SUPPLEMENTAL FIGURES AND TABLES:

Figure S1: Schematic diagrams summarizing the breakdown of participants enrolled in this study. **(A)** Of the 102 asthmatic adults screened for this study, 42 atopic asthmatics (AAs) were enrolled. These subjects underwent specimen collection at baseline (prior to any treatment) and were then randomized to receive inhaled placebo or 250 mcg of fluticasone (ICS) twice daily for six weeks. **(B)** Of the 84 atopic non-asthmatic (ANAs) and non-atopic non-asthmatic healthy control (HCs) subjects screened, 21 from each group were enrolled in this study. **(C)** Enrolled participants were seen at multiple visits (indicated by arrows) in nine participating study centers, during which they underwent spirometry (S), methacholine provocation (MP), sputum induction (IS) and bronchoscopy (B). Following baseline assessment (visits 1 and 2) asthmatic patients underwent additional assessment post six weeks twice-daily treatment with ICS or placebo inhaler (post-treatment assessment visits 3 and 4). **(D)** A schematic diagram of the total bronchial brush samples (BBs) collected during bronchoscopy at baseline (visit 2) indicating the breakdown of subjects with sufficient bacterial 16S rRNA for bacterial profile. The proportion of sequenced to not-sequenced BB samples did not vary by subject group or clinical study site ($^{\#}$Chi-square test; $p>0.5$). **(E)** Breakdown of BBs collected from asthmatics post-treatment (visit 4) showing the proportion of sequenced to not sequenced samples, which did not vary between type of inhaler used ($^{\&}$Fishers exact test; $p>0.5$).

Figure S2: **(A)** Total serum IgE concentrations differentiate the three groups. **(B, C)** Atopic asthmatics show evidence of systemic eosinophilia. **(D)** Bacterial burden (normalized to ß-actin expression) in sequenced samples was significantly higher than in non-sequenced samples. **(E)** Bacterial burden in the second scope flush was indistinguishable between a random subset of sequenced and non-sequenced samples, while their paired brush 16S rRNA burden was significantly higher for the sequenced samples. **(F)** Bacterial burden (normalized to ß-actin expression) for sequenced samples did not significantly vary between study groups. **(G)** Bacterial richness did not significantly vary between study groups. **(H)** Bacterial diversity based on Shannon Index did not significantly vary between study groups. **(I)** Bacterial evenness based on Pielou's Index did not significantly vary between study groups. Statistical significance was determined using Wilcoxon rank sum test, $^{\&}$Wilcoxon matched-pairs signed rank test or $^{\$}$Welch's corrected t-test.

Figure S3. The bronchial microbiota of all groups is highly heterogeneous, but compositional variability is higher in the atopic asthmatic subjects. Principal coordinate analysis plots based on unweighted UniFrac distance, where bronchial brush samples **(A)** from all subjects (28 atopic asthmatics – AA; 15 atopic non asthmatics – ANA; 13 healthy controls – HC) are colored by group, which does not explain variation in community composition (PERMANOVA $p>0.05$); **(B)** from all subjects are colored by richness or **(C)** from AAs only colored by richness or **(D)** ANAs only colored by richness or **(E)** HC only colored by richness. Community richness (Observed species ranging from 219 to 1122 operational taxonomic units (OTUs), significantly explained variability in composition between samples in all groups (PERMANOVA, $p\leq0.01$). **(F)** Distance box plots based on weighted UniFrac distance matrix show greater compositional variability in the AA compared to both ANAs and HC subjects (F-test $p<0.05$).

Figure S4: Summary of bacterial taxa at a phylum level, significantly enriched or depleted in relative abundance (at least 2 fold) in **(A)** atopic asthmatic (AAs) patients (n=28) compared to healthy control subjects (HC, n=13); **(B)** atopic non-asthmatic (ANAs) subjects (n=15) compared to HC subjects; **(C)** AAs patients compared to ANAs subjects. The number of operational taxonomic units (OTU) included in each phyla are indicated by #OTU. Statistical significance was determined using Negative binomial regression model corrected for false discovery rate ($q<0.1$).

Figure S5: (A) ICS-responders showed increase in the dose of methacholine in the PC_{20} challenge after 6 weeks of treatment with fluticasone, but not ICS non-responders or asthmatics taking a placebo inhaler. **(B)** ICS-responders showed at least one doubling in the dose of methacholine after 6 weeks of treatment with fluticasone. **(C)** ICS-responders exhibited slightly higher T2-type inflammation at baseline compared to ICS non-responders. Subjects identified as T2-high asthmatics are colored in maroon. **(D)** ICS-responders showed significant decline in the three-gene signature after treatment with fluticasone compared to both ICS non-responders and placebo controls. Statistical significance was determined using Wilcoxon rank sum test and [&]Wilcoxon matched-pairs rank sum test.

Figure S6: (A) Treatment with ICS had no significant effect on the change in bacterial burden compared to placebo inhaler. Statistical significance was determined using Wilcoxon rank sum test. **(B)** Treatment with ICS had no significant effect on the change in Faith's phylogenetic diversity compared to placebo inhaler. Statistical significance was determined using Wilcoxon rank sum test. **(C)** Procrustes analysis plot based on unweighted UniFrac distance of asthmatics taking placebo treatment (n = 8) shows no significant similarity in community composition between pre- and post-treatment paired samples ($M^2 = 0.635$, $p>0.05$). **(D)** Procrustes analysis plot based on unweighted UniFrac distance shows no significant similarity in community composition between pre- and post-treatment paired samples ($M^2 = 0.504$, $p>0.05$) in ICS-responders (n = 8). **(E)** Analysis of paired unweighted UniFrac distance shows no significant difference in the magnitude of the community shift identified with treatment using fluticasone or a lactose containing placebo inhaler. Statistical significance was determined using Wilcoxon rank sum test.

Table S1: Breakdown of sensitivities to specific aeroallergens in the atopic asthmatics and atopic non-asthmatic subjects.

Variable	**Atopic asthmatics** (n = 42)	**Atopic non-asthmatics** (n = 21)	**Healthy controls** (n = 21)	**p-value**[#]
sIgE (Mite-1)	56%	50%	-	NS
sIgE (Mite-2)	54%	60%	-	NS
sIgE (Cat)	68%	40%	-	**<0.05**
sIgE (Dog)	59%	32%	-	**0.05**
sIgE (Mouse)	17%	0%	-	**0.05**
sIgE (Grass mix)	58%	37%	-	NS
sIgE (Cockroach)	28%	11%	-	NS
sIgE (Mold mix)	38%	16%	-	NS
sIgE (Tree mix 1)	42%	21%	-	NS
sIgE (Tree mix 2)	34%	21%	-	NS
sIgE (Weed)	34%	18%	-	NS
sIgE (Weed mix)	47%	29%	-	NS

Percentage of positive specific IgE (sIgE >0.35 kU/l) as tested by ImmunoCap assay. [#] Statistical significance was determined using Chi-square test.

Table S2: Responses to Prior clinical conditions questionnaire for atopic participants.

Questions about Prior conditions	**Atopic Asthmatics** (n=42)	**Atopic Non-asthmatics** (n=21)	**p-value**[#]
Have you ever had eczema/allergic dermatitis?			
Yes	31%	5%	**0.02**
No	69%	95%	
Have you ever had allergic rhinitis (hay fever)?			
Yes	53%	24%	**0.06**
No	48%	76%	
Do you have chronic or recurrent sinusitis (treated with antibiotics and/or surgery)?			
Yes	7%	0%	NS
No	93%	100%	
Have you ever had pneumonia?			
Yes	29%	10%	0.11
No	71%	91%	
Have you been diagnosed with sleep disordered breathing (sleep apnea)?			
Yes	5%	0%	NS
No	95%	100%	
Do you have gastroesophageal reflux disease (GERD)?			
Yes	10%	5%	NS
No	91%	95%	

[#] Statistical significance was determined using Chi-square test, where NS = p≥0.2.

Table S3: Responses to Environmental exposure questionnaire for atopic participants.

Environmental exposure questions	**Atopic Asthmatics** (n = 42)	**Atopic Non-asthmatics** (n = 21)	**p-value**[#]
Do you live within a mile of a farm?			
Yes	**17%**	**10%**	NS
No	**83%**	**91%**	
Do you live within a mile of a major highway?			
Yes	**67%**	**48%**	0.18
No	**33%**	**52%**	
Does the home you live in have a yard?			
Yes	**69%**	**57%**	NS
No	**31%**	**43%**	
Have you been around animals outside your home at least 2 days/week in the past 3 months?			
Yes	**36%**	**29%**	NS
No	**64%**	**71%**	
Are you frequently exposed (2 or more days/week) to tobacco smoke outside of your home?			
Yes	**17%**	**10%**	NS
No	**83%**	**91%**	
Has there been any mold or mildew, on any surfaces inside your house in the past 12 months?			
Yes	**35%**	**35%**	NS
No	**65%**	**65%**	
Does your household have any pets?			
Yes	**33%**	**43%**	NS
No	**67%**	**57%**	
In general, and on a regular basis, are you exposed to cats?			
Yes	**29%**	**43%**	NS
No	**71%**	**57%**	
In general, and on a regular basis, are you exposed to dogs?			
Yes	**50%**	**43%**	NS
No	**50%**	**57%**	
In general, and on a regular basis, are you exposed to other furry pets?			
Yes	**7%**	**5%**	NS
No	**93%**	**95%**	
In general, and on a regular basis, are you exposed to birds?			
Yes	**7%**	**5%**	NS
No	**93%**	**95%**	
In general, and on a regular basis, are you exposed to farm animals?			
Yes	**5%**	**0%**	NS
No	**95%**	**100%**	
Do you ever see cockroaches in your house?			
Yes	**14%**	**19%**	NS
No	**86%**	**81%**	
Do you ever see rodents or rodent droppings in your house?			
Yes	**14%**	**19%**	NS
No	**86%**	**81%**	
Do you ever see cockroaches OR rodents/rodent droppings in your house?			
Yes	**29%**	**33%**	NS
No	**71%**	**67%**	

[#] Statistical significance was determined using Chi-square test, where NS = p≥0.2.

Table S4: Specific bacterial taxa that differ in relative abundance between atopic asthmatic (AA) and healthy control (HC) subjects.

OTU ID	**AA$^{\#}$**	**HC$^{\#}$**	**AA-HC**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
2714267	356.8	61.5	**295.3**	0.0610	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	*tannerae*
4406393	243.8	1.0	**242.8**	0.0041	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
2438396	192.5	1.7	**190.8**	3.00E-106	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4440404	176.8	0.2	**176.7**	1.66E-21	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	-
4405869	196.0	47.4	**148.6**	0.0347	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4296424	137.9	37.8	**100.2**	0.0759	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
240049	48.2	0.8	**47.3**	0.0011	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
1541939	47.9	2.0	**45.9**	0.0011	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
71146	43.4	1.4	**42.0**	0.0231	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
4448211	32.6	6.5	**26.1**	0.0476	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
4388775	31.8	6.8	**24.9**	0.0297	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Veillonella*	*dispar*
4468500	24.4	2.5	**21.9**	1.02E-34	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	*Anaerovorax*	-
642465	21.4	0.3	**21.1**	0.0041	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
70671	87.4	67.5	**19.9**	2.66E-09	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
73875	25.5	7.4	**18.1**	4.02E-28	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
41911	17.7	0.2	**17.4**	0.0027	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4297695	16.1	2.5	**13.6**	0.0667	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	-
495451	11.3	0.4	**10.9**	4.53E-12	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
250288	14.1	5.4	**8.8**	5.95E-12	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
1033013	9.8	1.1	**8.7**	6.48E-14	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4307228	9.1	0.8	**8.3**	0.0550	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
1398	8.2	0.4	**7.8**	0.0277	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
949816	9.2	1.7	**7.5**	0.0622	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4480775	8.4	1.0	**7.4**	0.0231	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	-
4331815	7.5	0.5	**7.0**	3.60E-10	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	-	-
3859	11.6	4.9	**6.7**	1.42E-08	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	*amylovorum*
855912	6.6	1.2	**5.5**	3.46E-09	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-

