Subgroup analysis: a look at the SEAMOS approach

SEAMOS: Standardised Effects Adjusted for Multiple Overlapping Subgroups

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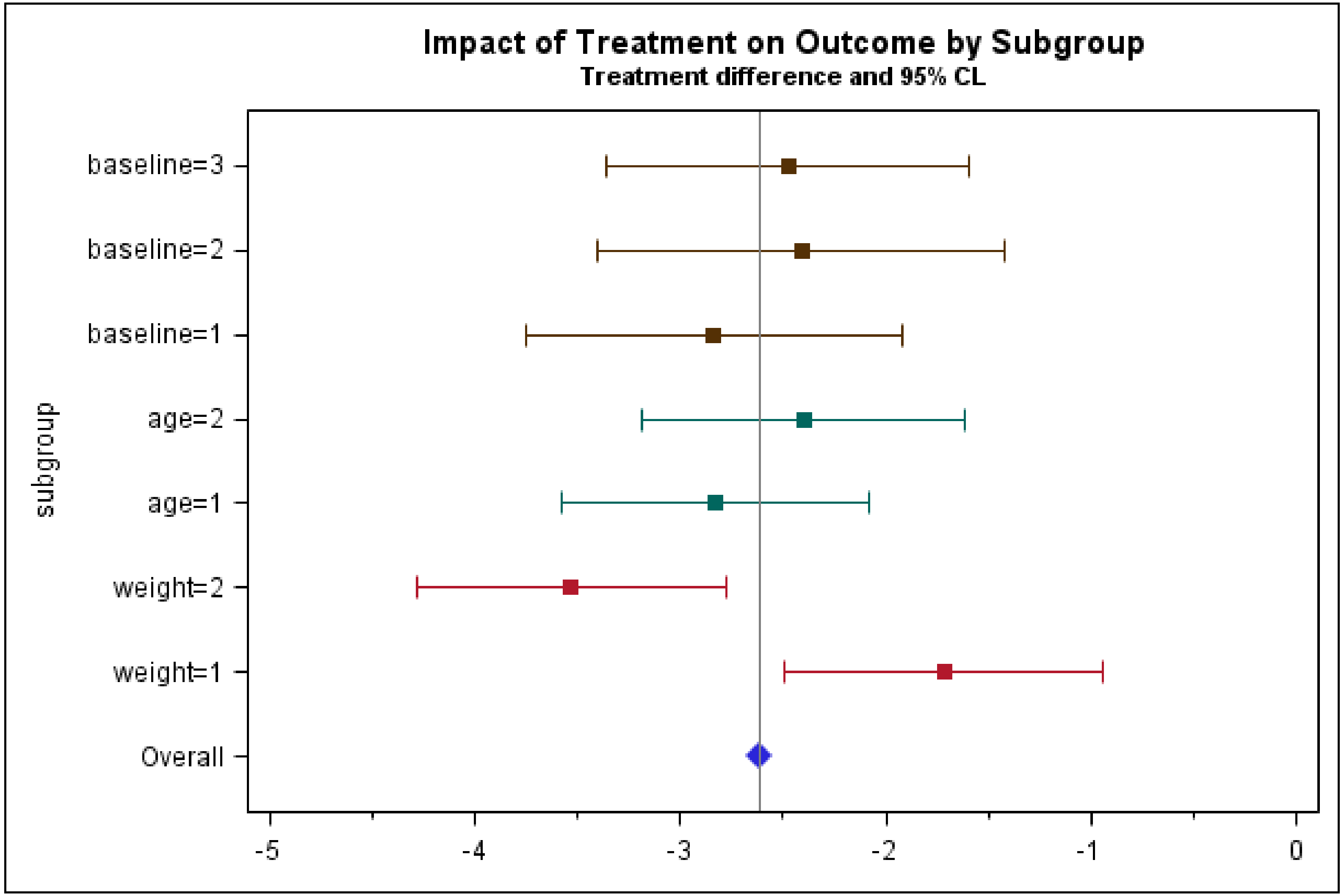
Acknowledgements

- For their ideas, advice, insights, comments and discussion:
  - Tom Parke, Berry Consultants
  - Ilya Lipkovich, Eli Lilly
  - David Svensson, AstraZeneca
  - Jonathan Bartlett, University of Bath

The problem: a standard clinical-trial output

The problem


Impact of Treatment on Outcome by Subgroup
Treatment difference and 95% CL
subgroup
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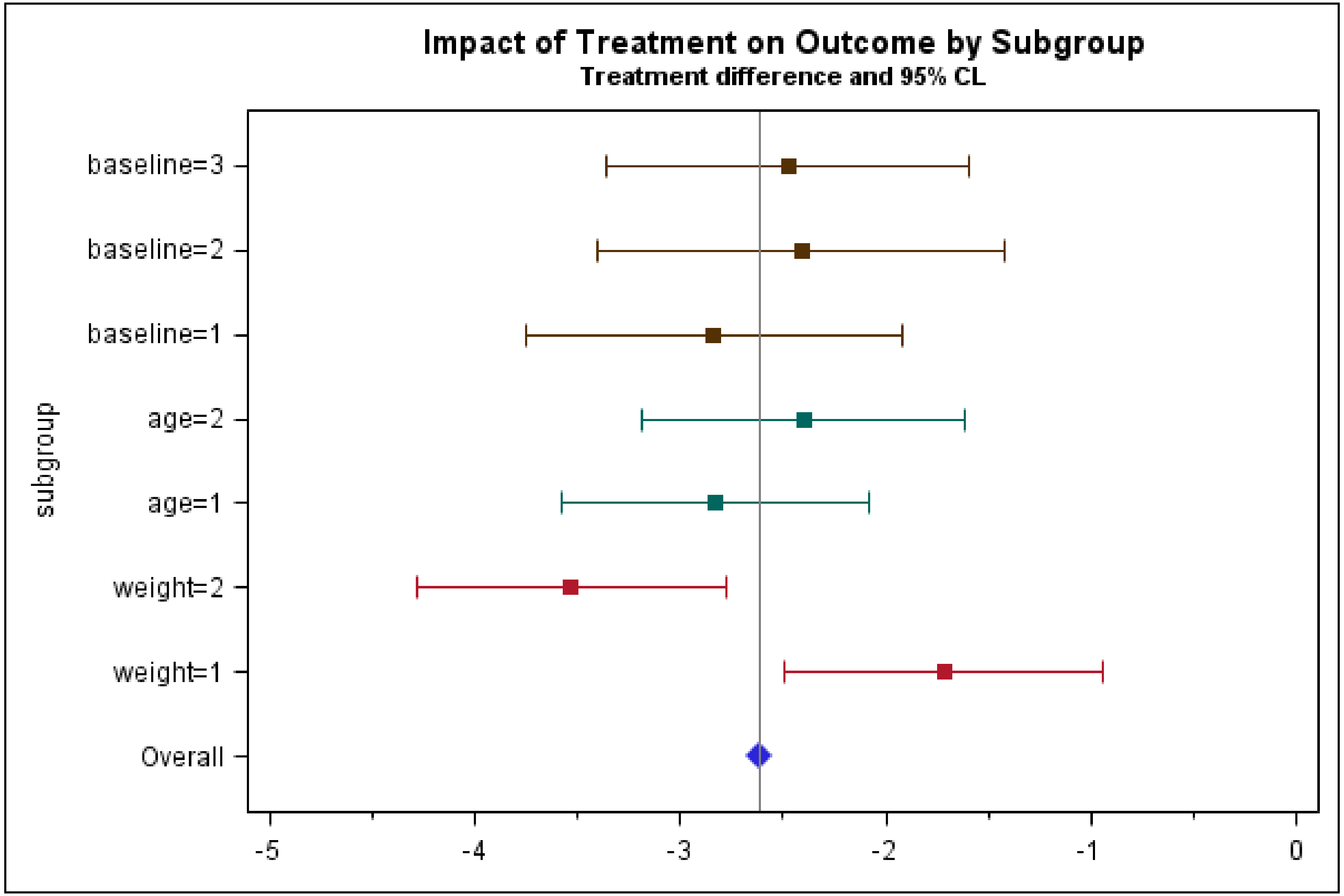
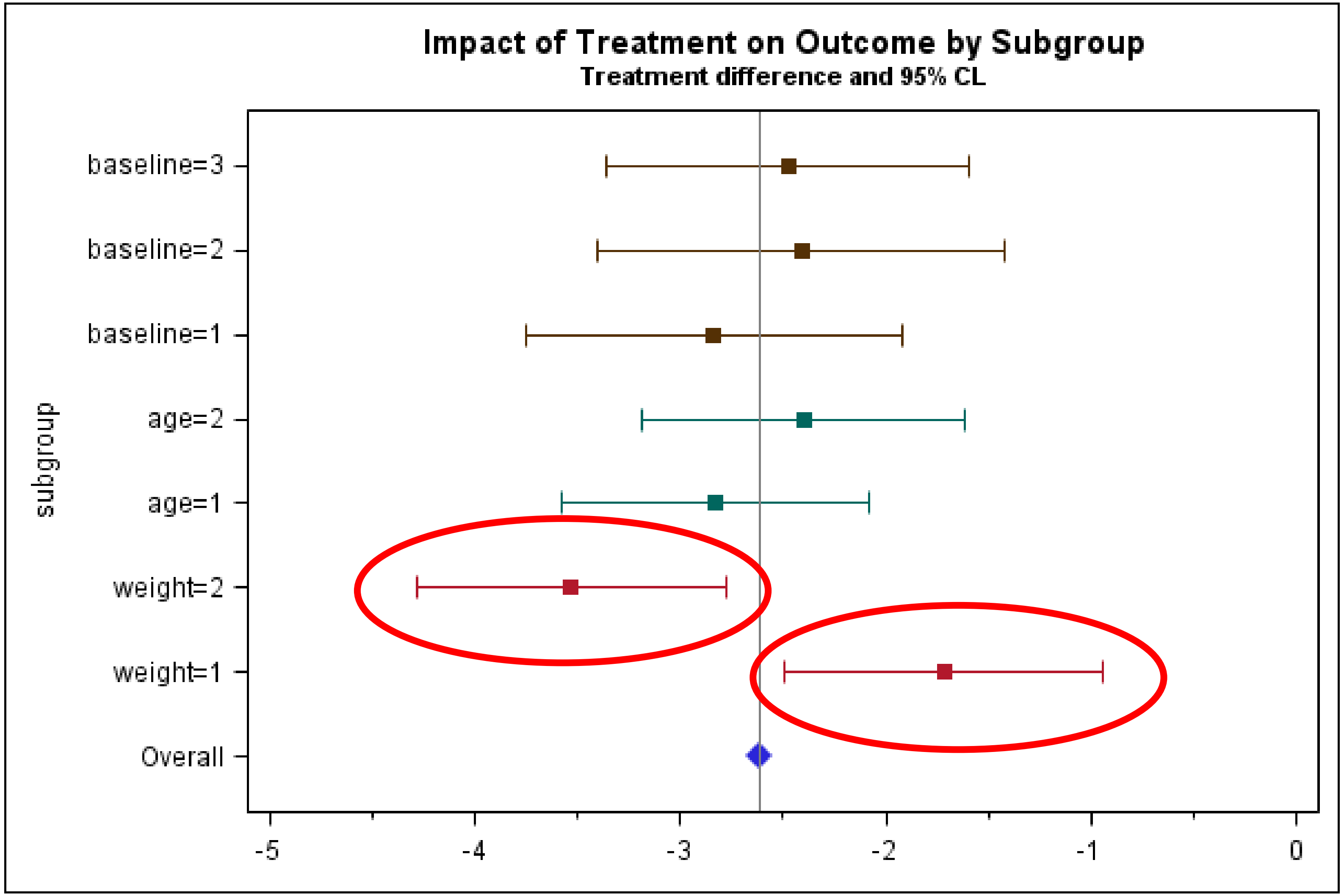
“Move along, nothing to see here”?



