Online Supplement

# An interpretable cluster-based logistic regression model, with application to the characterization of response to therapy in severe eosinophilic asthma

Massimo Bilancia[1*]
Andrea Nigri[2]
Barbara Cafarelli[2]
Danilo Di Bona[3]

[1]University of Bari Aldo Moro – Department of Precision and Regenerative Medicine and Jonian Area (DiMePRe-J), Bari, Italy
[2]University of Foggia – Department of Economics, Management and Territory (DEMeT), Foggia, Italy
[3]University of Foggia – Department of Medical and Surgical Sciences (DSMC), Foggia, Italy

[*]Corresponding author: massimo.bilancia@uniba.it; massi.bilancia@gmail.com

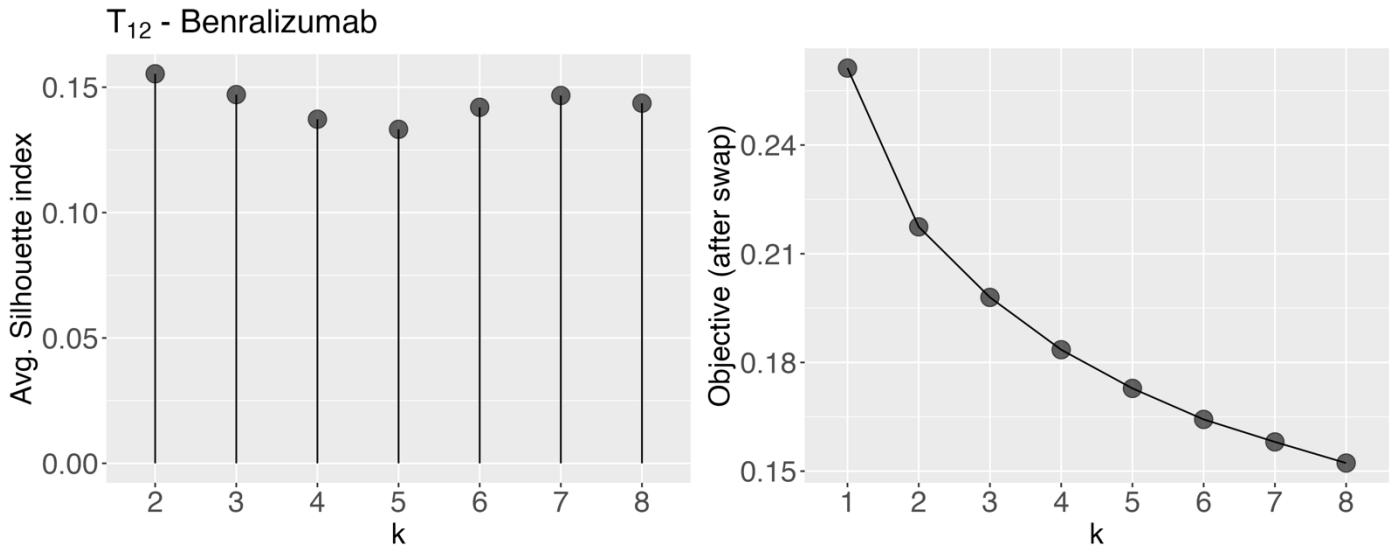
# Benralizumab

Descriptive statistics, $n = 157$ patients:

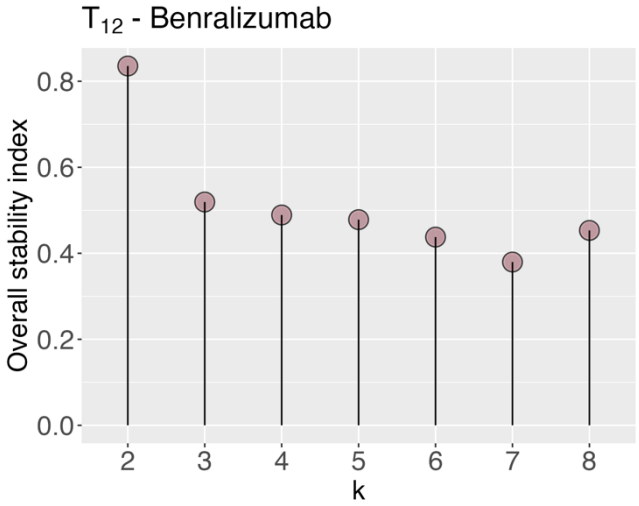
| Variable | n | Mean | SD | Test |
|---|---|---|---|---|
| Age | 157 | 54 | 13 | |
| Sex | 157 | | | |
| ... F | 96 | 61% | | |
| ... M | 61 | 39% | | |
| Body mass index | 157 | 26 | 5 | |
| Smoke | 157 | | | |
| ... no | 106 | 68% | | |
| ... yes | 51 | 32% | | |
| Asthma: age at onset | 157 | 34 | 14 | |
| Hereditariety | 157 | | | |
| ... no | 79 | 50% | | |
| ... yes | 78 | 50% | | |
| Prick test | 157 | | | |
| ... no | 70 | 45% | | |
| ... yes | 87 | 55% | | |
| N. exacerbations per year | 157 | 4 | 3 | |
| Oral corticosteroid | 157 | | | |
| ... no | 46 | 29% | | |
| ... yes | 111 | 71% | | |
| Asthma control test | 157 | 14 | 4 | |
| FEV1prePERC | 157 | 68 | 22 | |
| Blood eosinophils | 157 | 796 | 860 | |
| IgE total | 157 | 325 | 574 | |
| Bronchiecstasis | 157 | | | |
| ... no | 125 | 80% | | |
| ... yes | 32 | 20% | | |
| Chronic rhinosinusitis with nasal polyposis | 157 | | | |
| ... no | 79 | 50% | | |
| ... yes | 78 | 50% | | |
| ER=0 | 157 | | | |
| ... NON_RESPONDER_A | 48 | 31% | | |
| ... RESPONDER_A | 109 | 69% | | |
| ER=0 and OCS=0 | 157 | | | |
| ... NON_SUPER_RESPONDER_A | 50 | 32% | | |
| ... SUPER_RESPONDER_A | 107 | 68% | | |
| ER=0 and OCS=0 and ACT >= 20 | 157 | | | |
| ... NON_RESPONDER_B | 60 | 38% | | |
| ... RESPONDER_B | 97 | 62% | | |
| ER=0 and OCS=0 and ACT >= 20 and FEV1prePerc >= 80 | 157 | | | |
| ... NON_SUPER_RESPONDER_B | 105 | 67% | | |
| ... SUPER_RESPONDER_B | 52 | 33% | | |
| Statistical significance markers: * p<0.1; ** p<0.05; *** p<0.01 | | | | |

Determination of the optimal number of groups:

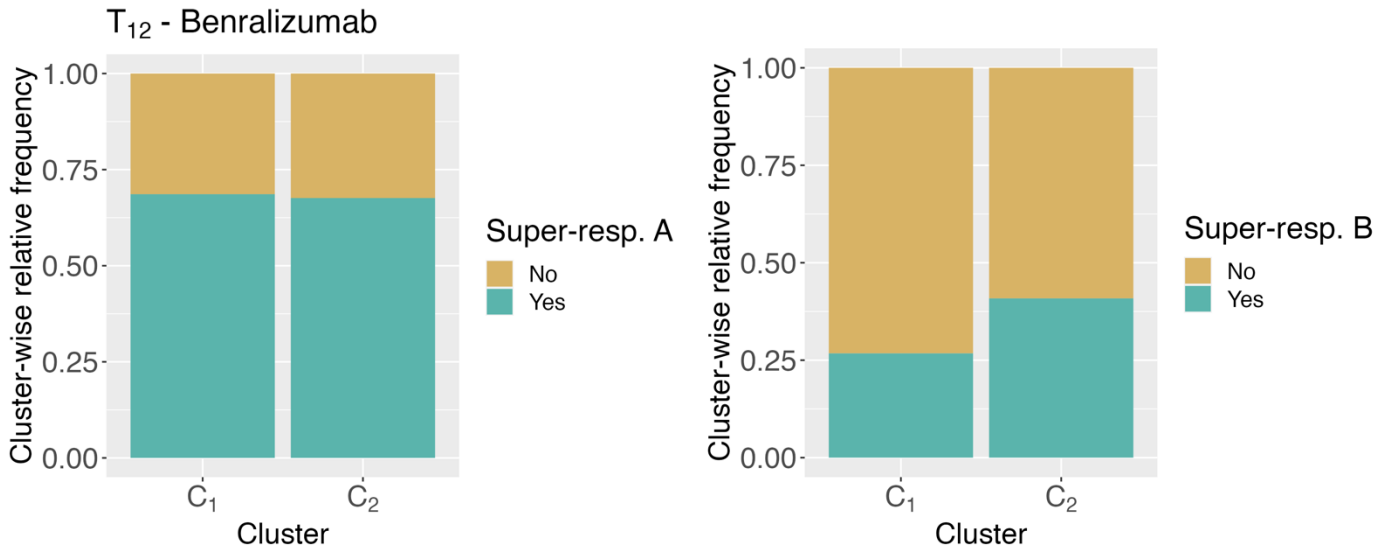
Average Silhouette index, $k^{\star} = 2$