OTU ID	AA[#]	HC[#]	AA-HC	q-value	Phylum	Class	Order	Family	Genus	Species
267852	5.9	0.6	**5.3**	1.96E-08	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingopyxis*	*alaskensis*
1033687	5.1	0.3	**4.8**	0.0914	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
292057	6.3	1.5	**4.7**	1.07E-07	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	-
328	4.9	0.4	**4.5**	0.0498	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
851668	4.5	0.1	**4.4**	0.0017	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4093791	14.5	10.7	**3.8**	0.0469	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
4410166	3.1	0.1	**3.0**	0.0073	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*copri*
1304	3.0	0.1	**2.9**	0.0082	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	*subflava*
2377731	3.2	0.5	**2.6**	0.0002	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
832	3.1	0.8	**2.3**	0.0010	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
130864	2.7	0.4	**2.3**	0.0009	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*iners*
29566	2.3	0.1	**2.2**	0.0200	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Sneathia*	-
1062051	2.6	0.8	**1.8**	0.0083	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
1116069	2.4	0.6	**1.8**	0.0072	Bacteroidetes	Cytophagia	Cytophagales	Cytophagaceae	-	-
1135830	2.6	1.1	**1.5**	0.0603	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
4375000	0.5	1.5	**-0.9**	0.0713	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
165489	0.5	1.5	**-1.0**	0.0333	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
160203	0.3	1.3	**-1.0**	0.0108	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	*Kocuria*	*palustris*
538185	0.5	1.8	**-1.3**	0.0165	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4469627	0.9	2.2	**-1.3**	0.0204	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
4335450	1.4	3.3	**-1.9**	0.0041	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	-	-
51646	0.4	2.6	**-2.2**	2.96E-06	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
3799784	0.9	3.2	**-2.3**	1.43E-05	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
521996	0.3	2.8	**-2.6**	0.0252	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
710275	0.8	3.5	**-2.6**	8.49E-07	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	-
849642	0.2	4.0	**-3.8**	1.67E-09	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
4417996	1.4	5.5	**-4.1**	2.22E-10	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
399903	2.4	6.7	**-4.3**	1.20E-08	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
242070	1.7	6.2	**-4.4**	1.53E-10	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-

OTU ID	**AA**[#]	**HC**[#]	**AA-HC**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
851961	1.9	7.3	**-5.5**	1.38E-13	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
114510	2.8	11.6	**-8.9**	6.38E-23	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
100791	2.7	12.2	**-9.6**	1.98E-25	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
4333897	3.6	15.9	**-12.3**	3.51E-32	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
4477971	3.8	17.7	**-13.9**	1.85E-37	Firmicutes	Clostridia	Clostridiales	-	-	-
74407	1.3	16.9	**-15.6**	1.69E-44	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4396717	2.5	25.6	**-23.1**	8.72E-68	Proteobacteria	Alphaproteobacteria	Rhizobiales	Methylobacteriaceae	*Methylobacterium*	-
4469032	21.9	45.3	**-23.4**	2.20E-34	Firmicutes	Bacilli	Lactobacillales	-	-	-
70628	0.4	24.3	**-24.0**	2.55E-37	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
55854	0.2	24.9	**-24.7**	0.0610	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
98258	0.7	26.7	**-26.0**	0.0186	Cyanobacteria	4C0d-2	MLE1-12	-	-	-
269930	22.8	81.1	**-58.3**	8.82E-139	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	-	-
684	1.6	61.8	**-60.3**	0.0001	Firmicutes	Bacilli	Lactobacillales	-	-	-
114813	1.0	66.9	**-66.0**	6.31E-102	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4404577	372.8	441.8	**-69.0**	4.03E-23	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Peptostreptococcus*	-
4480189	10.0	98.2	**-88.2**	1.23E-259	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*zeae*
4335578	221.3	332.8	**-111.6**	6.19E-92	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
4404220	336.1	452.3	**-116.2**	5.61E-69	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Actinobacillus*	-
4400260	2.3	123.2	**-120.9**	0.0333	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4307006	11.1	246.5	**-235.4**	0	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-

[#] mean relative abundance

Table S5: Specific bacterial taxa that differ in relative abundance between atopic non-asthmatic (ANA) and healthy control (HC) subjects.

OTU ID	**ANA$^{\#}$**	**HC$^{\#}$**	**ANA-HC**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
4432431	963.7	55.5	**908.3**	0.0029	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	*segnis*
828676	315.3	0.1	**315.3**	0.0036	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
978067	292.5	12.1	**280.4**	0.0302	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	-	-
4483015	218.4	18.0	**200.4**	0.0143	Firmicutes	Bacilli	Lactobacillales	Carnobacteriaceae	*Granulicatella*	-
4306587	158.2	11.7	**146.5**	0.0758	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
134265	119.2	7.2	**112.0**	2.37E-152	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4296424	141.9	37.8	**104.1**	0.0613	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
495067	103.4	3.6	**99.8**	1.74E-111	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4372058	105.2	5.6	**99.6**	0.0007	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
4459993	102.7	4.5	**98.2**	0.0854	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
976838	98.5	29.9	**68.5**	5.39E-95	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Flexispira*	-
2466322	65.7	0.2	**65.6**	0.0092	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
4388775	70.5	6.8	**63.7**	0.0047	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Veillonella*	*dispar*
1015518	55.8	1.8	**54.0**	4.86E-58	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4469627	55.3	2.2	**53.0**	8.15E-63	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
4297222	47.9	4.3	**43.6**	1.36E-65	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
995	44.7	2.5	**42.2**	0.0242	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
1053321	75.5	36.6	**38.9**	3.63E-38	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	-
4364176	47.9	11.3	**36.6**	1.91E-55	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Sharpea*	-
267852	33.8	0.6	**33.2**	1.47E-27	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingopyxis*	*alaskensis*
4419634	33.3	2.3	**31.0**	0.0302	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
1102	33.7	3.8	**29.9**	0.0583	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*nanceiensis*
575	28.0	0.5	**27.5**	0.0014	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
2438396	28.2	1.7	**26.5**	4.60E-36	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
1044611	24.1	0.8	**23.3**	0.0434	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
4353757	24.0	1.3	**22.7**	0.0043	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	-

OTU ID	ANA$^{\#}$	HC$^{\#}$	ANA-HC	q-value	Phylum	Class	Order	Family	Genus	Species
787709	24.9	3.7	**21.2**	0.0192	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
4412630	22.1	1.3	**20.8**	0.0132	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
876114	24.1	3.8	**20.3**	2.50E-32	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	-	-
71146	18.1	1.4	**16.7**	0.0714	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
4333897	32.1	15.9	**16.2**	1.12E-15	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
3859	20.6	4.9	**15.7**	9.42E-24	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	*amylovorum*
63117	14.7	1.9	**12.8**	2.17E-20	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	-
4373910	18.9	7.0	**11.9**	4.85E-15	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	-
89	11.4	0.1	**11.3**	1.40E-05	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
1124080	11.5	1.0	**10.5**	7.55E-16	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
161677	10.4	0.3	**10.1**	1.07E-10	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	-
4468500	12.4	2.5	**9.9**	1.12E-15	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	*Anaerovorax*	-
124932	10.9	1.5	**9.4**	4.42E-15	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
3931	10.7	2.1	**8.6**	1.20E-13	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
956702	9.1	1.2	**7.9**	1.11E-12	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*influenzae*
4460505	10.2	3.3	**6.9**	1.93E-09	Synergistetes	Synergistia	Synergistales	Dethiosulfovibrionaceae	*TG5*	-
41911	6.6	0.2	**6.4**	0.0562	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
114510	17.7	11.6	**6.1**	0.0007	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
4309323	6.8	1.0	**5.8**	0.0164	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
520222	5.5	0.1	**5.5**	0.0005	Proteobacteria	Betaproteobacteria	Burkholderiales	Oxalobacteraceae	-	-
4313608	11.3	6.0	**5.3**	7.30E-05	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
4351304	5.9	0.5	**5.3**	3.12E-08	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
1052181	6.8	1.9	**4.9**	3.64E-07	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*nanceiensis*
4374322	5.8	0.9	**4.9**	6.14E-08	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	-
4419380	5.6	1.1	**4.5**	2.81E-07	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Bulleidia*	*p-1630-c5*
4331815	4.8	0.5	**4.3**	7.69E-07	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	-	-
517	4.3	0.2	**4.1**	0.0462	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
544313	4.3	0.3	**4.0**	7.71E-06	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
328	4.0	0.4	**3.6**	0.0478	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-

OTU ID	ANA$^{\#}$	HC$^{\#}$	ANA-HC	q-value	Phylum	Class	Order	Family	Genus	Species
3799784	6.5	3.2	**3.2**	0.0031	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
325027	5.1	2.0	**3.1**	0.0007	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Comamonas*	-
43339	7.0	4.4	**2.6**	0.0562	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
2119418	2.7	0.1	**2.6**	0.0075	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
3600504	2.5	0.5	**2.0**	0.0031	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	-
165489	3.4	1.5	**1.9**	0.0241	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
4454619	2.3	0.8	**1.5**	0.0353	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
4412991	2.0	0.5	**1.5**	0.0247	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	-	-
4432889	2.1	0.6	**1.5**	0.0302	Actinobacteria	Actinobacteria	Actinomycetales	Intrasporangiaceae	-	-
495451	1.5	0.4	**1.2**	0.0613	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
51646	1.2	2.6	**-1.4**	0.0854	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
1010329	0.9	2.6	**-1.7**	0.0173	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	-
4426165	0.9	2.8	**-1.9**	0.0055	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
1595	1.4	3.6	**-2.2**	0.0051	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
941024	1.0	3.4	**-2.4**	8.94E-04	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4306356	0.2	3.0	**-2.8**	0.0001	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
4401957	1.9	6.2	**-4.2**	0.0920	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	-
851961	0.3	7.3	**-7.0**	4.95E-10	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
245523	9.7	17.8	**-8.0**	3.05E-07	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
923032	0.1	8.2	**-8.1**	0.0908	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4477971	6.3	17.7	**-11.4**	1.35E-15	Firmicutes	Clostridia	Clostridiales	-	-	-
100791	0.1	12.2	**-12.1**	5.90E-09	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
4443201	12.3	29.4	**-17.1**	9.85E-21	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Tannerella*	-
4396717	8.2	25.6	**-17.4**	1.91E-25	Proteobacteria	Alphaproteobacteria	Rhizobiales	Methylobacteriaceae	*Methylobacterium*	-
579608	0.1	18.7	**-18.6**	1.03E-10	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
615020	15.9	36.7	**-20.8**	3.31E-24	Tenericutes	Mollicutes	Mycoplasmatales	Mycoplasmataceae	*Mycoplasma*	-
4344371	35.3	57.7	**-22.4**	1.86E-16	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingomonas*	-
70628	0.2	24.3	**-24.1**	4.42E-15	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4297119	3.7	39.8	**-36.2**	0.0968	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-

OTU ID	ANA$^{\#}$	HC$^{\#}$	ANA-HC	q-value	Phylum	Class	Order	Family	Genus	Species
123320	0.1	36.8	**-36.8**	7.58E-09	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4480189	60.8	98.2	**-37.4**	1.28E-26	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*zeae*
1048420	7.0	46.4	**-39.4**	0.0149	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
28118	0.1	52.9	**-52.8**	0.0029	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
684	1.9	61.8	**-59.9**	0.0103	Firmicutes	Bacilli	Lactobacillales	-	-	-
4376637	8.1	73.5	**-65.4**	0.0785	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
269930	0.1	81.1	**-80.9**	0.0065	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	-	-
557974	10.1	96.8	**-86.8**	0.0812	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
69782	1.7	122.8	**-121.0**	6.05E-101	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Helicobacter*	-
3581175	3.0	133.8	**-130.8**	1.90E-137	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	-	-
1004910	93.5	260.4	**-166.9**	7.86E-226	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4331006	30.5	205.6	**-175.1**	0	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4377418	215.8	413.2	**-197.4**	4.13E-185	Firmicutes	Clostridia	Clostridiales	Tissierellaceae	*Parvimonas*	-
4307006	3.5	246.5	**-242.9**	5.60E-204	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
2613485	4.7	428.8	**-424.2**	0	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
252843	8.1	450.7	**-442.6**	0	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-

$^{\#}$mean relative abundance

Table S6: Specific bacterial taxa which differ in relative abundance between atopic asthmatic (AA) and atopic non-asthmatic (ANA) subjects.