Or is there a true subgroup effect hidden in the forest?



Objective, paradoxical for data visualisation session

- Can we find a statistic or statistics to help us assess this visual representation of subgroups?

Massive statistical literature on subgroup identification

- Objective
  - Check for homogeneity?
  - Search out promising subgroups?
  - Understand patterns linking treatment effect to population attributes?

Massive statistical literature on subgroup identification

- Objective
  - Check for homogeneity?
  - Search out promising subgroups?
  - Understand patterns linking treatment effect to population attributes?
- Complications
  - Correlated subgroups
  - Numbers of categories in a subgroup
  - Unequal N per subgroup

Massive statistical literature on subgroup identification

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Massive statistical literature on subgroup identification

- Objective
  - Check for homogeneity?
  - Search out promising subgroups? [machine learning, e.g. SIDES, etc.]
  - Understand patterns linking treatment effect to population attributes? [multivariate modelling]

Massive statistical literature on subgroup identification

- Objective
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Massive statistical literature on subgroup identification

- Objective
  - Check for homogeneity?
  - SEAMOS: Standardised Effects Adjusted for Multiple Overlapping Subgroups
  - Idea, focussed specifically on assessment of forest plots:
    - › Identify an overall measure of existence of subgroup in the plot
    - › Permute the subjects along with their subgroup attributes, preserving the treatment effect (i.e. treatment group and outcome are not permuted)
    - › Reject null hypothesis quantified by overall measure of existence of subgroup
    - › SEAMOS: overall measure is largest standardised subgroup treatment effect
  - Dane et al., (2018) Subgroup analysis: White paper of the EFSPI/PSI working group on subgroup analysis, *Pharmaceutical Statistics.*

SEAMOS

- SEAMOS: overall measure is largest standardised subgroup treatment effect, $\max(\Delta_{ij})$, where

$$\Delta_{ij} = \frac{\bar{\delta} - \delta_{ij}}{SE_{\delta_{ij}}}$$

- …and SE is the standard error, δ_{ij} is the estimate of treatment difference for category *j* of subgroup *i*, and $\bar{\delta}$ is the overall estimate of treatment difference ignoring subgroup.
- The permuting of the subgroup information in q=1, 2…Q permuted datasets allows access to a "null-hypothesis" scenario, percentiles of whose $\max(\Delta_{ijq})$ can be used to reject the null hypothesis of no subgroup as quantified by $\max(\Delta_{ij})$

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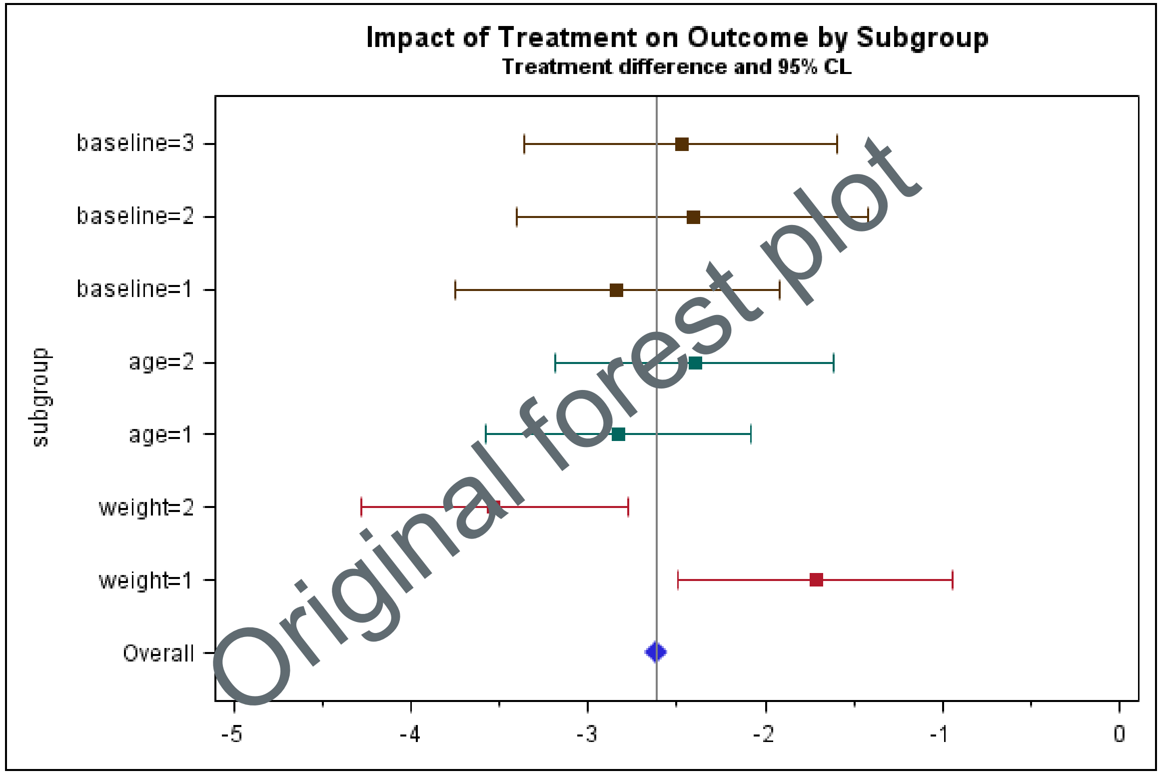

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Original forest plot

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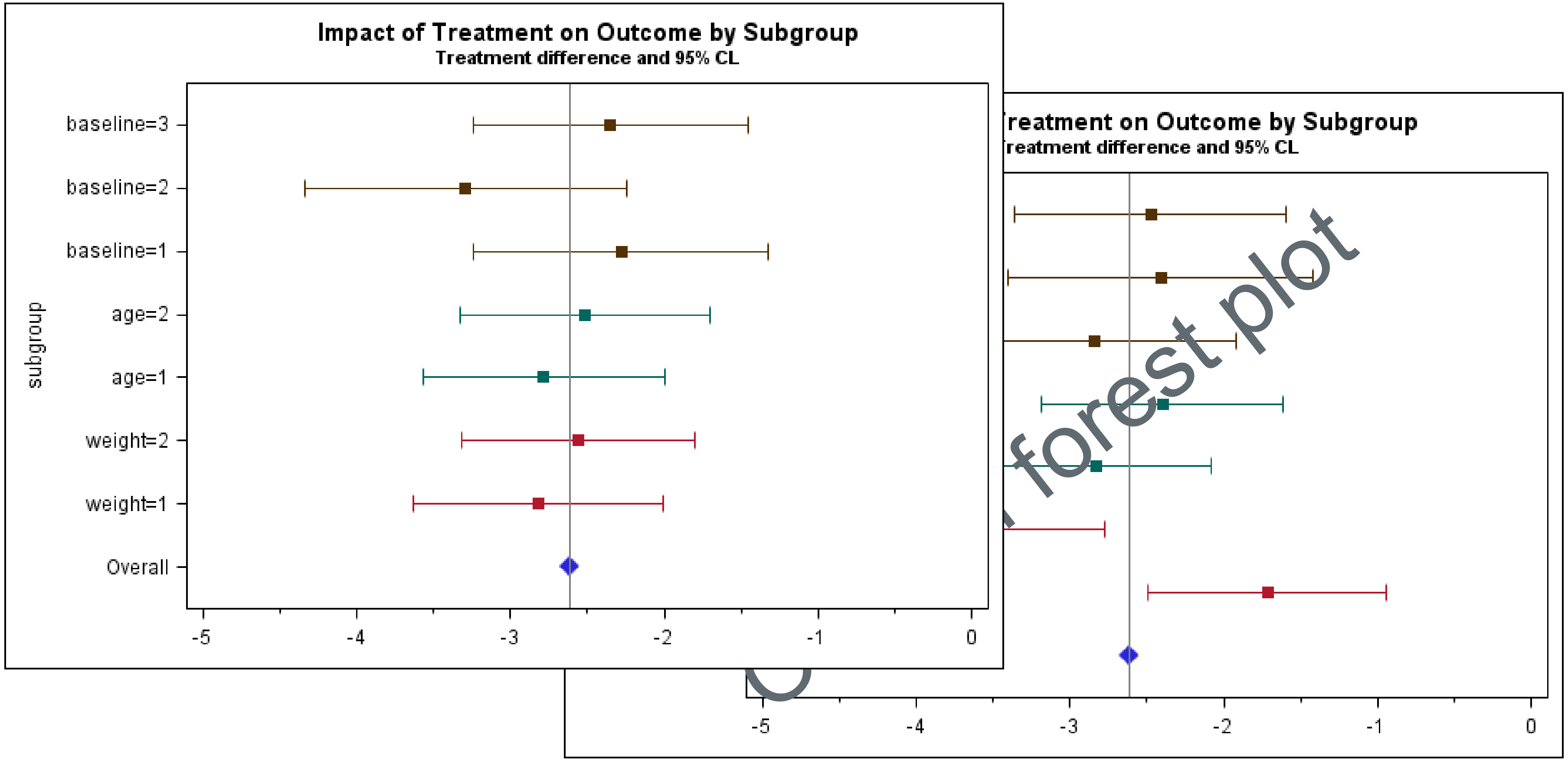
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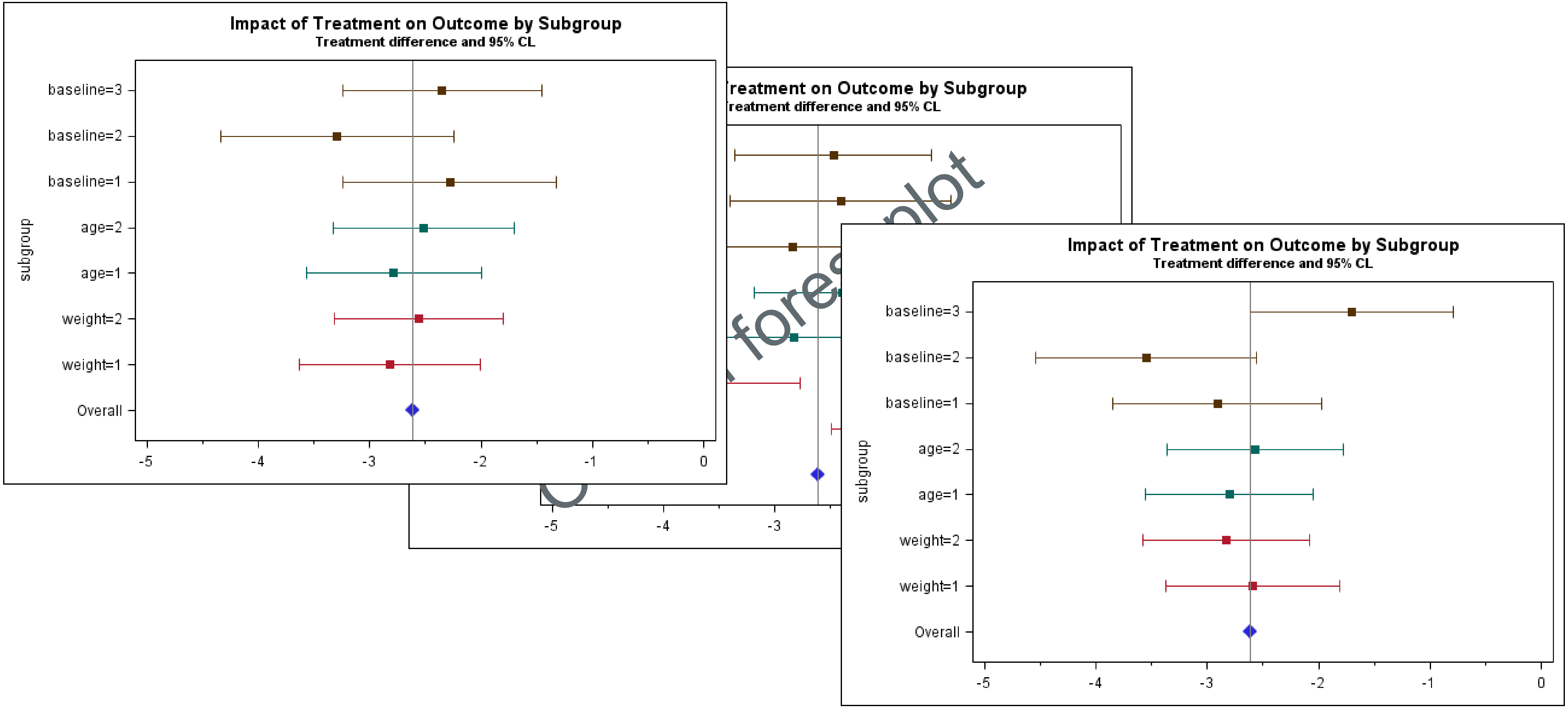

