# Long-Acting Beta-Agonists and Serious Asthma-Related Events Meta-Analysis

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# Outline

1. Goals/Objectives
2. Methods
   - Data Sources
   - Endpoints
   - Inclusion criteria
   - Comparisons and subgroups
   - Methods
3. Results
   - Trial and patient summaries
   - Event summaries
   - Meta-analysis
   - Subgroups
4. Limitations and comparisons with other meta-analyses
5. Conclusions

# Goal of Meta-Analysis

Provide risk information for a risk-benefit assessment of LABAs

- Benefits were to be derived from action packages of approved drugs
- Note: Only drugs and doses approved in United States were considered in this meta-analysis

# LABAs Approved for the Treatment of Asthma in the United States

| Brand Name | Sponsor | Active Ingredient(s) | Indication Summary |
|---|---|---|---|
| Advair | GSK | salmeterol, fluticasone | asthma, age ≥ 4 years; COPD |
| Serevent | GSK | salmeterol | asthma, age ≥ 4 years; COPD |
| Foradil | Novartis | formoterol | asthma, age ≥ 5 years; COPD |
| Symbicort | AstraZeneca | formoterol, budesonide | asthma, age ≥ 12 years |

# Objectives of Meta-Analysis (1)

Examine if LABAs are associated with increased risks of the following serious events:

- Asthma-related death
- Asthma-related intubation
- Asthma-related hospitalization

# Objectives of Meta-Analysis (2)

Examine the risks in the following subgroups:

- Inhaled corticosteroid (ICS) use
- Demographics (age, sex, and race)

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# Data Sources

- FDA requested patient- and trial-level data on LABA trials from sponsors of LABAs
  - Studied indication: asthma
  - Parallel placebo and/or active controlled trials with and without ICS use
- Sponsors were instructed to identify and adjudicate serious asthma events
  - Asthma-related death
  - Asthma-related intubation
  - Asthma-related hospitalization

# Endpoints

- Asthma-related death
- Asthma-related death or intubation
- Asthma-related hospitalization
- Asthma composite:
  - Asthma-related death
  - Asthma-related intubation
  - Asthma-related hospitalization

- Only events which occurred during protocol blinded treatment period were included

# Comparisons (1)

1. LABA v. No LABA

- No LABA includes :
  - ICS
  - Short-acting beta agonists
  - Other non-LABA treatments
  - Placebo
  - Combinations of the above treatments

# Comparisons (2)

2. LABA with randomized assigned ICS v. Randomized assigned ICS
   - Specific ICS and dose must be the same in both comparison arms within a trial
3. LABA without randomized assigned ICS v. No LABA

# Inclusion Criteria: Trial

- Studied indication: asthma
- Randomize blinded parallel trial or first period of crossover trial
- Must have both a LABA and a No LABA arm (Within trial control)
- LABA arm may have additional therapy if the non-LABA arm has the same therapy, including dosing
- Nominal blinded-treatment duration ≥ 7 days
- ≥ 20 subjects in both LABA and No LABA arms
- Subject-level data available

# Inclusion Criteria: Subject

- Assigned dose approved for the treatment of asthma
  - Delivery device is not part of criteria
- Age is in the approved age range for drug

# Subgroups

- Demographics
  - Age (4-11, 12-17, 18-64, ≥65)
  - Gender
  - Race
  - Location (United States, Non-United States)
- Baseline ICS use
- Nominal trial duration

  < 12 weeks of blinded treatment

  ≥ 12 weeks of blinded treatment

# Primary Analysis Method

- Mantel-Haenszel risk difference
  - Stratified method, maintains within trial control
  - Uses trials with no events
  - Assumes common risk difference across trials
- Details
  - Unit of analysis: subject
  - Primary display: risk difference (RD) and 95% CI

# Sensitivity Analysis

- Trial influence
  - Exclusion of SMART
  - Inclusion of SNS
- Statistical properties
  - Exact method for odds ratio (OR)
- Trial heterogeneity
  - Generalized linear mixed model (GLMM) with random treatment effect

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# Results:
# Trial and Patient Summaries

# Trial and Subject Counts

| | Trials N=110 n (%) | Subjects N=60954 n (%) |
|---|---|---|
| Advair | 36 (33) | 13212 (22) |
| Serevent | 66 (60) | 43824 (72) |
| Foradil | 14 (13) | 3765 (6) |
| Symbicort | 4 (4) | 1270 (2) |

# Nominal Trial Duration (Days)

- Mean = 172
- Median = 196
- Range = (7, 476)
- 50% of subjects in (84, 196)*

* (25%, 75%) quantiles

# Age

| Characteristic | | Total N=60954 n (%) |
|---|---|---|
| Age (Years) | 4-11 | 3415 (6) |
| | 12-17 | 6392 (11) |
| | 18-64 | 46878 (77) |
| | ≥ 65 | 4214 (7) |
| | Missing | 55 (0) |
| | Median (Min - Max) | 37 (4 – 100) |

# Race

| Characteristic | | Total N=60954 n (%) |
|---|---|---|
| Race | Asian | 2145 (4) |
| | Black/African American | 6852 (11) |
| | White/Caucasian | 43708 (72) |
| | Other/Unknown | 8249 (14) |

# Other Demographics

| Characteristic | | Total N=60954 n (%) |
|---|---|---|
| Gender | Female | 34705 (57) |
| | Missing | 298 (0) |
| Location | United States | 41975 (69) |
| | Missing | 1681 (3) |
| Nominal Trial Duration (weeks) | $\geq$ 12 | 57558 (94) |

# Baseline Characteristics

| Characteristic | | Total N=60954 n (%) |
|---|---|---|
| ICS Required at Baseline | Yes | 11923 (20) |
| Baseline ICS Use | Yes | 30394 (50) |
| | Missing | 5892 (10) |

# Actual Treatment Duration

| Characteristic | | No LABA N=30806 | LABA N=30148 | Total N=60954 |
|---|---|---|---|---|
| Treatment Duration (days) | Mean | 153 | 155 | 154 |
| | Median | 169 | 169 | 169 |
| | Min - Max | 1 – 506 | 1 – 506 | 1 – 506 |
| | 50% Range | 85 – 198 | 85 – 198 | 85 – 198 |
| | Missing | 620 | 573 | 1193 |

# Selected Summaries by Drug

| | Advair N=13212 | Serevent N=43824 | Foradil N=3765 | Symbicort N=1270 |
|---|---|---|---|---|
| Median Treatment Duration (days) | 104 | 193 | 85 | 85 |
| Location US (%) | 27 | 84 | 48 | 38 |
| ICS Required at Baseline (%) | 49 | 10 | 16 | 100 |

# Results: Event Summaries

# Overall Events

| | No LABA N=30806 n (%) | LABA N=30148 n (%) | Total N=60954 n (%) |
|---|---|---|---|
| Asthma Death | 4 (.01) | 16 (.05) | 20 (.03) |
| Asthma Death/Intubation | 27 (.09) | 44 (.15) | 71 (.12) |
| Asthma Hospitalization | 299 (.97) | 369 (1.22) | 668 (1.10) |
| Asthma Composite | 304 (.99) | 381 (1.26) | 685 (1.12) |
| All Cause Death | 40 (.13) | 51 (.17) | 91 (.15) |

# Advair Trial Events

| | No LABA N=6564 n (%) | LABA N=6648 n (%) | Total N=13212 n (%) |
|---|---|---|---|
| Asthma Death | 0 (0) | 0 (0) | 0 (0) |
| Asthma Death/Intubation | 0 (0) | 0 (0) | 0 (0) |
| Asthma Hospitalization | 20 (.30) | 21 (.32) | 41 (.31) |
| Asthma Composite | 20 (.30) | 21 (.32) | 41 (.31) |
| All Cause Death | 4 (.06) | 3 (.05) | 7 (.05) |

# Serevent Trial Events

| | No LABA N=22716 n (%) | LABA N=21108 n (%) | Total N=43824 n (%) |
|---|---|---|---|
| Asthma Death | 4 (.02) | 16 (.08) | 20 (.05) |
| Asthma Death/Intubation | 27 (.12) | 44 (.21) | 71 (.16) |
| Asthma Hospitalization | 265 (1.17) | 324 (1.53) | 589 (1.34) |
| Asthma Composite | 270 (1.19) | 336 (1.59) | 606 (1.38) |
| All Cause Death | 35 (.15) | 48 (.23) | 83 (.19) |

# Foradil Trial Events

| | No LABA N=2139 n (%) | LABA N=1626 n (%) | Total N=3765 n (%) |
|---|---|---|---|
| Asthma Death | 0 (0) | 0 (0) | 0 (0) |
| Asthma Death/Intubation | 0 (0) | 0 (0) | 0 (0) |
| Asthma Hospitalization | 14 (.65) | 18 (1.11) | 32 (.85) |
| Asthma Composite | 14 (.65) | 18 (1.11) | 32 (.85) |
| All Cause Death | 1 (.05) | 0 (.00) | 1 (.03) |

# Symbicort Trial Events

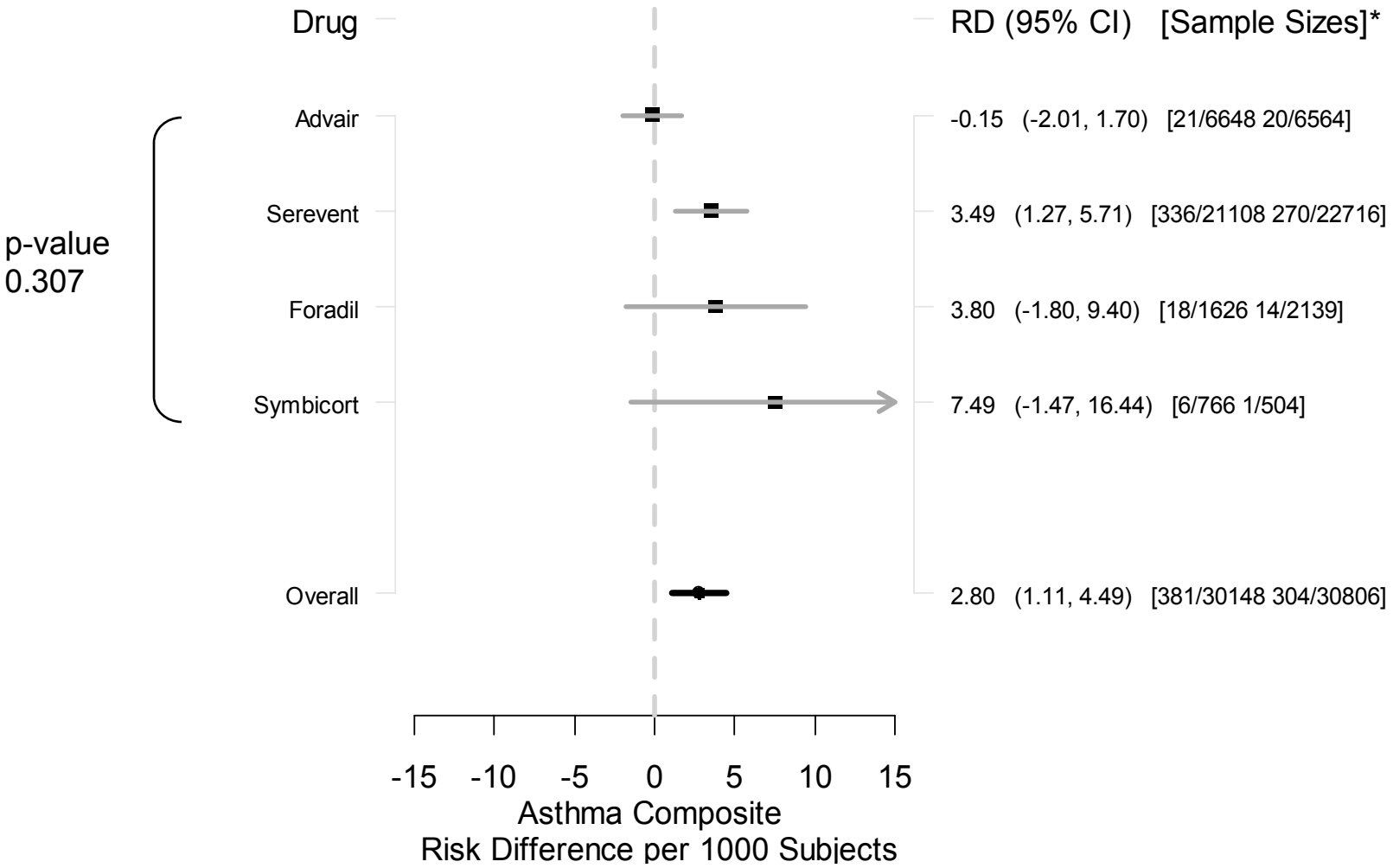
| | No LABA N=504 n (%) | LABA N=766 n (%) | Total N=1270 n (%) |
|---|---|---|---|
| Asthma Death | 0 (0) | 0 (0) | 0 (0) |
| Asthma Death/Intubation | 0 (0) | 0 (0) | 0 (0) |
| Asthma Hospitalization | 1 (.20) | 6 (.78) | 7 (.55) |
| Asthma Composite | 1 (.20) | 6 (.78) | 7 (.55) |
| All Cause Death | 0 (0) | 0 (0) | 0 (0) |

# Results: Meta-Analysis

# Asthma Endpoints
# Risk Difference Estimates

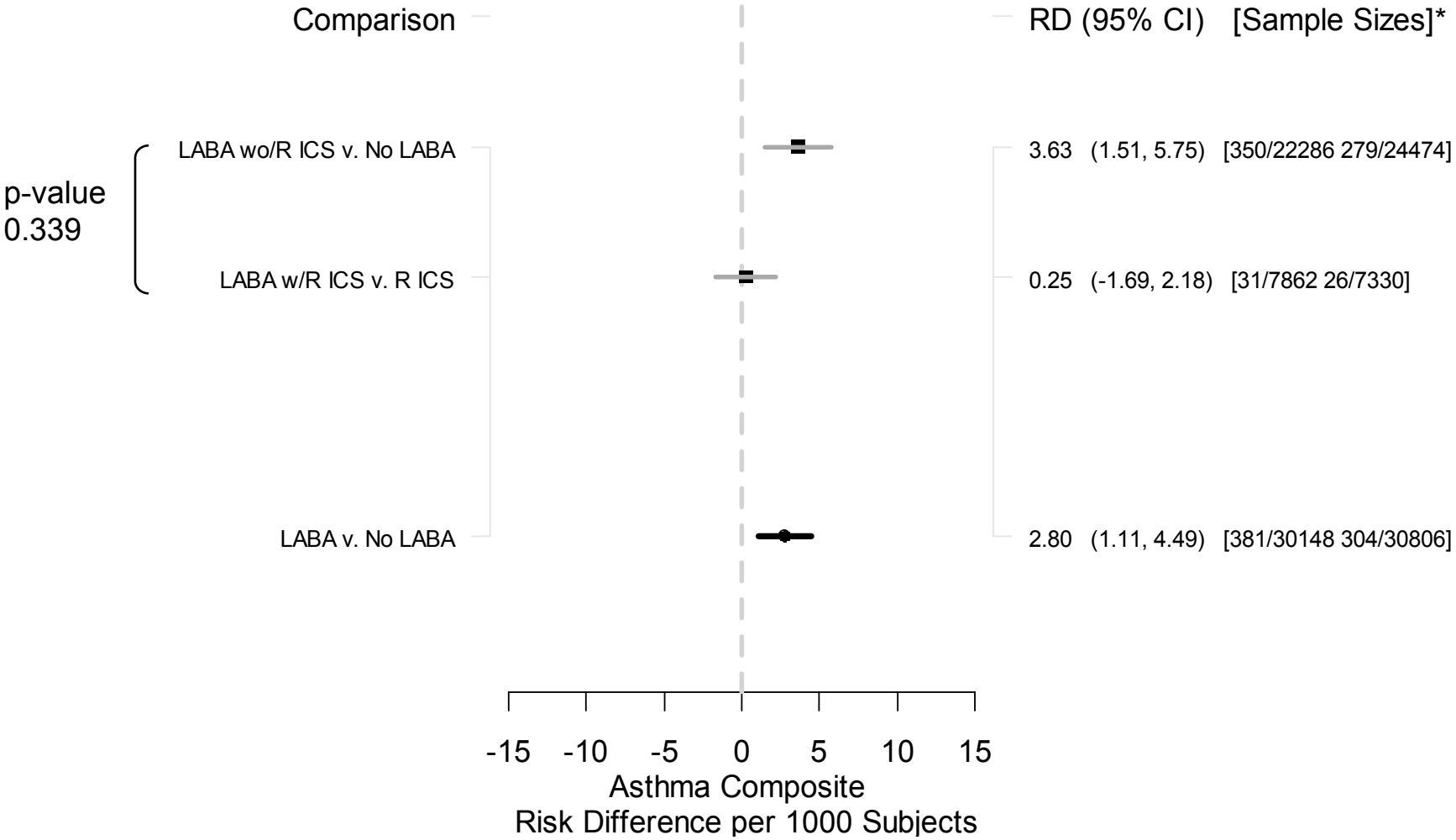
| | Risk Difference Per 1000 Subjects | |
|---|---|---|
| Endpoint | Estimate | 95% CI |
| Asthma Death | 0.40 | 0.11 - 0.69 |
| Asthma Death/Intubation | 0.57 | 0.01 - 1.12 |
| Asthma Hospitalization | 2.57 | 0.90 - 4.23 |
| Asthma Composite | 2.80 | 1.11 - 4.49 |