OTU ID	**AA$^{\#}$**	**ANA$^{\#}$**	**AA-ANA**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
252843	503.7	8.1	**495.6**	0.0255	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4307790	518.8	119.1	**399.7**	0.0255	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
4338372	363.6	86.0	**277.6**	0.0132	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4406393	243.8	1.8	**242.0**	0.0014	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
2438396	192.5	28.2	**164.3**	0	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4405869	196.0	57.4	**138.6**	0.0711	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4393181	141.3	3.4	**137.9**	0.0004	Tenericutes	Mollicutes	Mycoplasmatales	Mycoplasmataceae	*Mycoplasma*	-
4382476	126.9	7.0	**119.9**	0.0014	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4297119	93.6	3.7	**89.9**	0.0014	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
525942	94.6	16.9	**77.6**	0.0194	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
4426165	59.0	0.9	**58.1**	0.0373	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4318284	60.2	6.1	**54.1**	0.0599	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Dialister*	-
923032	31.0	0.1	**30.9**	0.0255	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
269930	22.8	0.1	**22.6**	0.0256	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	-	-
4452538	24.3	4.5	**19.7**	0.0077	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4307309	19.5	7.5	**12.0**	1.93E-18	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4468500	24.4	12.4	**12.0**	1.75E-14	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	*Anaerovorax*	-
495451	11.3	1.5	**9.7**	1.92E-18	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
4346863	10.9	1.2	**9.7**	0.0094	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
245523	18.9	9.7	**9.1**	6.69E-11	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
69782	10.4	1.7	**8.7**	1.25E-16	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Helicobacter*	-
28118	7.7	0.1	**7.5**	0.0255	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
1580	7.1	0.6	**6.5**	0.0808	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
4426163	7.7	1.6	**6.1**	0.0425	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
1033687	5.1	0.3	**4.8**	0.0689	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
92316	6.0	1.5	**4.5**	3.52E-08	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	-	-
62513	4.4	0.1	**4.3**	3.52E-05	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Moryella*	-

OTU ID	**AA$^{\#}$**	**ANA$^{\#}$**	**AA-ANA**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
523025	4.6	0.9	**3.7**	0.0787	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
989074	3.4	0.1	**3.2**	0.0002	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	-
1304	3.0	0.1	**2.9**	0.0044	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	*subflava*
4331815	7.5	4.8	**2.7**	0.0212	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	-	-
100791	2.7	0.1	**2.5**	0.0009	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
55917	3.6	1.1	**2.5**	0.0004	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
831	2.5	0.3	**2.2**	0.0897	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
2377731	3.2	1.1	**2.0**	0.0029	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
1465	2.1	0.1	**2.0**	0.0033	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*intermedia*
4353264	3.8	1.8	**2.0**	0.0135	Proteobacteria	Alphaproteobacteria	Caulobacterales	Caulobacteraceae	-	-
4414261	2.1	0.5	**1.6**	0.0044	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	-
1066621	2.2	0.6	**1.6**	0.0925	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
1188	1.4	0.1	**1.4**	0.0449	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
104313	1.2	0.3	**0.9**	0.0696	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
540269	0.6	1.7	**-1.1**	0.0190	Firmicutes	Bacilli	Bacillales	Exiguobacteraceae	-	-
4423236	0.1	1.3	**-1.2**	0.0894	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	*segnis*
57758	0.5	1.7	**-1.2**	0.0047	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Flavobacterium*	*columnare*
4483174	0.7	2.0	**-1.3**	0.0092	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
671258	0.4	2.1	**-1.7**	8.43E-05	Actinobacteria	Actinobacteria	Actinomycetales	Gordoniaceae	*Gordonia*	-
3359884	1.5	3.3	**-1.8**	0.0043	Cyanobacteria	Chloroplast	Streptophyta	-	-	-
4375000	0.5	2.7	**-2.2**	2.70E-06	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
470724	0.4	3.8	**-3.4**	2.37E-10	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	-
339015	0.3	4.1	**-3.8**	3.65E-11	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Hydrogenophaga*	-
669486	0.8	5.3	**-4.4**	2.19E-13	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
1052181	1.8	6.8	**-5.0**	4.58E-13	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*nanceiensis*
4335450	1.4	6.5	**-5.1**	2.75E-14	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	-	-
4343627	0.3	5.7	**-5.4**	1.07E-14	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*fragilis*
903686	2.8	8.3	**-5.5**	0.0689	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	*segnis*
4440670	19.8	25.3	**-5.5**	0.0055	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Veillonella*	-

OTU ID	AA$^{\#}$	ANA$^{\#}$	AA-ANA	q-value	Phylum	Class	Order	Family	Genus	Species
3799784	0.9	6.5	**-5.6**	6.52E-17	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
4309323	1.1	6.8	**-5.7**	0.0588	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
242070	1.7	8.2	**-6.5**	2.34E-18	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
521996	0.3	7.1	**-6.9**	0.0007	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
571873	0.4	7.6	**-7.2**	1.32E-18	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
95168	1.4	8.9	**-7.5**	1.36E-22	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
543491	0.3	8.1	**-7.8**	6.36E-19	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	-	-
898611	1.0	9.3	**-8.3**	3.23E-25	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	-
4428313	6.5	15.3	**-8.8**	3.16E-16	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	-
3859	11.6	20.6	**-9.0**	3.10E-11	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	*amylovorum*
956702	0.1	9.1	**-9.0**	0.0615	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*influenzae*
4303688	4.1	14.5	**-10.4**	8.09E-26	Proteobacteria	Betaproteobacteria	Burkholderiales	Burkholderiaceae	*Lautropia*	-
561636	0.1	10.9	**-10.8**	0.0232	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
63117	1.9	14.7	**-12.9**	3.41E-39	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	-
4386920	0.0	15.0	**-15.0**	0.0255	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
2510538	1.6	17.5	**-15.9**	0.0254	Firmicutes	Bacilli	Lactobacillales	Carnobacteriaceae	-	-
4430639	7.5	24.6	**-17.1**	0.0254	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*parainfluenzae*
353459	0.0	17.4	**-17.4**	0.087	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*copri*
4443200	0.8	19.3	**-18.5**	8.79E-45	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*ochracea*
4412630	2.0	22.1	**-20.1**	0.0271	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
171157	8.6	31.3	**-22.7**	1.72E-57	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Flexispira*	-
259631	0.0	23.0	**-23.0**	0.0686	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Ruminococcus*	*gnavus*
245	0.2	25.1	**-25.0**	0.0043	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
575	2.5	28.0	**-25.5**	0.032	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
4301566	10.6	37.3	**-26.7**	0.0172	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
886735	21.0	47.9	**-26.9**	1.18E-47	Firmicutes	Bacilli	Lactobacillales	Aerococcaceae	*Alloiococcus*	-
267852	5.9	33.8	**-27.9**	1.99E-82	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingopyxis*	*alaskensis*
4469032	21.9	50.2	**-28.3**	1.74E-50	Firmicutes	Bacilli	Lactobacillales	-	-	-
995	4.0	44.7	**-40.6**	0.010	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*

OTU ID	AA$^{\#}$	ANA$^{\#}$	AA-ANA	q-value	Phylum	Class	Order	Family	Genus	Species
4297222	7.1	47.9	**-40.9**	2.03E-123	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4364176	1.3	47.9	**-46.6**	1.99E-97	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Sharpea*	-
4480189	10.0	60.8	**-50.8**	1.45E-151	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*zeae*
1015518	3.1	55.8	**-52.7**	5.83E-143	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4466150	5.5	63.3	**-57.9**	5.08E-05	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
4337755	30.6	94.8	**-64.2**	0.0255	Firmicutes	Bacilli	Gemellales	Gemellaceae	-	-
1925094	8.2	75.5	**-67.4**	5.19E-204	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	-	-
260397	3.7	77.7	**-74.0**	2.51E-191	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Allobaculum*	-
4372058	17.6	105.2	**-87.6**	0.026	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
976838	7.3	98.5	**-91.2**	2.41E-263	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Flexispira*	-
4335578	221.3	313.5	**-92.2**	1.94E-70	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
4459993	3.5	102.7	**-99.1**	0.0010	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
495067	1.8	103.4	**-101.7**	2.20E-171	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
134265	1.0	119.2	**-118.2**	9.40E-137	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4306587	12.7	158.2	**-145.5**	0.0156	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
4400869	10.9	167.7	**-156.8**	0.0960	SR1	-	-	-	-	-
891034	31.5	270.0	**-238.5**	0.0806	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	-
4432431	91.3	963.7	**-872.4**	0.0006	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	*segnis*

$^{\#}$mean relative abundance

Table S7: Clinical and immunological comparison of T2-high compared to T2-low asthma patients.

Variable	**T2-high asthmatics** (n = 10)	**T2-low asthmatics** (n = 30)	**p-value**[#]
Age (yrs)	28 (24-33)	37 (27-43)	**<0.05**
Age of Asthma diagnosis (yrs)	9 (5-24)	9 (5-22)	NS
Duration of Asthma (yrs)	18 (9-23)	23 (14-29)	NS
ACQ Score (Baseline)*	1.0 (0.8 - 1.3)	0.5 (0.2 - 0.7)	**<0.05**
% Male	50%	47%	NS[€]
% White	60%	60%	NS[€]
BMI	26 (23 - 30)	26 (23 - 29)	NS
FEV1 % pre-Ab (Baseline)	91 (68 - 110)	86 (76 - 96)	NS
FEV1 % post-Ab (Baseline)	102 (93 - 114)	105 (83 - 105)	NS
Change in FEV % (Baseline)	15 (7 - 25)	7 (5 - 12)	**<0.05**
FEV1 % pre-Ab (post-ICS)	88 (79 - 97)	95 (90 - 106)	NS
FEV1 % post-Ab (post-ICS)	98 (91 - 105)	103 (98 - 115)	NS
Change in FEV % pre-Ab	3 (-4 - 13)	1 (-6 - 4)	NS
Change in FEV % post-Ab	1 (-3 - 5)	0 (-5 - 6)	NS
PC_{20} (Baseline)	0.9 (0.2 - 3.8)	1.3 (0.4 - 2.7)	NS
PC_{20} (post ICS)	6.1 (1.6 - 12.4)	1.9 (0.3 - 5.8)	NS
Change in PC_{20}	4.9 (1.2 - 11.5)	0.3 (-0.2 - 1.5)	**<0.01**
Blood eosinophils (absolute)	400 (245 - 600)	130 (100 - 293)	**<0.01**
Blood eosinophils (%)	6.9 (4.6 - 10.3)	2.7 (1.3 - 4.2)	**<0.001**
Blood neutrophils (%)	53.5 (43.7 - 60.5)	56.1 (49.7 - 62.0)	NS
Sputum neutrophils (% Baseline)	53.6 (33.9 - 64.9)	55.8 (32.5 - 65.2)	NS
Sputum neutrophils (% post-ICS)	49.5 (32.8 - 59.9)	49.4 (25.1 - 60.3)	NS
Change in sputum neutrophils	0.0 (-24.9 - 16.0)	-9.6 (-18-1.8)	NS
Sputum eosinophils (% Baseline)	1.3 (0.4 - 3.8)	0.3 (0.0 - 1.0)	**<0.05**
Sputum eosinophils (% post-ICS)	0.0 (0.0 - 0.4)	0.0 (0.0 - 0.2)	NS
Change in sputum eosinophils	0.0 (-0.7 - 0.1)	-0.2 (-0.6 - 0.0)	NS
Serum IgE (IU/mL)	323.5 (184.3 - 560.5)	121.5 (49.0 - 231.3)	**<0.05**
Number of positive sIgE[¢]	5 (2-10)	6 (3-7)	NS[€]
% Eczema/Allergic dermatitis[§]	40%	27%	NS[€]
% Allergic rhinitis[§]	60%	39%	NS[€]

All values are medians (IQR). *ACQ, Asthma Control Questionnaire. [¢]Number of positive specific IgE (sIgE >0.35 kU/l) from a total of 12 aeroallergens tested by ImmunoCap assay. [§]Subjects with a positive history of allergic conditions specified (self-reported). Statistical significance was determined using [#] Mann-Whitney or [€] Fisher's exact test.

Table S8: Clinical and immunological comparison of ICS-responders compared to ICS non-responders.

Variable	**ICS responders** (n = 15)	**ICS non-responders** (n = 10)	**p-value**$^{\#}$
Age (yrs)	32 (27-43)	29 (20-39)	NS
Age of Asthma diagnosis (yrs)	8 (5-22)	5 (2-9)	NS
Duration of Asthma (yrs)	25 (18-27)	21 (13-26)	NS
ACQ Score (Baseline)*	0.8 (0.2 - 1.2)	0.6 (0.1 - 1.0)	NS
ACQ Score (post ICS)*	0.3 (0.0 - 0.5)	0.2 (0.0 - 0.7)	NS
% Male	40%	40%	NS$^{€}$
% White	47%	70%	NS$^{€}$
BMI	26 (23 - 29)	26 (24 - 28)	NS
FEV1 % pre-Ab (Baseline)	86 (71 - 95)	99 (94 - 110)	**<0.05**
FEV1 % post-Ab (Baseline)	101 (85 - 105)	105 (100 - 114)	NS
Change in FEV with Ab % (Baseline)	12 (8 - 15)	6 (5 - 7)	**<0.05**
FEV1 % pre-Ab (post-ICS)	88 (79 - 97)	95 (90 - 106)	NS
FEV1 % post-Ab (post-ICS)	98 (91 - 105)	103 (98 - 115)	NS
Change in FEV % with Ab (post-ICS)	12 (5 - 14)	10 (5 - 14)	NS
Change in FEV % pre-Ab	3 (-4 - 13)	1 (-6 - 4)	NS
Change in FEV % post-Ab	1 (-3 - 5)	0 (-5 - 6)	NS
% Change from baseline in pre-Alb FEV$_1$	3.2 (-4.7 – 11.7)	0.4 (-5.3 – 3.3)	NS
PC$_{20}$ (Baseline)	0.8 (0.3 - 1.2)	1.9 (0.3 - 4.1)	NS
PC$_{20}$ (post ICS)	6.1 (1.6 - 12.4)	1.9 (0.3 - 5.8)	NS
Change in PC$_{20}$	4.9 (1.2 - 11.5)	0.3 (-0.2 - 1.5)	**<0.01**
Blood eosinophils (absolute)	200 (100 - 400)	155 (100 - 315)	NS
Blood eosinophils (%)	3.8 (1.3 - 6.7)	3.0 (1.0 - 5.1)	NS
Blood neutrophils (%)	53.3 (49.8 - 61.0)	58.0 (50.4 - 64.3)	NS
Sputum neutrophils (% Baseline)	51.5 (25.6 - 64.2)	56.1 (35.0 - 66.7)	NS
Sputum neutrophils (% post-ICS)	49.5 (32.8 - 59.9)	49.4 (25.1 - 60.3)	NS
Change in sputum neutrophils	0.0 (-24.9 - 16.0)	-9.6 (-18-1.8)	NS
Sputum eosinophils (% Baseline)	0.2 (0.0 - 1.0)	0.4 (0.0 - 0.7)	NS
Sputum eosinophils (% post-ICS)	0.0 (0.0 - 0.4)	0.0 (0.0 - 0.2)	NS
Change in sputum eosinophils	0.0 (-0.7 - 0.1)	-0.2 (-0.6 - 0.0)	NS
Serum IgE (IU/mL)	153.0 (93.0 - 261.0)	188.0 (66.8 - 310.8)	NS

All values are medians (IQR). *ACQ, Asthma Control Questionnaire. Statistical significance was determined using $^{\#}$ Mann-Whitney or $^{€}$ Fisher's exact test.