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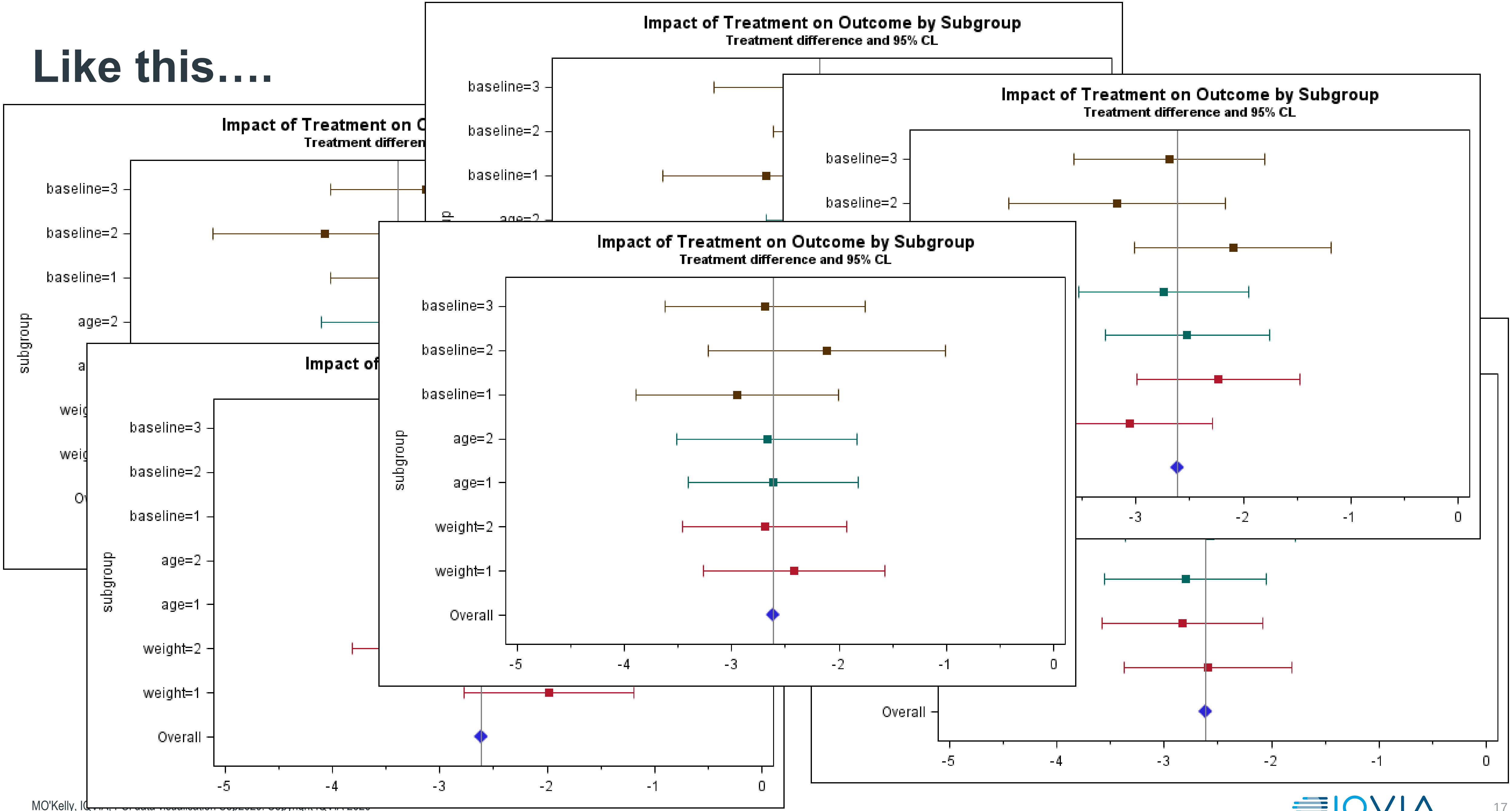

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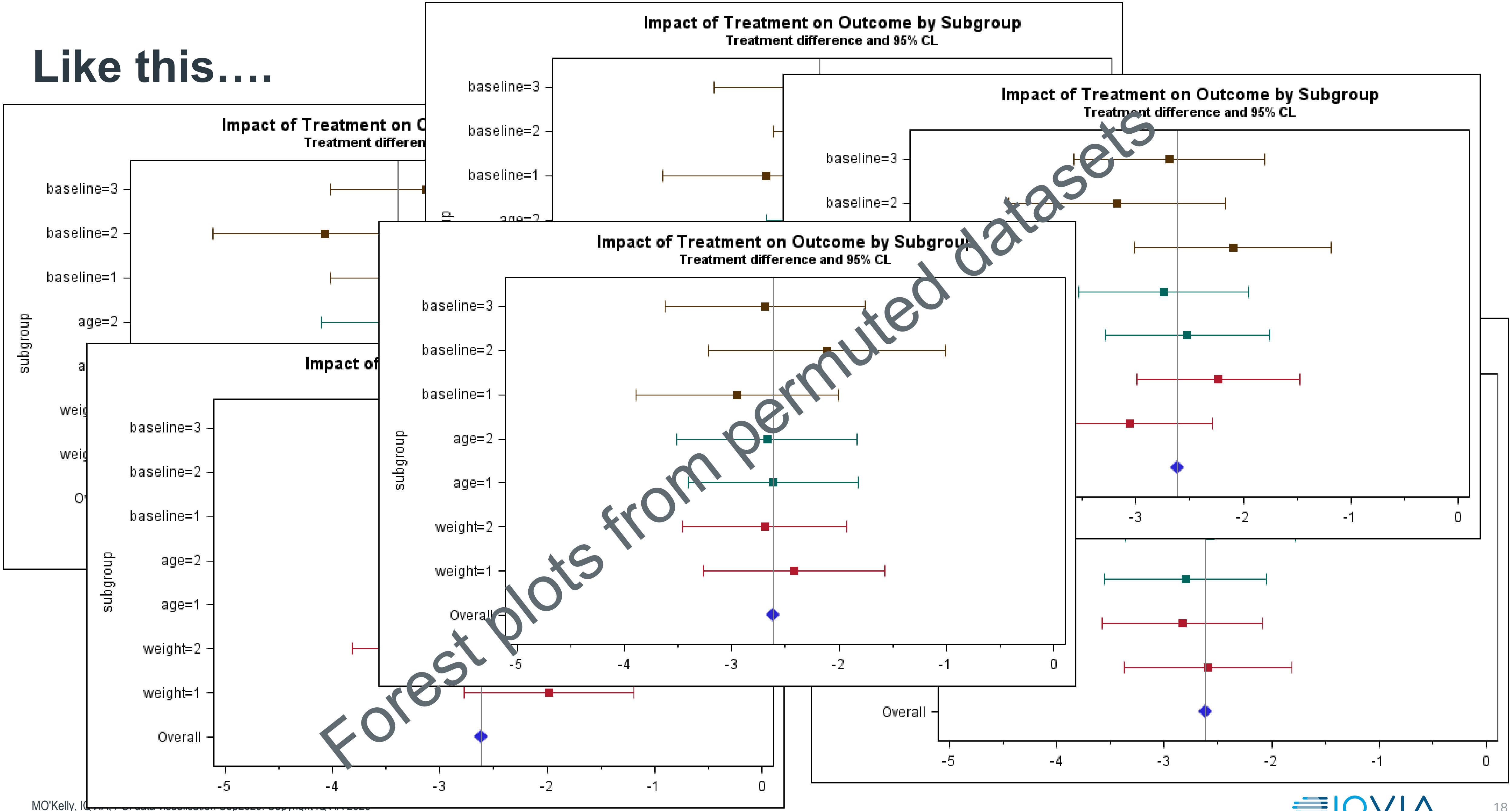

Forest plots from permuted datasets
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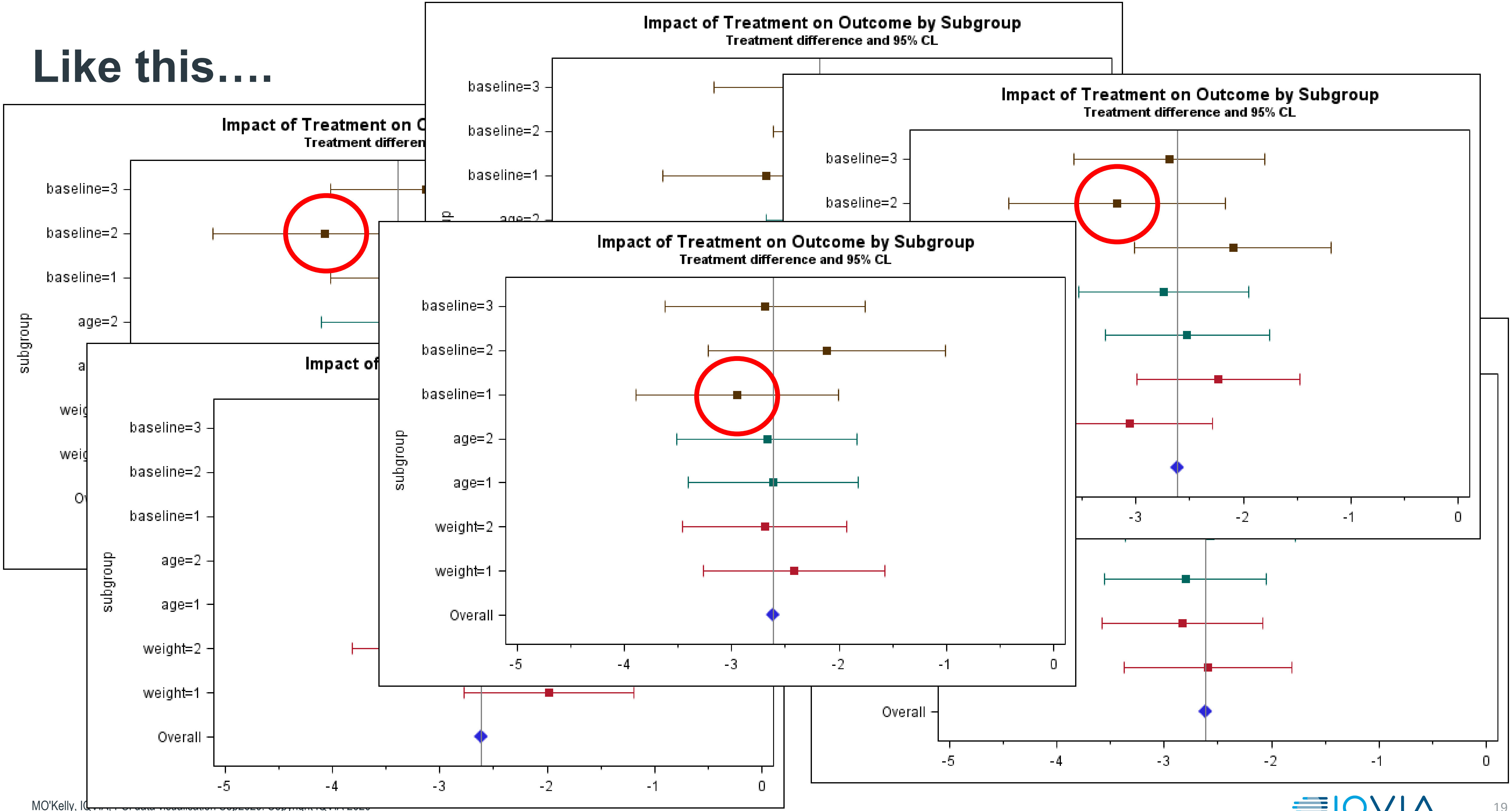

