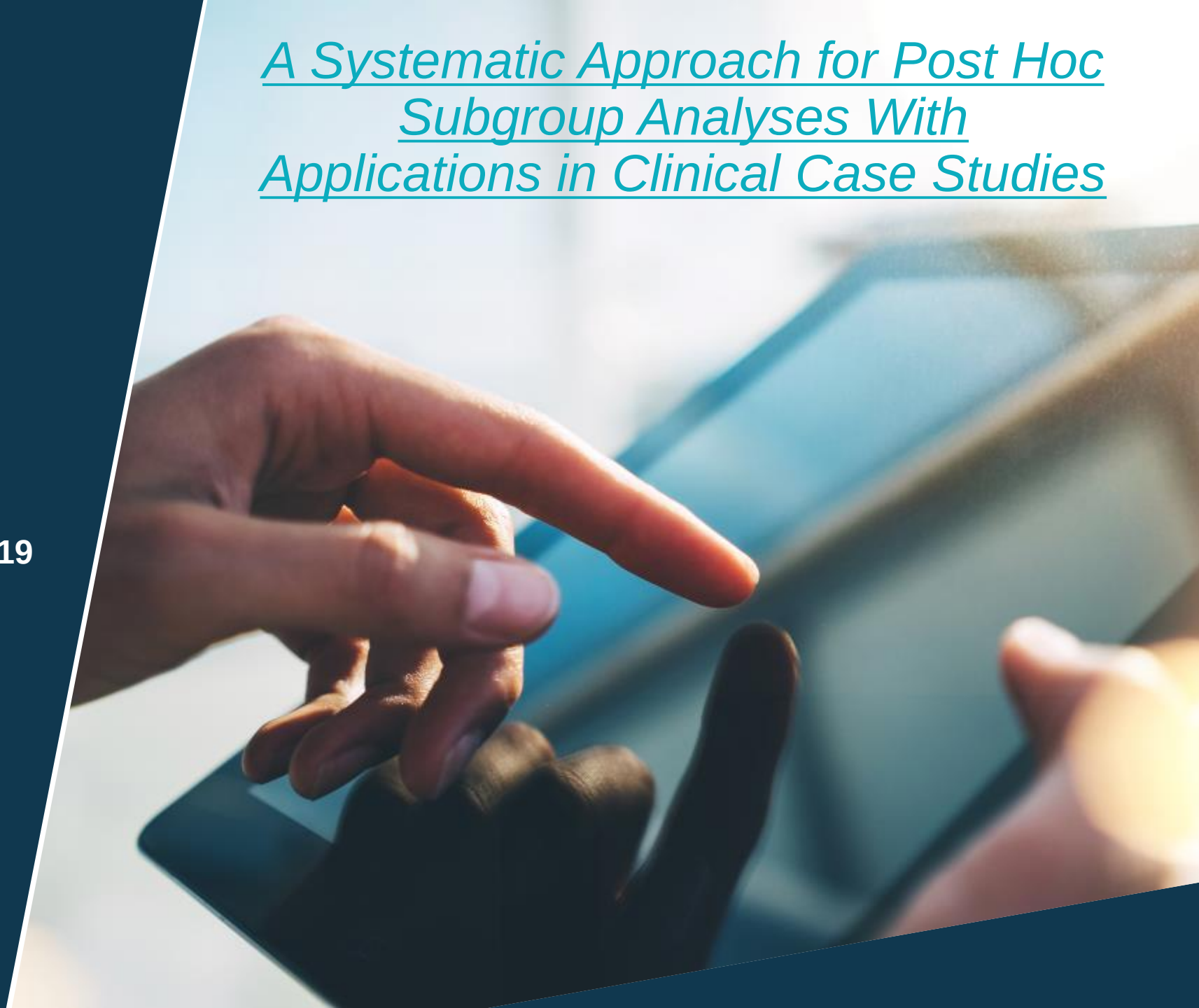
A Systematic Approach for Post Hoc Subgroup Analyses With Applications in Clinical Case Studies



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PSI / DIA webinar • October 2019

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The next 20 minutes

- The demand for subgroup analyses
- The ‘Subgroup Explorer’ (tool)
- The ‘Subgroup Screening’ (procedure)

Subgroup Analyses

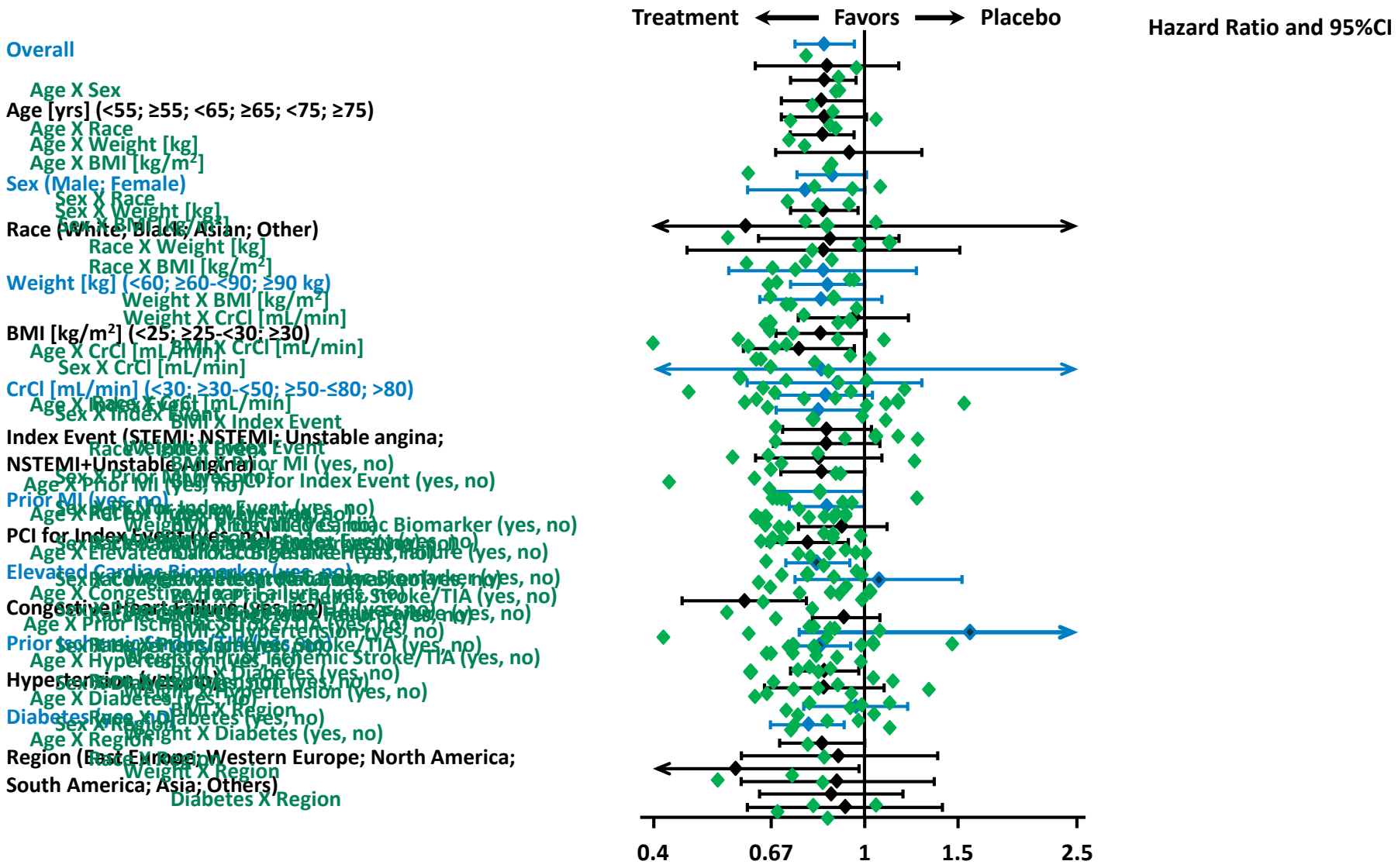
medically important -- regulatory requirement -- many stakeholders