Table S9: Specific taxa differentially expressed in ICS non-responders (ICS non-R) compared to ICS responders (ICS-R) at baseline.

OTU ID	ICS non-R$^{\#}$	ICS-R$^{\#}$	ICS non-R- R	q-value	Phylum	Class	Order	Family	Genus	Species
12297	9157.6	0.5	**9157.1**	1.05E-104	Actinobacteria	Actinobacteria	Actinomycetales	Microbacteriaceae	-	-
4406393	1111.8	0.7	**1111.1**	1.29E-82	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	-
4459021	221	7.1	**213.9**	0.0658	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Tannerella*	-
4465803	210.2	3.7	**206.5**	1.06E-126	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
923032	164	3.8	**160.2**	7.45E-112	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4426165	154	8.7	**145.3**	3.64E-140	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
2654263	116.4	4.5	**111.9**	0.0129	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*parainfluenzae*
4437399	137.4	58.4	**79**	2.55E-50	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
4404220	410.2	333.7	**76.5**	5.54E-12	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Actinobacillus*	-
14920	60.6	0.2	**60.4**	2.48E-14	Firmicutes	Bacilli	Gemellales	Gemellaceae	*Gemella*	-
73875	84.6	26.9	**57.7**	4.06E-47	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
71146	108.6	52.6	**56**	1.06E-30	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
2613485	60.8	6.3	**54.5**	2.20E-58	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
4419376	54.4	0.6	**53.8**	4.08E-26	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*ochracea*
548730	114.4	62.3	**52.1**	3.75E-24	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
949816	37.4	2.6	**34.8**	0.0389	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4376637	82.6	47.8	**34.8**	1.24E-14	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
968873	33.8	0.1	**33.7**	1.63E-07	Bacteroidetes	Flavobacteriia	Flavobacteriales	Weeksellaceae	-	-
325027	33.6	1.4	**32.2**	0.0454	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Comamonas*	-
4459265	42.8	12.9	**29.9**	2.28E-25	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
1013316	29.8	0.9	**28.9**	8.09E-23	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	-	-
4480189	27.2	0.4	**26.8**	3.05E-15	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*zeae*
4468500	58.2	36.4	**21.8**	6.44E-08	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	*Anaerovorax*	-
4446973	21.8	0.1	**21.7**	0.0716	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Paludibacter*	-
4313722	20.4	0.4	**20**	0.0059	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4449458	23.6	5.6	**18**	0.0545	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	-
4422512	19.6	2.1	**17.5**	5.90E-19	Tenericutes	Mollicutes	Mycoplasmatales	Mycoplasmataceae	*Mycoplasma*	-
886735	20.2	3.6	**16.6**	2.32E-17	Firmicutes	Bacilli	Lactobacillales	Aerococcaceae	*Alloiococcus*	-

OTU ID	ICS non-R$^{\#}$	ICS-R$^{\#}$	ICS non-R- R	q-value	Phylum	Class	Order	Family	Genus	Species
46	17.6	1.3	**16.3**	6.34E-17	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
4329788	33.2	19.3	**13.9**	6.48E-06	Firmicutes	Clostridia	Clostridiales	-	-	-
269930	43.2	32.5	**10.7**	0.0181	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	-	-
1157	11	1.1	**9.9**	8.65E-11	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4299087	8.2	0.3	**7.9**	0.0389	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*ochracea*
1609	7.6	0.3	**7.3**	1.60E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
1076969	11.8	4.5	**7.3**	2.31E-05	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4306773	9.8	3.3	**6.5**	2.74E-05	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4329957	5.8	0.2	**5.6**	8.21E-05	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
137183	6.8	1.4	**5.4**	1.37E-05	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	-	-
886264	2.6	0.6	**2**	0.0398	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	*Rothia*	*mucilaginosa*
43339	0.8	3.6	**-2.8**	0.0550	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
645055	0.6	3.6	**-3**	0.0390	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
968954	0.6	4.2	**-3.6**	0.0389	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
1015518	1.2	4.9	**-3.7**	0.0176	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4306356	2.2	6	**-3.8**	0.0325	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
4399781	1.2	5.1	**-3.9**	0.0130	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
989074	1.2	6.4	**-5.2**	0.0016	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	-
1580	2.2	7.6	**-5.4**	0.0022	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
591583	0.2	5.6	**-5.4**	0.0545	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
4341205	3.8	9.4	**-5.6**	0.0056	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	-	-
965500	2.4	8.9	**-6.5**	0.0004	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
254888	3.6	10.5	**-6.9**	0.0005	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	-	-
1935279	0.8	9.1	**-8.3**	0.0125	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
851935	0.4	9	**-8.6**	0.0916	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
610111	3.4	13.1	**-9.7**	3.71E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
851824	1.2	12.1	**-10.9**	7.99E-07	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Bulleidia*	-
124932	1.8	12.8	**-11**	3.19E-07	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
4306587	0.2	11.5	**-11.3**	0.0325	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-

OTU ID	ICS non-R$^{\#}$	ICS-R$^{\#}$	ICS non-R- R	q-value	Phylum	Class	Order	Family	Genus	Species
22951	6.4	18.2	**-11.8**	1.15E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4297119	0.2	15	**-14.8**	0.0131	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4373910	0.8	16	**-15.2**	8.52E-08	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	-
4440670	2.6	19.9	**-17.3**	3.30E-11	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Veillonella*	-
1044611	1.6	23.9	**-22.3**	1.61E-12	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
537098	125.6	150.9	**-25.3**	0.0020	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	-	-
86	1.4	28.5	**-27.1**	0.0155	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
4310395	25.8	57.8	**-32**	3.94E-15	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Oribacterium*	-
4466006	5.2	46.9	**-41.7**	0.0863	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	*Rothia*	*dentocariosa*
4313608	12.8	56.4	**-43.6**	1.16E-27	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
245523	0.2	47.7	**-47.5**	1.07E-06	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
642465	0.2	52.1	**-51.9**	0.0233	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
2438396	21.2	98.8	**-77.6**	1.93E-49	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4330849	6.6	92.4	**-85.8**	2.08E-48	SR1	-	-	-	-	-
4344371	2	94.1	**-92.1**	4.52E-32	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingomonas*	-
1053321	17	110.2	**-93.2**	5.59E-60	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	-
4335578	117.4	236	**-118.6**	6.17E-50	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
4404577	253.4	388.7	**-135.3**	3.41E-38	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Peptostreptococcus*	-
4455767	56.8	206.1	**-149.3**	0.0597	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-
252843	54.4	215.3	**-160.9**	2.22E-99	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
4448497	0.8	165.9	**-165.1**	0.0006	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	*tannerae*
4308793	35.2	270.2	**-235**	0.0389	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
4363066	9.8	333.7	**-323.9**	0.0568	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	-
2469654	41.2	399.4	**-358.2**	1.68E-219	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
4439603	1030	2727.2	**-1697.2**	0.0127	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	-

$^{\#}$mean relative abundance

Table S10: Predicted KEGG pathways enriched in ICS non-responders compared to ICS responders at baseline.

ICS non-responders	ICS-responders	ICS non-responders - responders	KEGG Super-pathways	KEGG pathways
96668	6133	**90535**	Amino Acid Metabolism	Alanine, aspartate and glutamate metabolism
346121	163683	**182438**	Amino Acid Metabolism	Amino acid related enzymes
67400	48235	**19165**	Amino Acid Metabolism	Arginine and proline metabolism
171954	78691	**93263**	Amino Acid Metabolism	Cysteine and methionine metabolism
231976	121154	**110822**	Amino Acid Metabolism	Glycine, serine and threonine metabolism
54604	16710	**37894**	Amino Acid Metabolism	Lysine degradation
46299	268	**46031**	Amino Acid Metabolism	Phenylalanine metabolism
159693	49782	**109911**	Amino Acid Metabolism	Phenylalanine, tyrosine and tryptophan biosynthesis
44	12	**32**	Amino Acid Metabolism	Tryptophan metabolism
51684	20667	**31017**	Amino Acid Metabolism	Tyrosine metabolism
317294	205019	**112275**	Amino Acid Metabolism	Valine, leucine and isoleucine biosynthesis
276968	119360	**157608**	Amino Acid Metabolism	Valine, leucine and isoleucine degradation
46198	546	**45652**	Biosynthesis of Other Secondary Metabolites	Novobiocin biosynthesis
4388	18964	**-14576**	Biosynthesis of Other Secondary Metabolites	Penicillin and cephalosporin biosynthesis
9285	36231	**-26946**	Biosynthesis of Other Secondary Metabolites	Phenylpropanoid biosynthesis
149876	160184	**-10308**	Carbohydrate Metabolism	Amino sugar and nucleotide sugar metabolism
93433	4694	**88739**	Carbohydrate Metabolism	Ascorbate and aldarate metabolism
413978	211294	**202684**	Carbohydrate Metabolism	Butanoate metabolism
151818	133288	**18530**	Carbohydrate Metabolism	C5-Branched dibasic acid metabolism
510250	246694	**263556**	Carbohydrate Metabolism	Citrate cycle (TCA cycle)
91488	115716	**-24228**	Carbohydrate Metabolism	Fructose and mannose metabolism
26877	108183	**-81306**	Carbohydrate Metabolism	Galactose metabolism
542521	327948	**214573**	Carbohydrate Metabolism	Glycolysis / Gluconeogenesis
83375	82142	**1233**	Carbohydrate Metabolism	Inositol phosphate metabolism
116722	70965	**45757**	Carbohydrate Metabolism	Pentose and glucuronate interconversions
309090	182603	**126487**	Carbohydrate Metabolism	Pentose phosphate pathway
96668	6133	**90535**	Carbohydrate Metabolism	Propanoate metabolism
455675	229990	**225685**	Carbohydrate Metabolism	Pyruvate metabolism

ICS non-responders	ICS-responders	ICS non-responders - responders	KEGG Super-pathways	KEGG pathways
14444	64173	**-49729**	Carbohydrate Metabolism	Starch and sucrose metabolism
109950	42064	**67886**	Cell Motility	Bacterial motility proteins
62488	39219	**23269**	Cellular Processes and Signaling	Electron transfer carriers
2	57	**-55**	Cellular Processes and Signaling	Germination
57202	31502	**25700**	Cellular Processes and Signaling	Inorganic ion transport and metabolism
29671	112498	**-82827**	Cellular Processes and Signaling	Membrane and intracellular structural molecules
79239	102277	**-23038**	Cellular Processes and Signaling	Other ion-coupled transporters
46318	902	**45416**	Cellular Processes and Signaling	Other transporters
101147	21454	**79693**	Cellular Processes and Signaling	Signal transduction mechanisms
37	155	**-118**	Cellular Processes and Signaling	Sporulation
85232	82785	**2447**	Energy Metabolism	Carbon fixation in photosynthetic organisms
48202	4851	**43351**	Energy Metabolism	Carbon fixation pathways in prokaryotes
64518	40288	**24230**	Energy Metabolism	Methane metabolism
61571	38894	**22677**	Energy Metabolism	Nitrogen metabolism
373876	9573	**364303**	Energy Metabolism	Oxidative phosphorylation
1540	420	**1120**	Energy Metabolism	Photosynthesis
396	108	**288**	Energy Metabolism	Photosynthesis - antenna proteins
54942	11504	**43438**	Energy Metabolism	Photosynthesis proteins
332715	262004	**70711**	Enzyme Families	Peptidases
63873	37500	**26373**	Enzyme Families	Protein kinases
188379	99634	**88745**	Folding, Sorting and Degradation	Protein export
67735	42062	**25673**	Folding, Sorting and Degradation	RNA degradation
103067	21437	**81630**	Folding, Sorting and Degradation	Sulfur relay system
48173	2656	**45517**	Genetic Information Processing	Protein folding and associated processing
120672	63480	**57192**	Genetic Information Processing	Replication, recombination and repair proteins
166228	69731	**96497**	Genetic Information Processing	Translation proteins
10512	43144	**-32632**	Glycan Biosynthesis and Metabolism	Glycosaminoglycan degradation
62858	48757	**14101**	Glycan Biosynthesis and Metabolism	Glycosyltransferases