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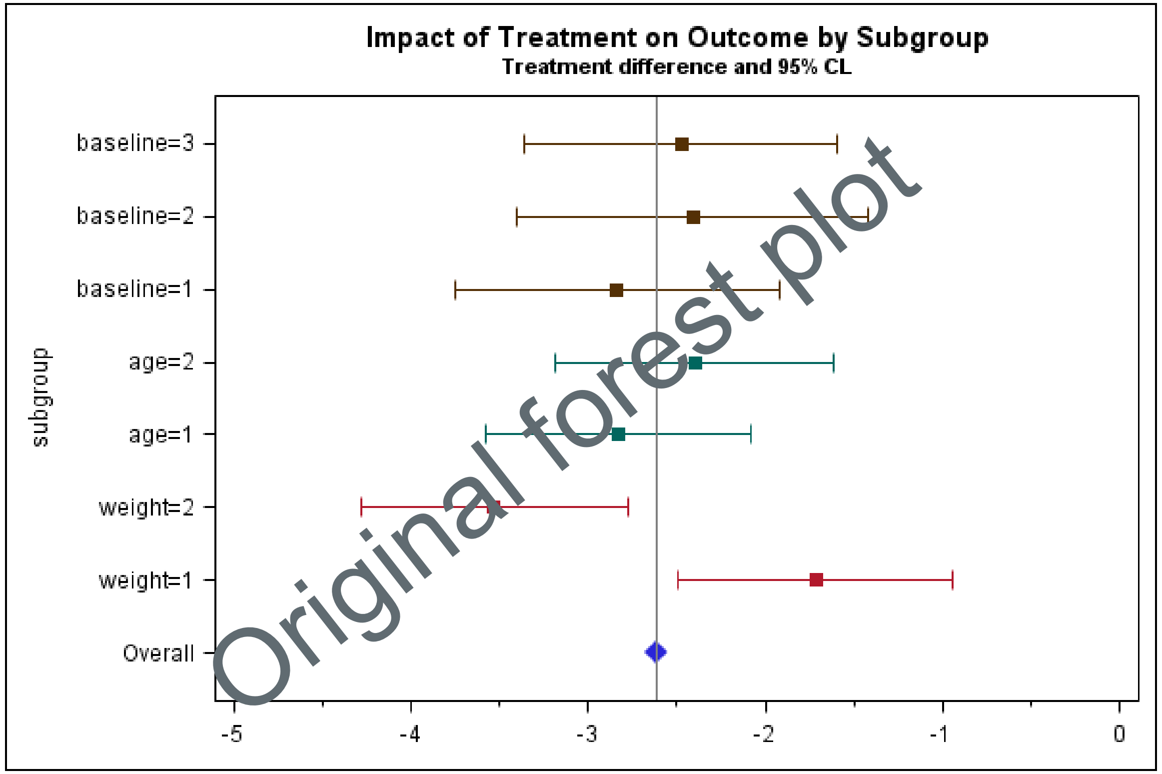

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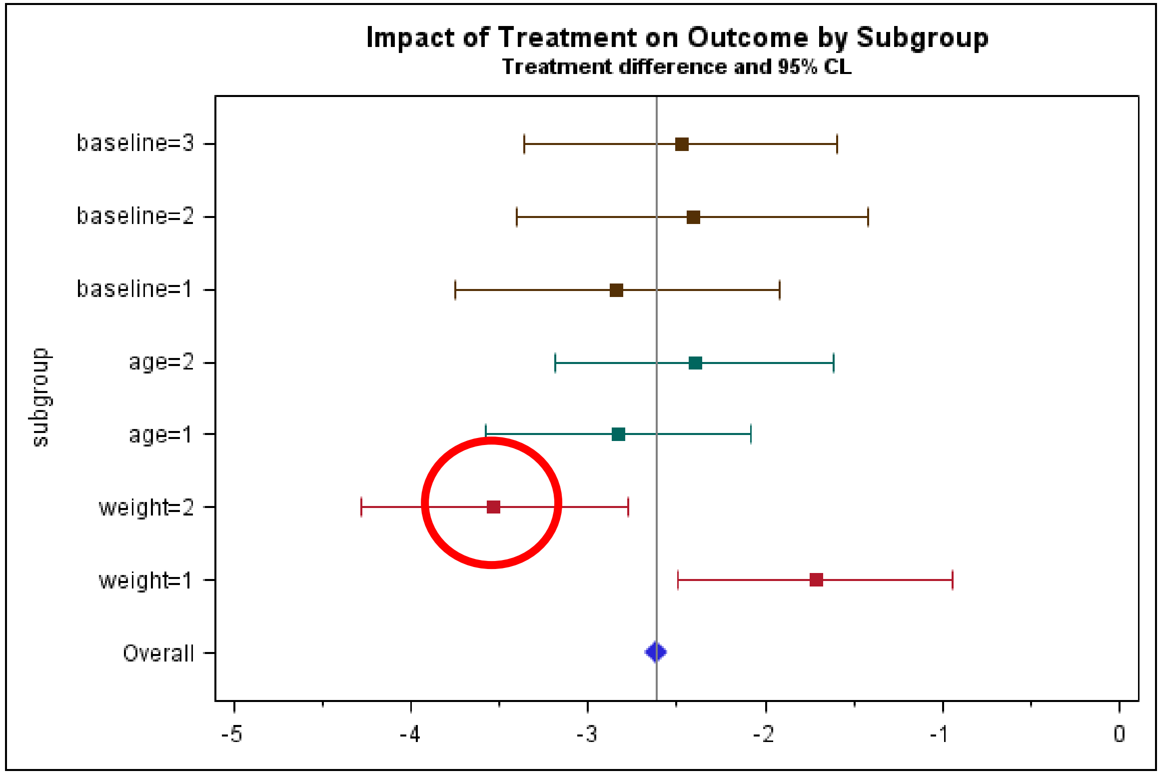
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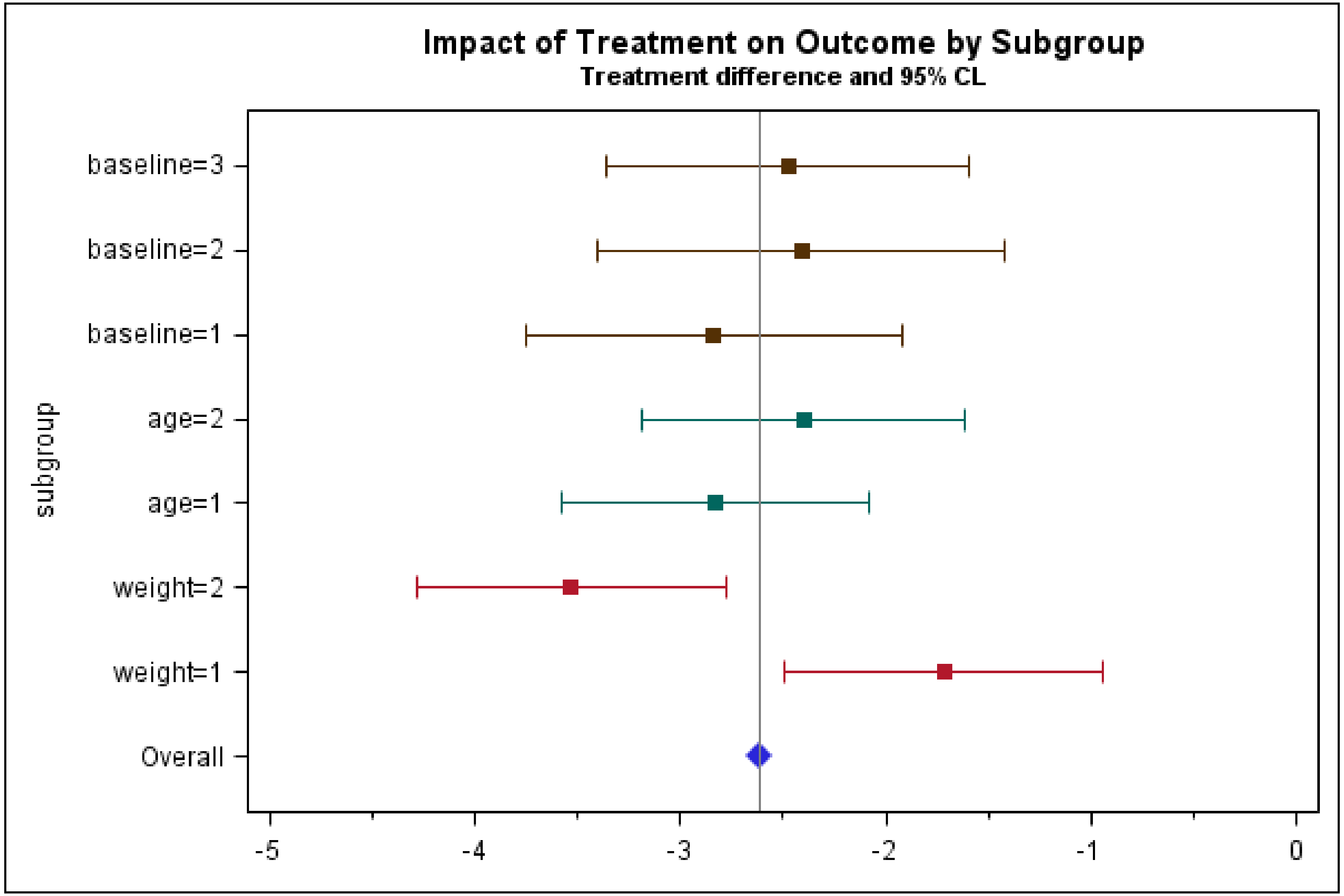
Actual SEAMOS approach, takes observed forest plot…



