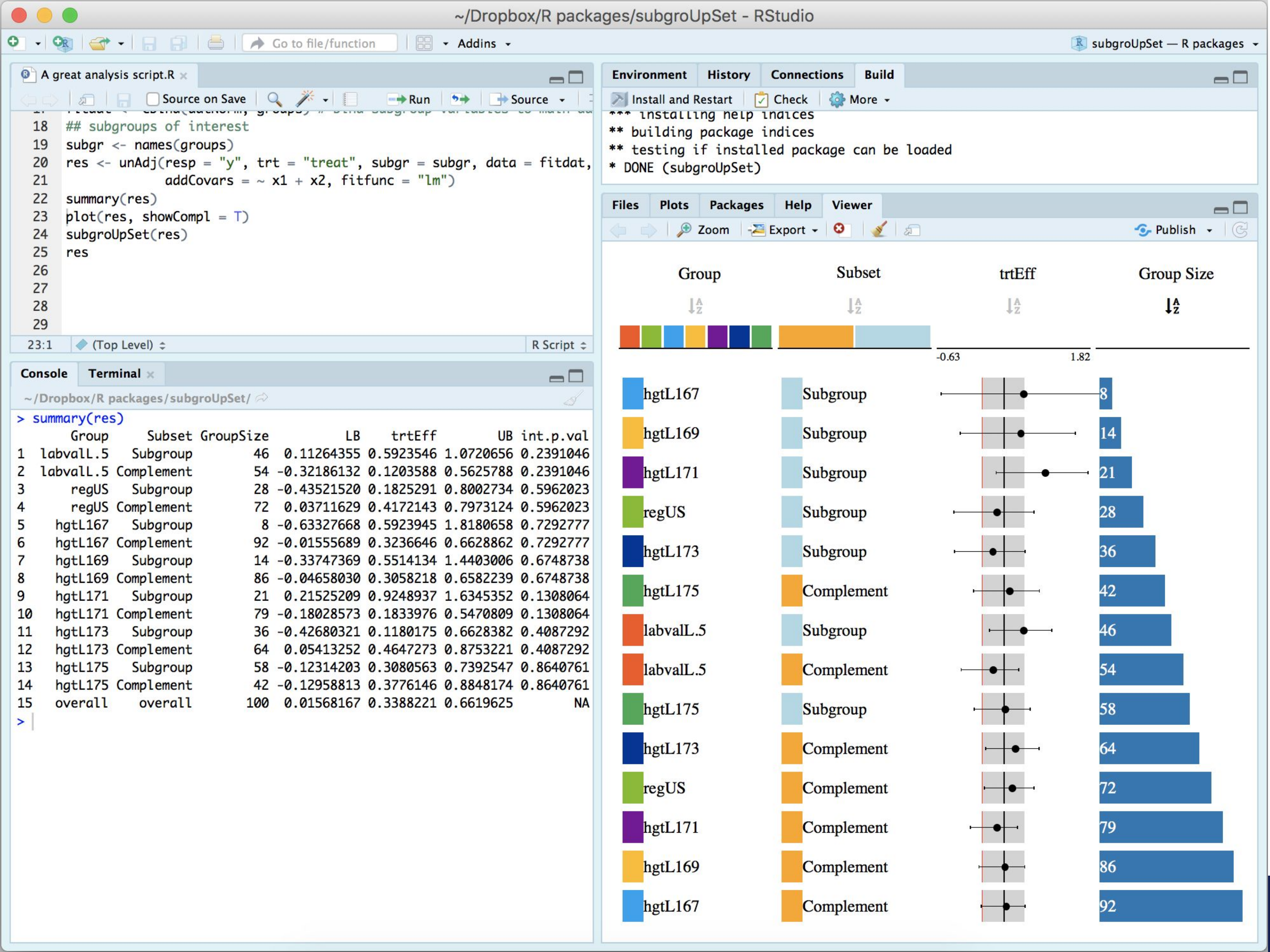
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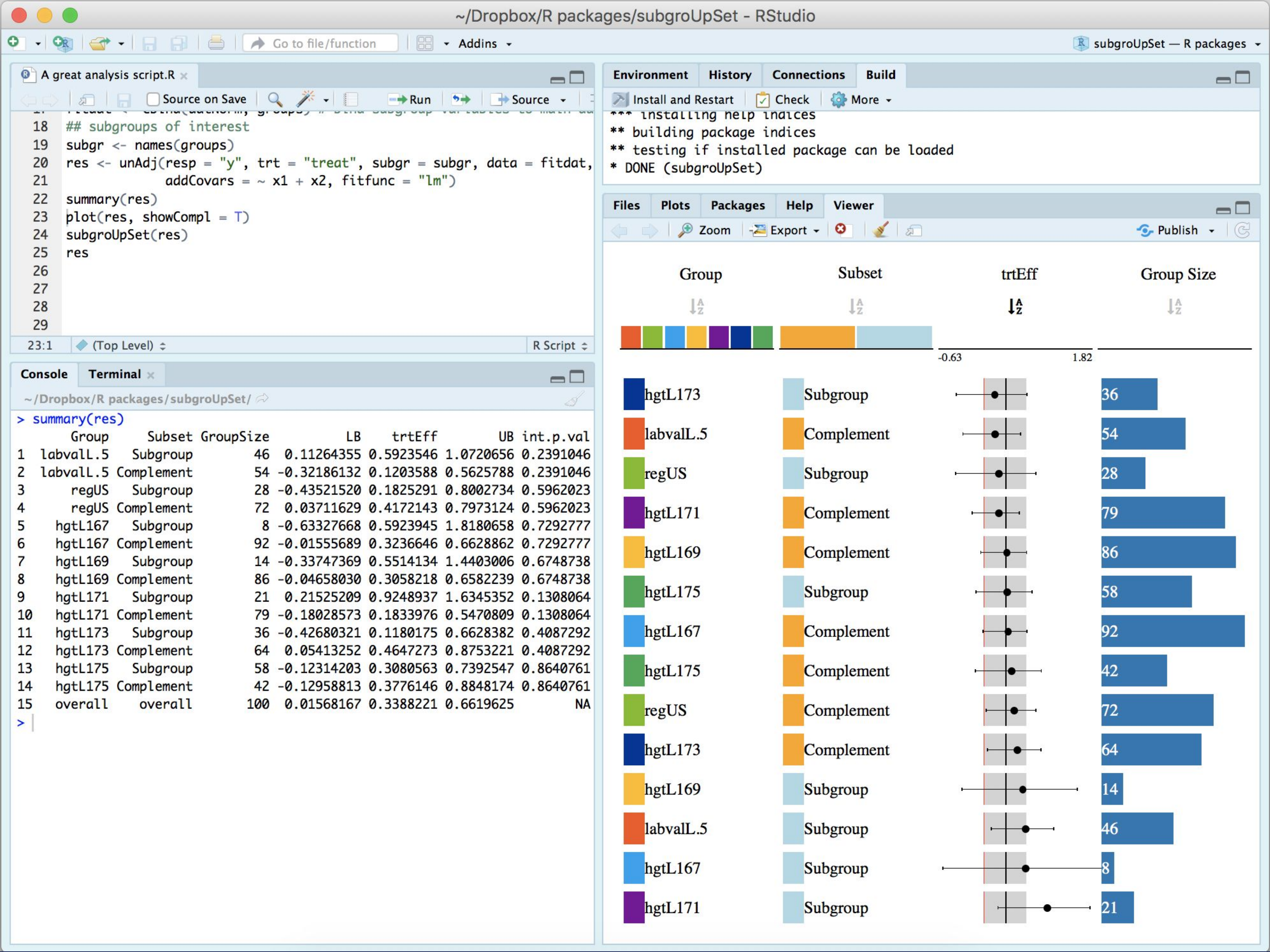
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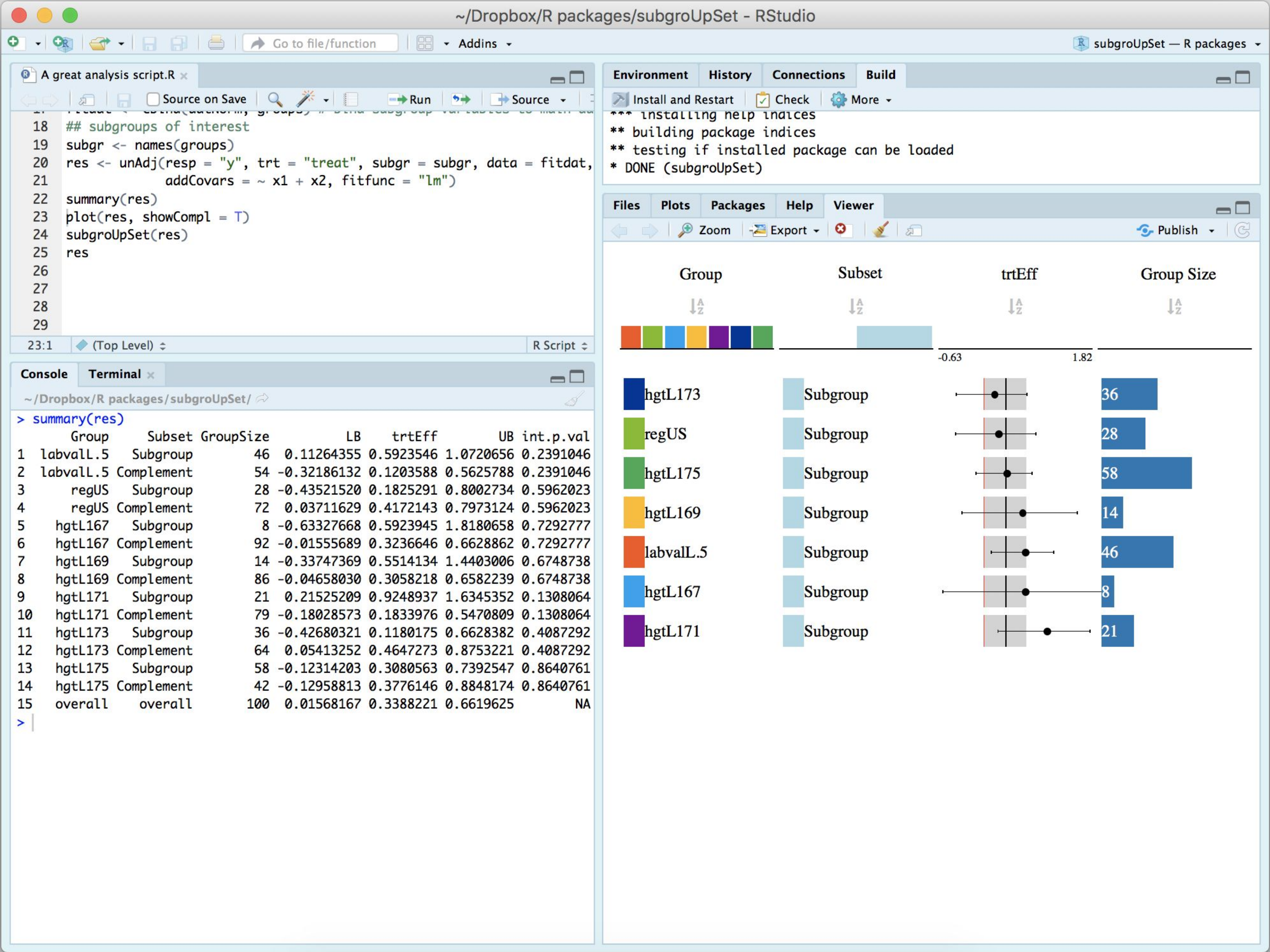
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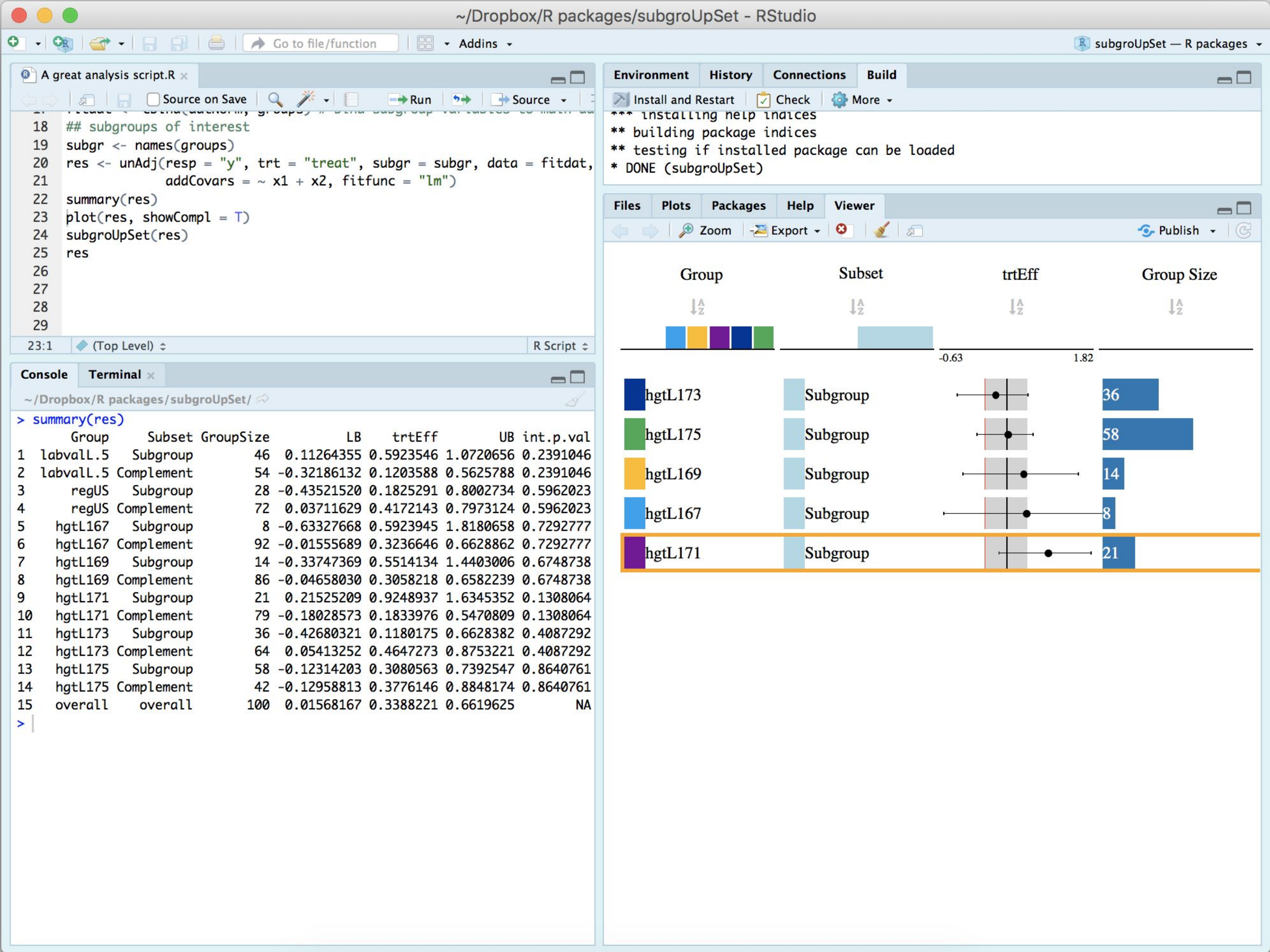
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hgtL175
Subgroup
58
hgtL169
Subgroup
14
hgtL167
Subgroup
8
hgtL171
Subgroup
21

Summary

Summary

- Many graphical approaches for subgroup analysis were assessed
- Modified UpSet plots and forest plots seem to be the most useful tools to check for treatment effect heterogeneity
- Other plots can complement the results

Summary

- Open software (R package) available

  https://cran.r-project.org/package=SubgrPlots

- A manuscript under peer review

Thank you for your attention!

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contact: nicolas.ballarini@meduniwien.ac.at

References

[1] Committee for Medicinal Products for Human Use et al. Guideline on the investigation of subgroups in confirmatory clinical trials. London: European Medicines Agency, 2014.

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