ICS non-responders	**ICS-responders**	**ICS non-responders - responders**	**KEGG Super-pathways**	**KEGG pathways**
5520	22647	**-17127**	Glycan Biosynthesis and Metabolism	Lipopolysaccharide biosynthesis proteins
191120	126883	**64237**	Glycan Biosynthesis and Metabolism	Peptidoglycan biosynthesis
50687	12248	**38439**	Lipid Metabolism	Fatty acid biosynthesis
51658	20661	**30997**	Lipid Metabolism	Fatty acid metabolism
44	12	**32**	Lipid Metabolism	Glycerolipid metabolism
4	140	**-136**	Lipid Metabolism	Lipid biosynthesis proteins
25	12	**13**	Lipid Metabolism	Steroid biosynthesis
1036463	799357	**237106**	Membrane Transport	ABC transporters
188379	99634	**88745**	Membrane Transport	Bacterial secretion system
42102	177864	**-135762**	Membrane Transport	Phosphotransferase system (PTS)
480439	264215	**216224**	Membrane Transport	Secretion system
1233749	1031431	**202318**	Membrane Transport	Transporters
7503	30877	**-23374**	Metabolism	Amino acid metabolism
44	12	**32**	Metabolism	Biosynthesis and biodegradation of secondary metabolites
53520	15503	**38017**	Metabolism	Carbohydrate metabolism
70507	69838	**669**	Metabolism	Energy metabolism
88	24	**64**	Metabolism	Lipid metabolism
3010	11274	**-8264**	Metabolism	Metabolism of cofactors and vitamins
53	21	**32**	Metabolism	Nucleotide metabolism
315074	248847	**66227**	Metabolism	Others
127273	82607	**44666**	Metabolism of Cofactors and Vitamins	Folate biosynthesis
121296	59194	**62102**	Metabolism of Cofactors and Vitamins	Lipoic acid metabolism
61527	38882	**22645**	Metabolism of Cofactors and Vitamins	Nicotinate and nicotinamide metabolism
128513	82153	**46360**	Metabolism of Cofactors and Vitamins	One carbon pool by folate
209922	168515	**41407**	Metabolism of Cofactors and Vitamins	Pantothenate and CoA biosynthesis
448003	159144	**288859**	Metabolism of Cofactors and Vitamins	Porphyrin and chlorophyll metabolism
51658	20661	**30997**	Metabolism of Cofactors and Vitamins	Retinol metabolism
404632	189043	**215589**	Metabolism of Cofactors and Vitamins	Riboflavin metabolism

ICS non-responders	ICS-responders	ICS non-responders - responders	KEGG Super-pathways	KEGG pathways
988	642	**346**	Metabolism of Cofactors and Vitamins	Thiamine metabolism
53810	15689	**38121**	Metabolism of Cofactors and Vitamins	Ubiquinone and other terpenoid-quinone biosynthesis
96668	6133	**90535**	Metabolism of Other Amino Acids	beta-Alanine metabolism
9285	36231	**-26946**	Metabolism of Other Amino Acids	Cyanoamino acid metabolism
244909	142175	**102734**	Metabolism of Other Amino Acids	Glutathione metabolism
1731	602	**1129**	Metabolism of Other Amino Acids	Phosphonate and phosphinate metabolism
68889	57393	**11496**	Metabolism of Other Amino Acids	Selenocompound metabolism
53634	15641	**37993**	Metabolism of Terpenoids and Polyketides	Biosynthesis of siderophore group nonribosomal peptides
195	50	**145**	Metabolism of Terpenoids and Polyketides	Carotenoid biosynthesis
319432	117227	**202205**	Metabolism of Terpenoids and Polyketides	Prenyltransferases
368339	126713	**241626**	Metabolism of Terpenoids and Polyketides	Terpenoid backbone biosynthesis
409304	360629	**48675**	Nucleotide Metabolism	Purine metabolism
170310	80320	**89990**	Nucleotide Metabolism	Pyrimidine metabolism
306381	206945	**99436**	Replication and Repair	Base excision repair
306381	206945	**99436**	Replication and Repair	DNA repair and recombination proteins
44	12	**32**	Signal Transduction	Calcium signaling pathway
180412	87533	**92879**	Signal Transduction	Two-component system
10512	43144	**-32632**	Signaling Molecules and Interaction	Bacterial toxins
257807	183480	**74327**	Transcription	Transcription factors
642256	442093	**200163**	Translation	Aminoacyl-tRNA biosynthesis
270199	206858	**63341**	Translation	Ribosome Biogenesis
54816	18151	**36665**	Translation	Ribosome biogenesis in eukaryotes
79	2	**77**	Xenobiotics Biodegradation and Metabolism	Aminobenzoate degradation
578	146	**432**	Xenobiotics Biodegradation and Metabolism	Benzoate degradation
26	6	**20**	Xenobiotics Biodegradation and Metabolism	Caprolactam degradation
51658	20661	**30997**	Xenobiotics Biodegradation and Metabolism	Chloroalkane and chloroalkene degradation
51658	20661	**30997**	Xenobiotics Biodegradation and Metabolism	Drug metabolism - cytochrome P450
51685	21169	**30516**	Xenobiotics Biodegradation and Metabolism	Metabolism of xenobiotics by cytochrome P450

ICS non-responders	ICS-responders	ICS non-responders - responders	KEGG Super-pathways	KEGG pathways
51658	20661	**30997**	Xenobiotics Biodegradation and Metabolism	Naphthalene degradation
121	27	**94**	Xenobiotics Biodegradation and Metabolism	Polycyclic aromatic hydrocarbon degradation
26	6	**20**	Xenobiotics Biodegradation and Metabolism	Toluene degradation
26	6	**20**	Xenobiotics Biodegradation and Metabolism	Xylene degradation

Table S11: Specific taxa differentially expressed in placebo treated asthmatics post-treatment compared to baseline (pre-treatment) visit.

OTU ID	Post-$^{\#}$	Pre-$^{\#}$	Post - Pre	q-value	Phylum	Class	Order	Family	Genus	Species
4401186	195.3	0.5	**194.8**	0.0013	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Eikenella*	-
4404731	241.0	71.6	**169.4**	3.27E-140	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4469492	183.6	16.4	**167.3**	0.0009	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Delftia*	-
269930	129.9	12.0	**117.9**	0.0051	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	-	-
615020	39.4	0.9	**38.5**	7.57E-31	Tenericutes	Mollicutes	Mycoplasmatales	Mycoplasmataceae	*Mycoplasma*	-
87506	31.3	4.1	**27.1**	0.0904	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Eikenella*	-
4366487	23.4	2.6	**20.8**	0.0951	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	-
1566691	16.8	0.8	**16.0**	0.0040	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
495451	19.5	10.6	**8.9**	0.0009	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	-
245523	14.0	6.3	**7.8**	0.0004	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
63117	10.1	2.6	**7.5**	0.0010	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	-
240252	7.6	0.6	**7.0**	2.40E-05	Proteobacteria	Alphaproteobacteria	Rhodospirillales	Acetobacteraceae	*Acidocella*	-
1052181	7.8	2.9	**4.9**	1.47E-09	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*nanceiensis*
763967	5.0	0.1	**4.9**	0.0658	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4305935	5.9	1.4	**4.5**	0.0066	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Paludibacter*	-
399903	5.4	0.9	**4.5**	0.0010	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
937813	4.5	0.3	**4.3**	0.0241	Firmicutes	Clostridia	Clostridiales	Tissierellaceae	*Anaerococcus*	-
458	4.9	0.8	**4.1**	0.0099	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*	-
886735	6.0	2.1	**3.9**	0.0154	Firmicutes	Bacilli	Lactobacillales	Aerococcaceae	*Alloiococcus*	-
676367	3.8	0.3	**3.5**	0.0423	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Schwartzia*	-

OTU ID	**Post-**[#]	**Pre-**[#]	**Post - Pre**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
839	3.4	0.3	**3.1**	0.0013	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	-	-
4365143	3.1	0.1	**3.0**	0.0792	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
686900	4.4	1.8	**2.6**	0.0059	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Oribacterium*	-
4312347	2.4	0.6	**1.8**	0.0350	Proteobacteria	Gammaproteobacteria	Cardiobacteriales	Cardiobacteriaceae	*Cardiobacterium*	-
92721	1.9	0.6	**1.3**	0.0029	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
887744	1.9	0.6	**1.3**	0.0404	Bacteroidetes	Flavobacteriia	Flavobacteriales	Weeksellaceae	-	-
4420570	1.8	1.6	**0.1**	0.0902	Cyanobacteria	Chloroplast	Streptophyta	-	-	-
844535	0.8	2.0	**-1.3**	0.0350	Proteobacteria	Alphaproteobacteria	Caulobacterales	Caulobacteraceae	*Asticcacaulis*	-
2758	0.4	2.1	**-1.8**	0.0137	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
299830	0.8	3.0	**-2.3**	0.0904	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*copri*
506	0.3	3.3	**-3.0**	0.0668	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
551109	0.3	3.4	**-3.1**	0.0658	Proteobacteria	Alphaproteobacteria	Caulobacterales	Caulobacteraceae	*Asticcacaulis*	-
1066621	1.0	4.3	**-3.3**	0.0951	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
425	0.3	3.6	**-3.4**	0.0409	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
1536	0.5	4.3	**-3.8**	0.0423	Firmicutes	Bacilli	Gemellales	-	-	-
943	0.3	4.0	**-3.8**	0.0608	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	-
1643	0.4	4.8	**-4.4**	0.0404	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
4457085	0.5	5.0	**-4.5**	2.30E-05	GN02	BD1-5	-	-	-	-
301	0.1	4.6	**-4.5**	0.0792	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
68416	0.1	4.8	**-4.6**	0.0340	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
3530625	0.3	6.0	**-5.8**	0.0071	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	-
250288	5.8	11.5	**-5.8**	6.95E-12	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
133961	0.5	7.3	**-6.8**	9.90E-05	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	-
105	0.8	8.4	**-7.6**	0.0608	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
274365	0.3	9.5	**-9.3**	0.0010	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	-	-
4459265	2.3	11.6	**-9.4**	1.49E-23	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
734	2.4	13.8	**-11.4**	0.0404	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	-
43339	4.5	24.9	**-20.4**	4.64E-11	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
594026	2.6	65.9	**-63.3**	0.0552	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-

$^{\#}$mean relative abundance

Table S12: Specific taxa differentially expressed in ICS treated asthmatics post-treatment compared to baseline (pre-treatment) visit.