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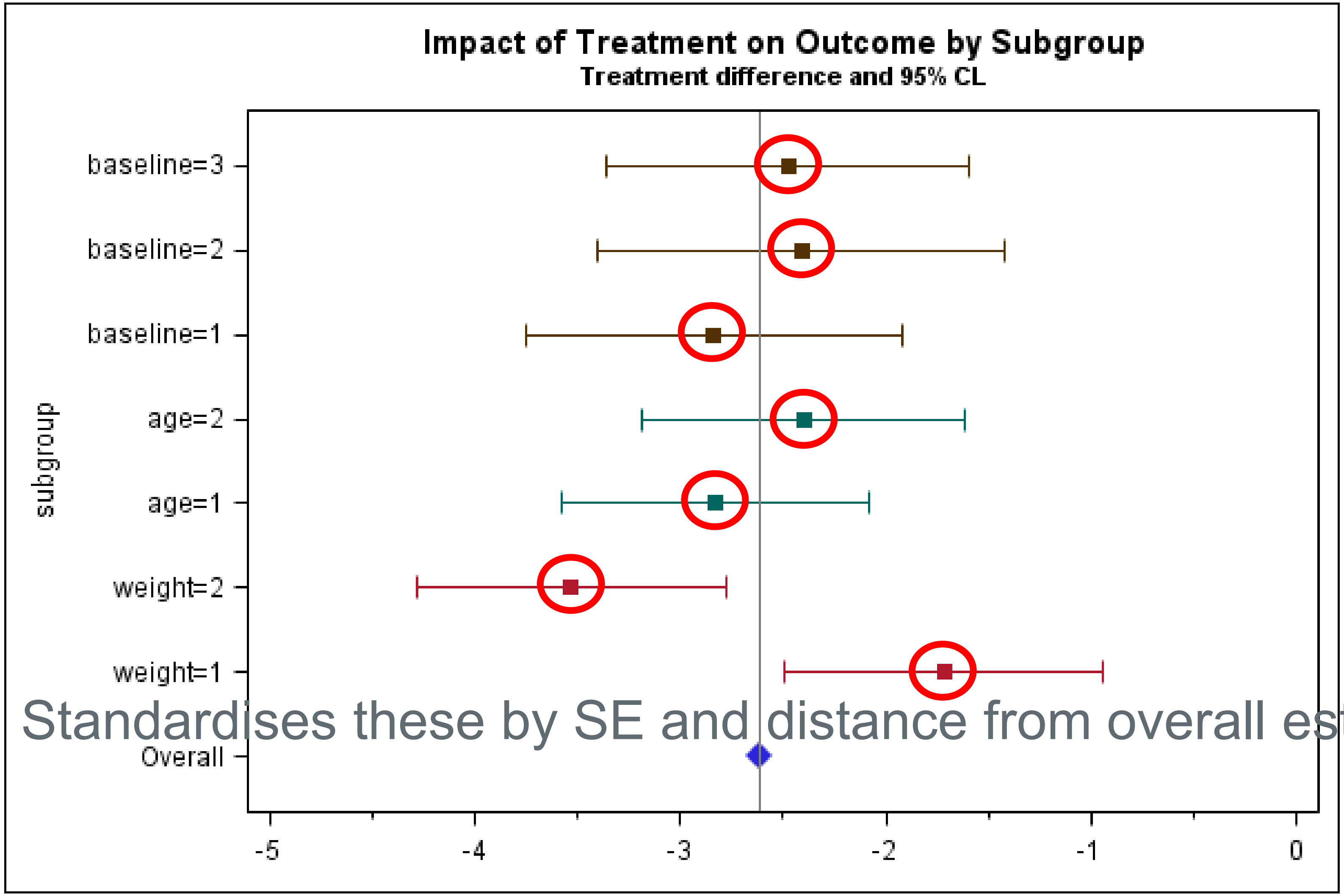
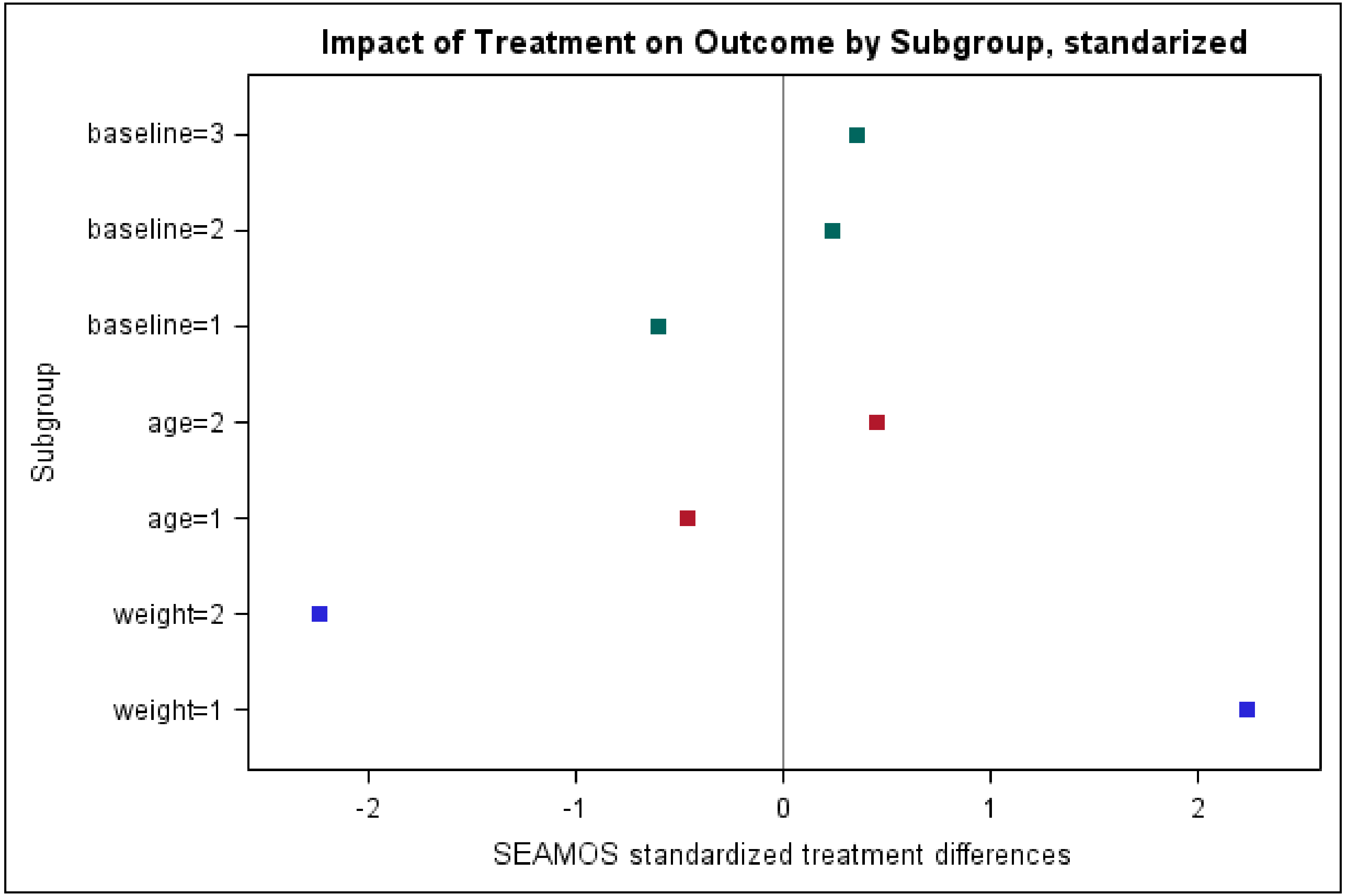
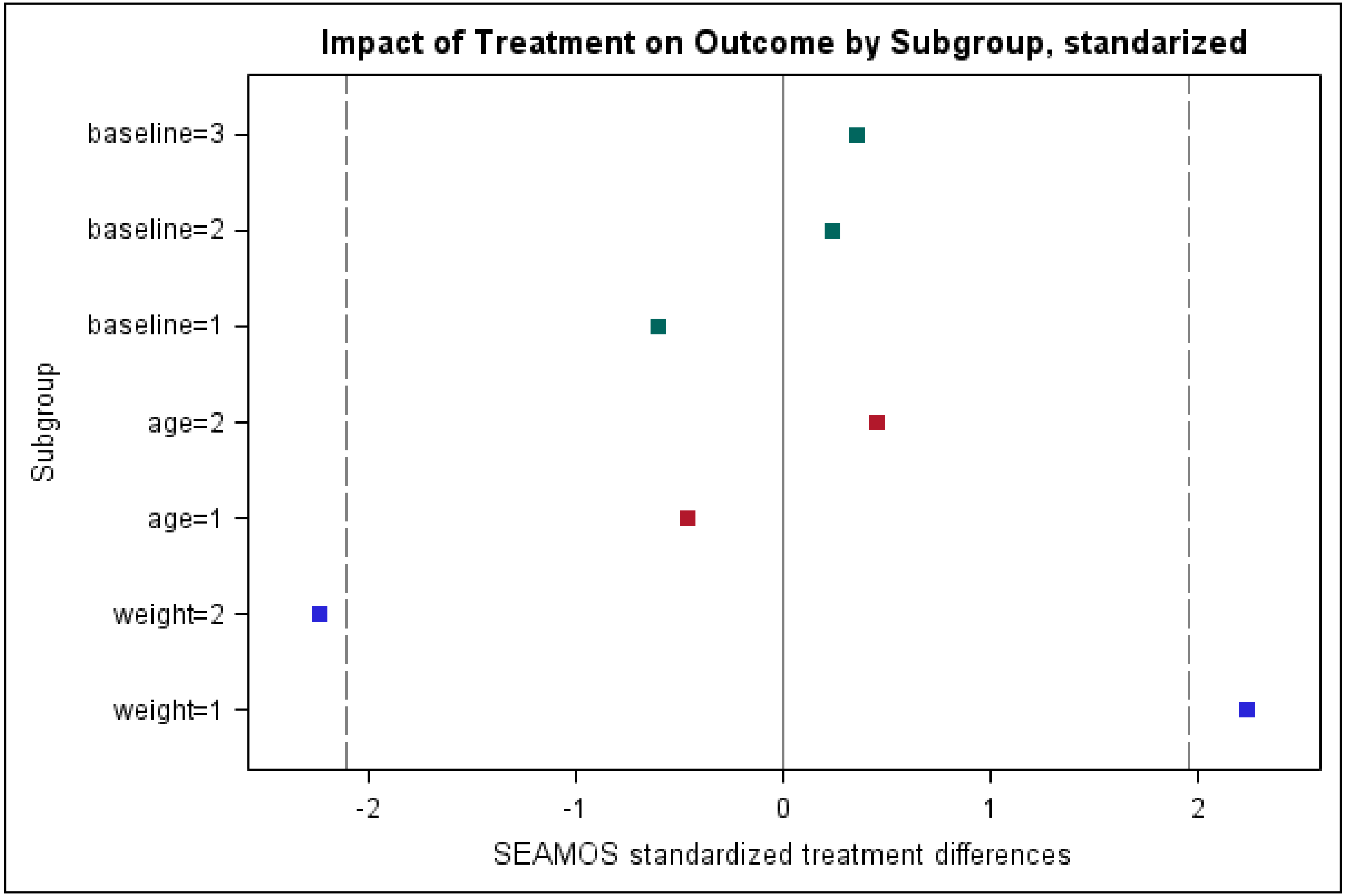


Standardises these by SE and distance from overall estimate, to get…

Actual SEAMOS standardised estimates



SEAMOS estimates with limits = 2.5% and 97.5% percentiles of permuted SEAMOS estimates