# Asthma Composite by Drug
# Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Assigned ICS Comparison Risk Difference Estimates



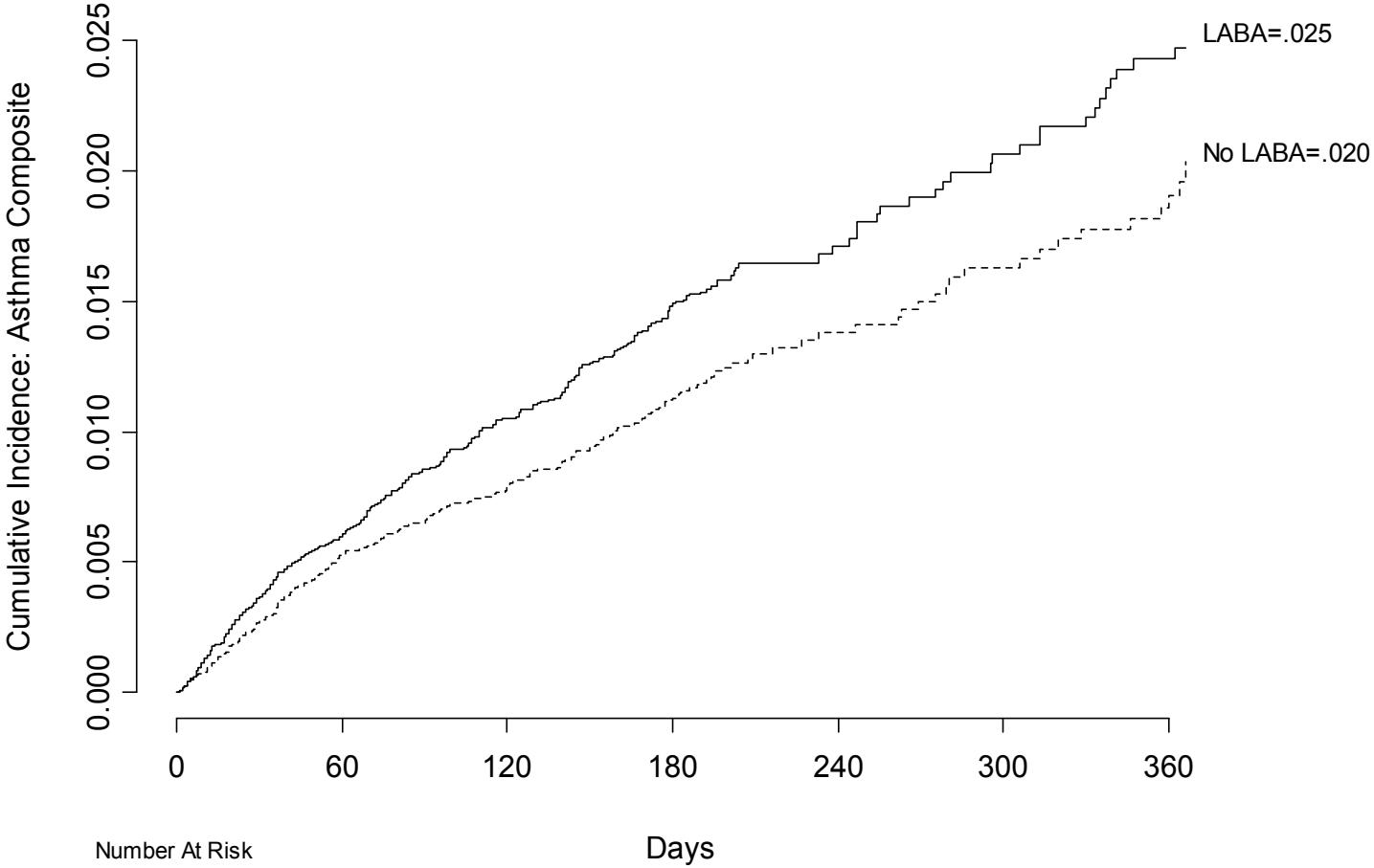



*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite
# Life Table Estimates
# Hazard per 1000 Subjects

| | No LABA | | | LABA | | |
|---|---|---|---|---|---|---|
| Days | Events | Subjects | Hazard | Events | Subjects | Hazard |
| 0 - 89 | 177 | 24493 | 0.08 | 228 | 24085 | 0.11 |
| 90 - 179 | 76 | 16226 | 0.05 | 100 | 16067 | 0.07 |
| 180 - 269 | 26 | 8531 | 0.03 | 26 | 8404 | 0.03 |
| 270 - 366 | 13 | 2201 | 0.06 | 16 | 2126 | 0.08 |

# Asthma Composite
# Kaplan-Meier Cumulative Incidence Curves

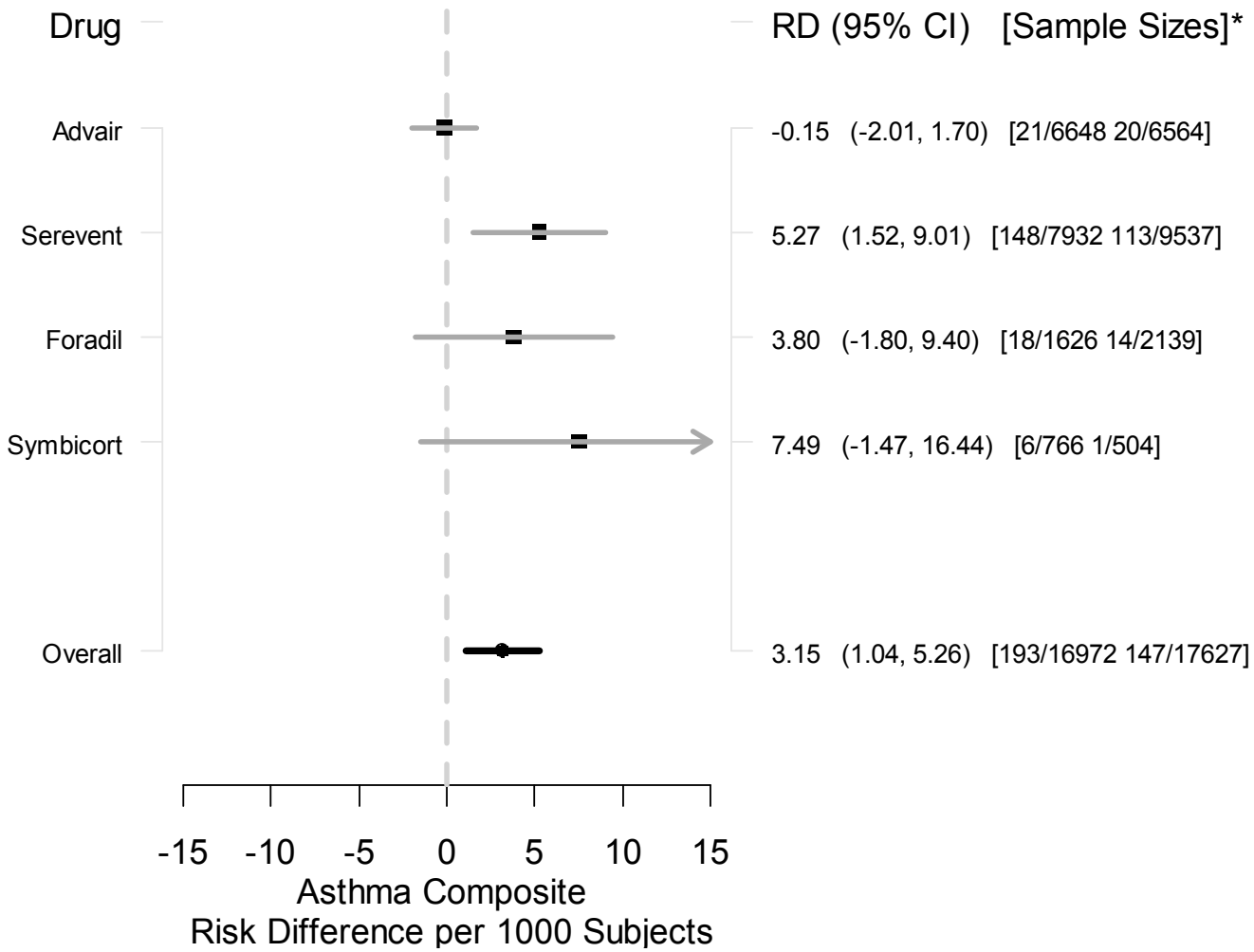



Number At Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 29578 | 25138 | 15990 | 13670 | 3164 | 2789 | 2282 | LABA |
| 30189 | 25294 | 16211 | 13755 | 3341 | 2702 | 2137 | No LABA |

# Sensitivity Analysis

# Asthma Composite by Drug
# Risk Difference Estimates
# Without SMART




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

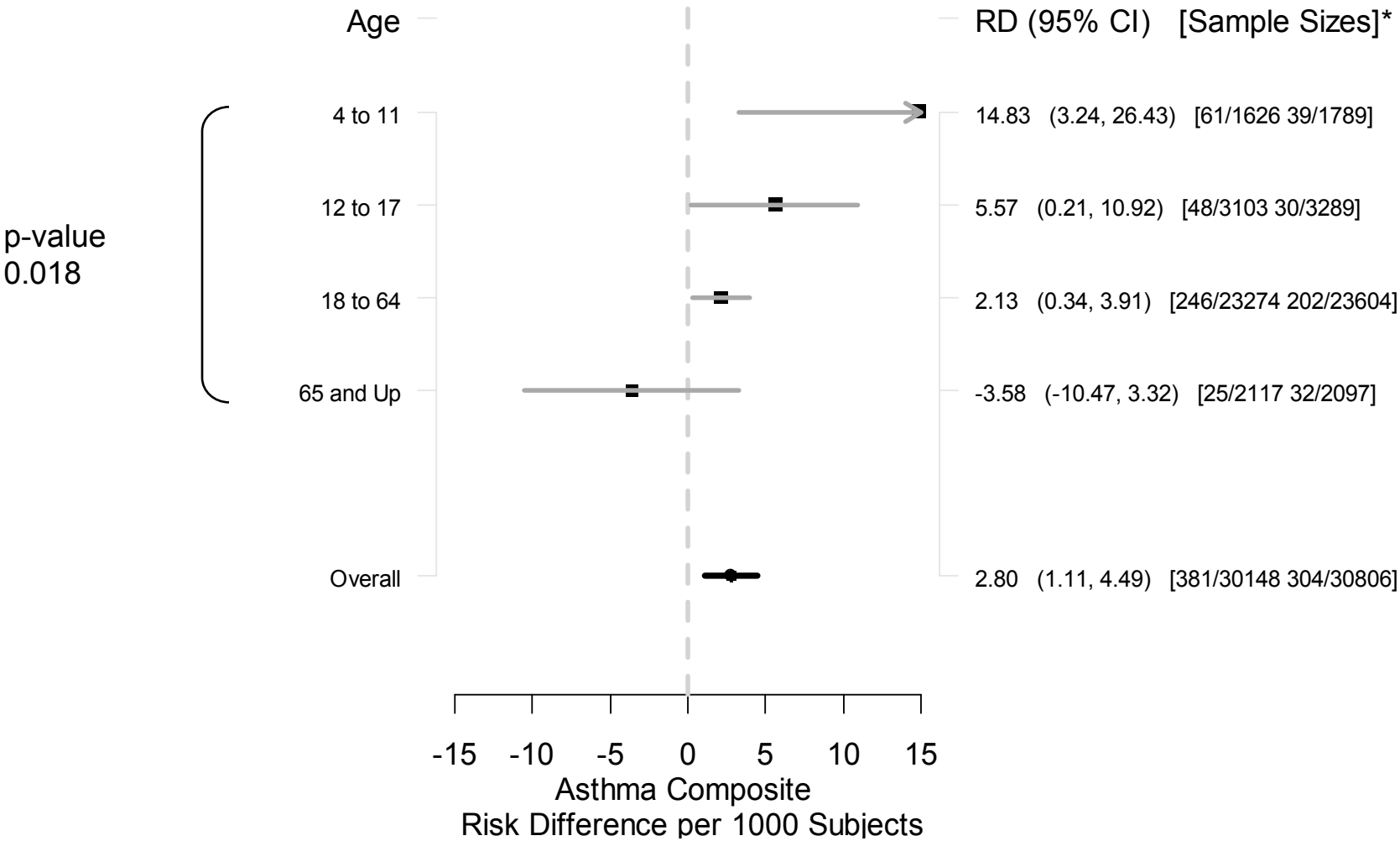
# Sensitivity Analyses

Results were robust to statistical method:

- Exact OR
- GLMM

# Results: Subgroups

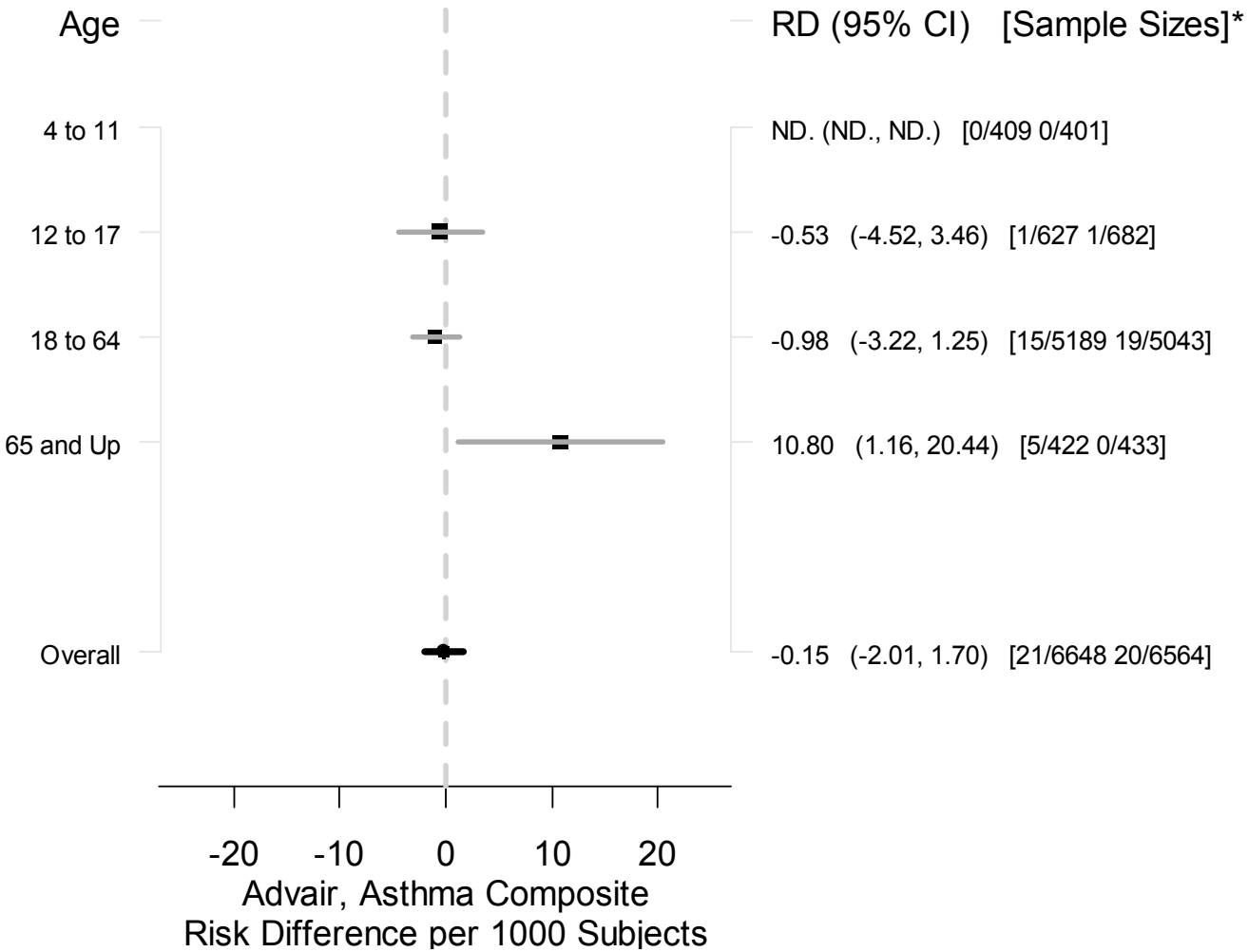
# Asthma Composite by Age Subgroup
# Risk Difference Estimates





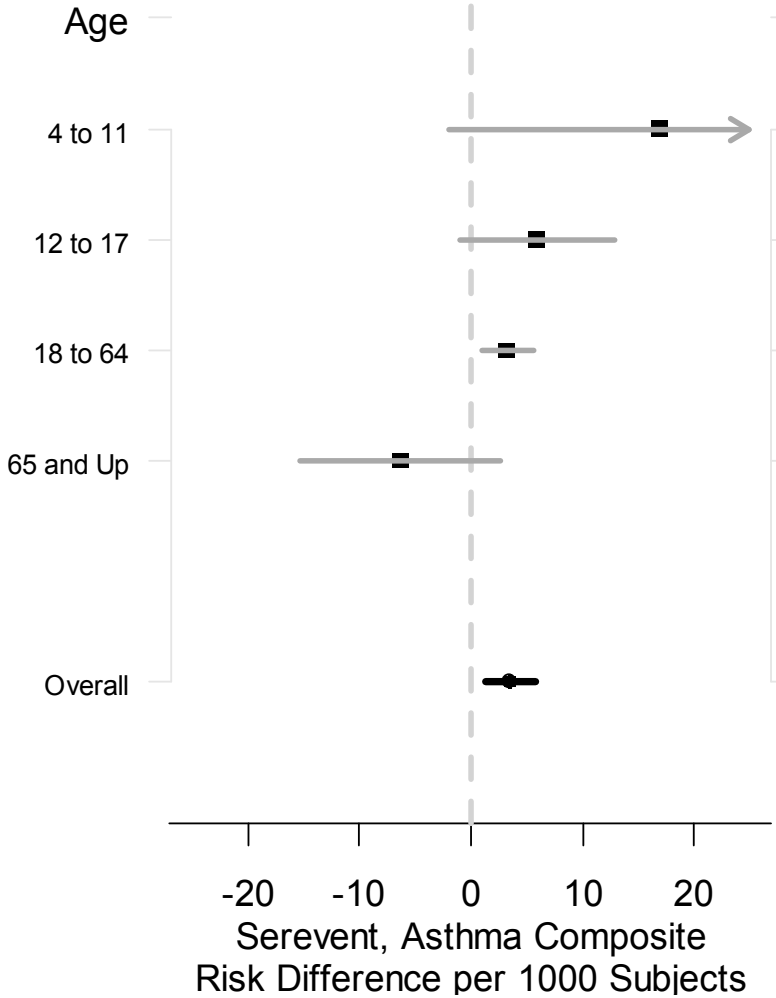

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Age Subgroup
# Risk Difference Estimates
# Advair




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

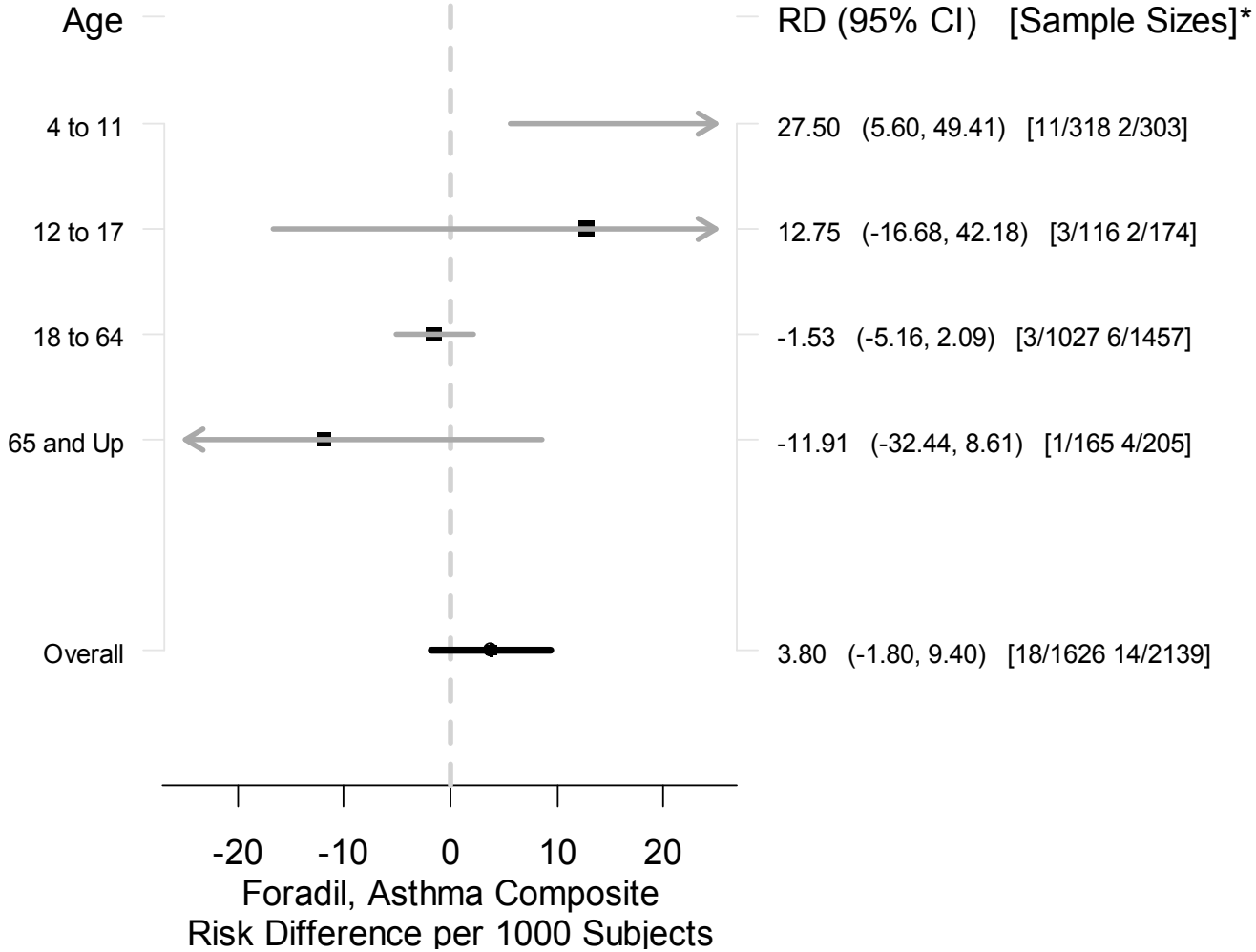
# Asthma Composite by Age Subgroup
# Risk Difference Estimates
# Serevent




| Age | RD (95% CI) | [Sample Sizes]* |
|---|---|---|
| 4 to 11 | 16.97 (-1.94, 35.88) | [50/899 37/1085] |
| 12 to 17 | 5.88 (-1.07, 12.83) | [41/2205 27/2411] |
| 18 to 64 | 3.27 (0.94, 5.60) | [225/16492 177/17696] |
| 65 and Up | -6.38 (-15.38, 2.63) | [19/1485 28/1502] |
| Overall | 3.49 (1.27, 5.71) | [336/21108 270/22716] |

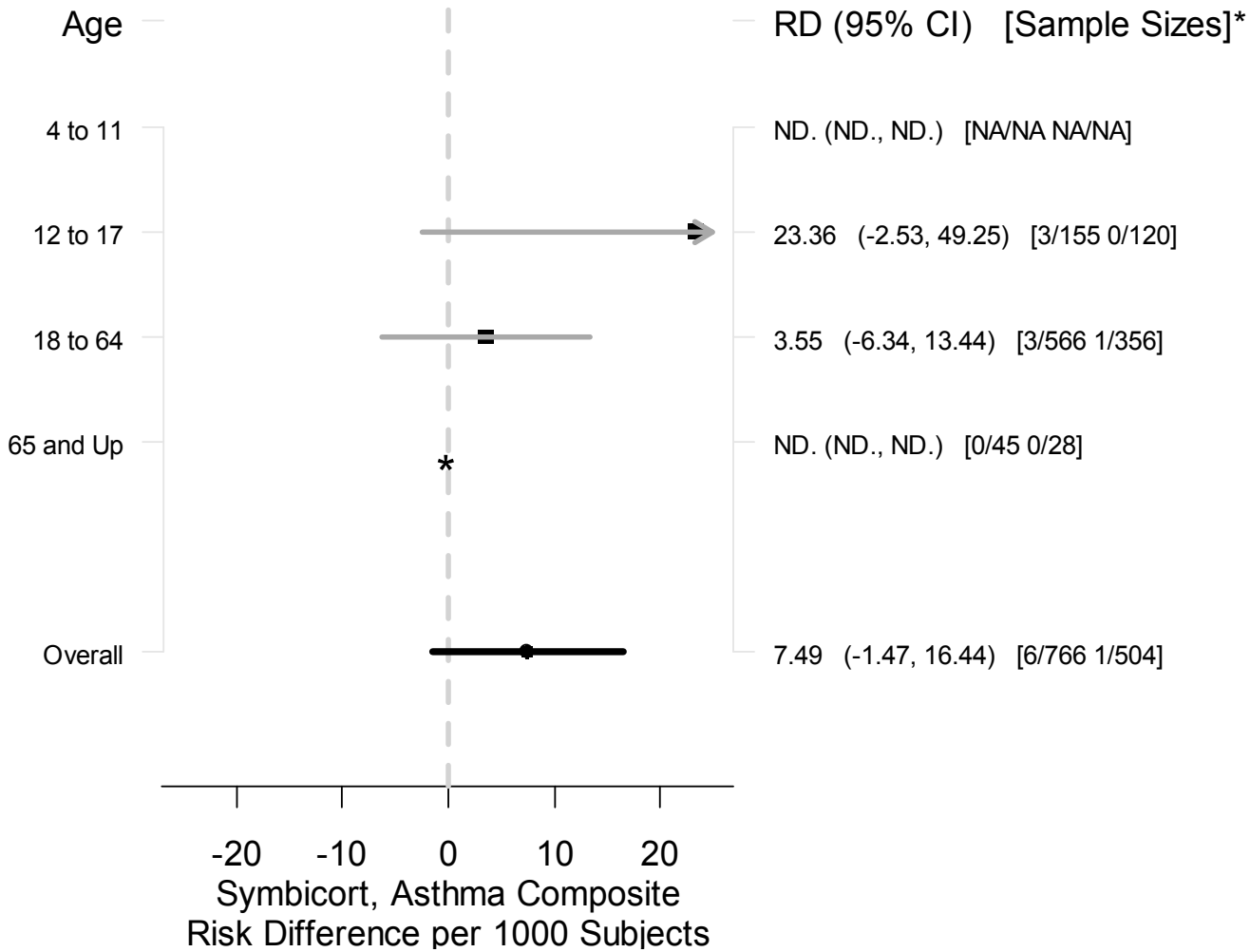
*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Age Subgroup
# Risk Difference Estimates
# Foradil