OTU ID	**Post-$^{\#}$**	**Pre-$^{\#}$**	**Post - Pre**	**q-value**	**Phylum**	**Class**	**Order**	**Family**	**Genus**	**Species**
12297	5944.5	0.6	**5943.9**	1.08E-09	Actinobacteria	Actinobacteria	Actinomycetales	Microbacteriaceae	-	-
4318672	233.9	46.3	**187.6**	0.0071	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	-
855912	34.5	1.4	**33.1**	8.01E-23	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
246528	103.4	73.0	**30.4**	1.67E-08	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	-
3931	17.8	1.8	**16.0**	3.35E-14	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
3860	13.5	0.8	**12.8**	1.13E-09	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	*amylovorum*
930422	13.0	1.9	**11.1**	4.45E-10	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	-
114813	11.3	3.3	**8.0**	2.30E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
4472050	7.3	2.0	**5.3**	1.51E-14	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	-	-
773109	5.6	1.4	**4.3**	5.83E-08	Tenericutes	Mollicutes	Mycoplasmatales	Mycoplasmataceae	*Mycoplasma*	-
4364176	2.4	1.5	**0.9**	0.0821	Firmicutes	Erysipelotrichi	Erysipelotrichales	Erysipelotrichaceae	*Sharpea*	-
1105876	1.3	2.1	**-0.9**	0.0922	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Dialister*	-
148695	0.8	1.8	**-1.0**	0.0848	GN02	BD1-5	-	-	-	-
23709	0.3	1.5	**-1.3**	0.0520	Bacteroidetes	Bacteroidia	Bacteroidales	-	-	-
4411875	5.3	6.6	**-1.4**	0.0020	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Scardovia*	-
1465	1.3	3.5	**-2.3**	1.34E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*intermedia*
62513	0.9	3.4	**-2.5**	0.0699	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Moryella*	-
495067	0.8	3.5	**-2.8**	0.0539	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	*Corynebacterium*	-
4380570	1.0	3.9	**-2.9**	0.0358	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	-
645055	1.4	4.5	**-3.1**	0.0293	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-
43339	1.0	4.5	**-3.5**	0.0159	Firmicutes	Clostridia	Clostridiales	Mogibacteriaceae	-	-
422455	0.8	4.8	**-4.0**	0.0020	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	-
1580	1.4	5.6	**-4.3**	0.0111	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*melaninogenica*
399903	2.4	7.5	**-5.1**	0.0009	Spirochaetes	Spirochaetes	Spirochaetales	Spirochaetaceae	*Treponema*	-
4004098	1.8	7.6	**-5.9**	5.69E-05	Tenericutes	RF3	ML615J-28	-	-	-

130864	3.3	9.3	**-6.0**	5.11E-12	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*iners*
92316	1.3	9.6	**-8.4**	0.0006	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	-	-
4426165	2.3	10.9	**-8.6**	1.25E-07	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	-
893048	1.9	10.9	**-9.0**	4.04E-08	Firmicutes	Clostridia	Clostridiales	-	-	-
1044611	10.4	29.9	**-19.5**	3.10E-14	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	-	-
4421864	5.1	26.3	**-21.1**	0.0597	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Selenomonas*	-
398192	0.3	23.1	**-22.9**	2.93E-06	Bacteroidetes	Bacteroidia	Bacteroidales	Paraprevotellaceae	*Prevotella*	-
4440670	1.5	24.9	**-23.4**	1.74E-18	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Veillonella*	-
4318284	3.9	69.1	**-65.3**	0.0359	Firmicutes	Clostridia	Clostridiales	Veillonellaceae	*Dialister*	-
2438396	12.5	123.5	**-111.0**	1.93E-102	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	-

[#] mean relative abundance

SUPPLEMENTAL METHODS:

Study Population and Sample Collection:

Of 186 adults screened for eligibility at nine "AsthmaNet" clinical centers, 84 subjects were enrolled (**Figure S1A-C**). Each participating clinical center (Brigham and Women's Hospital, Boston, MA; Northwestern University, Chicago, IL; National Jewish Health, Denver, CO; University of Wisconsin, Madison, WI; University of Pittsburgh, Pittsburgh, PA; Washington University, St. Louis, MO; University of California San Francisco, San Francisco, CA; Duke University, Durham, NC; Duke University, Durham, NC and Wake Forest University, Winston-Salem, NC) enrolled a median of 10 (IQR of 8-11) subjects of whom 50% (IQR of 39-64) were asthmatic. The study center was not a significant contributor to any of the differences in bacterial community composition reported in this study. Each subject signed informed consent approved by the center's IRB, and an NHLBI-appointed Data Safety Monitoring Board (DSMB) oversaw the study conduct.

Adult subjects with mild atopic asthma (AA; n=42) were enrolled who had demonstrated serologic evidence of sensitivity (>0.35 kU/l) to at least one of 12 aeroallergens (**Table S1**) identified using ImmunoCAP specific IgE test (Thermo scientific); and airway hyper-responsiveness (methacholine PC_{20} ≤8 mg/mL), or bronchodilator reversibility (FEV_1 improvement ≥12% in response to albuterol). Asthmatic subjects had stable asthma for preceding 3 months, an Asthma Control Questionnaire (ACQ) score of <1.5 (1) and no use of a controller medication (such as an inhaled corticosteroid) in the preceding 6 months. Atopic non-asthmatic subjects (ANA; n=21) had sensitivity to at least one aeroallergen but no evidence of airway hyper-responsiveness, (PC_{20} >16 mg/mL) or bronchodilator reversibility, and no history of chronic sinusitis (for responses to additional prior clinical conditions and environmental exposure for AA and ANA subjects see **Tables S2-S3**). Healthy control subjects (HC; n=21) had no history of atopic symptoms, negative serologic tests for all aeroallergens tested, and no history of chronic respiratory or other disease. Exclusion criteria for all subjects included smoking, symptoms of respiratory tract infection (including acute sinusitis and bronchitis) in the previous 6 weeks, and antibiotic use in the previous 3 months.

All subjects underwent spirometry, blood sampling, and sputum induction at visit 1 **(Figure S1C)**. At visit 2, prior to bronchoscopy, oral wash samples (OW) consisting of a tongue scraping followed by oral rinse and gargle with sterile saline (10 mL), were collected as previously described (2). To evaluate for instrument carryover of oral bacterial DNA contamination during sample collection, a 10mL flush of sterile saline through the suction channel of the bronchoscope ("scope flush") was collected following application of topical anesthesia to the vocal cords when the instrument was withdrawn before proceeding to collection of 4 protected bronchial brush (BB) samples as described previously (3). Asthmatic subjects were subsequently randomized in a 2:1 ratio to treatment with inhaled fluticasone propionate (250 mcg; GlaxoSmithKline) or placebo (lactose alone) from a dry powder inhaler twice daily for six weeks. Repeat assessments were then performed (visits 3 and 4). All samples intended for microbial analysis were stored in RNA*later* (Ambion, Inc. Austin, TX) at -80°C until processing.

Nucleic acid extraction:

For the focus of this study, nucleic acids from OW and 3 BB's were extracted as previously described (2, 3) using a bead-beating protocol and the AllPrep kit (Qiagen, CA), to purify DNA and RNA in parallel. Reagent controls including 10mL aliquots of the lidocaine and sterile saline used during bronchoscopy, and from "scope flush" samples were extracted for DNA and tested by quantitative PCR (Q-PCR) using universal bacterial primers (see below) for bacterial contamination, with all reagents demonstrating no evidence of significant bacterial contamination

(<35 16S rRNA gene copy number). Each extraction batch also included a blank control; these went through all the steps in preparation for 16S rRNA sequencing (as described below) and were sequenced. DNA and RNA were quantified on a NanoDrop2000 (ThermoFisher, CA).

Quantitation of 16S rRNA and β-actin copy number:
16S rRNA gene copy number was assessed by quantitative PCR (Q-PCR) using the 16S rRNA universal primers P891F, P1033R and TaqMan UniProbe as previously described (4) in triplicate using TaqMan Universal Master Mix (Life Technologies). Mammalian β-actin copy numbers were evaluated using primers bActin-F (5'- CCTGGCACCCAGCACAAT-3') and bActin-R (5'-GCCGATCCACACGGAGTACT-3') and bActin-TMP probe (5-FAM/TCAAGATCATTGCTCCTCCTGAGCGC/3BHQ) (5). Total 16S rRNA and β-actin copy number was calculated against a standard curve of known 16SrRNA or β-actin copy numbers (1x10^2 – 1x10^8). Regression coefficients for all standard curves were > 0.98.

16S rRNA-based airway and oral microbiota profiling using Illumina MiSeq:
The variable region 4 (V4) of the 16S rRNA gene was amplified using 10 ng/□l of OW and 100 ng/□l of BB DNA template and 515F/806R primer combination as previously described (6, 7). Those samples without visible evidence of 16s rRNA PCR product on the first screen underwent repeat PCR screening with a bacterial-DNA control to rule out presence of sample-specific PCR inhibition. Amplicons were purified using SPRI beads (Beckman Coulter) or in the presence of multiple bands, gel-extracted with a Qiagen Gel Extraction kit (Qiagen) per manufacturer protocol, analyzed on Bioanalyzer (Aligent), quantified using the Qubit HS dsDNA kit (Invitrogen). Samples with amplicons <10ng were not sequenced. Blank control DNA extracts were also amplified, bead purified and included in each MiSeq run. Samples with sufficient 16S rRNA amplicon were pooled at 50 ng per sample, with 30-35 samples and a blank control. The barcoded, pooled library was quantified using the Qubit HS dsDNA kit (Invitrogen), denatured and 5pM was loaded onto the Illumina MiSeq cartridge (V3) in combination with a 15% (v/v) of denatured 12.5pM PhiX for sequencing.

Paired-end sequences were combined using FLASh version 1.2.7 (8). Sequence analysis was performed using the Quantitative Insights into Microbial Ecology (QIIME) pipeline version 1.8.0 (9). Raw sequences were de-multiplexed by barcode and quality filtered by removing low quality sequences. Sequences with three or more consecutive bases with a Q score < 30 were truncated and discarded if the length was less than 75% of the original 250 bp read length. Sequences were aligned using PyNAST (10) and operational taxonomic units (OTUs) were picked at 97% sequence identity using uclust against the latest release of the Greengenes database (13_5) (11, 12). Reads that failed to hit the reference sequence collection were retained and clustered de novo. PyNAST-aligned sequences were chimera checked using ChimeraSlayer and putative chimeras as well as OTUs identified in negative controls or where not from kingdom Bacteria were removed from the OTU table. A phylogenetic tree was built using FastTree (13) and used to compute Faith's Phylogenetic Diversity on OTU table multiply rarefied 100 times to 52,317 sequences per sample.

Statistical analysis:
All statistical analysis was performed as indicated in QIIME (9), R environment or using PRISM software. Welch's corrected t-test, Kruskal-Wallis or Wilcoxon rank sum test and Chi-square or Fisher's exact test where appropriate were used to determine significant differences in metadata between study groups conducted in PRISM. Ordination was visualized using Principle Coordinates Analysis (PCoA) on unweighted UniFrac distance matrix and plotted using Emperor in QIIME (14). Significant differences in beta-diversity between paired OW and BB samples were calculated on unweighted UniFrac PC1 coordinates (as a response variable) using Linear mixed

effects (LME) model ((15) using *lmerTest* package in R). PERMANOVA ((16)*; vegan* package function *Adonis* in R) was used to evaluate significant differences in beta-diversity between groups of independent samples. Negative binomial (NB) regression model (17, 18) was used to identify specific OTUs (present in at least 3 samples) that differed in relative abundance between groups of subjects. Only OTUs having a false discovery (FDR) corrected using Benjamini Hochberg method, q-value of <0.1, were retained and declared as significantly differentially enriched taxa. Pearson correlations were performed to determine relationships between relative abundance of OTUs and study variables with q-value correction for false discovery. Phylogenetic tree constructed with taxa of interest in QIIME were annotated using Interactive tree of Life (19). Metagenome prediction from normalized 16S rRNA representative sequences was performed using PICRUSt (20). NB regression model with Benjamini Hochberg FDR correction for multiple comparisons was used to determine Kyoto Encyclopedia of Genes and Genomes (KEGG) gene orthologs (KO's) that were significantly enriched in each group of interest. Zero-inflated negative binomial (ZINB) model (21,22) corrected for false discovery (Benjamini Hochberg, q-value of <0.1) was used to identify specific OTUs in paired samples before and after treatment with ICS or placebo inhaler. Procrustes analysis (23) based on unweighted UniFrac distance was used to compare community composition between paired samples in each treatment group.