Bootstrap-based cluster stability criteria, $k^{\star} = 2$



Distribution of the outcome variables across the two clusters:




Testing the difference between proportions:

```
> table(partition_final)
partition_final
C1 C2
86 71

    NON_SUPER_RESPONDER_A SUPER_RESPONDER_A
C1                    27                59
C2                    23                48

    NON_SUPER_RESPONDER_A SUPER_RESPONDER_A
C1                  31.4              68.6
C2                  32.4              67.6

     Pearson's Chi-squared test with Yates' continuity correction

data:  a
X-squared = 0, df = 1, p-value = 1


    NON_SUPER_RESPONDER_B SUPER_RESPONDER_B
C1                    63                23
C2                    42                29

    NON_SUPER_RESPONDER_B SUPER_RESPONDER_B
C1                  73.3              26.7
C2                  59.2              40.8

     Pearson's Chi-squared test with Yates' continuity correction

data:  b
X-squared = 2.8835, df = 1, p-value = 0.08949
```

Cluster-wise descriptive statistics:

| | C1 | | | | C2 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Mean** | **Sd** | **Min** | **Max** | **Mean** | **Sd** | **Min** | **Max** | **Test** |
| Age | 52 | 13 | 20 | 79 | 56 | 12 | 23 | 79 | F=5.174** |
| Sex | 86 | | | | 71 | | | | X2=0.919 |
| ... F | 56 | 65% | | | 40 | 56% | | | |
| ... M | 30 | 35% | | | 31 | 44% | | | |
| Body mass index | 27 | 5 | 17 | 46 | 26 | 4 | 18 | 47 | F=0.371 |
| Smoke | 86 | | | | 71 | | | | X2=2.442 |
| ... no | 53 | 62% | | | 53 | 75% | | | |
| ... yes | 33 | 38% | | | 18 | 25% | | | |
| Asthma: age at onset | 31 | 14 | 3 | 65 | 39 | 13 | 5 | 68 | F=14.184*** |
| Hereditariety | 86 | | | | 71 | | | | X2=40.217*** |
| ... no | 23 | 27% | | | 56 | 79% | | | |
| ... yes | 63 | 73% | | | 15 | 21% | | | |
| Prick test | 86 | | | | 71 | | | | X2=80.684*** |
| ... no | 10 | 12% | | | 60 | 85% | | | |
| ... yes | 76 | 88% | | | 11 | 15% | | | |
| N. exacerbations per y ear | 5 | 3 | 0 | 20 | 4 | 3 | 0 | 12 | F=1.864 |
| Oral corticosteroid | 86 | | | | 71 | | | | X2=0.011 |
| ... no | 26 | 30% | | | 20 | 28% | | | |
| ... yes | 60 | 70% | | | 51 | 72% | | | |
| Asthma control test | 14 | 4 | 5 | 24 | 14 | 4 | 6 | 25 | F=1.879 |
| FEV1prePERC | 65 | 22 | 28 | 131 | 71 | 22 | 26 | 124 | F=2.848* |
| Blood eosinophils | 748 | 534 | 11 | 3320 | 854 | 1138 | 17 | 9190 | F=0.589 |
| IgE total | 435 | 702 | 0.02 | 3406 | 191 | 322 | 15 | 1889 | F=7.312*** |
| Bronchiecstasis | 86 | | | | 71 | | | | X2=0.652 |
| ... no | 71 | 83% | | | 54 | 76% | | | |
| ... yes | 15 | 17% | | | 17 | 24% | | | |
| CRNP | 86 | | | | 71 | | | | X2=15.374*** |
| ... no | 56 | 65% | | | 23 | 32% | | | |
| ... yes | 30 | 35% | | | 48 | 68% | | | |
| Statistical significance markers: * p<0.1; ** p<0.05; *** p<0.01 | | | | | | | | | |

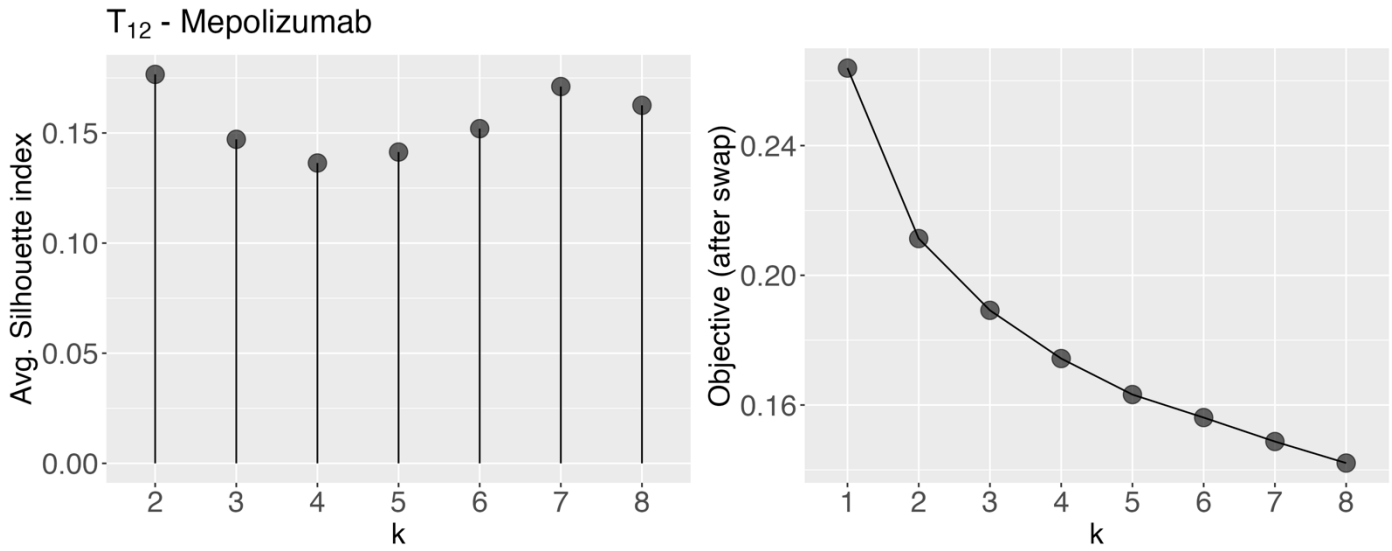
# Mepolizumab

Descriptive statistics, $N = 144$ pazienti:

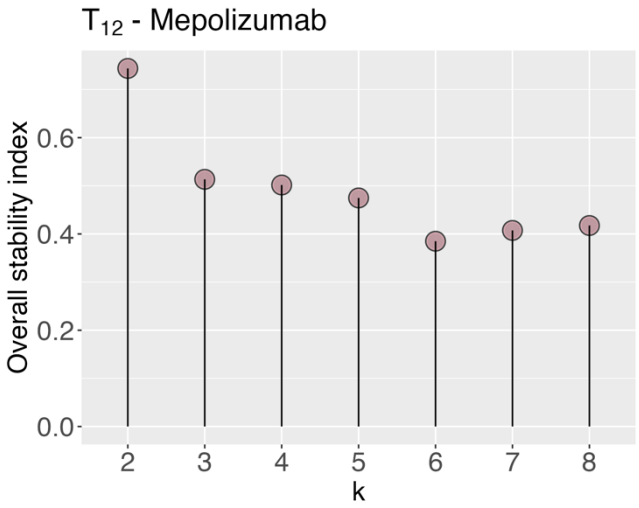
| Variable | N | Mean | SD | Test |
|---|---|---|---|---|
| Age | 144 | 57 | 13 | |
| Sex | 144 | | | |
| ... F | 100 | 69% | | |
| ... M | 44 | 31% | | |
| Body mass index | 144 | 27 | 6 | |
| Smoke | 144 | | | |
| ... no | 88 | 61% | | |
| ... yes | 56 | 39% | | |
| Asthma: age at onset | 144 | 36 | 16 | |
| Hereditariety | 144 | | | |
| ... no | 73 | 51% | | |
| ... yes | 71 | 49% | | |
| Prick test | 144 | | | |
| ... no | 49 | 34% | | |
| ... yes | 95 | 66% | | |
| N. exacerbations per year | 144 | 5 | 4 | |
| Oral corticosteroid | 144 | | | |
| ... no | 47 | 33% | | |
| ... yes | 97 | 67% | | |
| Asthma control test | 144 | 14 | 4 | |
| FEV1prePERC | 144 | 72 | 20 | |
| Blood eosinophils | 144 | 659 | 479 | |
| IgE total | 144 | 719 | 3321 | |
| Bronchiecstasis | 144 | | | |
| ... no | 127 | 88% | | |
| ... yes | 17 | 12% | | |
| Chronic rhinosinusitis with nasal polyposis | 144 | | | |
| ... no | 81 | 56% | | |
| ... yes | 63 | 44% | | |
| ER=0 | 144 | | | |
| ... NON_RESPONDER_A | 44 | 31% | | |
| ... RESPONDER_A | 100 | 69% | | |
| ER=0 and OCS=0 | 144 | | | |
| ... NON_SUPER_RESPONDER_A | 50 | 35% | | |
| ... SUPER_RESPONDER_A | 94 | 65% | | |
| ER=0 and OCS=0 and ACT >= 20 | 144 | | | |
| ... NON_RESPONDER_B | 66 | 46% | | |
| ... RESPONDER_B | 78 | 54% | | |
| ER=0 and OCS=0 and ACT >= 20 and FEV1pr ePerc >= 80 | 144 | | | |
| ... NON_SUPER_RESPONDER_B | 93 | 65% | | |
| ... SUPER_RESPONDER_B | 51 | 35% | | |
| Statistical significance markers: * p<0.1; ** p<0.05; *** p<0.01 | | | | |

Determination of the optimal number of groups:

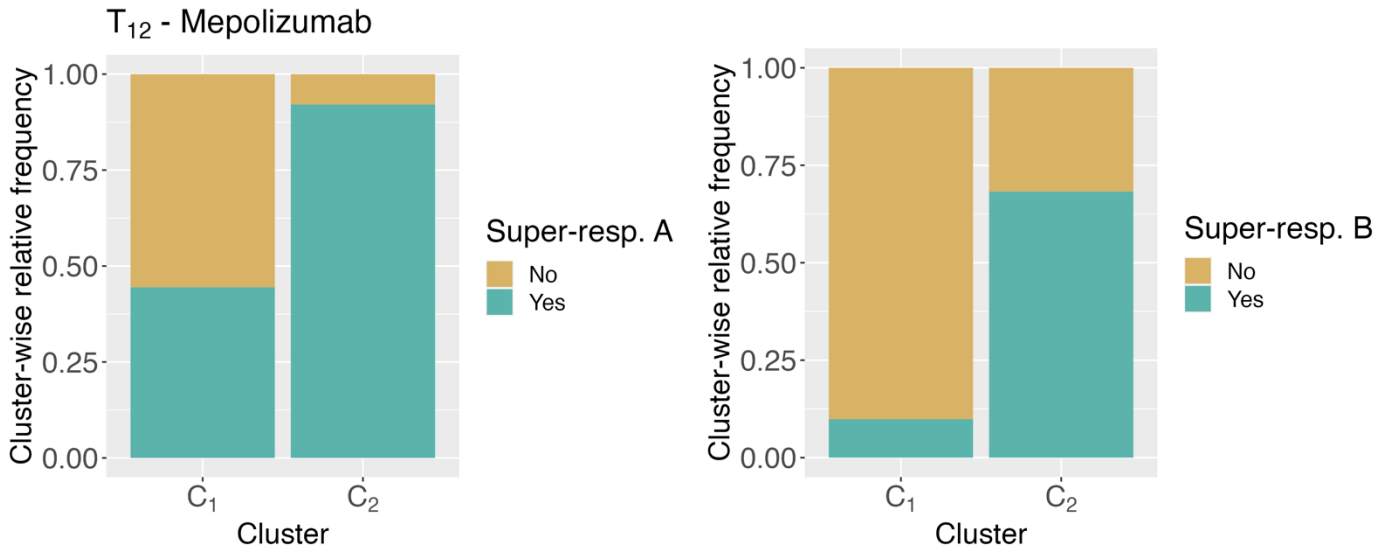
Average Silhouette index, $k^{\star} = 2$




Bootstrap-based cluster stability criteria, $k^{\star} = 2$



Distribution of the outcome variables across the two clusters:



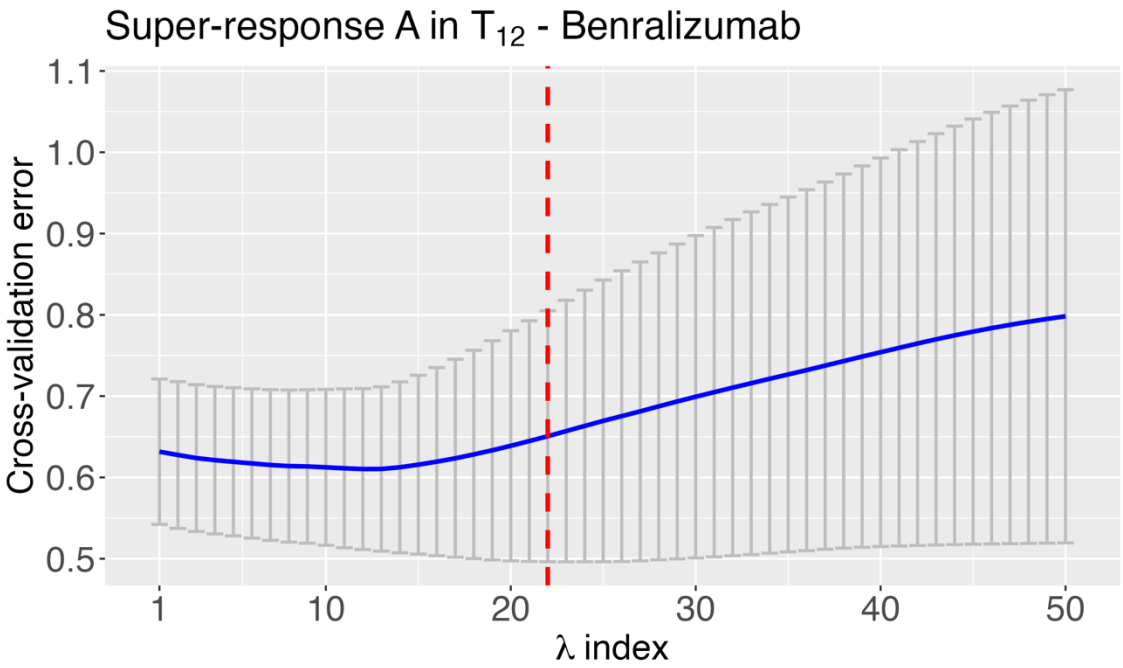

Testing the difference between proportions:

```
partition_final
C1 C2
81 63

    NON_SUPER_RESPONDER_A SUPER_RESPONDER_A
  C1                    45                 36
  C2                     5                 58

    NON_SUPER_RESPONDER_A SUPER_RESPONDER_A
  C1                  55.6               44.4
  C2                   7.9               92.1

      Pearson's Chi-squared test with Yates' continuity correction

data:  a
X-squared = 33.383, df = 1, p-value = 7.568e-09


    NON_SUPER_RESPONDER_B SUPER_RESPONDER_B
  C1                    73                  8
  C2                    20                 43

    NON_SUPER_RESPONDER_B SUPER_RESPONDER_B
  C1                  90.1                9.9
  C2                  31.7               68.3

      Pearson's Chi-squared test with Yates' continuity correction

data:  b
X-squared = 50.278, df = 1, p-value = 1.335e-12
```