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

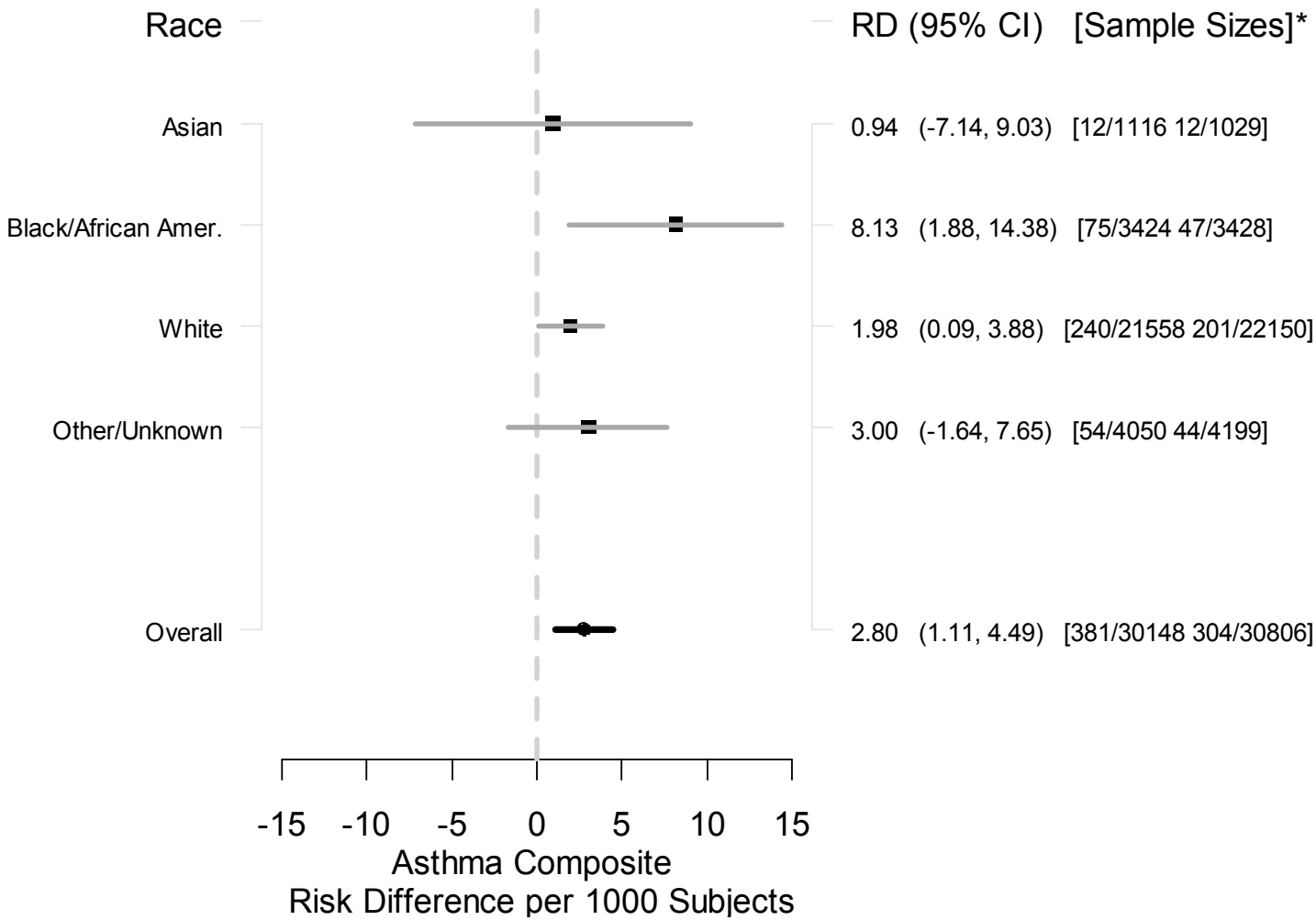
# Asthma Composite by Age Subgroup
# Risk Difference Estimates
# Symbicort





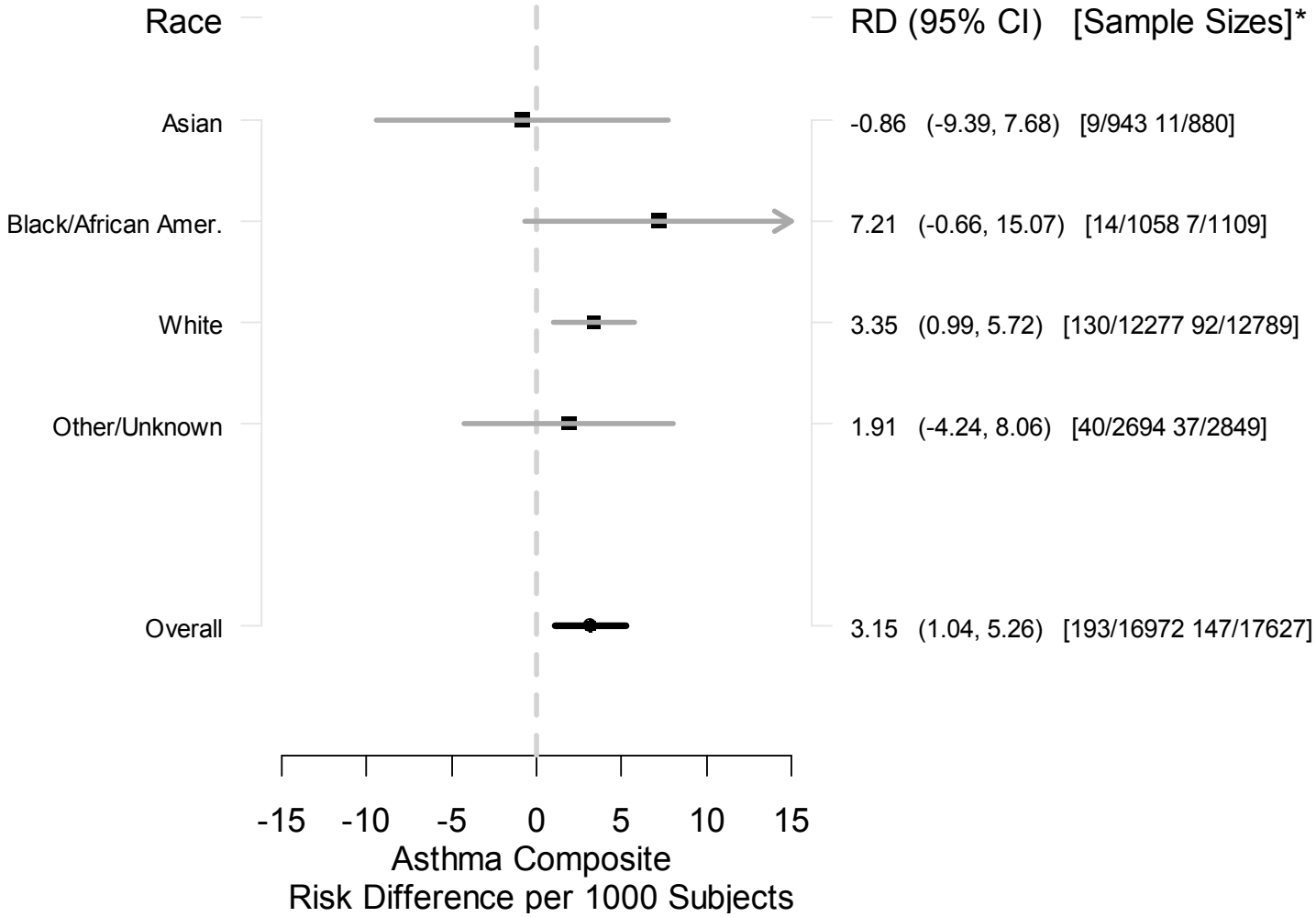

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Race Subgroup
# Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Race Subgroup Risk Difference Estimates Without SMART






*RD = Risk Difference Per 1000 Subjects
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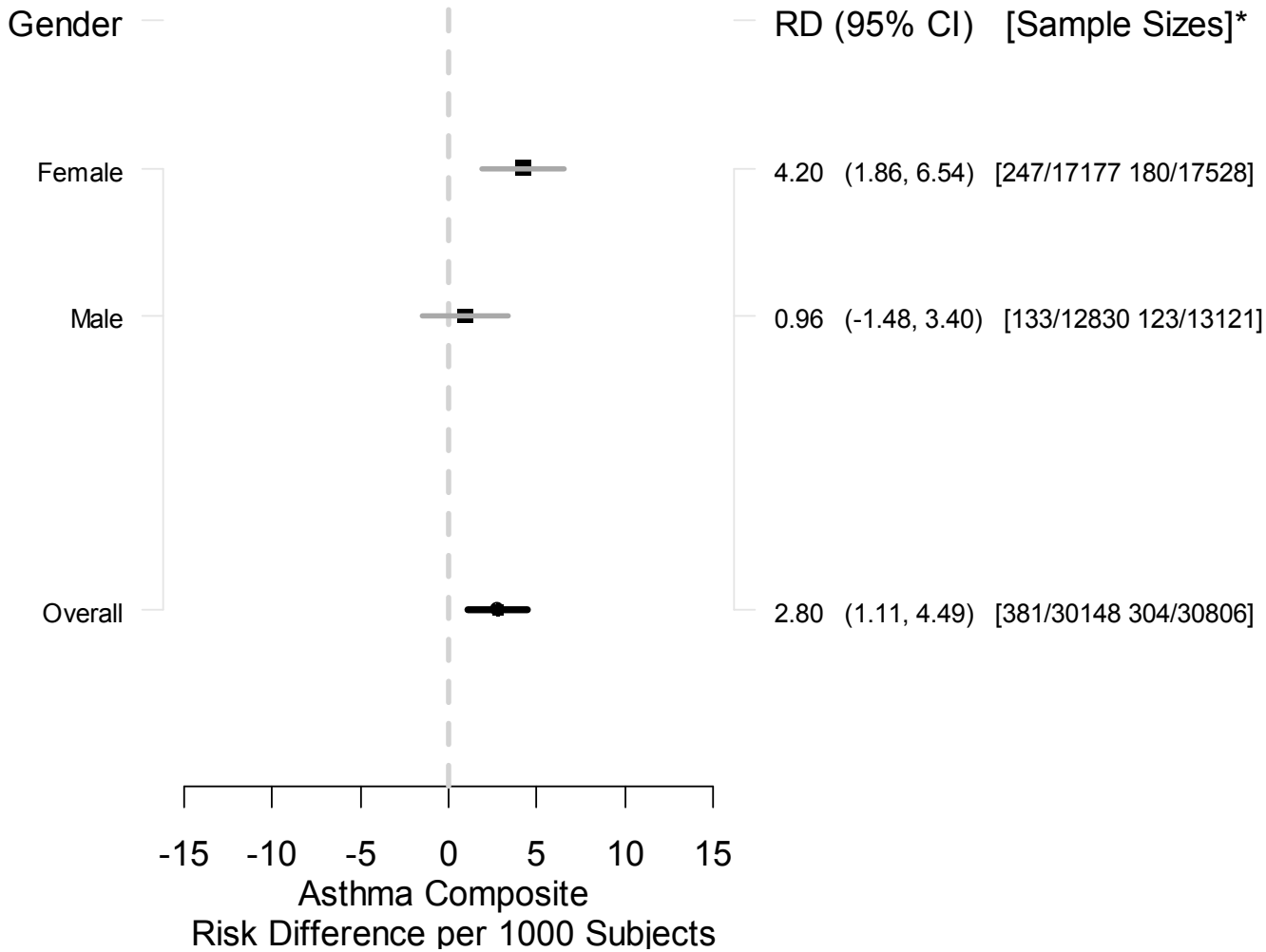
# Asthma Composite by Gender Subgroup Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Other Subgroups

- No notable differences among subgroups based on
  - Location
  - Nominal treatment duration
  - Baseline ICS use

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# Limitations

- Trials not designed for present purpose
  - Post-hoc identification and adjudication
- Information on subjects and trials limited
  - Dropout
  - Concomitant ICS use
- SMART results known prior to meta-analysis
- Exploratory and multiple testing issues

# Other Meta-Analyses

- Bateman et al. Ann Intern Med. 2008. (salmeterol+ICS)
- Salpeter et al. Ann Intern Med. 2006. (salmeterol and formoterol)
- Sears et al. Eur Respir J 2008. (formoterol)

# Bateman

- Drug: salmeterol+ICS
- Comparison: (salmeterol+ICS) v. ICS
  - No SMART
  - ICS did not have to be same drug or dose
- Included only approved doses
  - salmeterol: Yes
  - ICS: ?
- Asthma Hospitalization: RD 0.2 (95%CI: -1.9 – 2.3) per 1000 subjects
- FDA, Asthma Hospitalization, Advair: RD -0.15 (95%CI: -2.0 – 1.7) per 1000 subjects

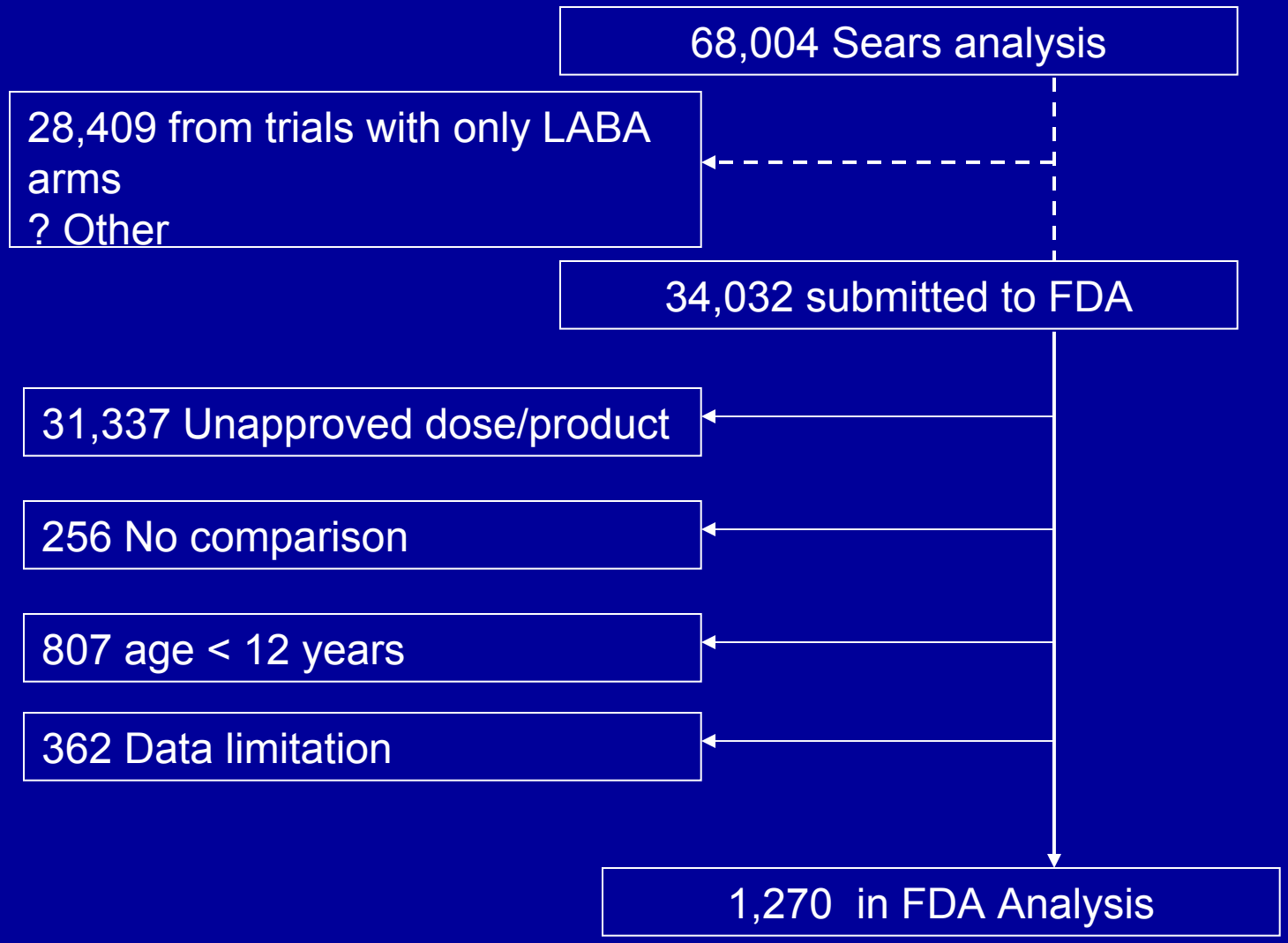
# Salpeter

- Drug: formoterol and salmeterol
- Comparison:
  - LABA v. placebo
  - Includes SMART
- Included only approved doses: No
- Asthma Hospitalization, LABA v. placebo: OR 2.6 (95%CI: 1.6 – 4.3)
- FDA, Asthma Hospitalization, LABA v. Non-LABA: OR 1.3 (95%CI: 1.1 – 1.5)

# Sears

- Drug: formoterol
- Comparison:
  - Formoterol w/ and wo/ ICS v. ICS, other non-LABA
  - Pooled analysis
  - Trials may not have had non-LABA control
- Included only approved doses: No