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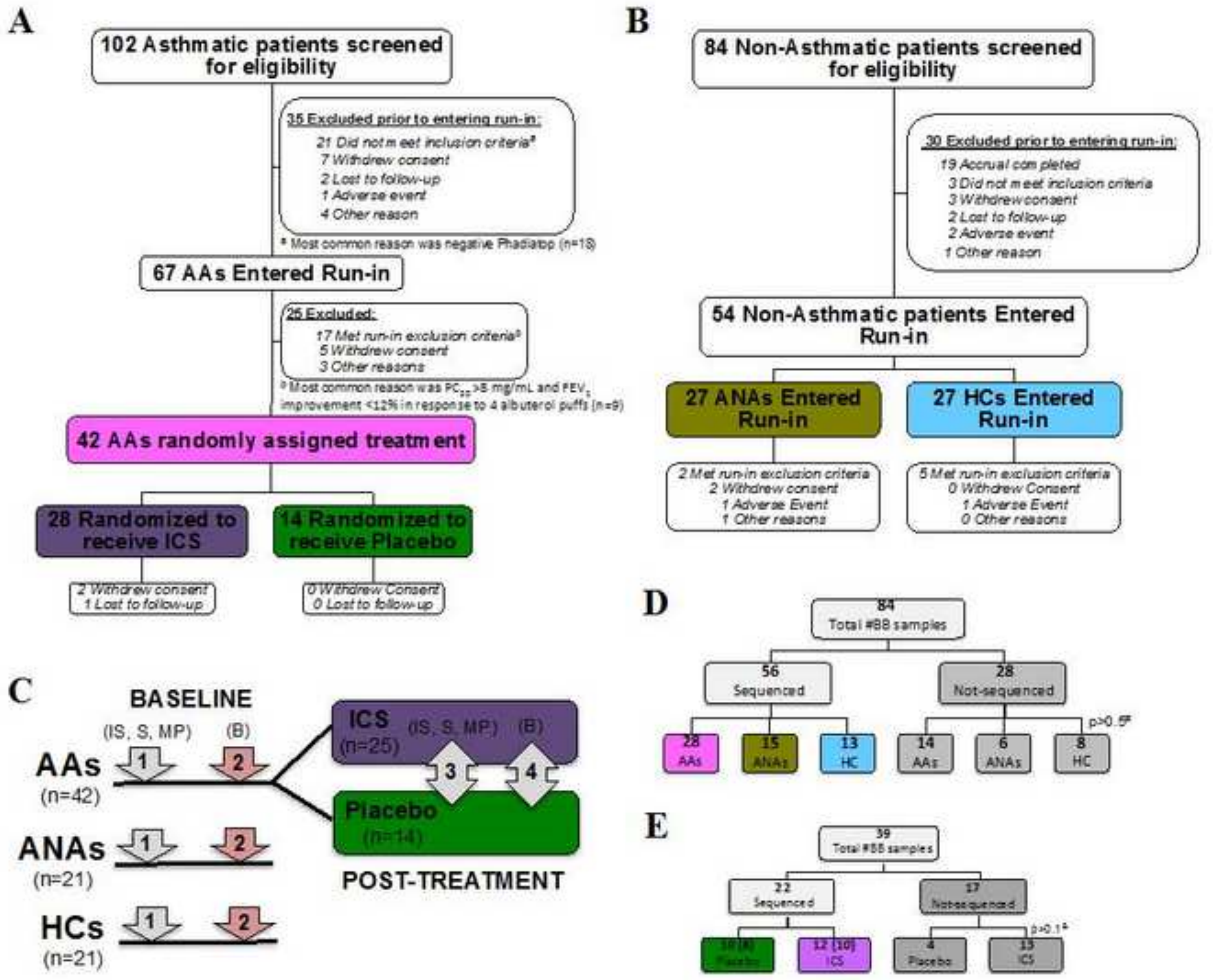
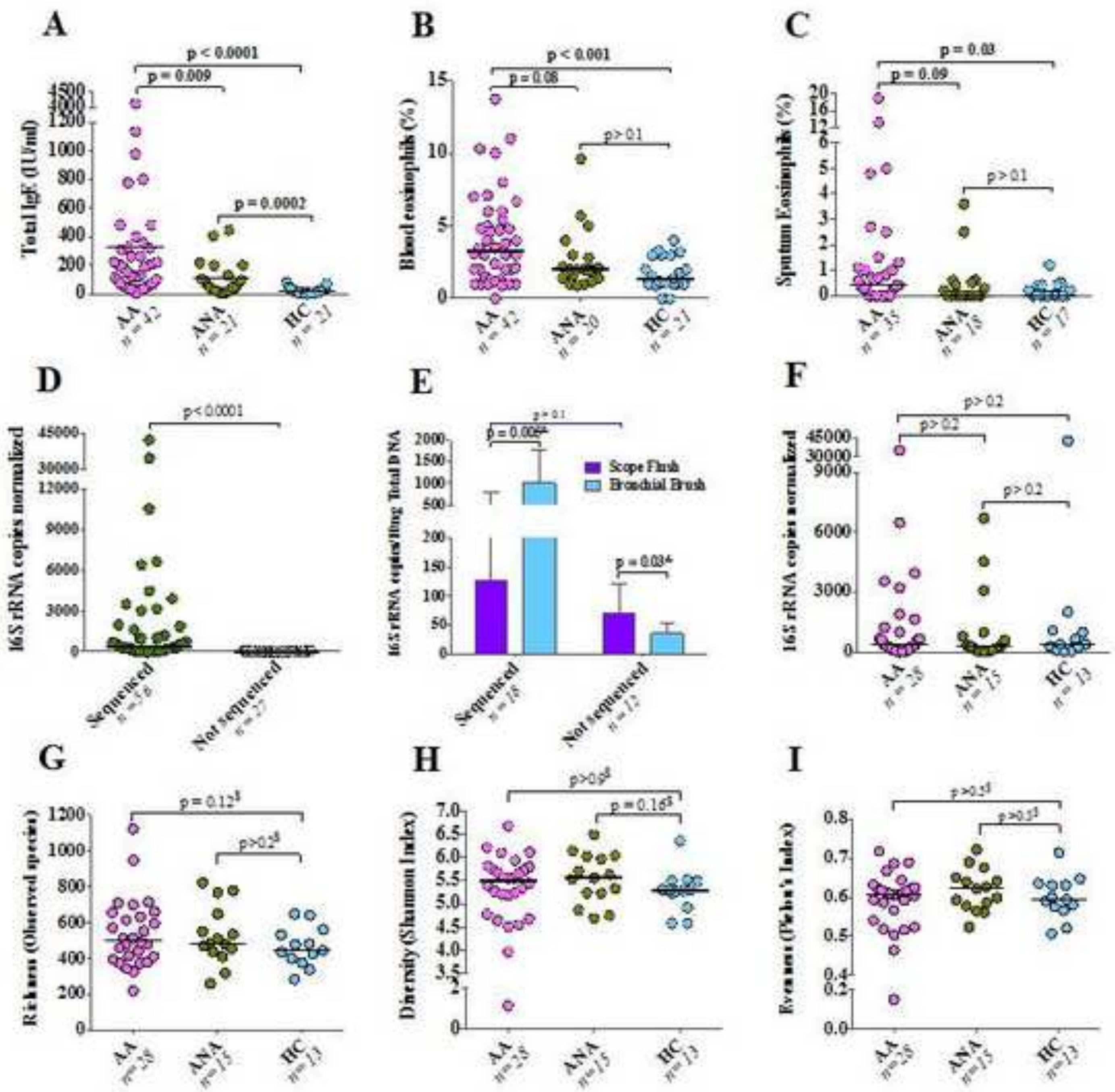
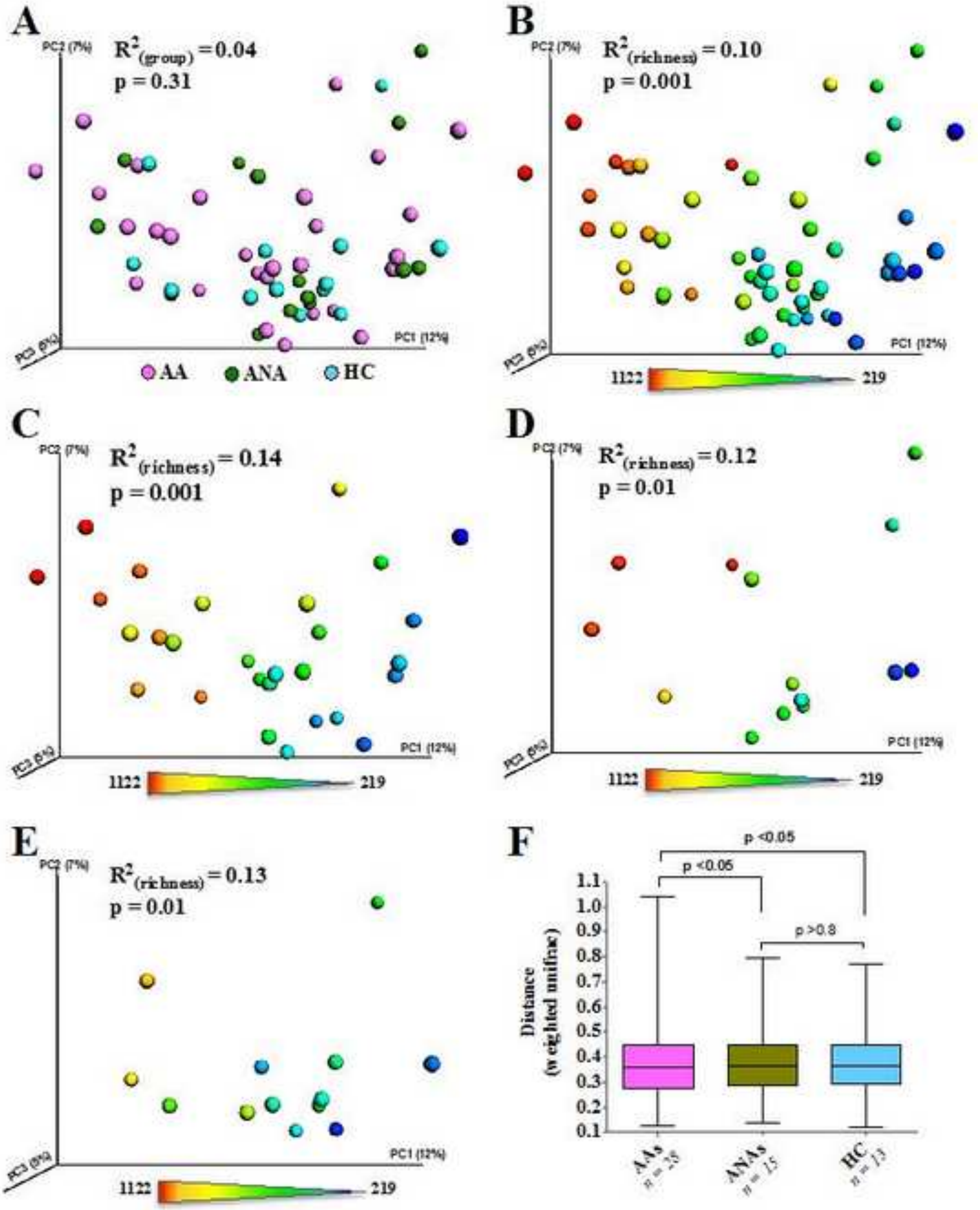
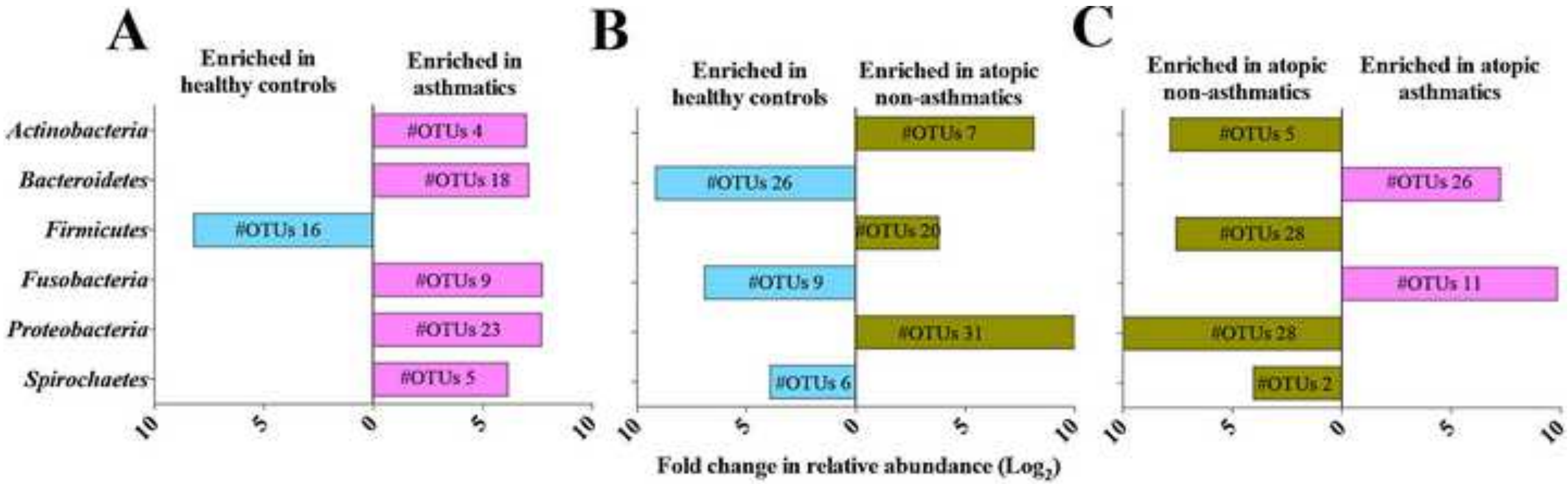
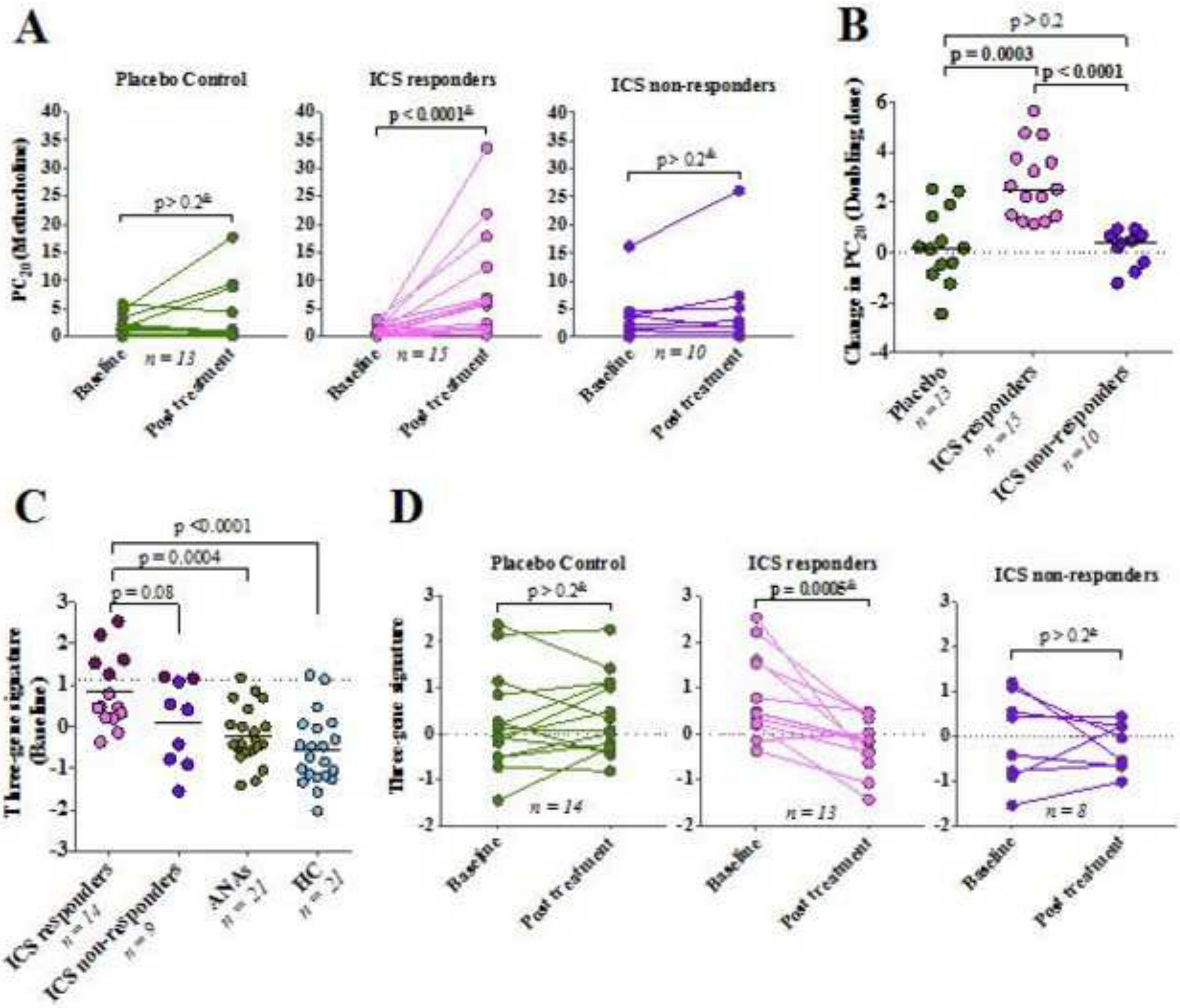
Repository - Unmarked E Figure No. 1