Cluster-wise descriptive statistics:

| | C1 | | | | C2 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Mean** | **Sd** | **Min** | **Max** | **Mean** | **Sd** | **Min** | **Max** | **Test** |
| Age | 58 | 13 | 18 | 84 | 56 | 11 | 24 | 78 | F=0.541 |
| Sex | 81 | | | | 63 | | | | X2=0.075 |
| ... F | 55 | 68% | | | 45 | 71% | | | |
| ... M | 26 | 32% | | | 18 | 29% | | | |
| Body mass index | 29 | 6 | 18 | 54 | 26 | 5 | 16 | 46 | F=8.88*** |
| Smoke | 81 | | | | 63 | | | | X2=0.119 |
| ... no | 51 | 63% | | | 37 | 59% | | | |
| ... yes | 30 | 37% | | | 26 | 41% | | | |
| Asthma: age at onset | 34 | 17 | 1 | 76 | 38 | 15 | 5 | 68 | F=1.837 |
| Hereditariety | 81 | | | | 63 | | | | X2=20.766*** |
| ... no | 27 | 33% | | | 46 | 73% | | | |
| ... yes | 54 | 67% | | | 17 | 27% | | | |
| Prick test | 81 | | | | 63 | | | | X2=32.432*** |
| ... no | 11 | 14% | | | 38 | 60% | | | |
| ... yes | 70 | 86% | | | 25 | 40% | | | |
| N. exacerbations per y ear | 6 | 4 | 0 | 20 | 4 | 3 | 0 | 15 | F=6.132** |
| Oral corticosteroid | 81 | | | | 63 | | | | X2=3.129* |
| ... no | 21 | 26% | | | 26 | 41% | | | |
| ... yes | 60 | 74% | | | 37 | 59% | | | |
| Asthma control test | 13 | 4 | 5 | 24 | 15 | 4 | 8 | 24 | F=8.863*** |
| FEV1prePERC | 68 | 21 | 27 | 118 | 76 | 19 | 26 | 113 | F=5.312** |
| Blood eosinophils | 671 | 554 | 120 | 3243 | 645 | 366 | 153 | 1840 | F=0.105 |
| IgE total | 469 | 617 | 2 | 2669 | 1041 | 4975 | 8 | 36395 | F=1.05 |
| Bronchiecstasis | 81 | | | | 63 | | | | X2=1.153 |
| ... no | 74 | 91% | | | 53 | 84% | | | |
| ... yes | 7 | 9% | | | 10 | 16% | | | |
| CRNP | 81 | | | | 63 | | | | X2=13.717*** |
| ... no | 57 | 70% | | | 24 | 38% | | | |
| ... yes | 24 | 30% | | | 39 | 62% | | | |
| Statistical significance markers: * p<0.1; ** p<0.05; *** p<0.01 | | | | | | | | | |

# Super-response A – Benralizumab




Active variables (best λ)

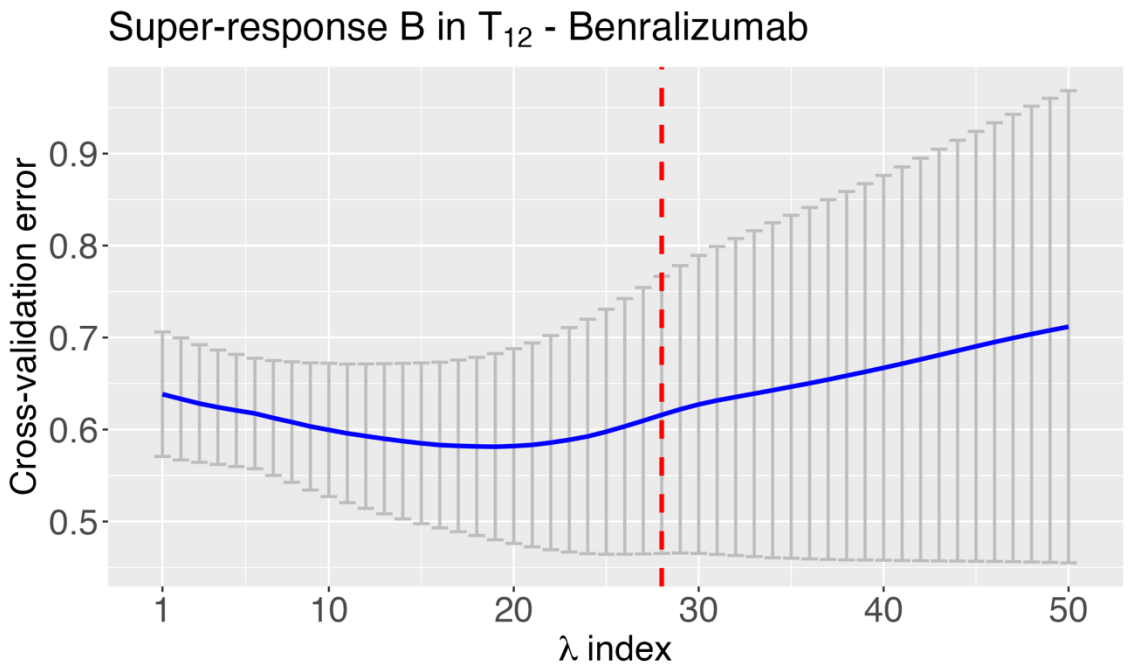
| categorical | continuous |
|---|---|
| Bronchiectasis (yes) | NO |
| CRNP (yes) | NA |

Legend. In this table, as in the others, NA is a placeholder to obtain the same number of lines on the left and right sides. In this case, the optimal model contains two categorical variables and no continuous variables.

Active variables ($p \leq 8$)

| categorical | continuous |
|---|---|
| Sex (male) | Age (Δ = 5 yrs.) |
| Smoke (yes/ex) | N.exacerb. YR |
| Hereditariety (yes) | NA |
| Prick test (positive) | NA |
| Bronchiectasis (yes) | NA |
| CRNP (yes) | NA |

# Super-response B – Benralizumab



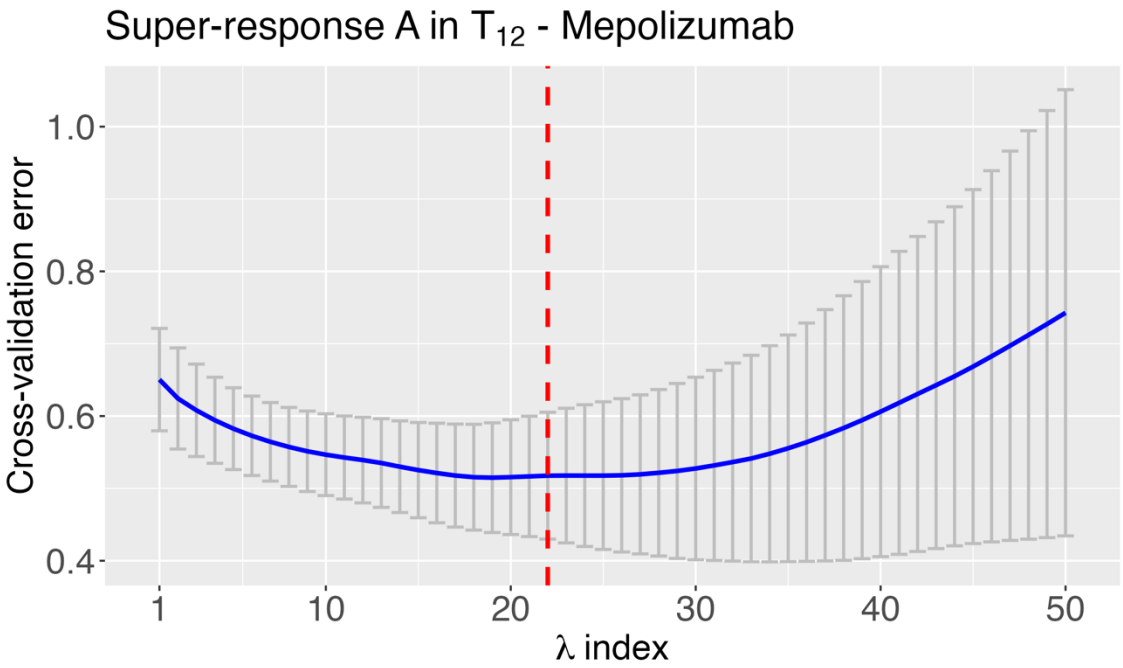

Active variables (best λ)

| categorical | continuous |
|---|---|
| Hereditariety (yes) | N.exacerb. YR |
| Bronchiectasis (yes) | NA |
| CRNP (yes) | NA |

Active variables ($p \leq 8$)

| categorical | continuous |
|---|---|
| Hereditariety (yes) | Age (Δ = 5 yrs.) |
| Bronchiectasis (yes) | BMI (Δ = 5 pts.) |
| CRNP (yes) | Asthma AAO (Δ = 5 yrs.) |
| NA | N.exacerb. YR |
| NA | IgE total (Δ = 100 IU/mL) |