Even ‘Important’ only Subgroups can be Overwhelming

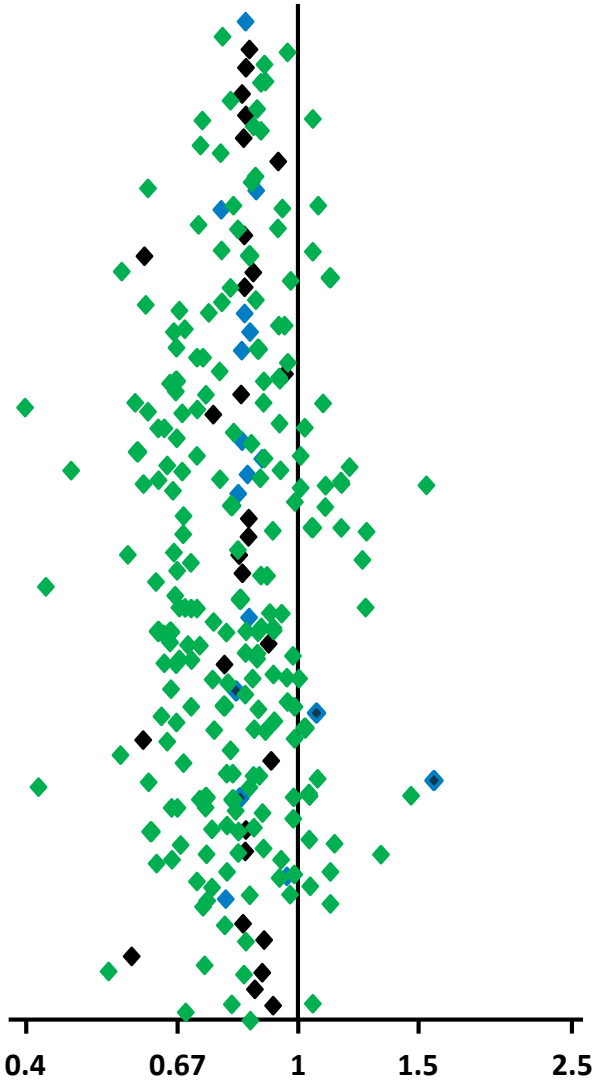
… factors used in **stratification randomisation** // factors with some **biological plausibility** or **external evidence where heterogeneous** response might be hypothesised // at least **demographic factors**, including **genomic factors**, related to the mechanism of action pharmacology // in addition, careful consideration should be given to other **factors that might plausibly be predictive for different response** to treatment **such as stage, severity or phenotype of disease**, use of **concomitant medications** and **possibly region**, country, or centre // truly exploratory analyses should be planned for the **spectrum of demographic, disease and clinical characteristics**, including those factors a particular factor there is good argumentation why homogeneity of response to treatment is plausible // analysis of the **complement subset** should also be displayed // review of **other exploratory analyses** // exploration of interactions and effects in subgroups **on different scales** // analyses of continuous variables using **different cut-offs** should routinely be performed … *

* EMA 2019, Guideline on the investigation of subgroups in confirmatory clinical trials

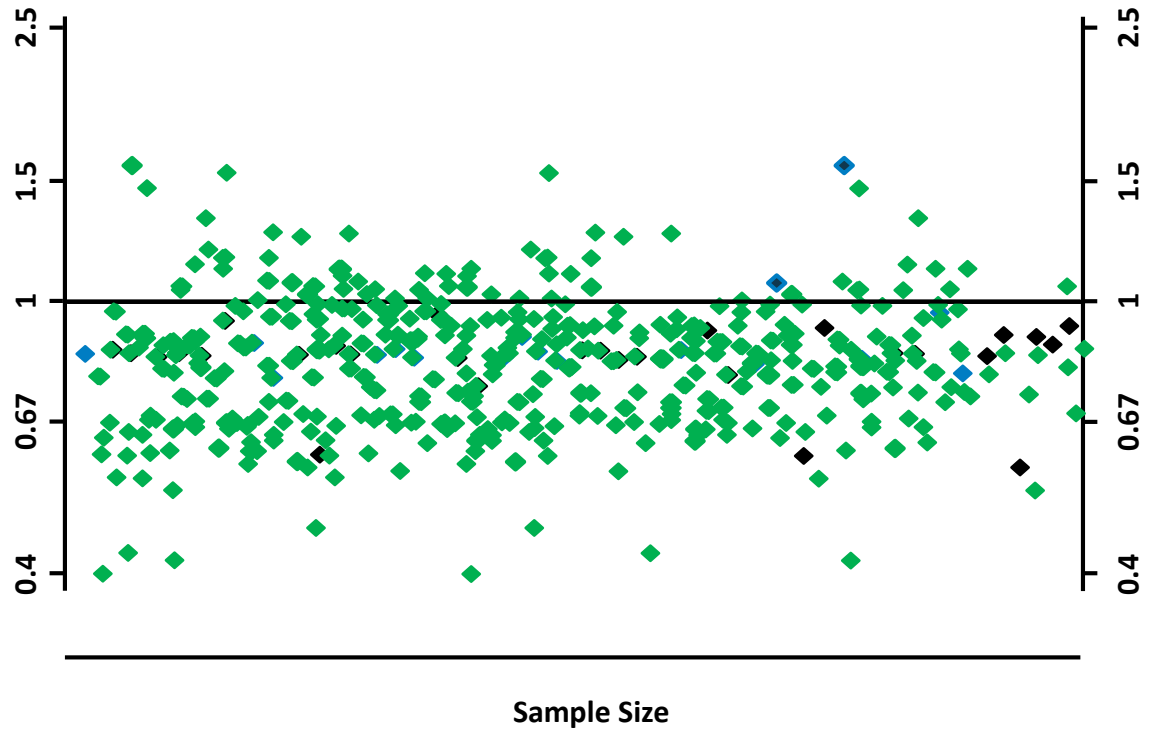
From Forest Plots to In-depth Subgroup Screening