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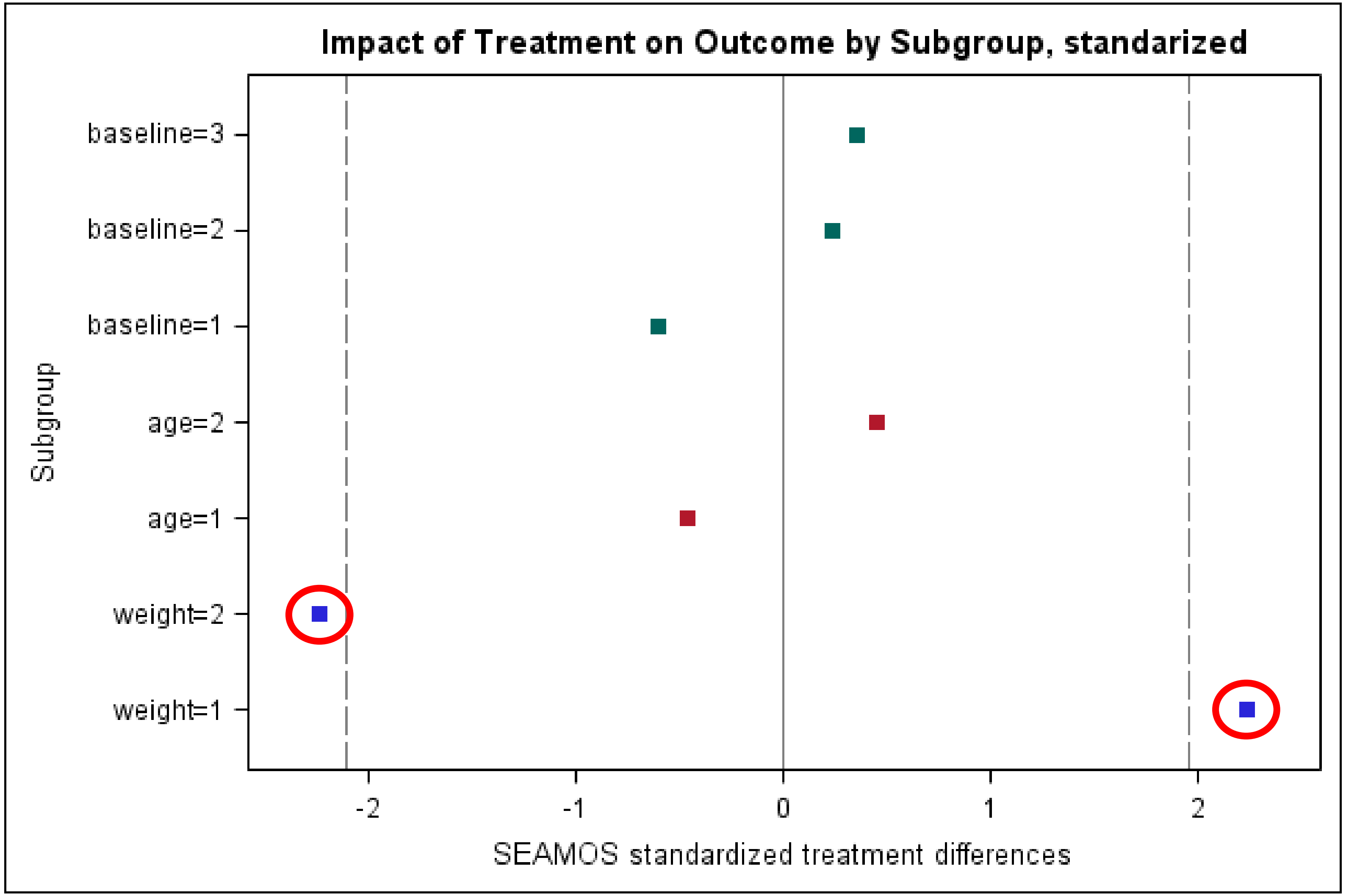
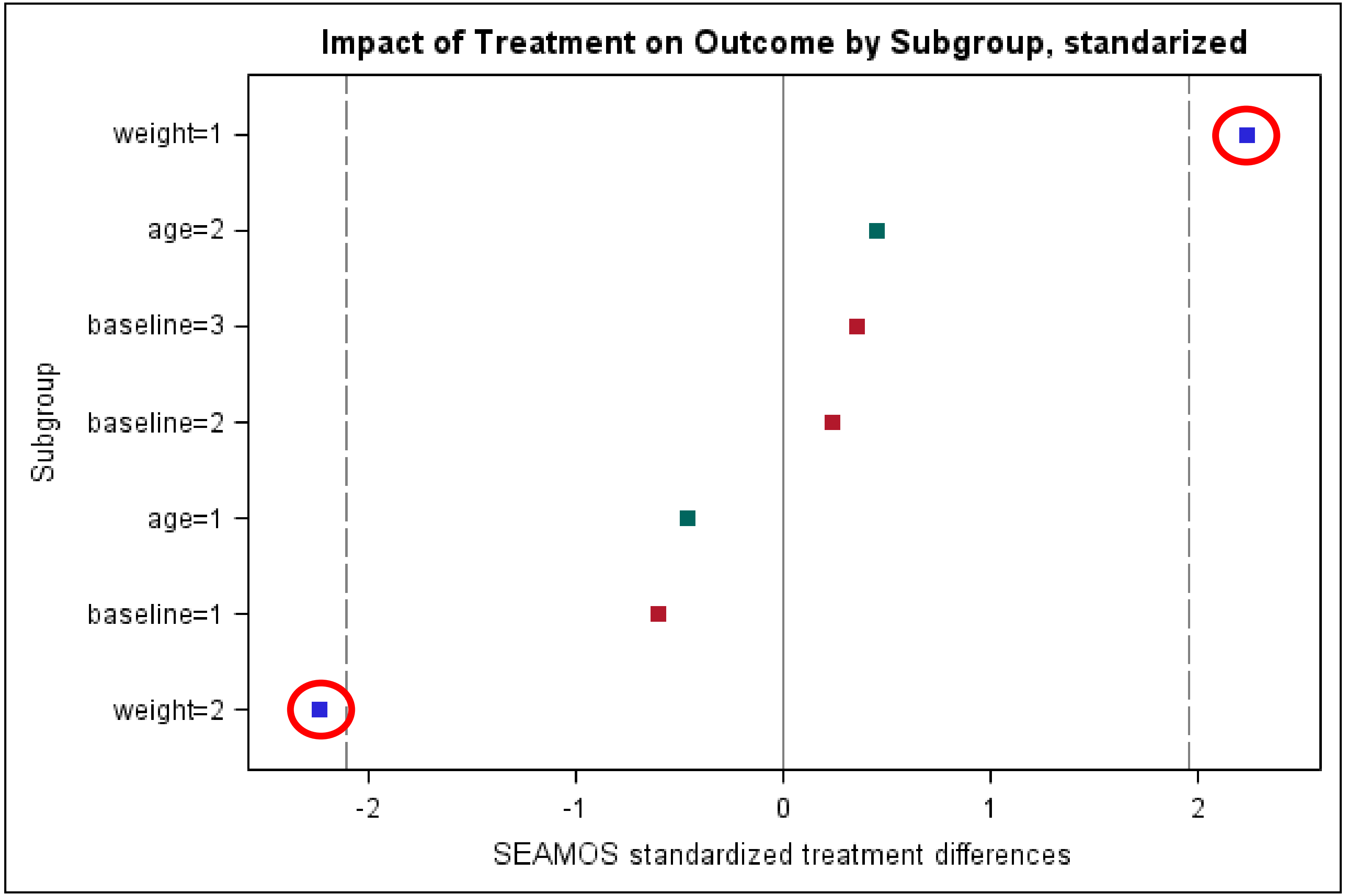


SEAMOS standardized differences are often presented ordered by difference



Objective of this research

- Dane et al. (2018) assess SEAMOS Type I error and power via simulated null-hypothesis and “true” subgroup scenarios
- Objective of this presentation:
  - Identify difficulties of SEAMOS’s model based approach, if any.
  - Further investigate nuances of Type I error
    - How numbers of *true* subgroups vs. numbers of subgroups *assessed*, affect Type I error and power
  - Compare the max(Δ_{ij}) statistic with alternative measures of existence of subgroup
    - Standard Type 3 sums of squares (SS) for the subgroup, Bonferroni corrected
    - Type 3 SS vs. Type 3 SS from permuted datasets

Simulations

- 1000 clinical trials simulated, each with 200 subjects per arm
- Outcome simulated as Y~ N(μ, σ^2)

$$Y = \beta_t T_t + \sum_{i=1,j=1}^{i=3,j=K_i} \beta_{ij} X_{ij} + \sum_{i=1,j=1,t=1}^{i=3,j=K_i,t=2} \beta_{ijt} X_{ij} T_t + e$$

- …where Y is the response, the β are coefficients for three subgroups X_i, i=1, 2, 3 (age (2 categories), weight (2 categories) and baseline value of Y (3 categories), i.e. K_1=2, K_2=2, and K_3=3; and T_t, t=1, 2 represents treatment group
- …with the β ε {0,1} depending upon scenario, and e ~ i.i.d N(0, 2^2)
- For some scenarios weight and age were correlated.
- Each simulated dataset permuted 200 times when estimating SEAMOS statistic.

Scenarios simulated, methods assessed

- Scenarios
  - Null hypothesis scenarios
    - With and without correlations $\rho=0.5$ between weight and age
  - Scenario with true subgroup(s)
    - Weight and age are true subgroups, but not baseline
      - Again, with and without correlations $\rho=0.5$ between weight and age
- Measures of existence of subgroup
  - SEAMOS's max(Δ_{ij})
  - Max(Type 3 SS) per subgroup, evaluated vs. permuted version of this statistic
  - Standard Type 3 SS (not permuted) with Bonferroni correction.
- One, two and three subgroups assessed.

Note on use of the permutation approach

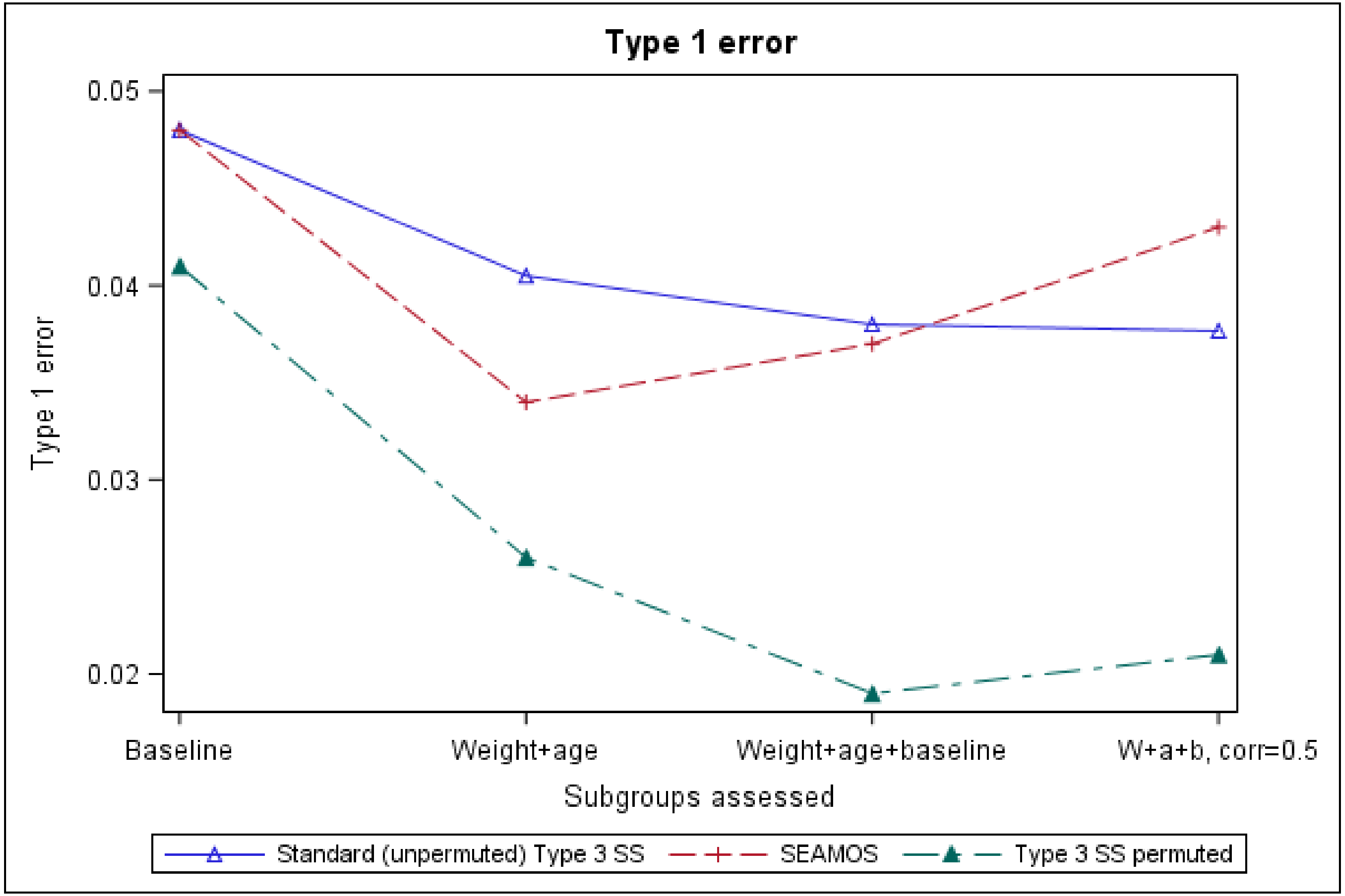
- In our scenarios, candidate subgroup variables are expected to be associated with outcome (i.e. expected to have a “main effect”).
- When a subgroup main effect is in the planned model, the permuted-dataset analysis cannot make use of this factor. Compared to the original non-permuted analysis, residual variance in permuted analysis is inflated: the Δ_{ij} and $\max(\Delta_{ij})$ in permuted datasets will tend to be smaller than that in the original forest plot.
  - =>Inflation of Type I error in identification of subgroups.
  - Solution: preserve the *original* subgroup variable for main subgroup effect, but using *permuted* subgroup variable for treatment-by-subgroup interaction.
  - Work ongoing on this by PSI Subgroups SIG.
- General principle: permuted test statistic should be estimated on same basis as original test statistic, except for existence of subgroup-by-treatment interaction.