# Super-response A – Mepolizumab



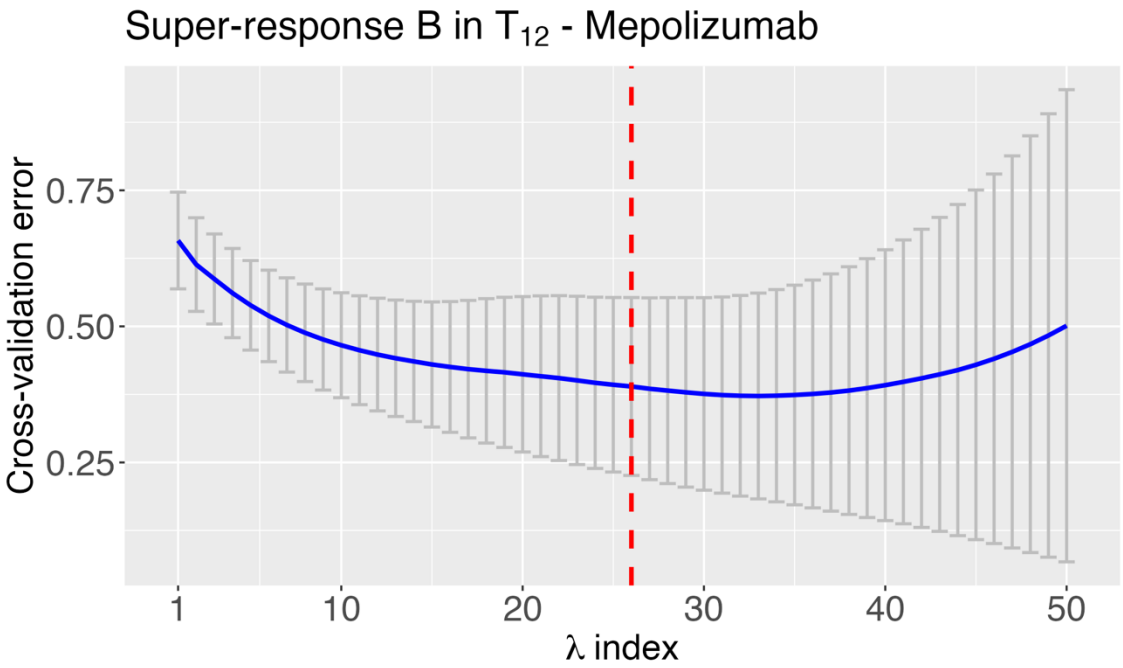

Active variables (best λ)

| categorical | continuous |
|---|---|
| Sex (male) | N.exacerb. YR |
| Smoke (yes/ex) | FEV1% pred. (Δ = 10 pts.) |
| Hereditariety (yes) | NA |

Active variables ($p \leq 8$)

| categorical | continuous |
|---|---|
| Sex (male) | N.exacerb. YR |
| Smoke (yes/ex) | ACT (Δ = 5 pts.) |
| Hereditariety (yes) | FEV1% pred. (Δ = 10 pts.) |
| Prick test (positive) | NA |
| Bronchiectasis (yes) | NA |
| CRNP (yes) | NA |

# Super-response B – Mepolizumab




Active variables

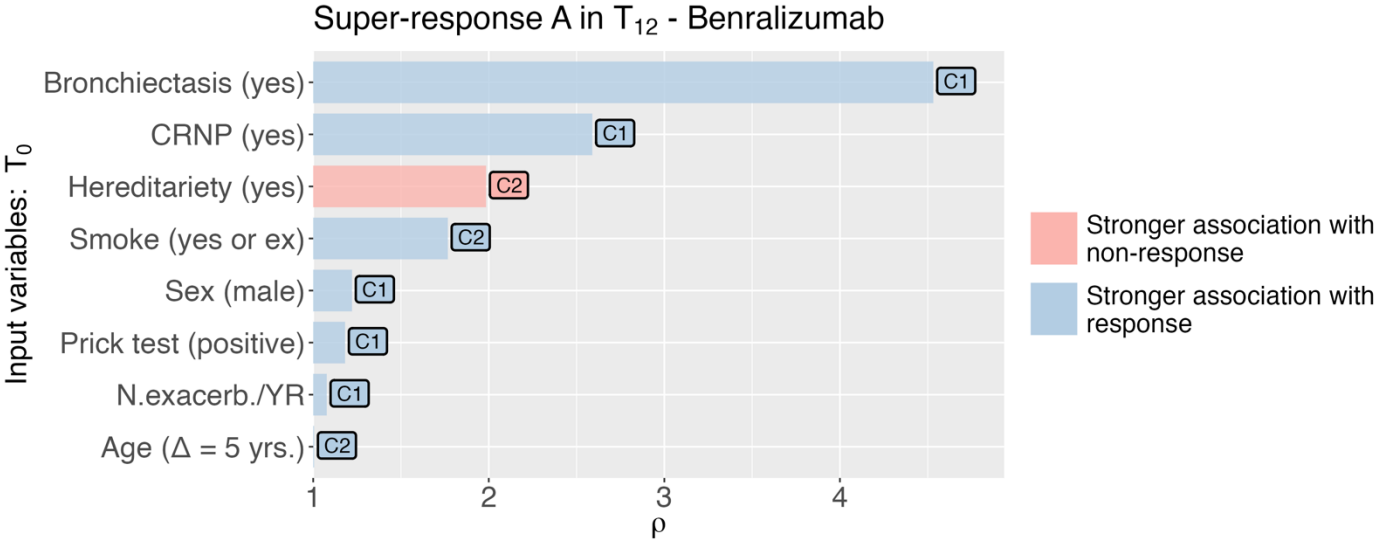
| categorical | continuous |
|---|---|
| Sex (male) | Age (Δ = 5 yrs.) |
| Smoke (yes/ex) | N.exacerb. YR |
| Prick test (positive) | FEV1% pred. (Δ = 10 pts.) |
| OCS (yes) | Blood EOS (Δ = 100 cells/µL) |
| Bronchiectasis (yes) | NA |

Active variables ($p \leq 8$)

| categorical | continuous |
|---|---|
| Sex (male) | FEV1% pred. (Δ = 10 pts.) |
| Smoke (yes/ex) | Blood EOS (Δ = 100 cells/µL) |
| Hereditariety (yes) | NA |
| Prick test (positive) | NA |
| OCS (yes) | NA |
| Bronchiectasis (yes) | NA |