# Symbicort Subject Flowchart



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# Conclusions (1)

- Overall effect for all asthma-related endpoints:
  - Asthma-related death
  - Asthma-related death or intubation
  - Asthma-related hospitalization
  - Asthma composite
- Asthma composite RD:
  2.8 (95%CI: 1.1 – 4.5) per 1000 subjects
- 3 of the 4 drugs have observed adverse signals
  - Sample size varies substantially among drugs
  - Difference among drug not statistically demonstrated
  - Observed differences may be related to trial or subject differences

# Conclusions (2)

- LABA with assigned ICS appeared to have less adverse effect
  - Difference not statistically demonstrated
  - Effect dominated by Advair
- Apparent age effect with youngest at greatest risk
- Meta-analysis has limitations
  - Ascertainment of events
  - Limited information
  - Exploratory
- Agreement or resolution among meta-analyses

# Extra

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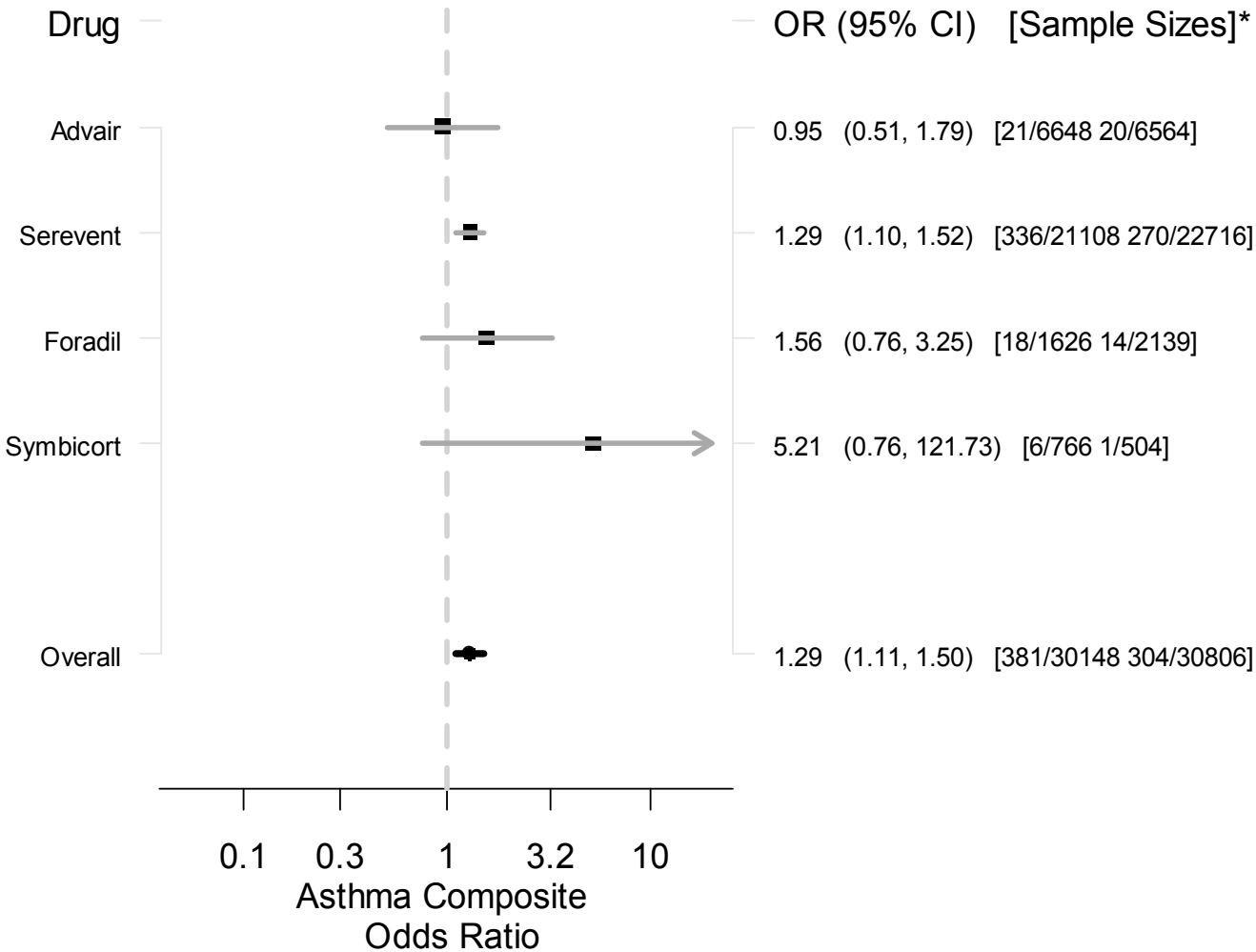
# Other Statistics

# Asthma Composite
# Odds Ratio Estimates






*[Treat. Events/Treat. n Plac. Events/Placebo n]

# Trial Heterogeneity
# Asthma Composite Endpoint

- Zelen's test: p-value = 0.018
- Random effect (GLMM) OR:
  1.53 (95% CI: 1.15 – 2.02)
- Fixed effect (exact) OR:
  1.29 (95% CI: 1.11 – 1.50)

# Mantel-Haenszel RD
# Greenland and Robins 1985

$$\hat{\delta}_{\mathrm{MH}} = \sum_k (x_k m_k / N_k - y_k n_k / N_k) \Big/ \left( \sum_k n_k m_k / N_k \right)$$

$$\widehat{\mathrm{var}}^{\mathrm{A}}(\hat{\delta}_{\mathrm{MH}}) = \sum_k L_k \Big/ \left( \sum_k n_k m_k / N_k \right)^2$$

$$L_k = [x_k(n_k - x_k)m_k^3 + y_k(m_k - y_k)n_k^3]/(n_k m_k N_k^2)$$

x : Events in exposed

y : Events in unexposed

n : Subjects in exposed

m : Subjects in unexposed

N = m + n

# SMART, SNS

# Serevent Trial Events

| | No LABA N=22716 n (%) | LABA N=21108 n (%) | Total N=43824 n (%) |
|---|---|---|---|
| Asthma Death | 4 (.02) | 16 (.08) | 20 (.05) |
| Asthma Death/Intubation | 27 (.12) | 44 (.21) | 71 (.16) |
| Asthma Hospitalization | 265 (1.17) | 324 (1.53) | 589 (1.34) |
| Asthma Composite | 270 (1.19) | 336 (1.59) | 606 (1.38) |
| All Cause Death | 35 (.15) | 48 (.23) | 83 (.19) |

# Serevent Trial Events: SMART

| | No LABA N=13179 n (%) | LABA N=13176 n (%) | Total N=26355 n (%) |
|---|---|---|---|
| Asthma Death | 3 (.02) | 13 (.10) | 16 (.06) |
| Asthma Death/Intubation | 22 (.17) | 37 (.28) | 59 (.22) |
| Asthma Hospitalization | 153 (1.16) | 176 (1.34) | 329 (1.25) |
| Asthma Composite | 157 (1.19) | 188 (1.43) | 345 (1.31) |
| All Cause Death | 32 (.24) | 42 (.32) | 74 (.28) |

# Serevent Trial Events: No SMART

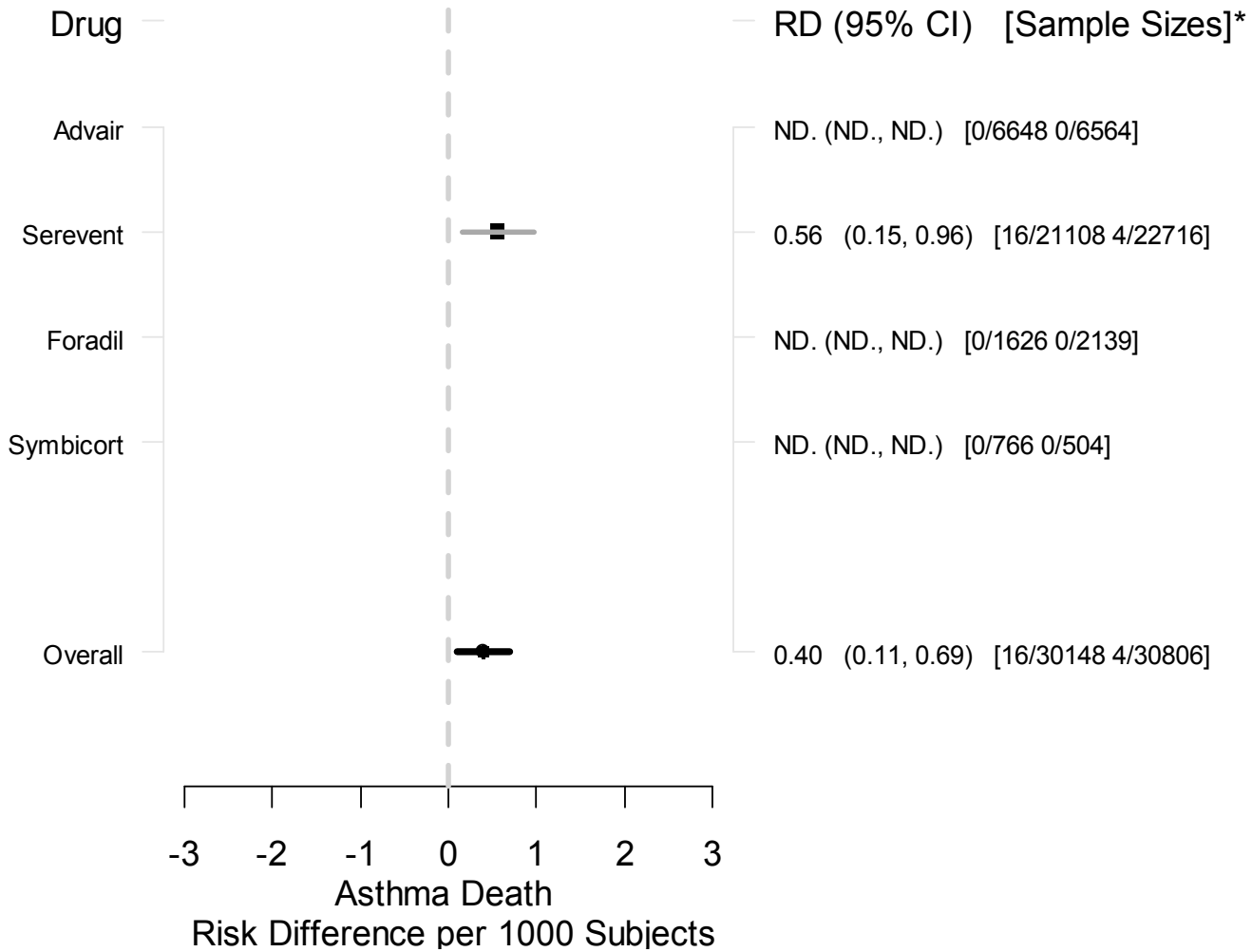
| | No LABA N=9537 n (%) | LABA N=7932 n (%) | Total N=17469 n (%) |
|---|---|---|---|
| Asthma Death | 1 (.01) | 3 (.04) | 4 (.02) |
| Asthma Death/Intubation | 5 (.05) | 7 (.09) | 12 (.07) |
| Asthma Hospitalization | 112 (1.17) | 148 (1.87) | 260 (1.49) |
| Asthma Composite | 113 (1.18) | 148 (1.87) | 261 (1.49) |
| All Cause Death | 3 (.03) | 6 (.08) | 9 (.05) |

# SNS Sensitivity

| Outcome | RD (95% CI) Per 1000 Subjects | |
|---|---|---|
| | Primary | With SNS |
| Asthma Death | 0.40 (0.11 – 0.69) | 0.42 (0.17 – 0.68) |
| Asthma Hospitalization | 2.57 (0.90 – 4.23) | 1.74 (0.30 – 3.18) |