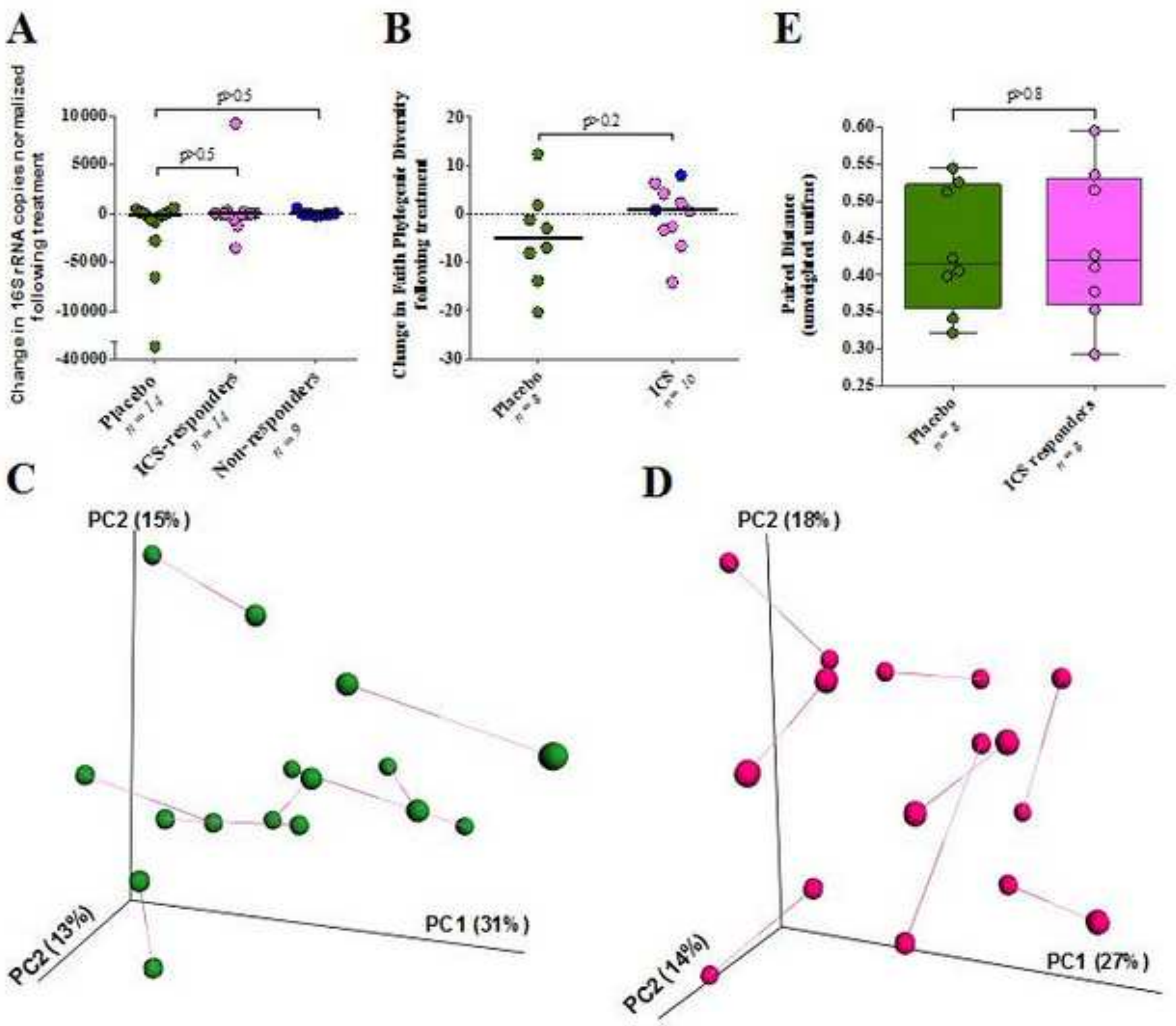



A
Total IgE (IU/ml)
4500
4000
1200
1000
800
600
400
200
0
p < 0.0001
p = 0.009
p = 0.0002
AA n = 42
ANA n = 21
HC n = 21
B
Blood eosinophils (%)
15
10
5
0
p < 0.001
p = 0.08
p > 0.1
AA n = 42
ANA n = 20
HC n = 21
C
Sputum Eosinophils (%)
20
16
12
6
5
4
3
2
1
0
p = 0.03
p = 0.09
p > 0.1
AA n = 35
ANA n = 18
HC n = 17
D
16S rRNA copies normalized
45000
30000
12000
9000
6000
3000
0
p < 0.0001
Sequenced n = 56
Not sequenced n = 27
E
16S rRNA copies/10ng Total DNA
2000
1500
1000
500
200
150
100
50
0
p > 0.1
p = 0.006^
p = 0.03^
Scope Flush
Bronchial Brush
Sequenced n = 18
Not sequenced n = 12
F
16S rRNA copies normalized
45000
30000
9000
6000
3000
0
p > 0.2
p > 0.2
p > 0.2
AA n = 28
ANA n = 15
HC n = 13
G
Richness (Observed species)
1200
1000
800
600
400
200
0
p = 0.12$
p > 0.2$
AA n = 28
ANA n = 15
HC n = 13
H
Diversity (Shannon Index)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
2
0
p > 0.9$
p = 0.16$
AA n = 28
ANA n = 15
HC n = 13
I
Evenness (Pielou's Index)
0.8
0.7
0.6
0.5
0.4
0.2
0.0
p > 0.5$
p > 0.5$
AA n = 28
ANA n = 15
HC n = 13


A
PC2 (7%)
$R^2_{(group)} = 0.04$
p = 0.31
PC3 (6%)
PC1 (12%)
● AA ● ANA ● HC
B
PC2 (7%)
$R^2_{(richness)} = 0.10$
p = 0.001
PC3 (6%)
PC1 (12%)
1122
219
C
PC2 (7%)
$R^2_{(richness)} = 0.14$
p = 0.001
PC3 (6%)
PC1 (12%)
1122
219
D
PC2 (7%)
$R^2_{(richness)} = 0.12$
p = 0.01
PC3 (6%)
PC1 (12%)
1122
219
E
PC2 (7%)
$R^2_{(richness)} = 0.13$
p = 0.01
PC3 (6%)
PC1 (12%)
1122
219
F
p <0.05
p <0.05
p >0.8
Distance (weighted unifrac)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
AAs n = 25
ANAs n = 15
HC n = 13


A
Enriched in healthy controls
Enriched in asthmatics
Actinobacteria
Bacteroidetes
Firmicutes
Fusobacteria
Proteobacteria
Spirochaetes
#OTUs 4
#OTUs 18
#OTUs 16
#OTUs 9
#OTUs 23
#OTUs 5
10
5
0
5
10
B
Enriched in healthy controls
Enriched in atopic non-asthmatics
#OTUs 7
#OTUs 26
#OTUs 20
#OTUs 9
#OTUs 31
#OTUs 6
10
5
0
5
10
C
Enriched in atopic non-asthmatics
Enriched in atopic asthmatics
#OTUs 5
#OTUs 26
#OTUs 28
#OTUs 11
#OTUs 28
#OTUs 2
10
5
0
5
10
Fold change in relative abundance (Log_2)


A
Placebo Control
ICS responders
ICS non-responders
PC20 (Methacholine)
p> 0.2&
p < 0.0001&
p> 0.2&
n = 13
n = 15
n = 10
Baseline
Post treatment
B
Change in PC20 (Doubling dose)
p > 0.2
p = 0.0003
p < 0.0001
Placebo n = 13
ICS responders n = 15
ICS non-responders n = 10
C
Three-gene signature (Baseline)
p <0.0001
p = 0.0004
p = 0.08
ICS responders n = 14
ICS non-responders n = 9
ANAs n = 21
HC n = 21
D
Three-gene signature
Placebo Control
ICS responders
ICS non-responders
p > 0.2&
p = 0.0006&
p > 0.2&
n = 14
n = 13
n = 8
Baseline
Post treatment


A
Change in 16S rRNA copies normalized following treatment
10000
5000
0
-5000
-10000
-40000
p>0.5
p>0.5
Placebo
n = 14
ICS-responders
n = 14
Non-responders
n = 9
B
Change in Faith Phylogenic Diversity following treatment
20
10
0
-10
-20
-30
p>0.2
Placebo
n = 8
ICS
n = 10
E
Paired Distance (unweighted unifrac)
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
p>0.8
Placebo
n = 8
ICS responders
n = 8
C
PC2 (15%)
PC1 (31%)
PC2 (13%)
D
PC2 (18%)
PC1 (27%)
PC2 (14%)

Graphical Abstract

Study Design

Atopic Asthmatic
(AA; steroid-naive)

Atopic-only

Non-atopic Healthy

Bronchoscopy #1

AA only

Randomized to fluticasone vs. placebo x 6 wks

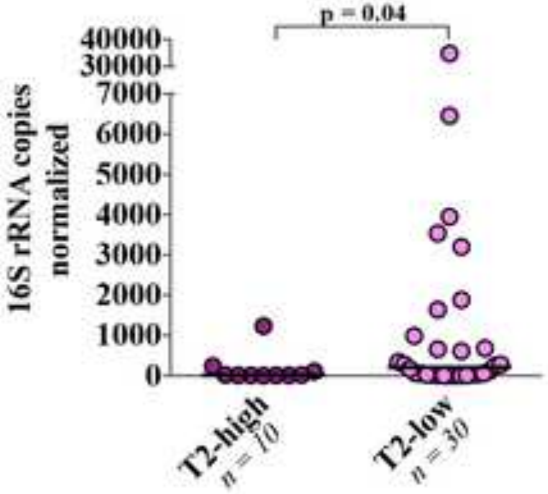
Bronchoscopy #2

Findings: Asthma-associated differences in the bronchial bacterial microbiome

① **Compositional differences in members of:**
- *Fusobacterium*
- *Haemophilus*
- *Neisseria*
- *Sphingomondaceae*
- *Lactobacillales*

② **Differences in predicted bacterial functions:**
- Amino acid and carbohydrate metabolism

③ **Lower bacterial burden in T2-high asthma**



④ **Response to fluticasone linked to baseline features of bronchial microbiota**