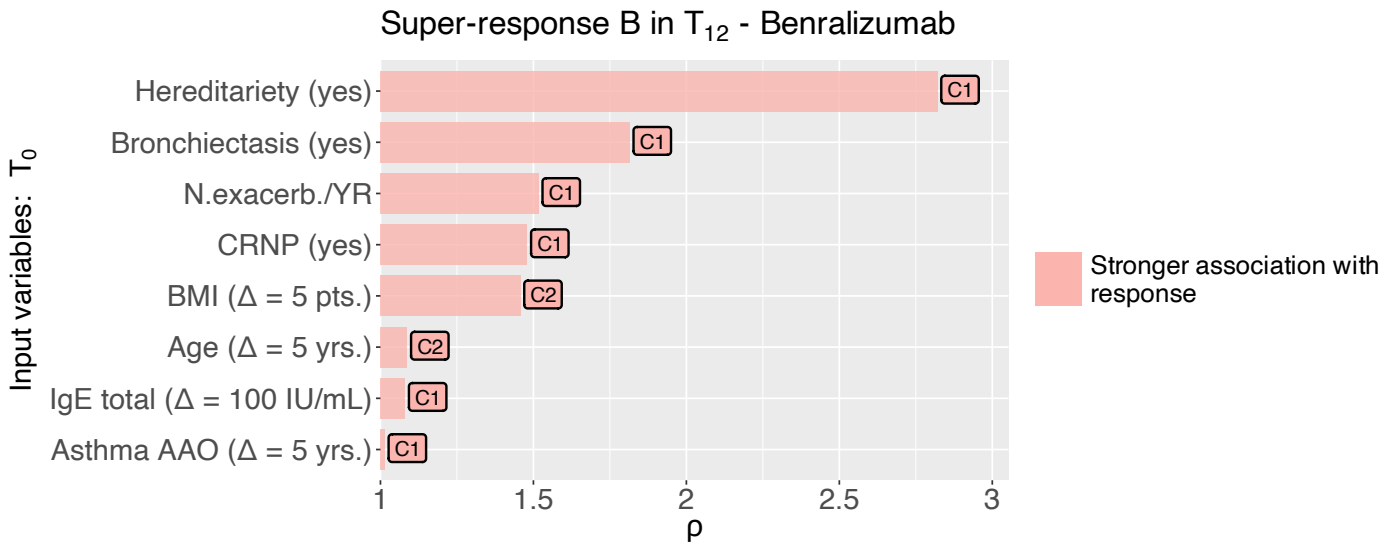
# Super-rensponse A – Benralizumab

| Variable | C1_OR | C2_OR | STRONGer | TYPE | TYPE2 | rho |
|---|---|---|---|---|---|---|
| Age (Δ = 5 yrs.) | 1.23 | 1.24 | C2 | ++ | Stronger association with response | 1.01 |
| N.exacerb./YR | 1.03 | 0.95 | C1 | +- | Stronger association with response | 1.08 |
| Prick test (positive) | 1.11 | 0.94 | C1 | +- | Stronger association with response | 1.18 |
| Sex (male) | 1.23 | 1.01 | C1 | ++ | Stronger association with response | 1.22 |
| Smoke (yes or ex) | 0.58 | 1.03 | C2 | -+ | Stronger association with response | 1.77 |
| Hereditariety (yes) | 0.97 | 0.49 | C2 | -- | Stronger association with non-response | 1.98 |
| CRNP (yes) | 4.78 | 1.84 | C1 | ++ | Stronger association with response | 2.59 |
| Bronchiectasis (yes) | 3.32 | 0.73 | C1 | +- | Stronger association with response | 4.53 |



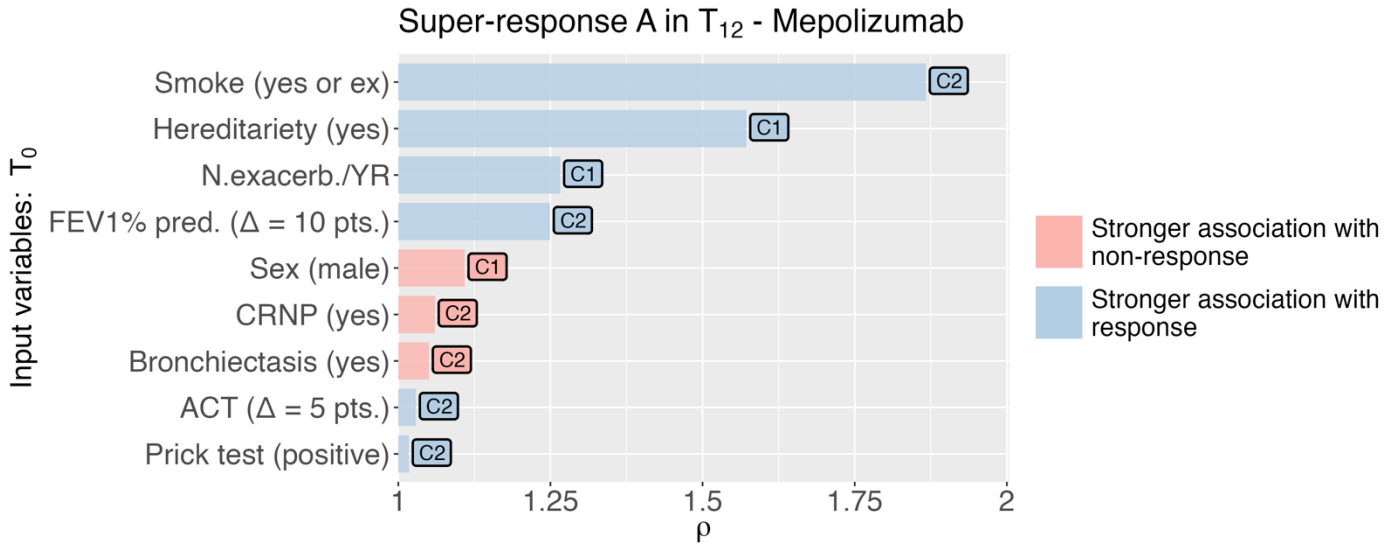
# Super-response B – Benralizumab

| Variable | C1_OR | C2_OR | STRONGer | TYPE | TYPE2 | rho |
|---|---|---|---|---|---|---|
| Asthma AAO (Δ = 5 yrs.) | 1.11 | 1.09 | C1 | ++ | Stronger association with response | 1.01 |
| IgE total (Δ = 100 IU/mL) | 1.04 | 0.96 | C1 | +- | Stronger association with response | 1.08 |
| Age (Δ = 5 yrs.) | 0.95 | 1.04 | C2 | -+ | Stronger association with response | 1.09 |
| BMI (Δ = 5 pts.) | 0.81 | 1.18 | C2 | -+ | Stronger association with response | 1.46 |
| CRNP (yes) | 1.75 | 1.19 | C1 | ++ | Stronger association with response | 1.48 |
| N.exacerb./YR | 1.20 | 0.79 | C1 | +- | Stronger association with response | 1.52 |
| Bronchiectasis (yes) | 2.40 | 1.32 | C1 | ++ | Stronger association with response | 1.81 |
| Hereditariety (yes) | 2.16 | 0.76 | C1 | +- | Stronger association with response | 2.82 |



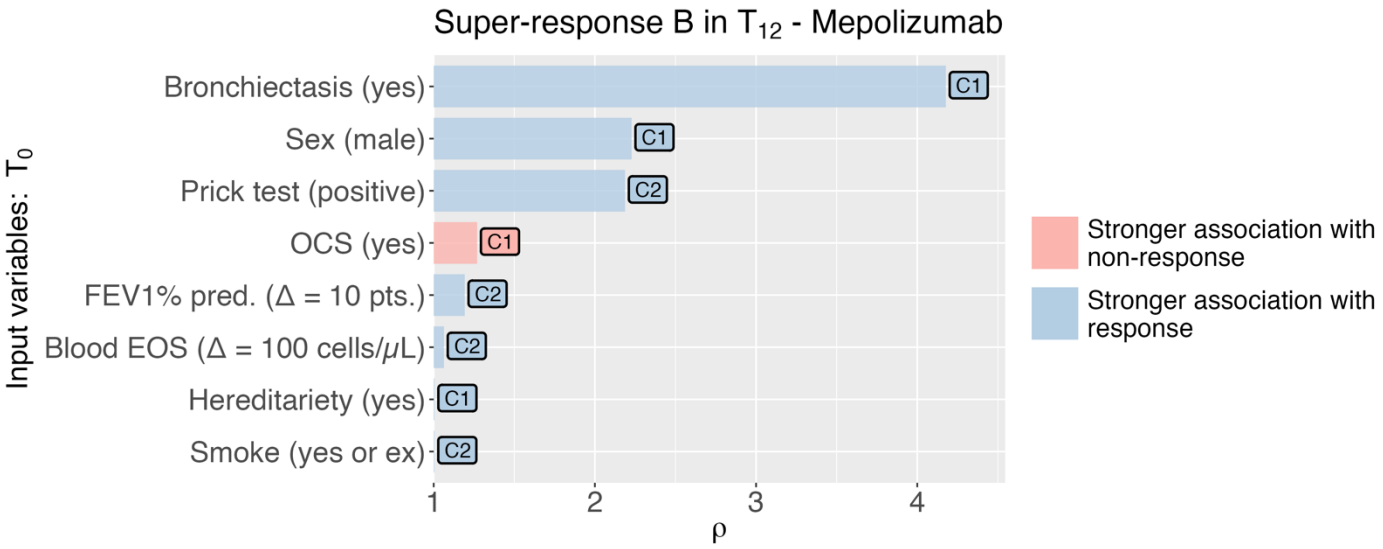
# Super-risposta A – Mepolizumab

| Variable | C1_OR | C2_OR | STRONGer | TYPE | TYPE2 | rho |
|---|---|---|---|---|---|---|
| Prick test (positive) | 1.03 | 1.05 | C2 | ++ | Stronger association with response | 1.02 |
| ACT (Δ = 5 pts.) | 0.98 | 1.01 | C2 | -+ | Stronger association with response | 1.03 |
| Bronchiectasis (yes) | 1.00 | 0.95 | C2 | -- | Stronger association with non-response | 1.05 |
| CRNP (yes) | 0.92 | 0.87 | C2 | -- | Stronger association with non-response | 1.06 |
| Sex (male) | 0.71 | 0.79 | C1 | -- | Stronger association with non-response | 1.11 |
| FEV1% pred. (Δ = 10 pts.) | 0.96 | 1.20 | C2 | -+ | Stronger association with response | 1.25 |
| N.exacerb./YR | 1.17 | 0.93 | C1 | +- | Stronger association with response | 1.27 |
| Hereditariety (yes) | 1.94 | 1.23 | C1 | ++ | Stronger association with response | 1.57 |
| Smoke (yes or ex) | 0.64 | 1.19 | C2 | -+ | Stronger association with response | 1.87 |