From Forest Plots to In-depth Subgroup Screening



From Forest Plots to In-depth Subgroup Screening

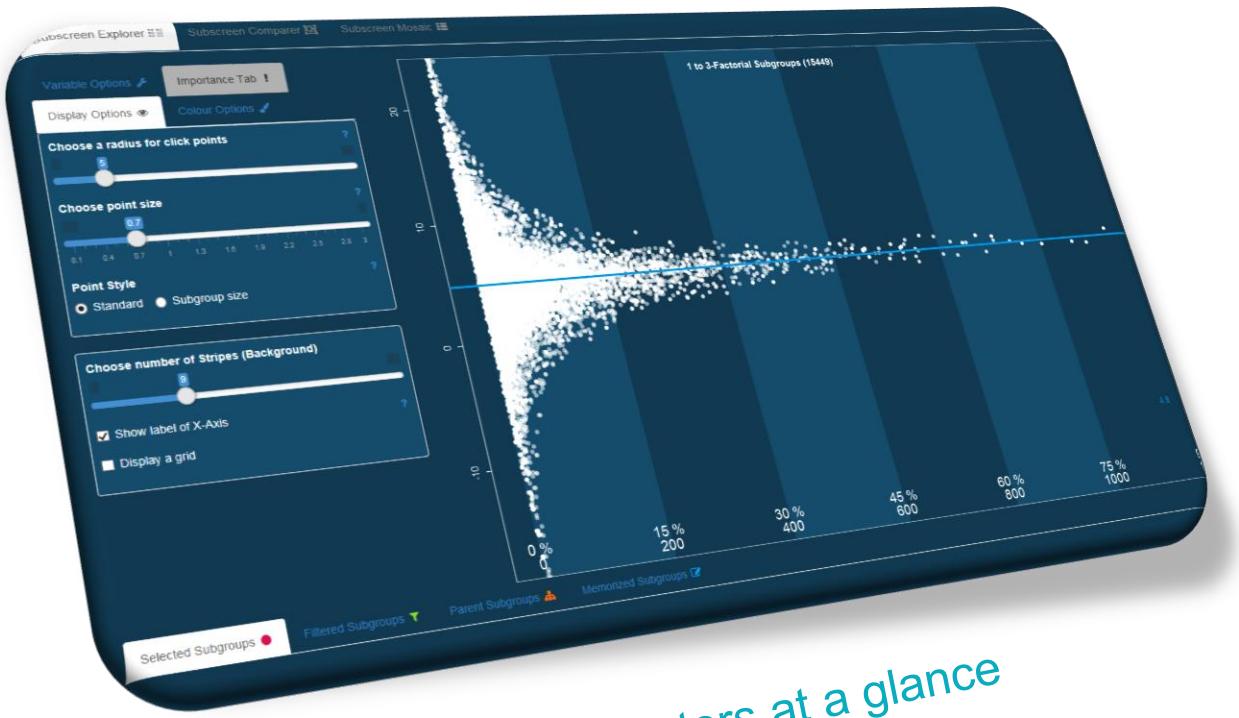


Subgroup Explorer

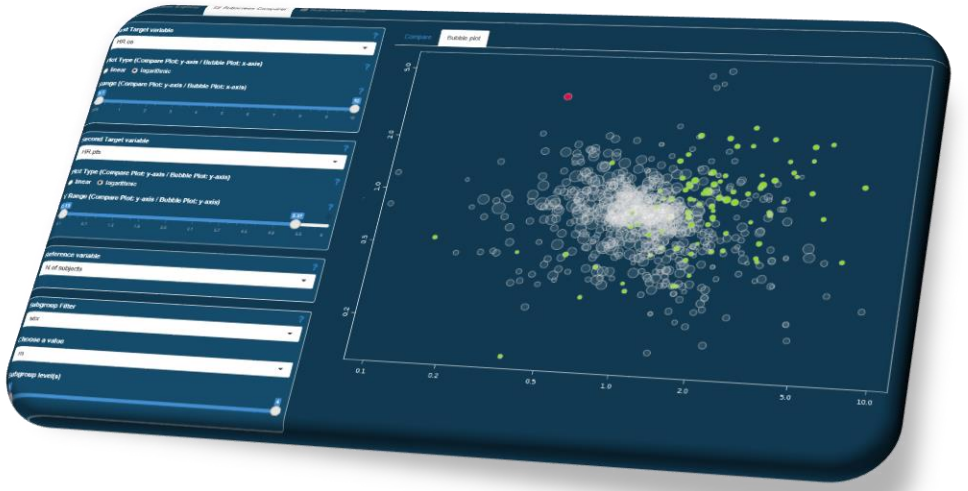
and the Exploration Hub

https://cran.r-project.org/web/packages/subscreen/

explore factor level combinations



exploration of all factors at a glance

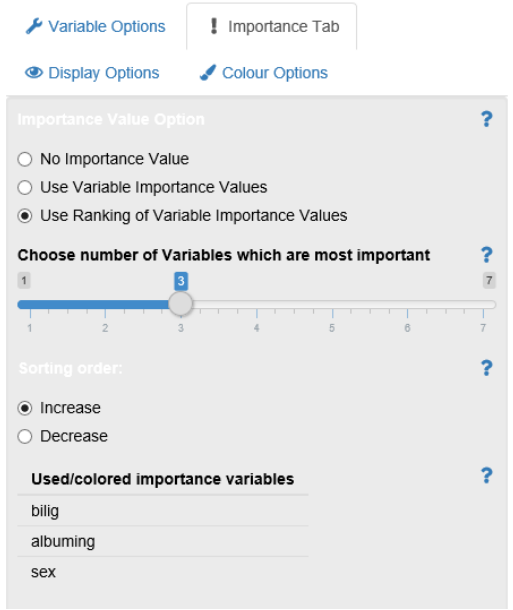


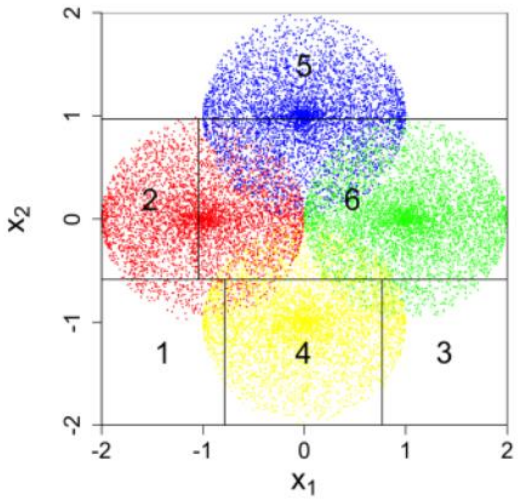
compare subgroups for two endpoints

Feature: Importance Tab

Machine learning based prioritization of analyzed factors