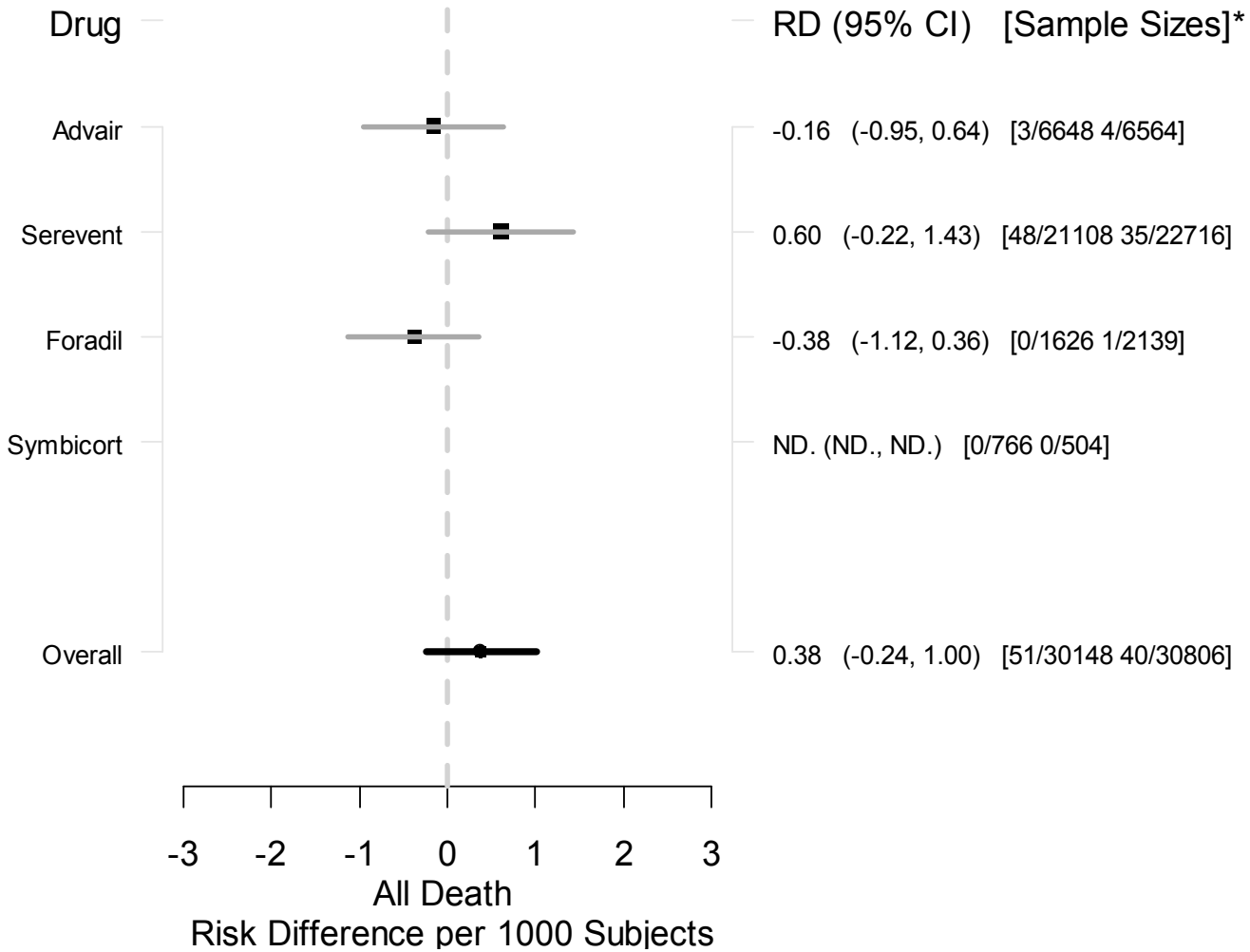
# Other Outcomes

# Asthma Death
# Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# All Death
# Risk Difference Estimates

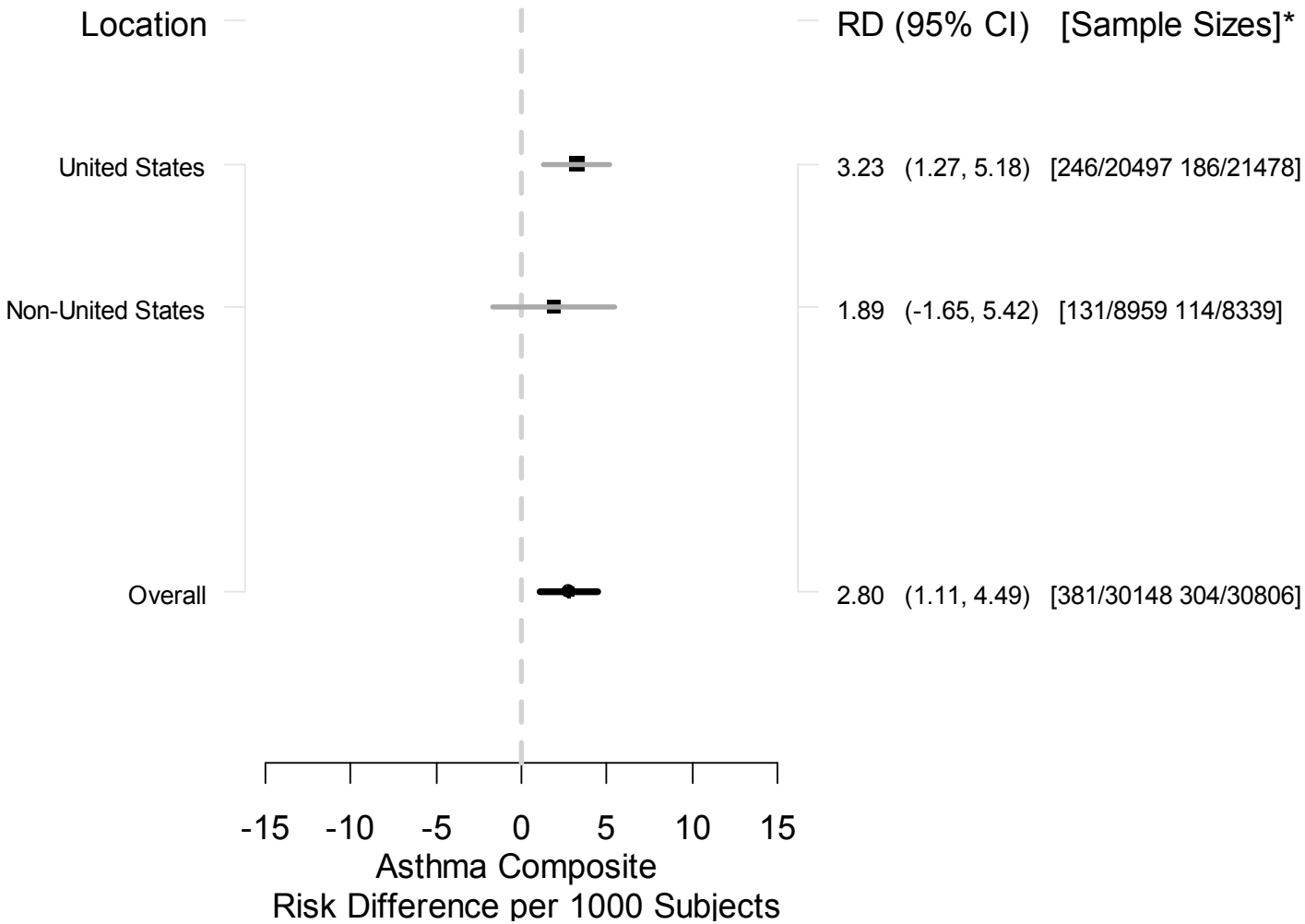





*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

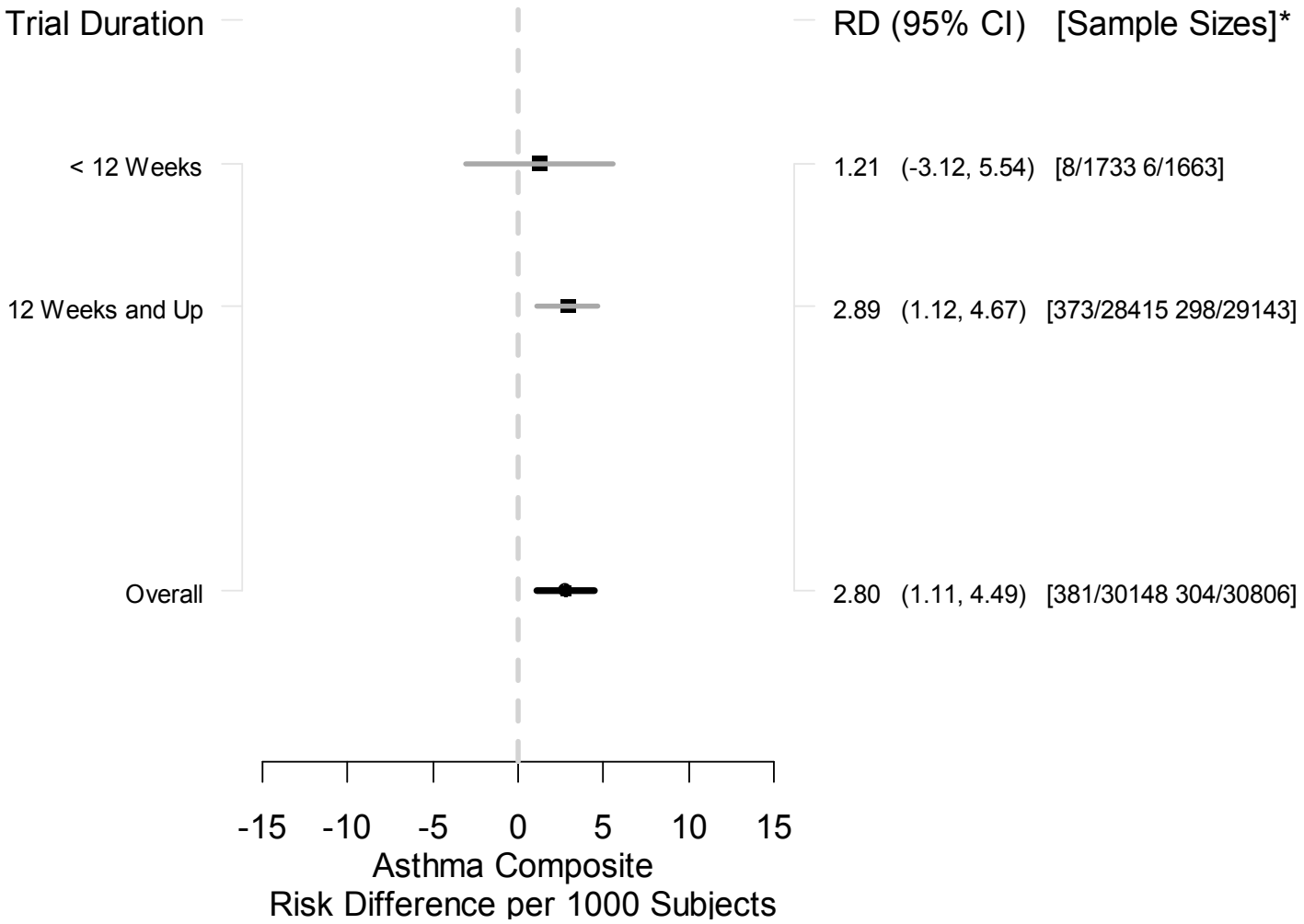
# Other Subgroups

# Asthma Composite by Location Subgroup Risk Difference Estimates



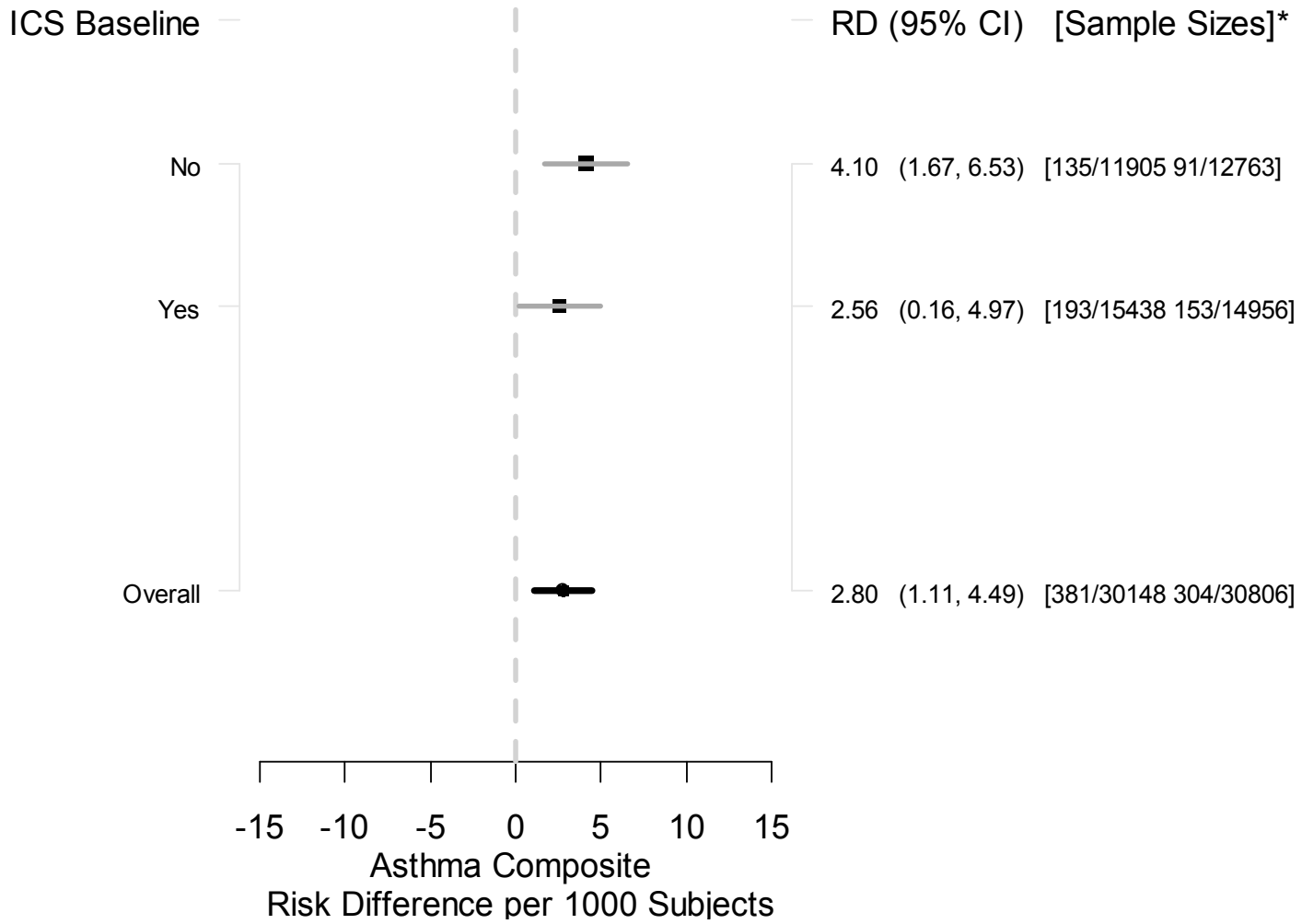

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Trial Duration Subgroup Risk Difference Estimates



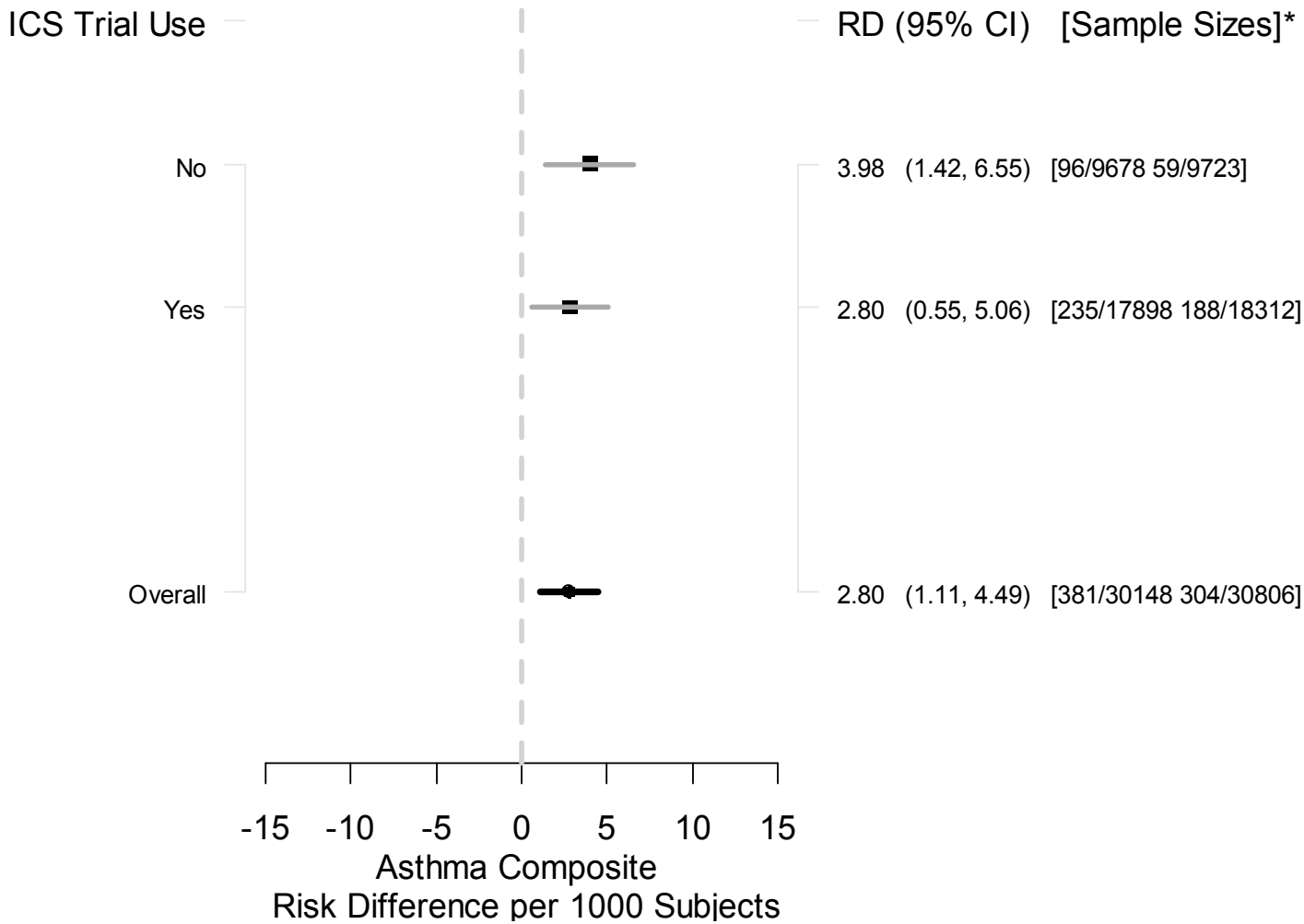

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by ICS Baseline Subgroup Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