# Super-response B – Mepolizumab

| Variable | C1_OR | C2_OR | STRONGer | TYPE | TYPE2 | rho |
|---|---|---|---|---|---|---|
| Smoke (yes or ex) | 1.00 | 1.00 | C2 | -+ | Stronger association with response | 1.00 |
| Hereditariety (yes) | 1.91 | 1.90 | C1 | ++ | Stronger association with response | 1.01 |
| Blood EOS (Δ = 100 cells/µL) | 1.04 | 1.10 | C2 | ++ | Stronger association with response | 1.06 |
| FEV1% pred. (Δ = 10 pts.) | 1.65 | 1.96 | C2 | ++ | Stronger association with response | 1.19 |
| OCS (yes) | 0.67 | 0.85 | C1 | -- | Stronger association with non-response | 1.27 |
| Prick test (positive) | 1.12 | 2.44 | C2 | ++ | Stronger association with response | 2.19 |
| Sex (male) | 1.15 | 0.52 | C1 | +- | Stronger association with response | 2.23 |
| Bronchiectasis (yes) | 1.18 | 0.28 | C1 | +- | Stronger association with response | 4.18 |



# Super-risposta A – Benralizumab

| Variable | C1_OR_boot | C1_BCa | C2_OR_boot | C2_BCa | STRONGer | TYPE | TYPE2 | Significance | rho |
|---|---|---|---|---|---|---|---|---|---|
| Bronchiectasis (yes) | 3.10 | (1.18, 20.26) | 1.04 | (0.61, 6.96) | C1 | ++ | Stronger association with response | YES | 2.97 |
| CRNP (yes) | 5.53 | (2.31, 43.36) | 2.30 | (0.89, 10.16) | C1 | ++ | Stronger association with response | YES | 2.40 |
| Hereditariety (yes) | 1.08 | (0.60, 3.65) | 0.62 | (0.14, 1.00) | C1 | +- | Stronger association with response | NO | 1.74 |
| Smoke (yes or ex) | 0.64 | (0.21, 1.01) | 1.05 | (0.54, 4.72) | C2 | -+ | Stronger association with response | NO | 1.65 |
| Prick test (positive) | 1.43 | (1.00, 11.47) | 0.97 | (0.17, 1.17) | C1 | +- | Stronger association with response | NO | 1.47 |
| Sex (male) | 1.48 | (1.00, 6.29) | 1.16 | (0.84, 3.37) | C1 | ++ | Stronger association with response | NO | 1.27 |
| OCS (yes) | 1.20 | (1.00, 5.13) | 1.01 | (0.98, 3.87) | C1 | ++ | Stronger association with response | NO | 1.19 |
| N.exacerb./YR | 1.05 | (0.86, 1.60) | 0.93 | (0.62, 1.12) | C1 | +- | Stronger association with response | NO | 1.13 |
| Asthma AAO (Δ = 5 yrs.) | 1.07 | (0.93, 1.70) | 0.97 | (0.55, 1.15) | C1 | +- | Stronger association with response | NO | 1.11 |
| Age (Δ = 5 yrs.) | 1.20 | (0.92, 1.85) | 1.33 | (1.00, 2.44) | C2 | ++ | Stronger association with response | NO | 1.10 |
| BMI (Δ = 5 pts.) | 1.00 | (0.69, 3.85) | 1.10 | (0.76, 4.32) | C2 | ++ | Stronger association with response | NO | 1.09 |
| ACT (Δ = 5 pts.) | 1.53 | (1.00, 7.11) | 1.41 | (0.88, 7.49) | C1 | ++ | Stronger association with response | NO | 1.09 |
| FEV1% pred. (Δ = 10 pts.) | 1.02 | (0.85, 1.69) | 1.10 | (0.91, 1.85) | C2 | ++ | Stronger association with response | NO | 1.09 |
| Blood EOS (Δ = 100 cells/μL) | 1.06 | (1.00, 1.26) | 1.05 | (0.97, 1.23) | C1 | ++ | Stronger association with response | NO | 1.01 |
| IgE total (Δ = 100 IU/mL) | 0.99 | (0.84, 1.07) | 0.99 | (0.79, 1.06) | C1 | -- | Stronger association with non-response | NO | 1.00 |

| | **Explanatory variables of response ($\rho$)** | **Responders** | **Most significant input variables in T0** |
|---|---|---|---|
| C1 vs. C2 | Bronchiectstasis (YES) +197% association with response | C1: 68.6% vs. C2: 67.6% | Asthma: age at onset (C1: 31 vs. C2: 39) ↓ |
| | CNRP (YES) +140% association with response | | Hereditariety (yes) (73% C1 vs. 21% C2) ↑ |
| | | | Prick test (yes) (88% C1 vs. 15% C2) ↑ |
| | | | IgE total (435 C1 vs. 191 C2) ↑ |
| | | | CNRP (yes) (35% C1 vs. 68% C2) ↓ |
| | | | |
| C2 vs. C1 | | | |

# Super-response B – Benralizumab

| Variable | C1_OR_boot | C1_BCa | C2_OR_boot | C2_BCa | STRONGer | TYPE | TYPE2 | Significance | rho |
|---|---|---|---|---|---|---|---|---|---|
| Hereditariety (yes) | 2.95 | (1.12, 59.23) | 0.91 | (0.27, 2.18) | C1 | +- | Stronger association with response | YES | 3.23 |
| Bronchiectasis (yes) | 3.06 | (1.14, 24.95) | 1.59 | (0.81, 7.63) | C1 | ++ | Stronger association with response | YES | 1.93 |
| BMI (Δ = 5 pts.) | 0.83 | (0.26, 1.42) | 1.38 | (1.00, 19.43) | C2 | -+ | Stronger association with response | NO | 1.66 |
| CRNP (yes) | 2.22 | (1.00, 10.90) | 1.42 | (0.77, 5.73) | C1 | ++ | Stronger association with response | YES | 1.57 |
| N.exacerb./YR | 1.21 | (0.93, 1.81) | 0.83 | (0.56, 1.13) | C1 | +- | Stronger association with response | NO | 1.47 |
| Age (Δ = 5 yrs.) | 0.93 | (0.60, 1.14) | 1.10 | (0.89, 2.26) | C2 | -+ | Stronger association with response | NO | 1.18 |
| ACT (Δ = 5 pts.) | 0.95 | (0.27, 1.87) | 0.82 | (0.21, 1.46) | C2 | -- | Stronger association with non-response | NO | 1.17 |
| Smoke (yes or ex) | 1.05 | (0.92, 4.53) | 1.22 | (1.00, 6.86) | C2 | ++ | Stronger association with response | NO | 1.16 |
| OCS (yes) | 0.89 | (0.21, 1.05) | 0.98 | (0.27, 1.18) | C1 | -- | Stronger association with non-response | NO | 1.10 |
| IgE total (Δ = 100 IU/mL) | 1.05 | (0.96, 1.28) | 0.96 | (0.59, 1.07) | C1 | +- | Stronger association with response | NO | 1.09 |
| FEV1% pred. (Δ = 10 pts.) | 1.96 | (1.30, 3.63) | 2.11 | (1.45, 4.32) | C2 | ++ | Stronger association with response | YES | 1.08 |
| Asthma AAO (Δ = 5 yrs.) | 1.15 | (1.00, 1.82) | 1.08 | (0.91, 1.73) | C1 | ++ | Stronger association with response | NO | 1.07 |
| Sex (male) | 1.41 | (0.99, 6.31) | 1.33 | (0.97, 5.11) | C1 | ++ | Stronger association with response | NO | 1.06 |
| Blood EOS (Δ = 100 cells/μL) | 1.18 | (1.05, 1.65) | 1.14 | (1.02, 1.45) | C1 | ++ | Stronger association with response | YES | 1.03 |
| Prick test (positive) | 0.95 | (0.09, 1.00) | 0.97 | (0.05, 1.00) | C1 | -- | Stronger association with non-response | NO | 1.02 |

| | Explanatory variables of response ($\rho$) | Responders | Most significant input variables in T0 |
|---|---|---|---|
| C1 vs. C2 | Hereditariety (YES) +223% association with response | C1: 26.7% vs. C2: 40.8% | Asthma: age at onset (C1: 31 vs. C2: 39) ↓ |
| | Bronchiectstasis (YES) +93% association with response | | Hereditariety (yes) (73% C1 vs. 21% C2) ↑ |
| | CNRP (YES) +57% association with response | | Prick test (yes) (88% C1 vs. 15% C2) ↑ |
| | Blood EOS (Δ = 100 cells/ml) +3% association with response | | IgE total (435 C1 vs. 191 C2) ↑ |
| | | | CNRP (yes) (35% C1 vs. 68% C2) ↓ |
| | | | |
| C2 vs. C1 | FEV1% pred (Δ = 10 pts.) +8% association with response | | |