information about variable importance based on a random forest algorithm





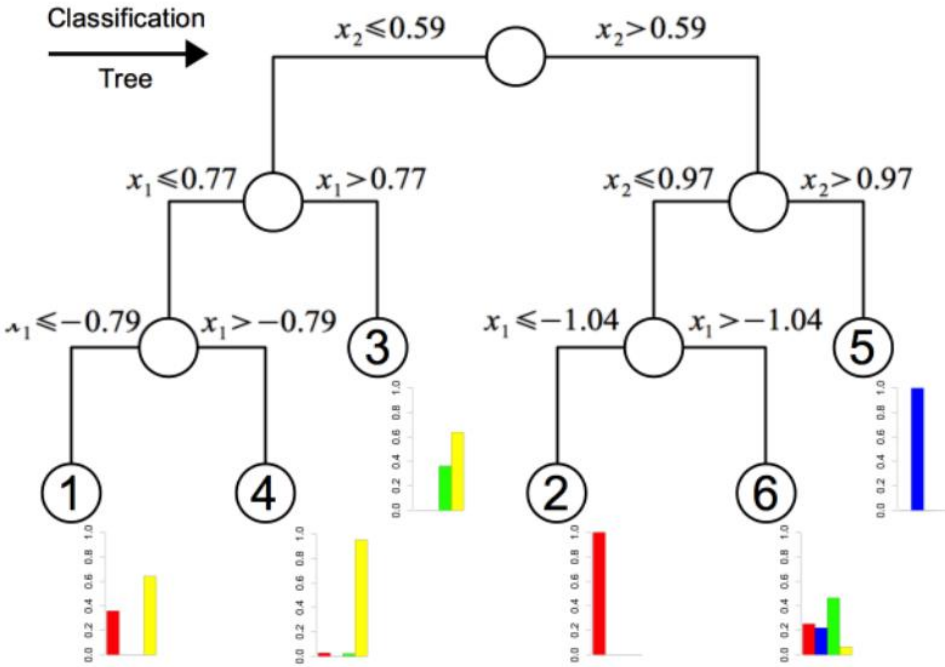


Illustration taken from Random Forest R-package
https://kogalur.github.io/randomForestSRC/theory.html

Subscreen Explorer | Subscreen Comparer | Subscreen Mosaic

Variable Options | Importance Tab !

Display Options | Colour Options

Target variable

Mean_changeTS_w52

Reference variable

Number.of.Subjects

Subgroup Filter

no selection

Subgroup level(s)

1 — 3

Plot Type

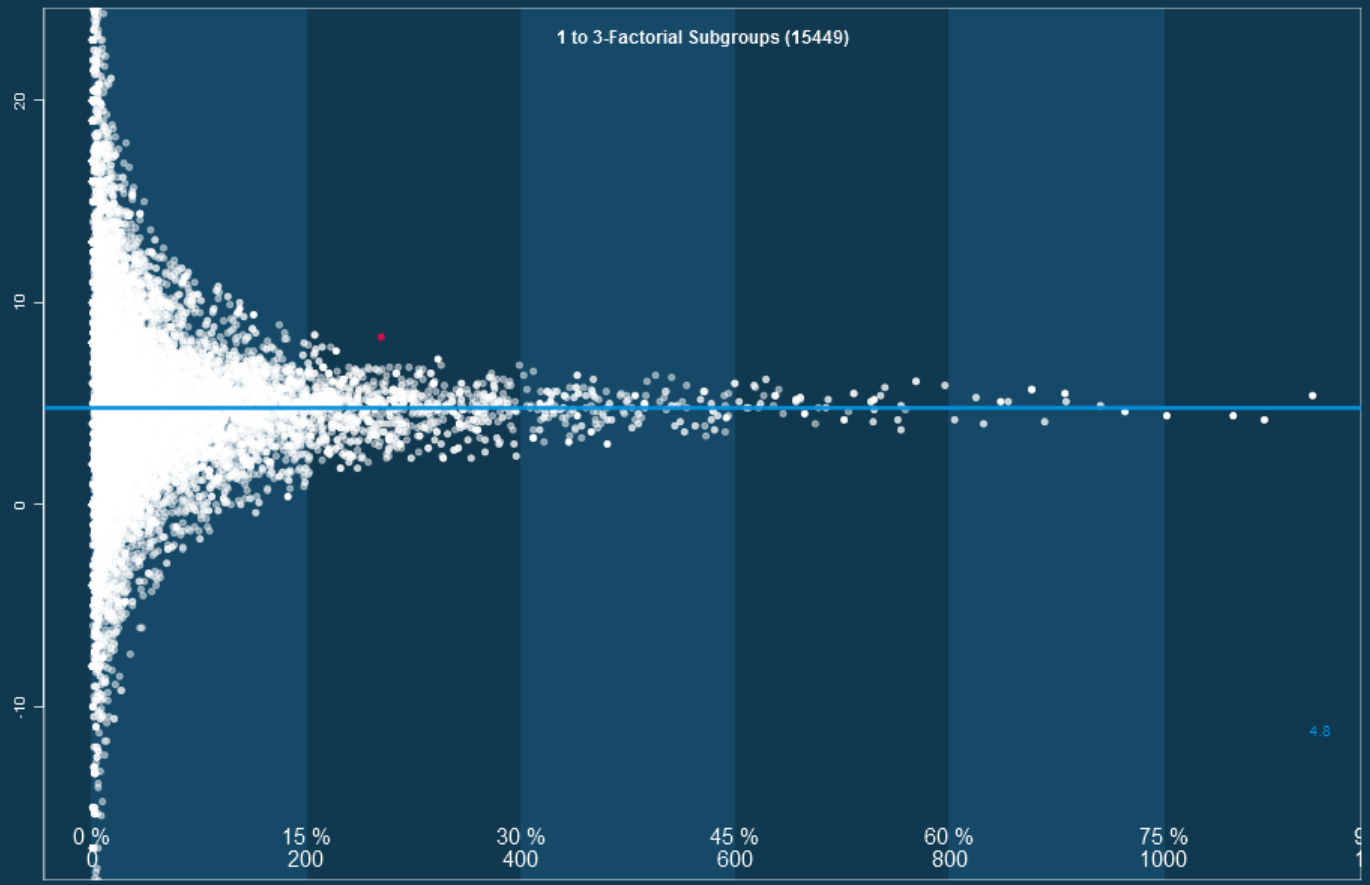
linear | logarithmic

Y Range

-17 — 23

-40 -31 -22 -13 -4 5 14 23 32 41 50

Help text:



Selected Subgroups | Filtered Subgroups | Parent Subgroups | Memorized Subgroups

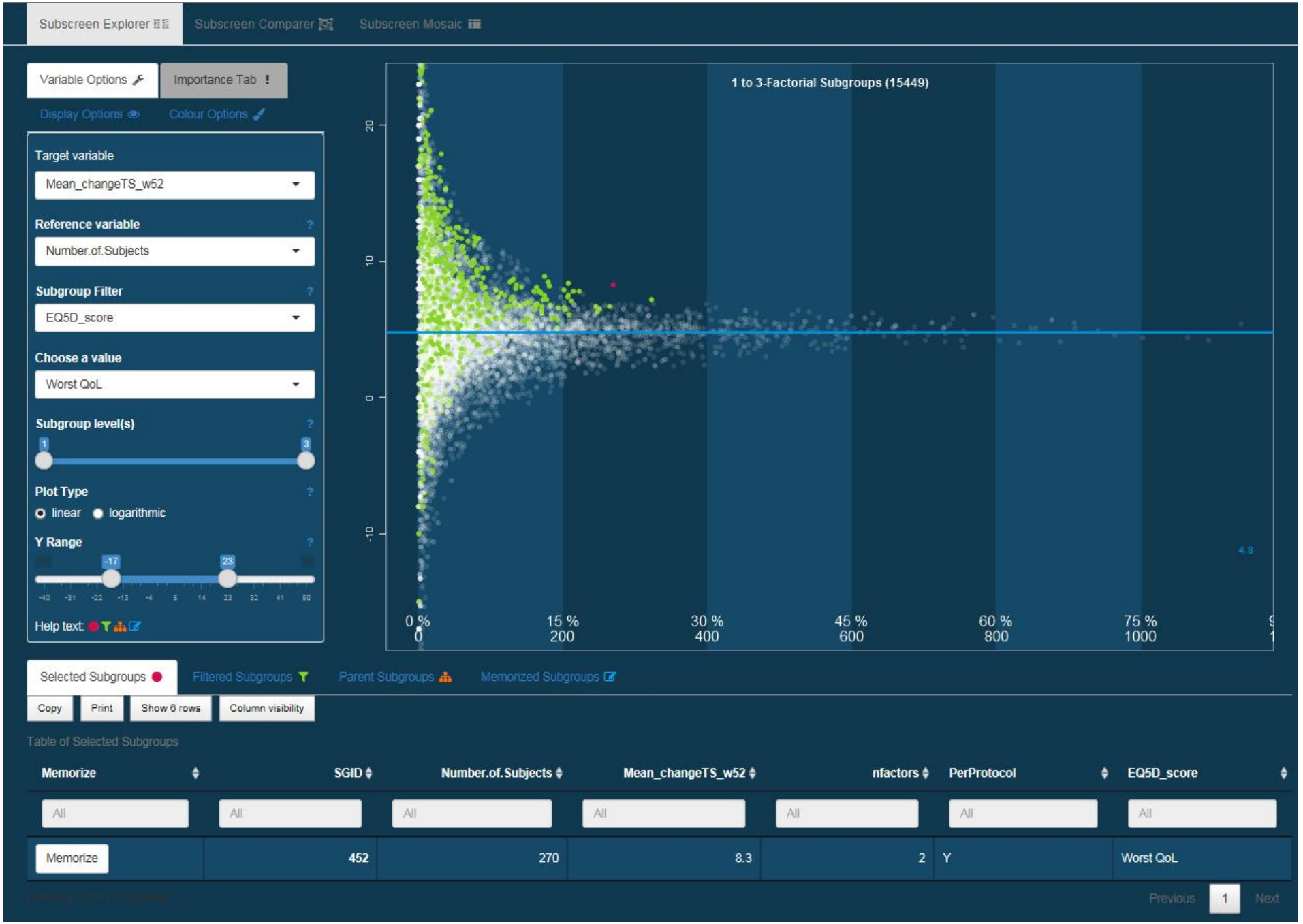
Copy | Print | Show 6 rows | Column visibility

Table of Selected Subgroups

Memorize	SGID	Number.of.Subjects	Mean_changeTS_w52	nfactors	PerProtocol	EQ5D_score
All	All	All	All	All	All	All
Memorize	452	270	8.3	2	Y	Worst QoL

Showing 1 to 1 of 1 entries

Previous 1 Next


Subscreen Explorer
Subscreen Comparer
Subscreen Mosaic
Variable Options
Importance Tab
Display Options
Colour Options
Target variable
Mean_changeTS_w52
Reference variable
Number.of.Subjects
Subgroup Filter
EQ5D_score
Choose a value
Worst QoL
Subgroup level(s)
1
3
Plot Type
linear
logarithmic
Y Range
-17
23
Help text:
1 to 3-Factorial Subgroups (15449)
20
10
0
-10
0 %
0
15 %
200
30 %
400
45 %
600
60 %
800
75 %
1000
4.8
Selected Subgroups
Filtered Subgroups
Parent Subgroups
Memorized Subgroups
Copy
Print
Show 6 rows
Column visibility
Table of Selected Subgroups
Memorize
SGID
Number.of.Subjects
Mean_changeTS_w52
nfactors
PerProtocol
EQ5D_score
All
Memorize
452
270
8.3
2
Y
Worst QoL
Previous
1
Next

Subscreen Explorer | Subscreen Comparer | Subscreen Mosaic

Variable Options | Importance Tab !

Display Options | Colour Options

Target variable

Mean_changeTS_w52

Reference variable

Number.of.Subjects

Subgroup Filter

EQ5D_score

Choose a value

Best QoL

Subgroup level(s)

1 2 3

Plot Type

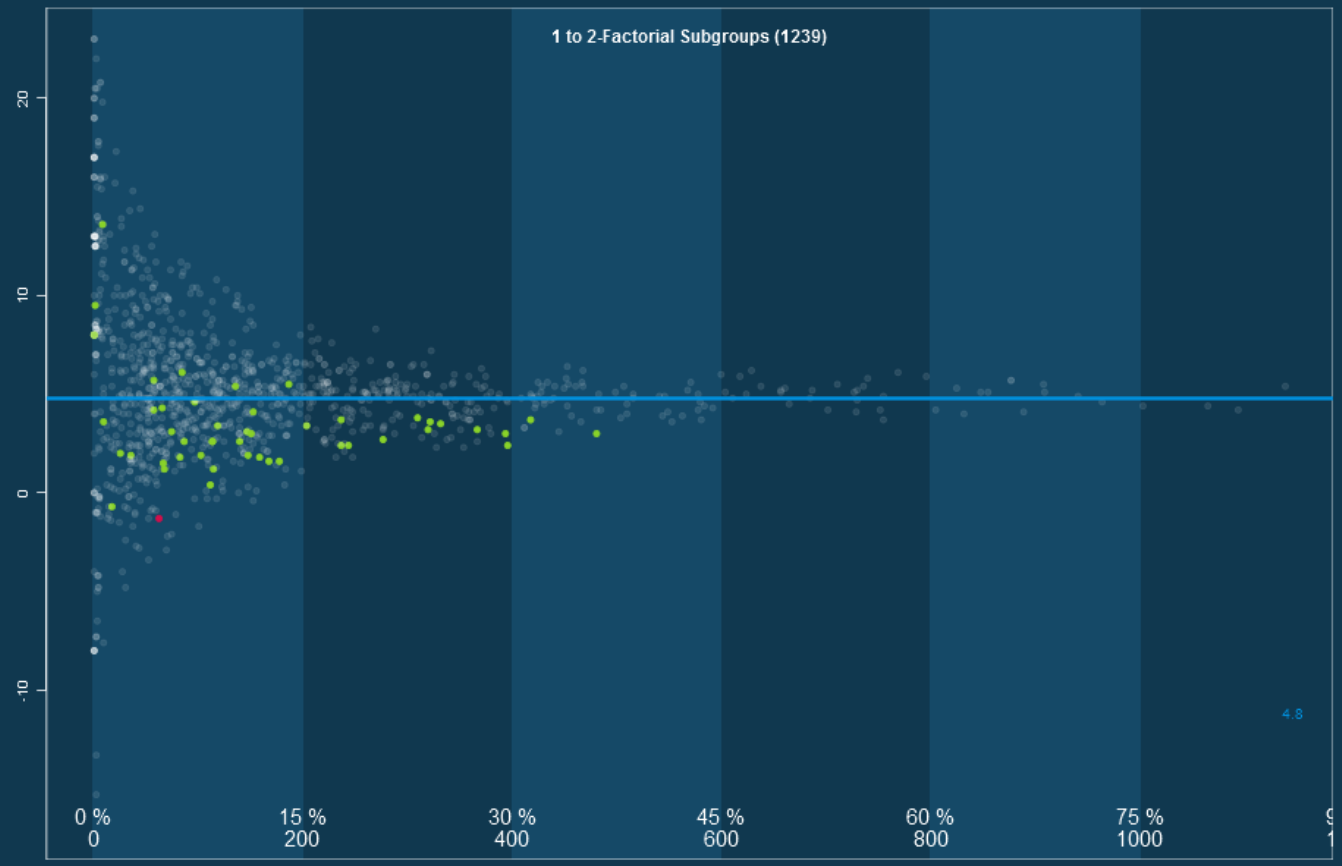
linear logarithmic

Y Range

-17 23

-40 -31 -22 -13 -4 5 14 23 32 41 50

Help text:



Selected Subgroups | Filtered Subgroups | Parent Subgroups | Memorized Subgroups

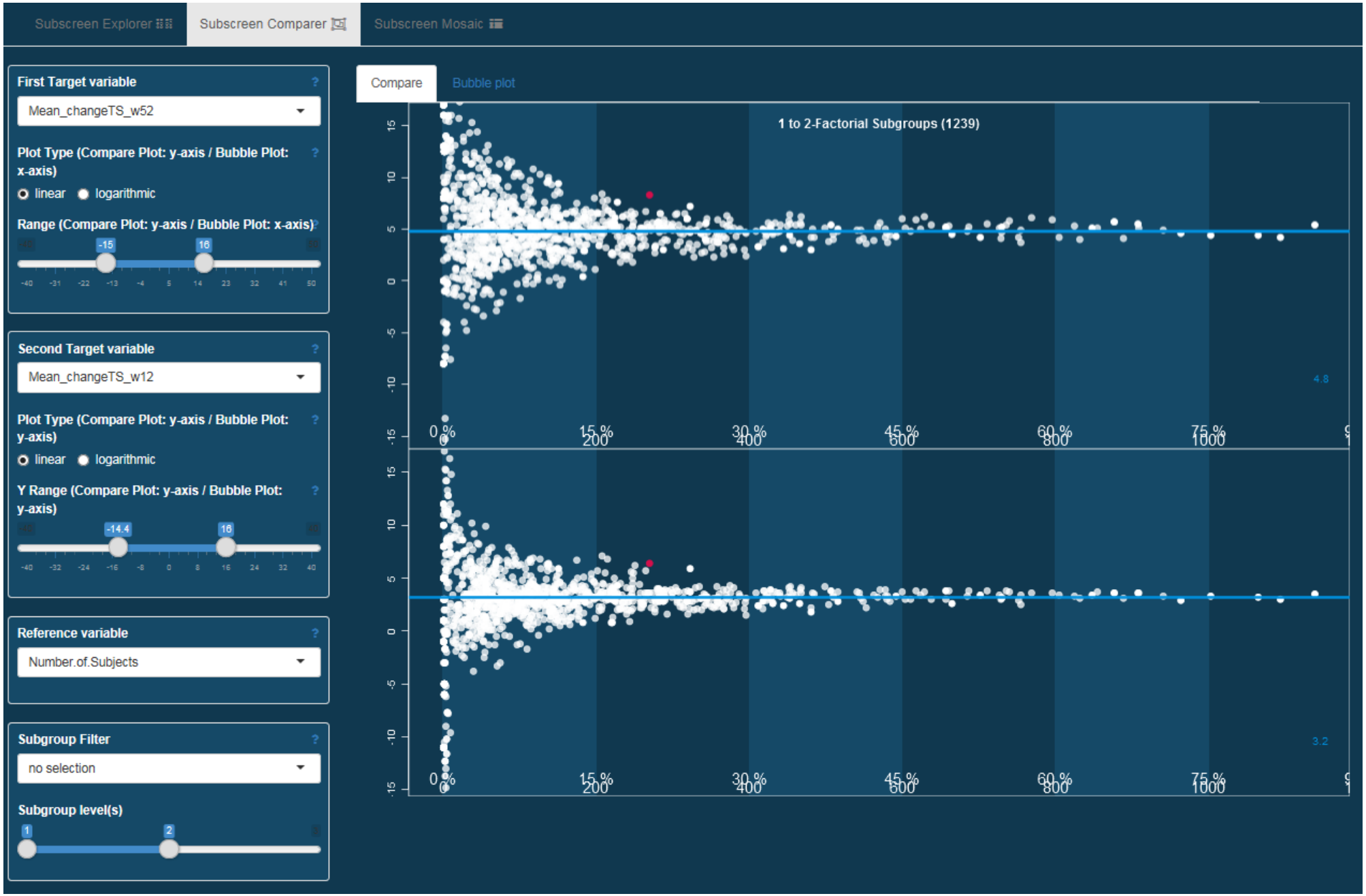
Copy | Print | Show 6 rows | Column visibility

Table of Selected Subgroups

Memorize	SGID	Number.of.Subjects	Mean_changeTS_w52	nfactors	PerProtocol	EQ5D_score
All	All	All	All	All	All	All
Memorize	445	63	-1.3	2	N	Best QoL

Showing 1 to 1 of 1 entries

Previous 1 Next


Subscreen Explorer
Subscreen Comparer
Subscreen Mosaic
First Target variable
Mean_changeTS_w52
Plot Type (Compare Plot: y-axis / Bubble Plot: x-axis)
linear
logarithmic
Range (Compare Plot: y-axis / Bubble Plot: x-axis)
-15
16
Second Target variable
Mean_changeTS_w12
Plot Type (Compare Plot: y-axis / Bubble Plot: y-axis)
linear
logarithmic
Y Range (Compare Plot: y-axis / Bubble Plot: y-axis)
-14.4
16
Reference variable
Number.of.Subjects
Subgroup Filter
no selection
Subgroup level(s)
1
2
Compare
Bubble plot
1 to 2-Factorial Subgroups (1239)
4.8
3.2
0 %
15 %
30 %
45 %
60 %
75 %

Subscreen Explorer | Subscreen Comparer | Subscreen Mosaic

First Target variable

Mean_changeTS_w52

Plot Type (Compare Plot: y-axis / Bubble Plot: x-axis)

linear logarithmic

Range (Compare Plot: y-axis / Bubble Plot: x-axis)

-15 16

-40 -31 -22 -13 -4 5 14 23 32 41 50

Second Target variable

Mean_changeTS_w12

Plot Type (Compare Plot: y-axis / Bubble Plot: y-axis)

linear logarithmic

Y Range (Compare Plot: y-axis / Bubble Plot: y-axis)