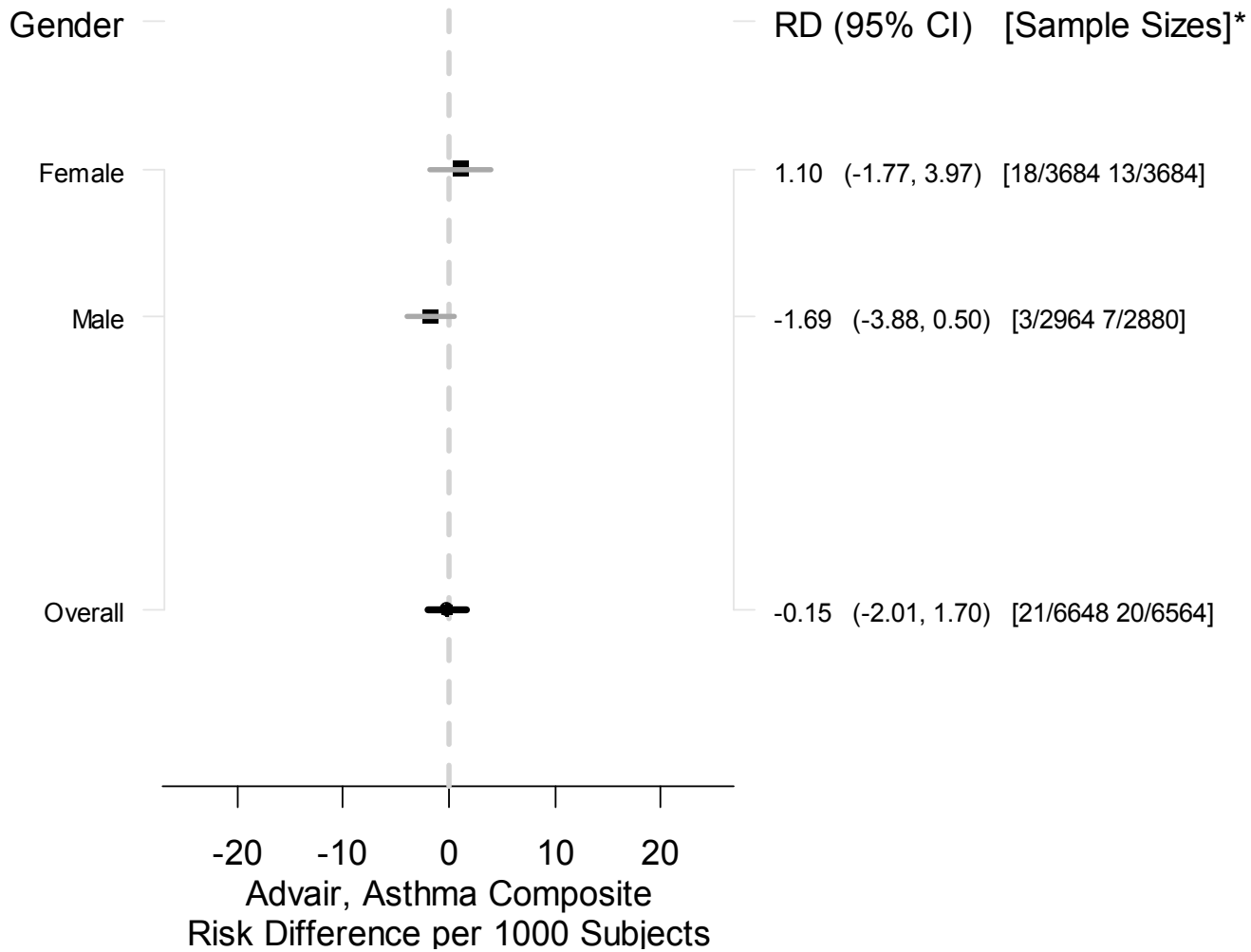
# Asthma Composite by ICS Trial Use Subgroup Risk Difference Estimates




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

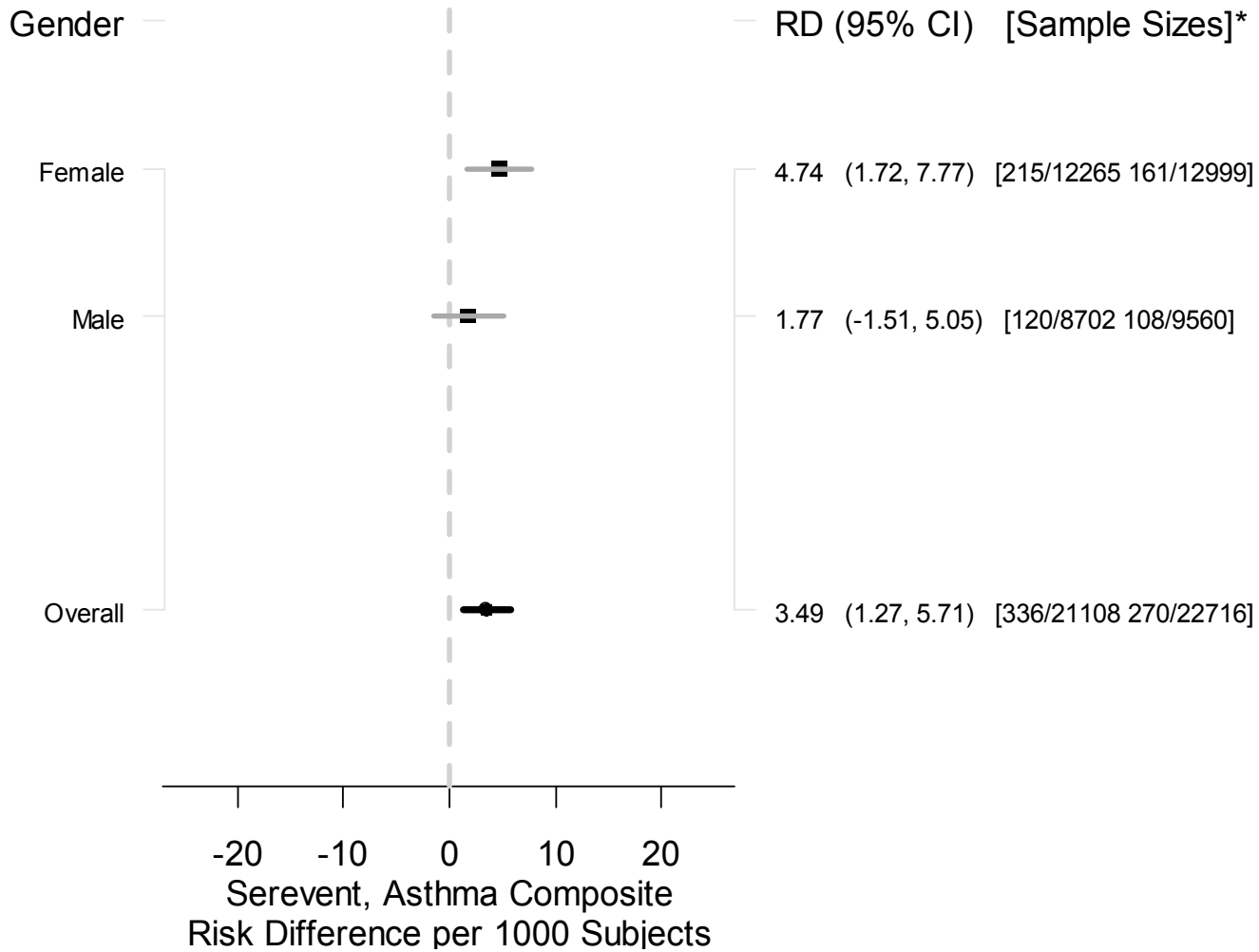
# Gender by Drug

# Asthma Composite by Gender Subgroup
# Risk Difference Estimates
# Advair



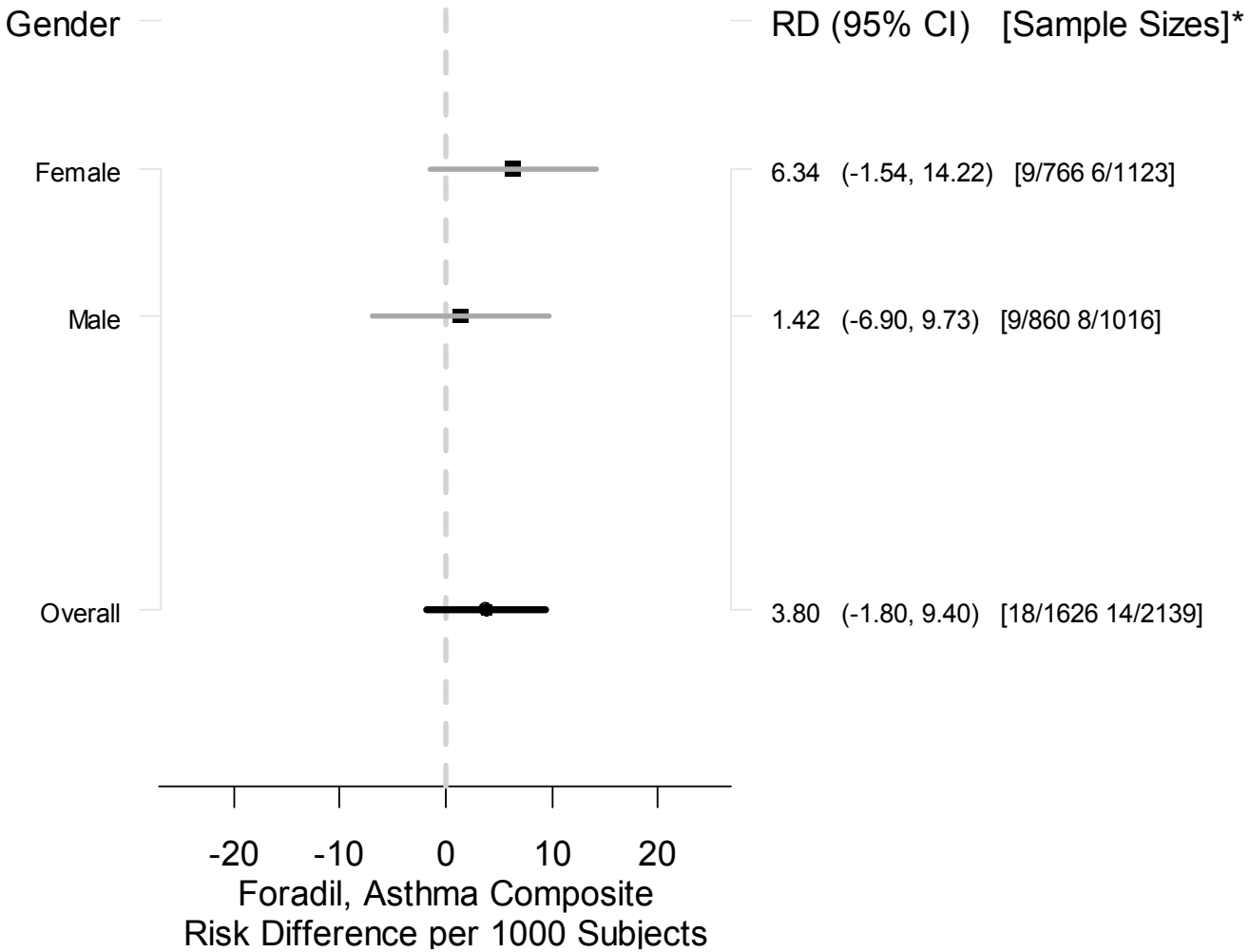

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Gender Subgroup
# Risk Difference Estimates
# Serevent




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

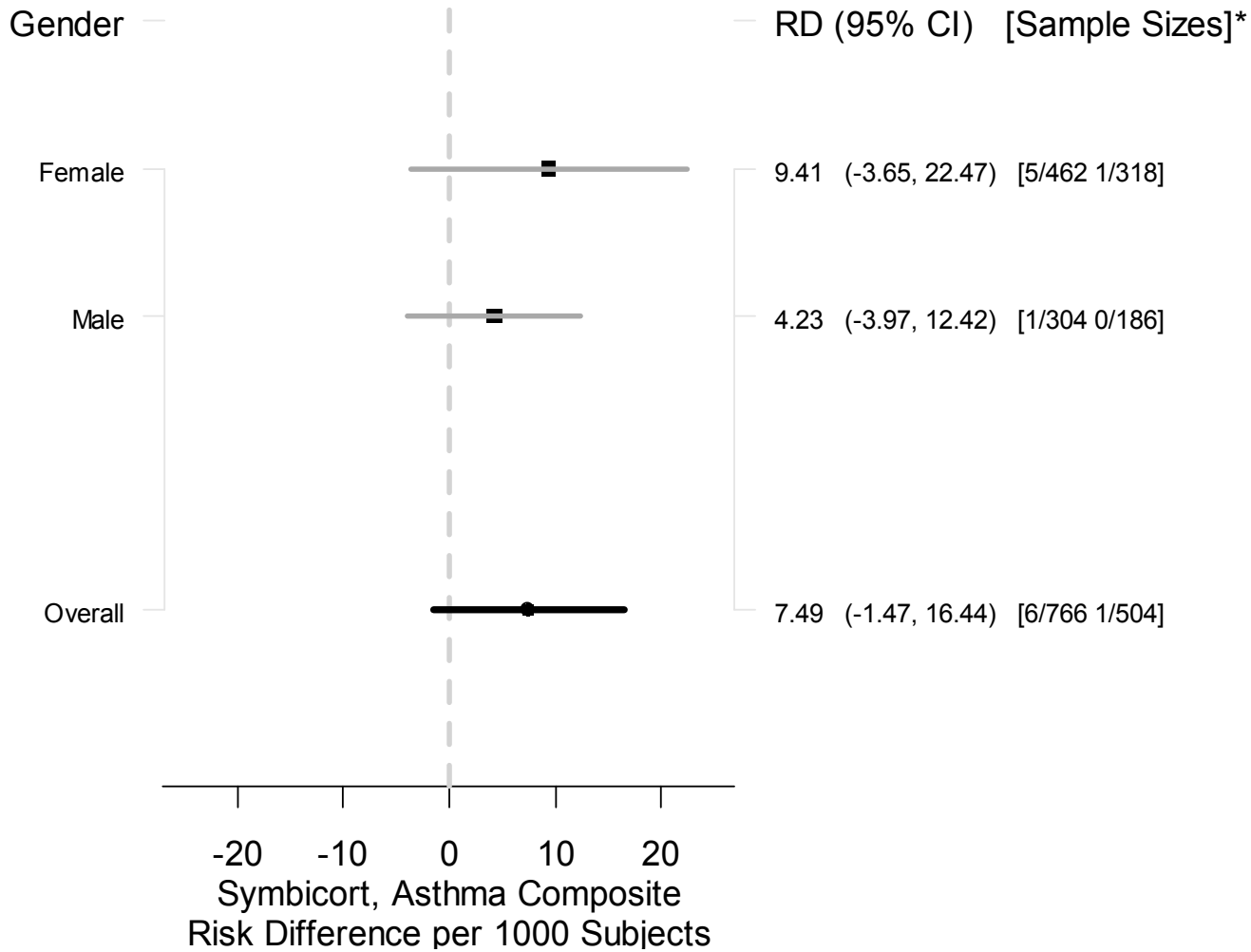
# Asthma Composite by Gender Subgroup
# Risk Difference Estimates
# Foradil






*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Gender Subgroup
# Risk Difference Estimates
# Symbicort