# Super-response A – Mepolizumab

| Variable | C1_OR_boot | C1_BCa | C2_OR_boot | C2_BCa | STRONGer | TYPE | TYPE2 | Significance | rho |
|---|---|---|---|---|---|---|---|---|---|
| Hereditariety (yes) | 3.15 | (1.37, 23.49) | 1.35 | (1.00, 8.08) | C1 | ++ | Stronger association with response | YES | 2.34 |
| Smoke (yes or ex) | 0.62 | (0.17, 1.00) | 1.40 | (1.00, 6.39) | C2 | -+ | Stronger association with response | NO | 2.24 |
| FEV1% pred. (Δ = 10 pts.) | 1.00 | (0.80, 2.00) | 1.32 | (1.00, 4.29) | C2 | ++ | Stronger association with response | NO | 1.32 |
| N.exacerb./YR | 1.22 | (1.00, 1.94) | 0.93 | (0.59, 1.03) | C1 | +- | Stronger association with response | NO | 1.31 |
| Bronchiectasis (yes) | 1.03 | (1.00, 7.63) | 0.83 | (0.10, 1.00) | C1 | +- | Stronger association with response | NO | 1.25 |
| ACT (Δ = 5 pts.) | 0.83 | (0.15, 1.07) | 1.01 | (0.73, 4.82) | C2 | -+ | Stronger association with response | NO | 1.22 |
| CRNP (yes) | 0.92 | (0.16, 1.12) | 0.78 | (0.13, 1.00) | C2 | -- | Stronger association with non-response | NO | 1.17 |
| BMI (Δ = 5 pts.) | 1.17 | (1.00, 3.52) | 1.02 | (0.98, 3.89) | C1 | ++ | Stronger association with response | NO | 1.15 |
| Sex (male) | 0.72 | (0.17, 1.02) | 0.80 | (0.13, 1.02) | C1 | -- | Stronger association with non-response | NO | 1.12 |
| OCS (yes) | 0.88 | (0.11, 1.00) | 0.93 | (0.22, 1.00) | C1 | -- | Stronger association with non-response | NO | 1.06 |
| Asthma AAO (Δ = 5 yrs.) | 0.96 | (0.58, 1.03) | 0.94 | (0.47, 1.00) | C2 | -- | Stronger association with non-response | NO | 1.03 |
| Blood EOS (Δ = 100 cells/μL) | 1.03 | (0.95, 1.38) | 1.01 | (0.99, 1.37) | C1 | ++ | Stronger association with response | NO | 1.02 |
| Age (Δ = 5 yrs.) | 1.03 | (1.00, 2.05) | 1.05 | (1.00, 2.90) | C2 | ++ | Stronger association with response | NO | 1.01 |
| IgE total (Δ = 100 IU/mL) | 1.00 | (1.00, 1.34) | 1.00 | (1.00, 1.34) | C2 | ++ | Stronger association with response | NO | 1.00 |
| Prick test (positive) | 1.30 | (1.00, 7.41) | 1.30 | (1.00, 7.56) | C1 | ++ | Stronger association with response | NO | 1.00 |

| | Explanatory variables of response (ρ) | Responders | Most significant input variables in T0 |
|---|---|---|---|
| C1 vs. C2 | Hereditariety (yes) +134% association with response | C1: 44.4% vs. C2: 92.1% ↓ | BMI (C1: 29 vs. C2: 26) ↑ |
| | | | Hereditariety (yes) (67% C1 vs. 27% C2) ↑ |
| | | | Prick test (yes) (86% C1 vs. 40% C2) ↑ |
| | | | ACT (Δ = 10 pts.) (13 C1 vs. 15 C2) ↓ |
| | | | CNRP (yes) (30% C1 vs. 62% C2) ↓ |
| C2 vs. C1 | | | |

# Super-response B – Mepolizumab

| Variable | C1_OR_boot | C1_BCa | C2_OR_boot | C2_BCa | STRONGer | TYPE | TYPE2 | Significance | rho |
|---|---|---|---|---|---|---|---|---|---|
| Sex (male) | 1.64 | (0.97, 14.66) | 0.52 | (0.06, 1.00) | C1 | +- | Stronger association with response | NO | 3.19 |
| Bronchiectasis (yes) | 1.19 | (0.82, 2.12) | 0.39 | (0.07, 1.00) | C1 | +- | Stronger association with response | NO | 3.09 |
| Prick test (positive) | 1.19 | (0.98, 6.83) | 3.09 | (1.04, 26.70) | C2 | ++ | Stronger association with response | YES | 2.60 |
| Smoke (yes or ex) | 0.80 | (0.12, 1.00) | 1.33 | (1.00, 13.84) | C2 | -+ | Stronger association with response | NO | 1.65 |
| FEV1% pred. (Δ = 10 pts.) | 1.89 | (1.13, 4.96) | 2.88 | (1.66, 22.40) | C2 | ++ | Stronger association with response | YES | 1.53 |
| Hereditariety (yes) | 3.89 | (1.46, 172.87) | 2.96 | (1.10, 38.05) | C1 | ++ | Stronger association with response | YES | 1.31 |
| OCS (yes) | 0.60 | (0.11, 1.03) | 0.75 | (0.10, 1.19) | C1 | -- | Stronger association with non-response | NO | 1.26 |
| ACT (Δ = 5 pts.) | 1.01 | (1.00, 18.10) | 0.84 | (0.06, 1.00) | C1 | +- | Stronger association with response | NO | 1.20 |
| BMI (Δ = 5 pts.) | 1.48 | (0.98, 5.22) | 1.29 | (0.98, 5.36) | C1 | ++ | Stronger association with response | NO | 1.15 |
| Blood EOS (Δ = 100 cells/µL) | 1.05 | (0.96, 1.71) | 1.17 | (1.00, 2.69) | C2 | ++ | Stronger association with response | NO | 1.11 |
| Age (Δ = 5 yrs.) | 1.05 | (1.00, 2.83) | 0.95 | (0.47, 1.00) | C1 | +- | Stronger association with response | NO | 1.10 |
| N.exacerb./YR | 1.05 | (1.00, 2.10) | 0.99 | (0.50, 1.00) | C1 | +- | Stronger association with response | NO | 1.06 |
| Asthma AAO (Δ = 5 yrs.) | 0.99 | (0.46, 1.00) | 0.96 | (0.52, 1.00) | C2 | -- | Stronger association with non-response | NO | 1.03 |
| CRNP (yes) | 0.66 | (0.15, 1.00) | 0.64 | (0.15, 1.00) | C2 | -- | Stronger association with non-response | NO | 1.02 |
| IgE total (Δ = 100 IU/mL) | 1.01 | (1.00, 1.45) | 1.00 | (1.00, 1.39) | C1 | ++ | Stronger association with response | YES | 1.01 |

| | Explanatory variables of response (ρ) | Responders | Most significant input variables in T0 |
|---|---|---|---|
| C1 vs. C2 | Hereditariety (yes) +31% association with response | C1: 9.9% vs. C2: 68.3% ↓ | BMI (C1: 29 vs. C2: 26) ↑ |
| | IgE Total + 1% association with response | | Hereditariety (yes) (67% C1 vs. 27% C2) ↑ |
| | | | Prick test (yes) (86% C1 vs. 40% C2) ↑ |
| | | | ACT (Δ = 10 pts.) (13 C1 vs. 15 C2) ↓ |
| | | | CNRP (yes) (30% C1 vs. 62% C2) ↓ |
| C2 vs. C1 | Prick test (positive) +160% association with response | | |