Model used in the analysis of the simulated data sets

- For each candidate subgroup, test statistic was estimated using the following model

$$Y = \beta_0 + \beta_t T_t + \sum_{i=1,j=1}^{i=3,j=K_i} \beta_{ij} X_{ij} + \sum_{i=1,j=1,t=1}^{i=3,j=K_i,t=2} \beta_{ijt} X_{ij} T_t + \mathrm{e}$$

Results: Type 1 error, nominally two-sided 5% or equivalent



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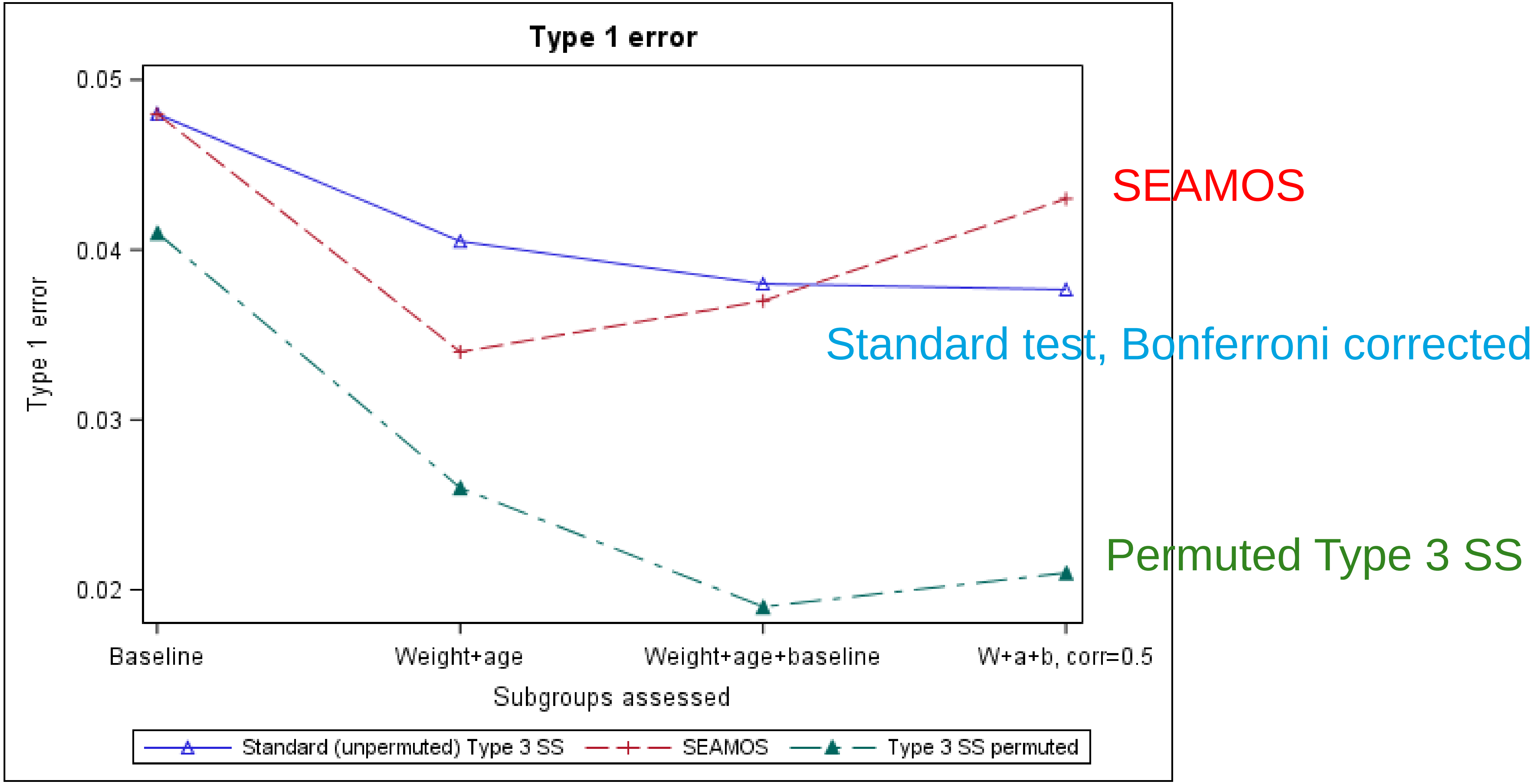
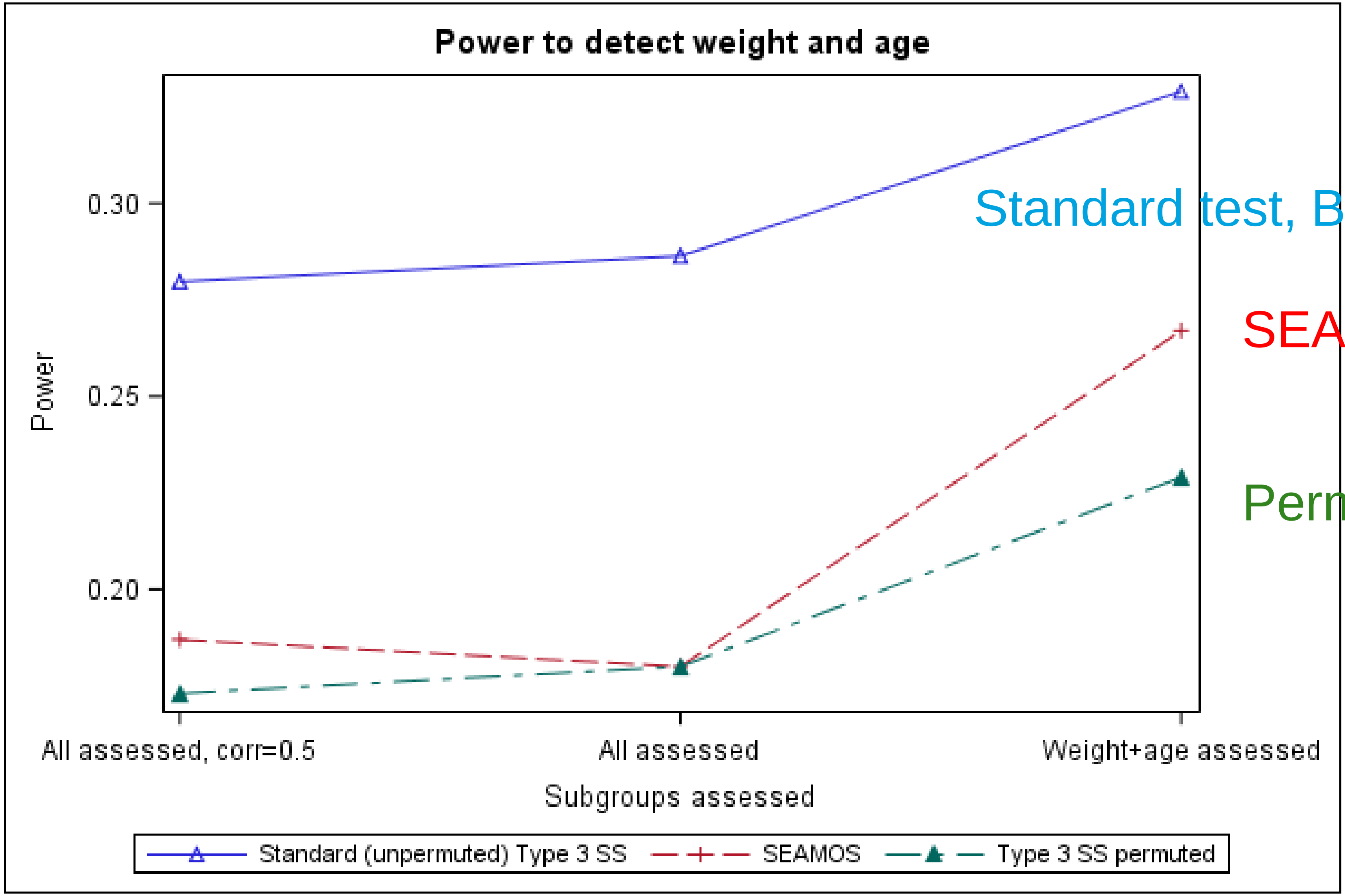