-14.4 16

-40 -32 -24 -16 -8 0 8 16 24 32 40

Reference variable

Number.of.Subjects

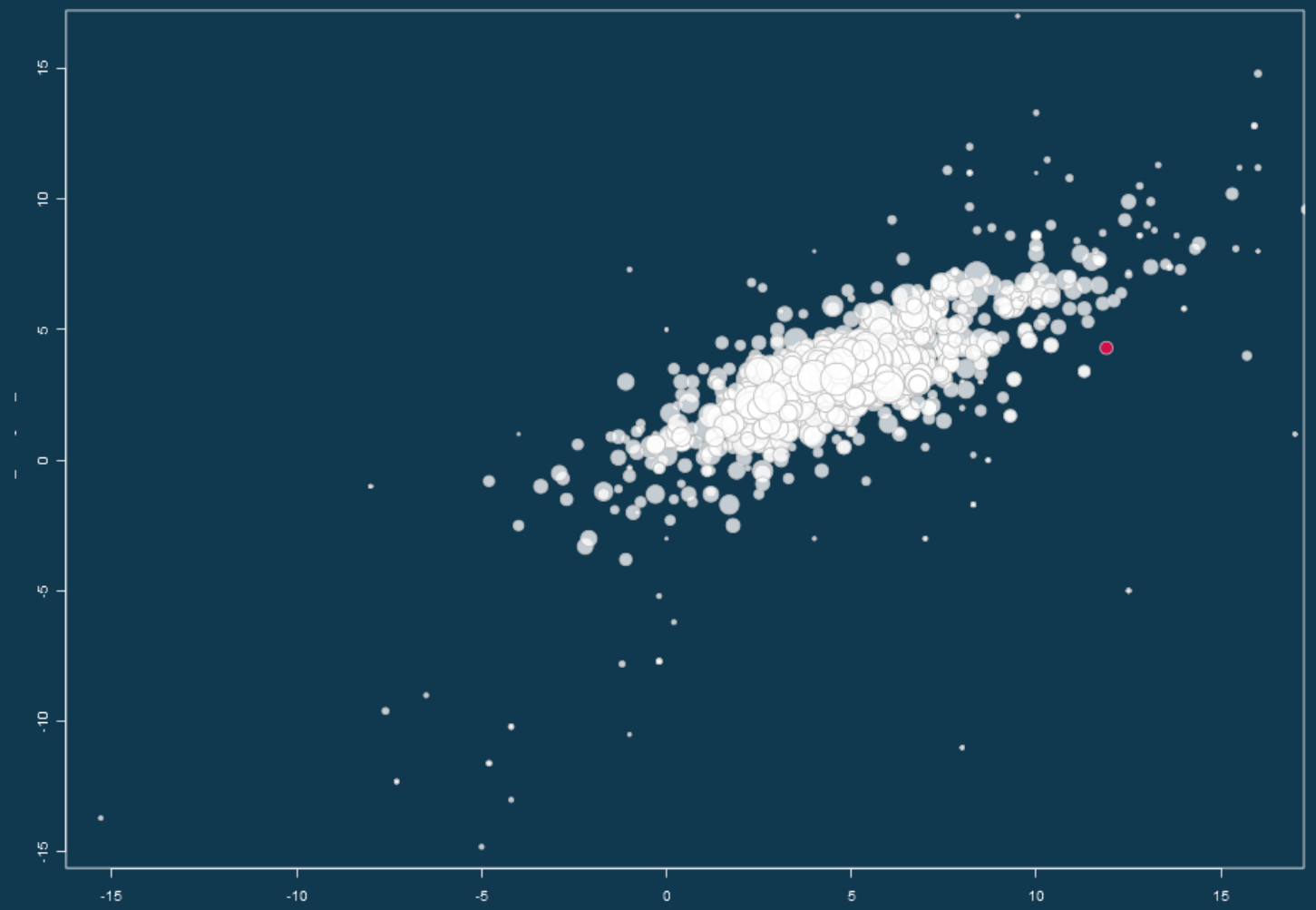
Subgroup Filter

no selection

Subgroup level(s)

1 2 3

Compare | Bubble plot



Subscreen Explorer | Subscreen Comparer | Subscreen Mosaic

First subgroup variable (x)

EQ5D_score

Second subgroup variable (y)

Region

Third subgroup variable (y2)

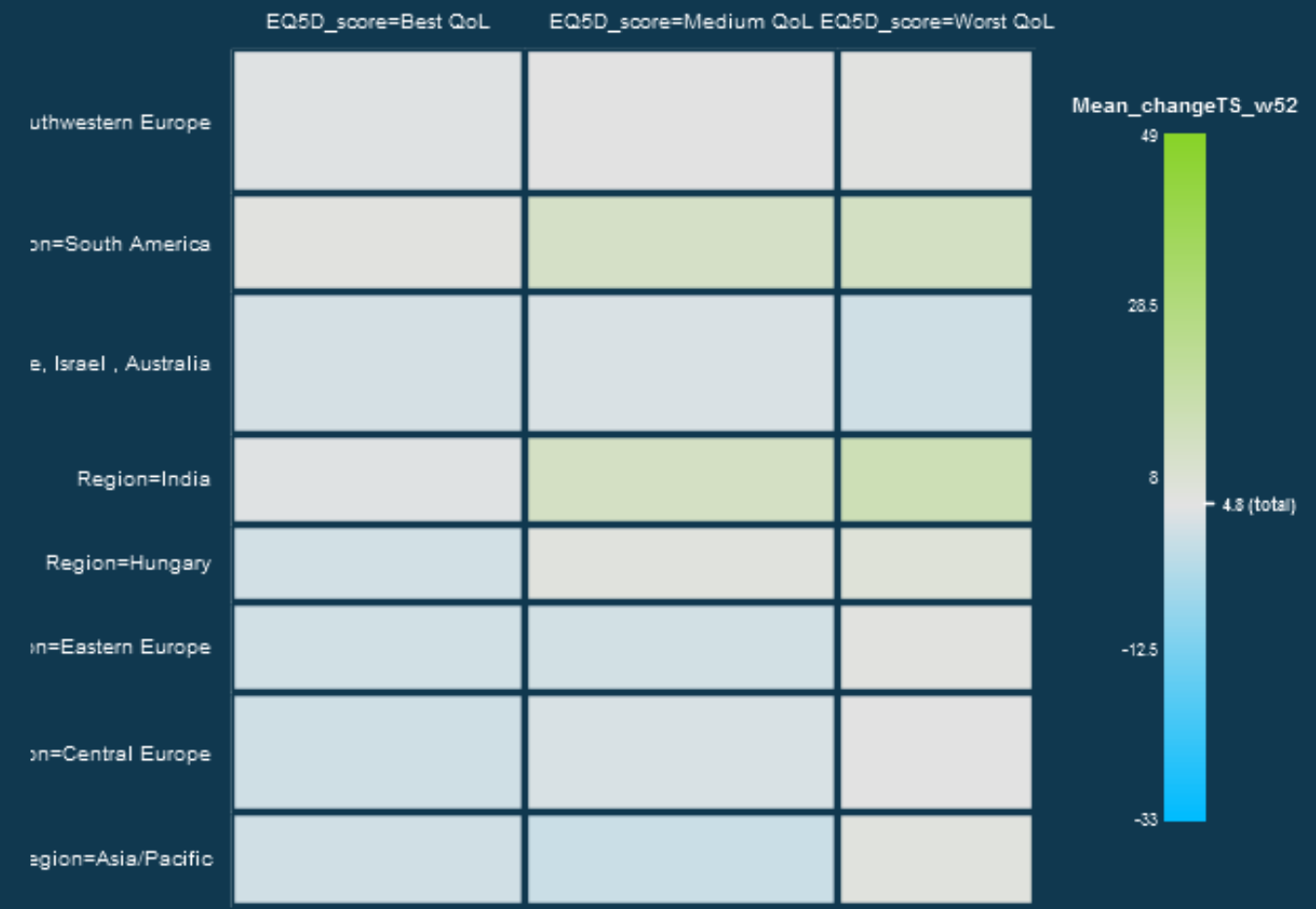
no selection

Reference variable (color)