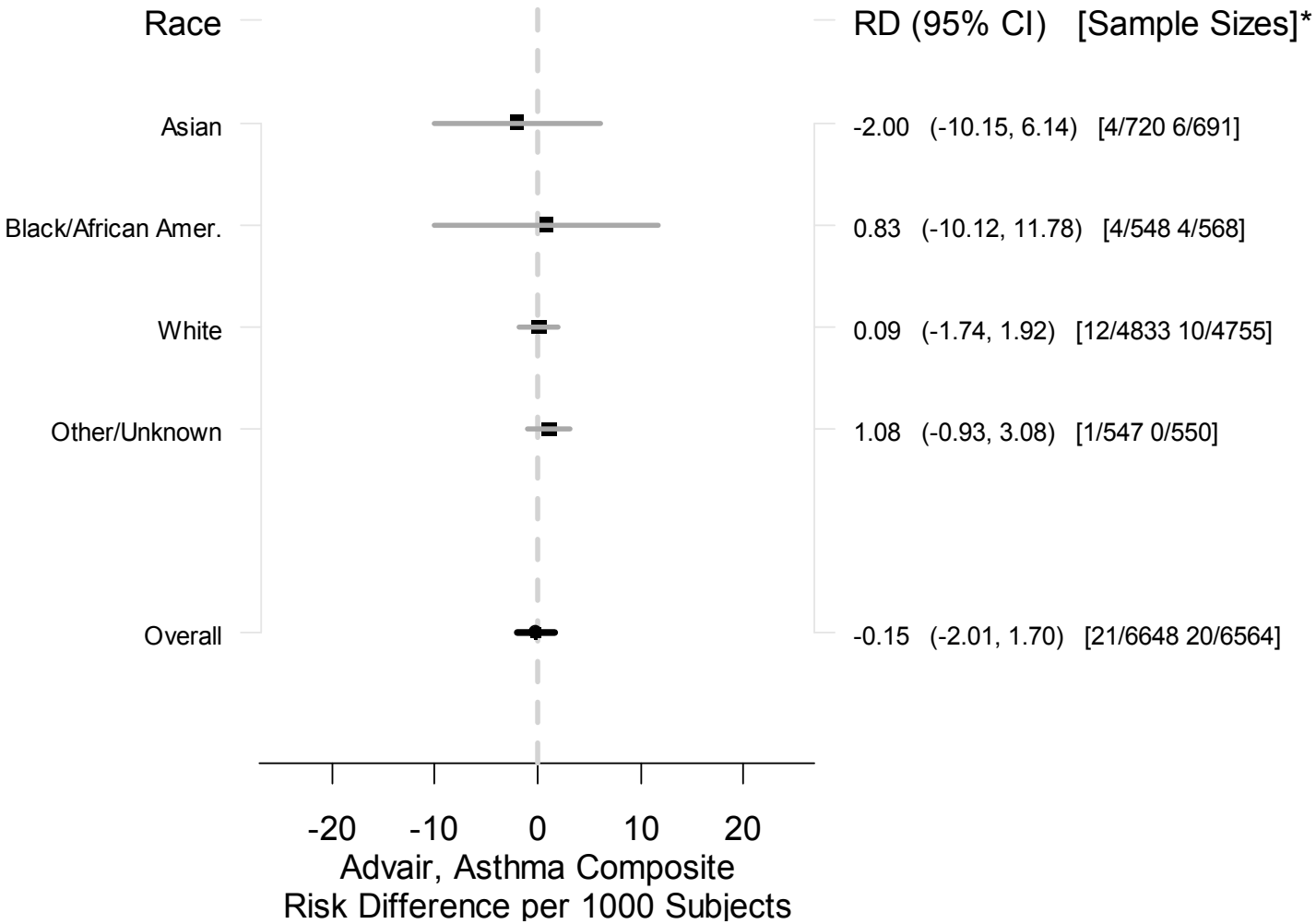





*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Race by Drug

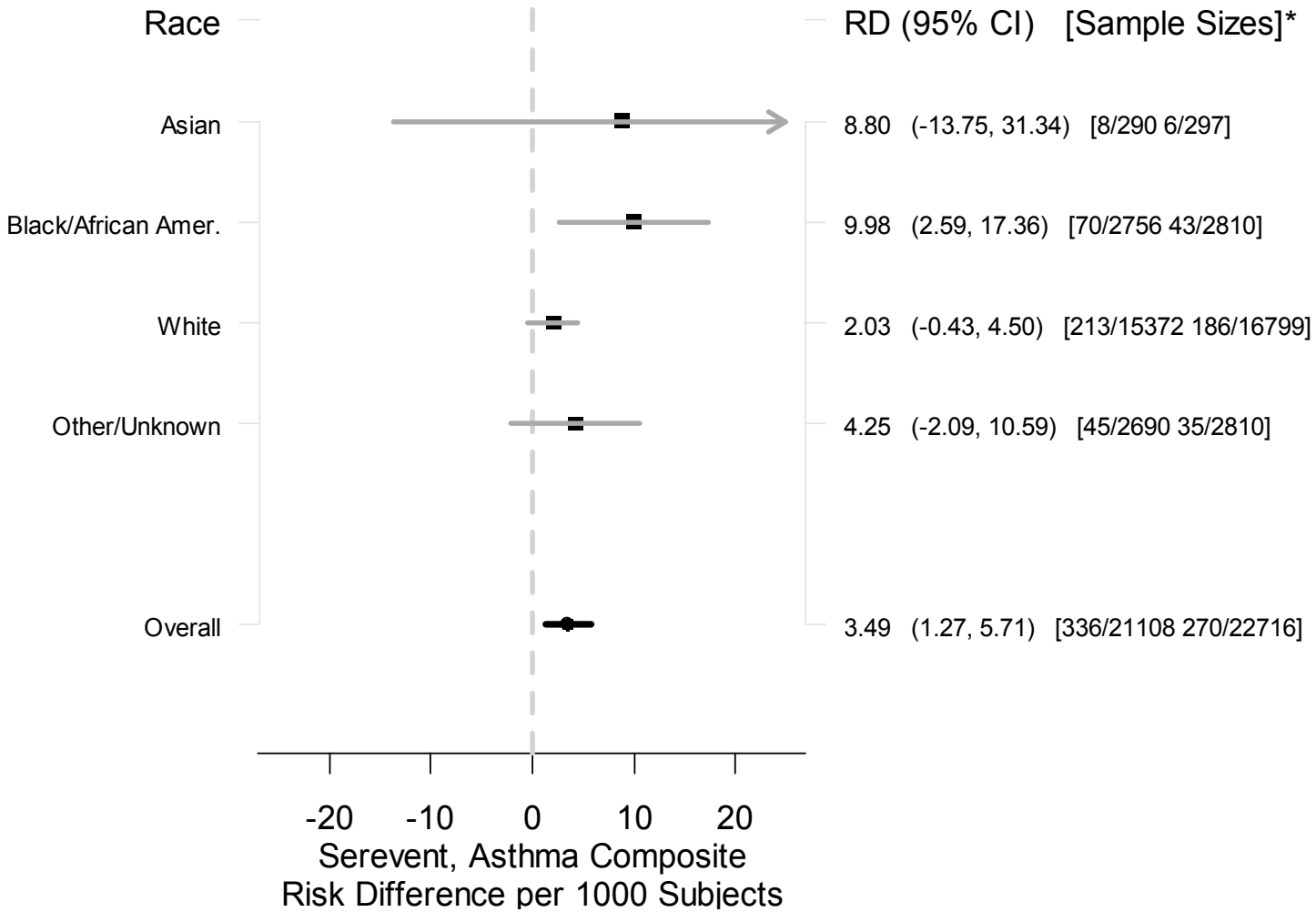
# Asthma Composite by Race Subgroup
# Risk Difference Estimates
# Advair





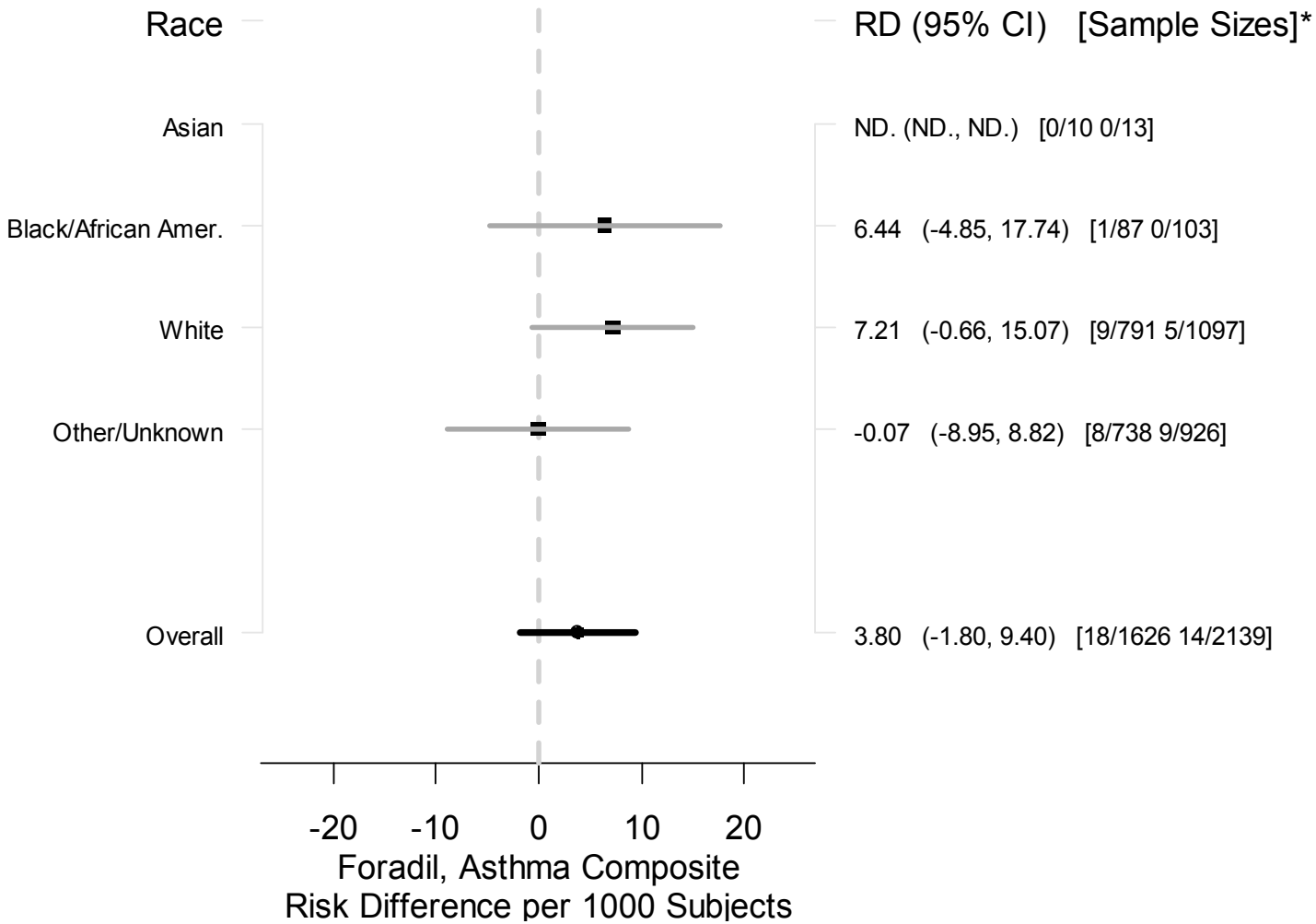

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Race Subgroup
# Risk Difference Estimates
# Serevent



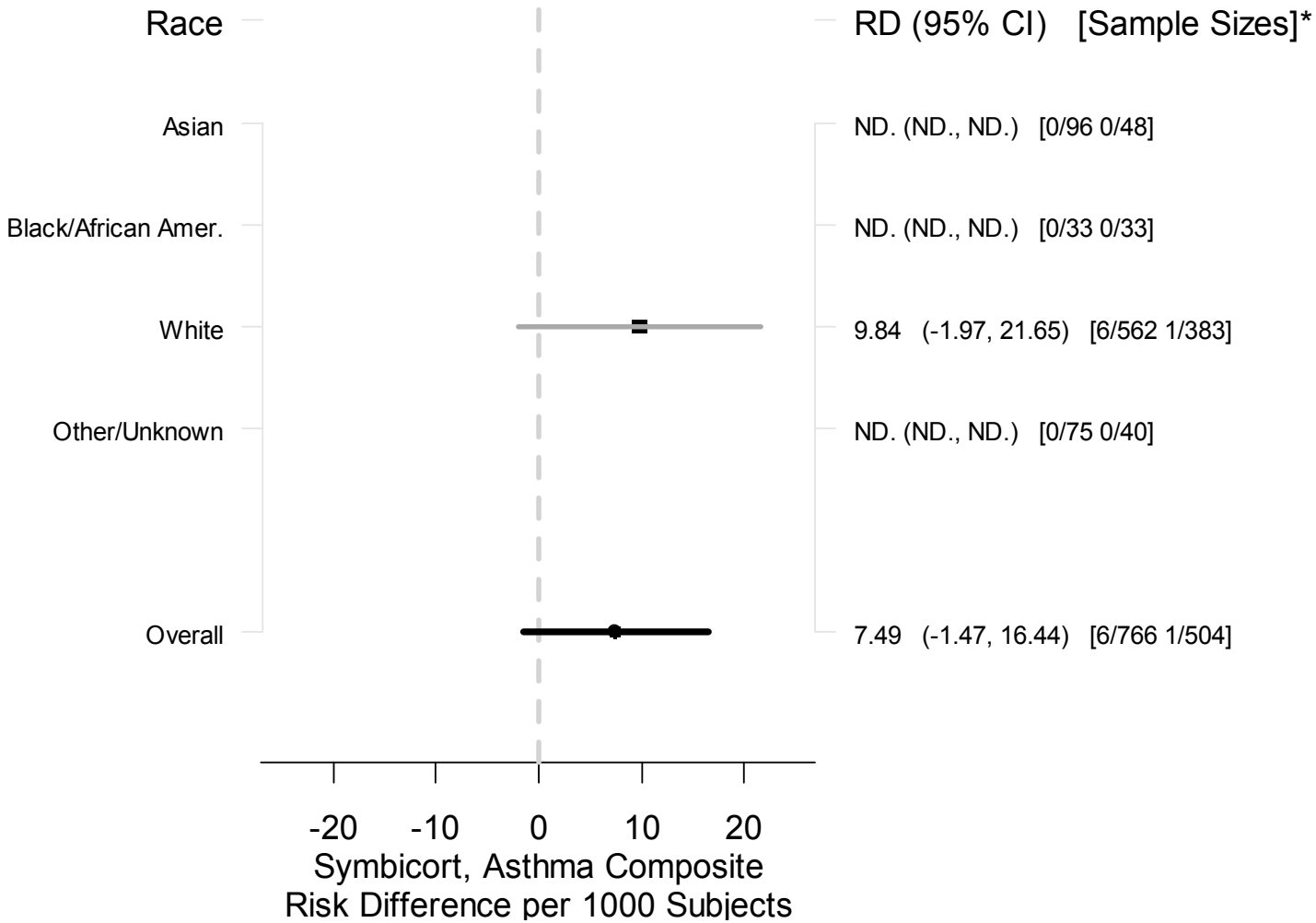

*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Race Subgroup
# Risk Difference Estimates
# Foradil




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

# Asthma Composite by Race Subgroup
# Risk Difference Estimates
# Symbicort




*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]