Results, power

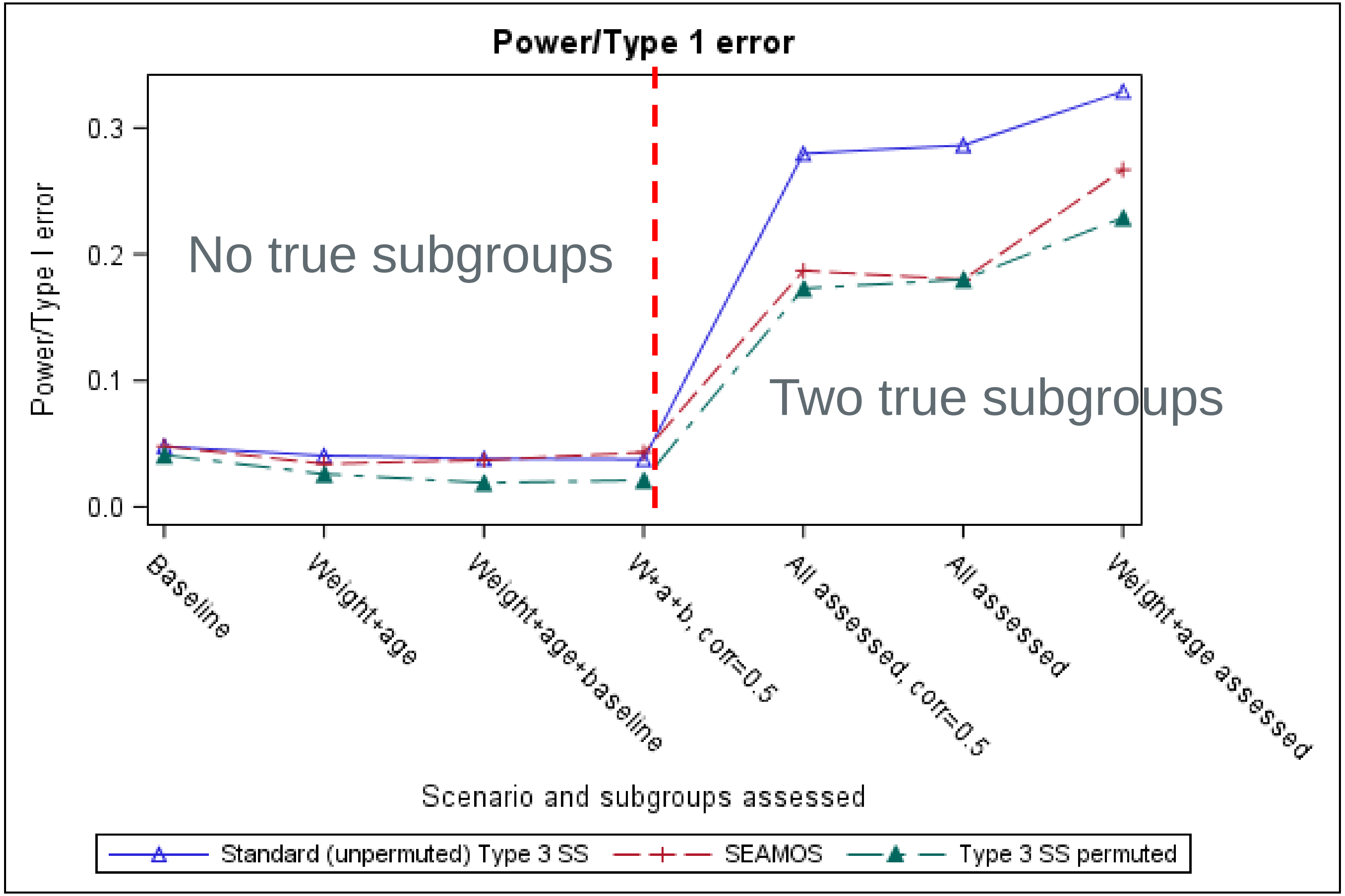


Standard test, Bonferroni corrected

SEAMOS

Permuted Type 3 SS

Results, combined



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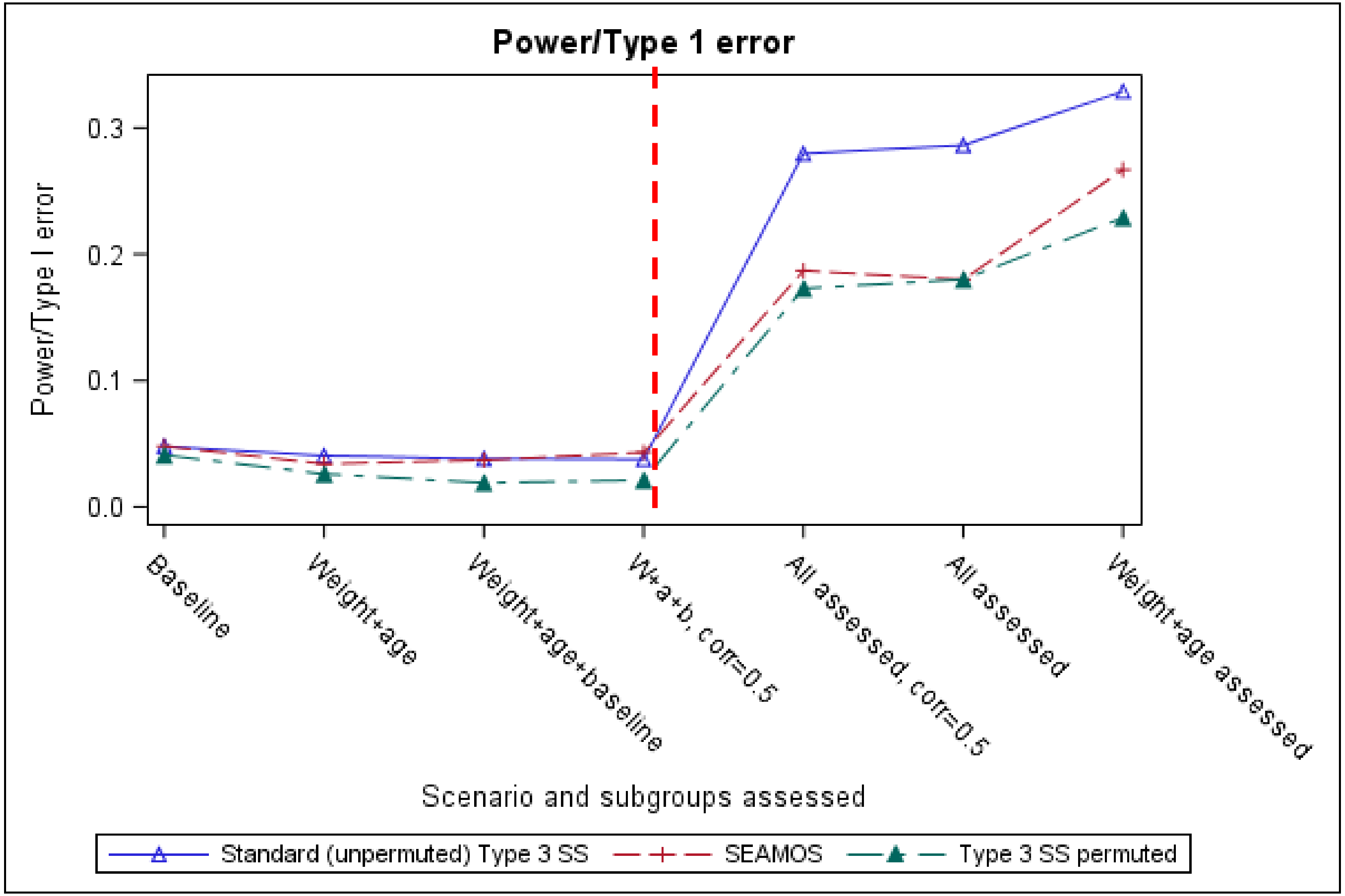

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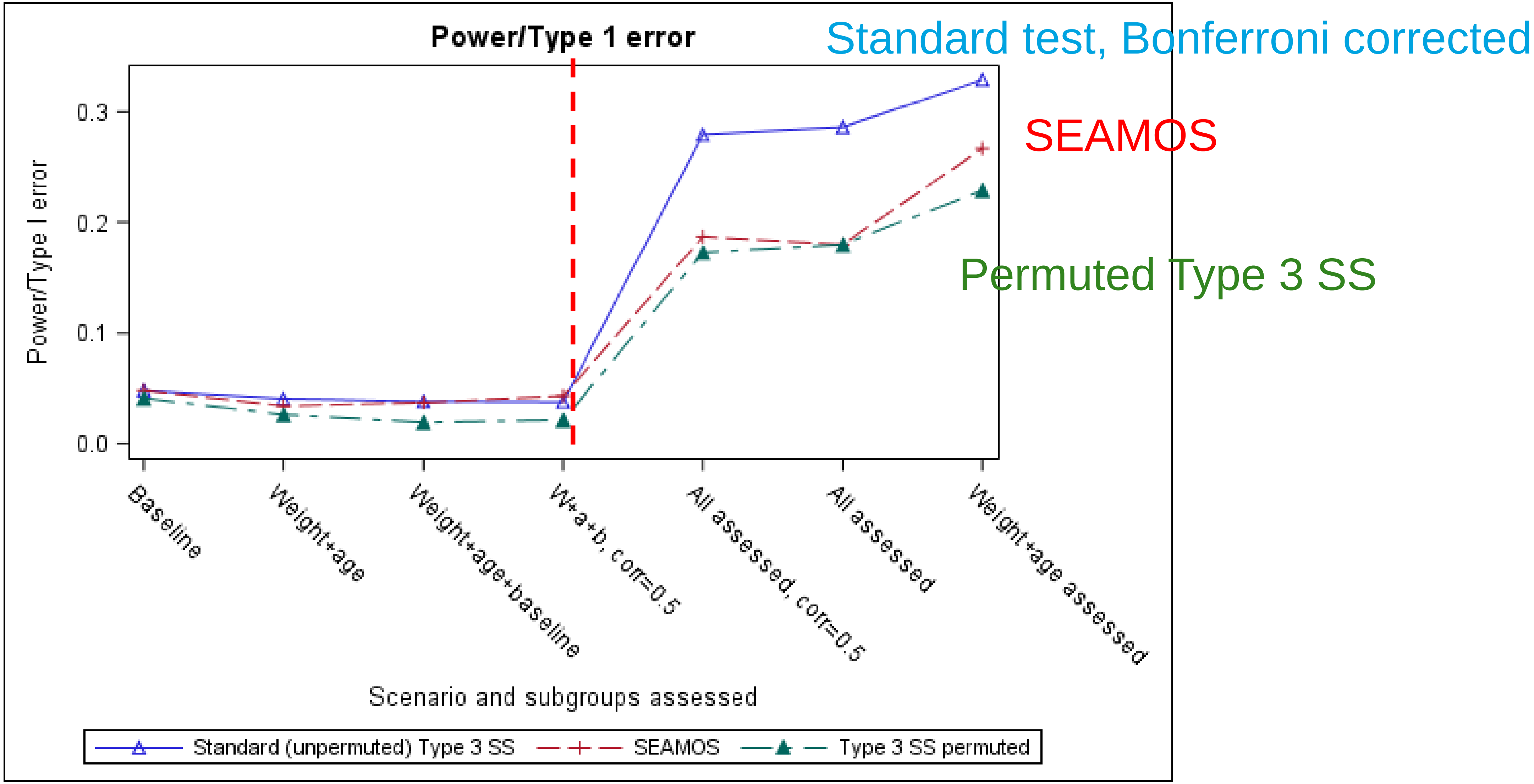

Limitations in our research

- This research was confined to a particular objective with regard to subgroup identification: assessment of forest plots.
- A relatively small number of subgroups were simulated/assessed.
- Scenarios where subgroups existed had relatively large proportion of true subgroups.
- Subgroups were assumed to have a main effect
- Did not compare the approaches with, e.g.,

  - bootstrap-based approach also described by Dane at al. (2018);

  - machine-learning approaches such as SIDES.
- Detection of existence of *any* subgroup in the forest plot was what was evaluated - did not evaluate whether the max(Δ_{ij}) came from a true subgroup.

Some learnings

- Standard Type 3 SS test for subgroups (with Bonferroni correction) controls “false positive” findings, even with correlated subgroups (as in Dane et al (2018)).
- Standard Type 3 SS test appears more sensitive than rival permutation-based approaches. (This test was less sensitive in the scenarios of Dane et al. (2018)).
- When using permutation based approaches, it is prudent to include unpermuted main effect of the subgroup when modelling the permuted datasets.
  - In our simulations, failing to do so inflated Type I error, where there is a subgroup main effect and main subgroup effect is in the model.
- For all approaches and scenarios assessed, presence/absence of correlation among subgroups has little association with changes in Type I error or power.
- As expected, the inclusion of extra “non-true” subgroups in the search erodes power for all approaches (e.g. 19% vs.27% for SEAMOS.

Some learnings

- SEAMOS is reasonably straightforward to implement in SAS.
  - Code created for this research is sharable, but user-friendly SAS macro has not been created.
- Permutation-based methods can be heavy on IT resources when used in simulations.
  - Hence our results limited to 200 permutations for each of the 1000 simulations.

Further research required

- Relative power of “standard” global interaction test (i.e. Type III SS test) vs. SEAMOS-type tests seems to vary depending on scenario – standard global test performed relatively well in the scenarios simulated here, compared to performance in scenarios of Dane et al. (2018).
  - Further work needed to identify characteristics of scenarios that suit standard subgroup approaches vs. SEAMOS-type approaches when assessing forest plots.

Questions?