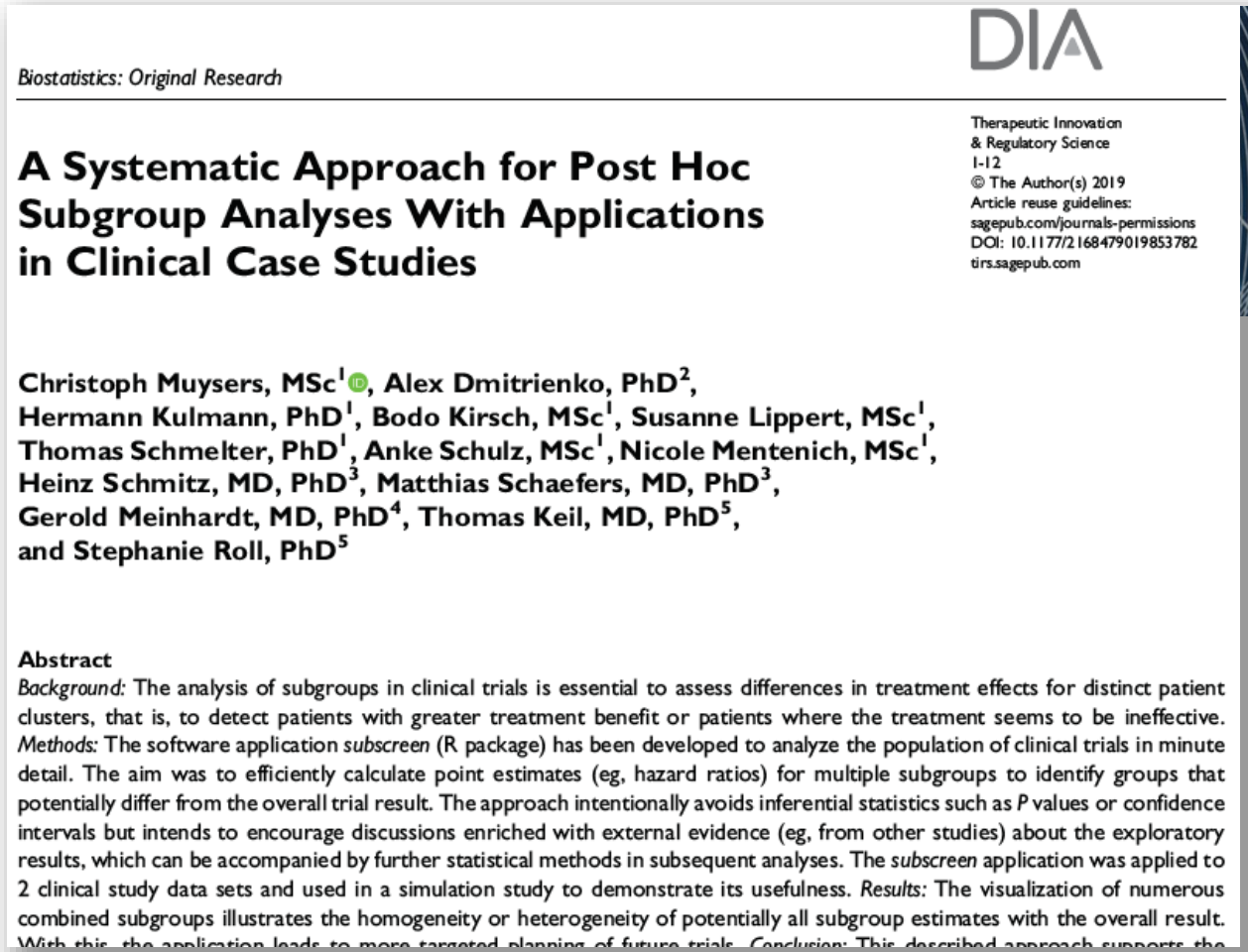
Mean_changeTS_w52

Plot Type

linear | logarithmic



More information in the article



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1-12

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A Systematic Approach for Post Hoc Subgroup Analyses With Applications in Clinical Case Studies

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Abstract

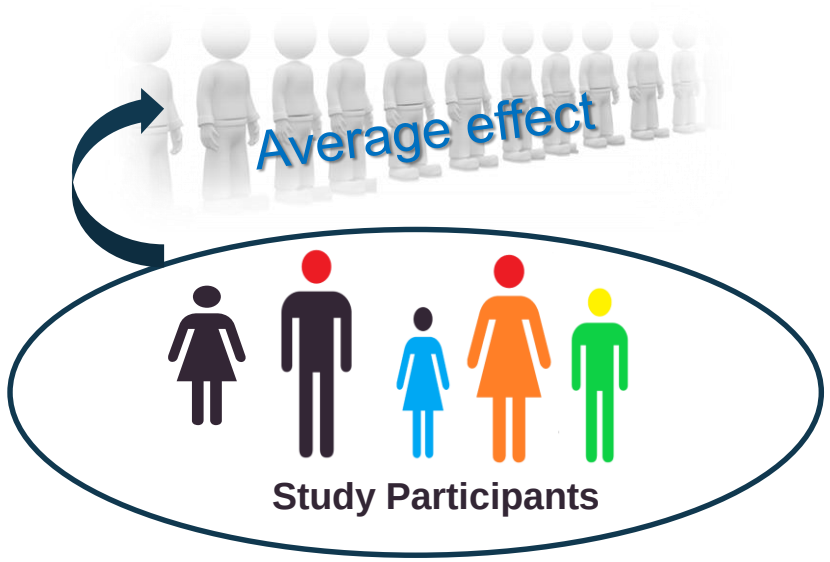
Background: The analysis of subgroups in clinical trials is essential to assess differences in treatment effects for distinct patient clusters, that is, to detect patients with greater treatment benefit or patients where the treatment seems to be ineffective. *Methods:* The software application *subscreen* (R package) has been developed to analyze the population of clinical trials in minute detail. The aim was to efficiently calculate point estimates (eg, hazard ratios) for multiple subgroups to identify groups that potentially differ from the overall trial result. The approach intentionally avoids inferential statistics such as *P* values or confidence intervals but intends to encourage discussions enriched with external evidence (eg, from other studies) about the exploratory results, which can be accompanied by further statistical methods in subsequent analyses. The *subscreen* application was applied to 2 clinical study data sets and used in a simulation study to demonstrate its usefulness. *Results:* The visualization of numerous combined subgroups illustrates the homogeneity or heterogeneity of potentially all subgroup estimates with the overall result. With this, the application leads to more targeted planning of future trials. *Conclusion:* This described approach supports the

THERAPEUTIC INNOVATION & REGULATORY SCIENCE

And on CRAN

subscreen (Vers 2.0.1): Systematic Screening of Study Data for Subgroup Effects

In the past we draw a single conclusion based on a heterogenous study population



Imagine a tool (such as ‘subscreen’) that allows efficient subgroup analyses for many stakeholders interactively

dedicated effect estimation

Sponsors

Health Authorities

Study Participants

Contributing in- and external Databases

HTAs

Investigator Researcher

Contact

e-mail: Bodo.Kirsch@bayer.com

R-PACKAGE: https://cran.r-project.org/web/packages/subscreen/index.html

Thank you!

at a glance

exemplary data