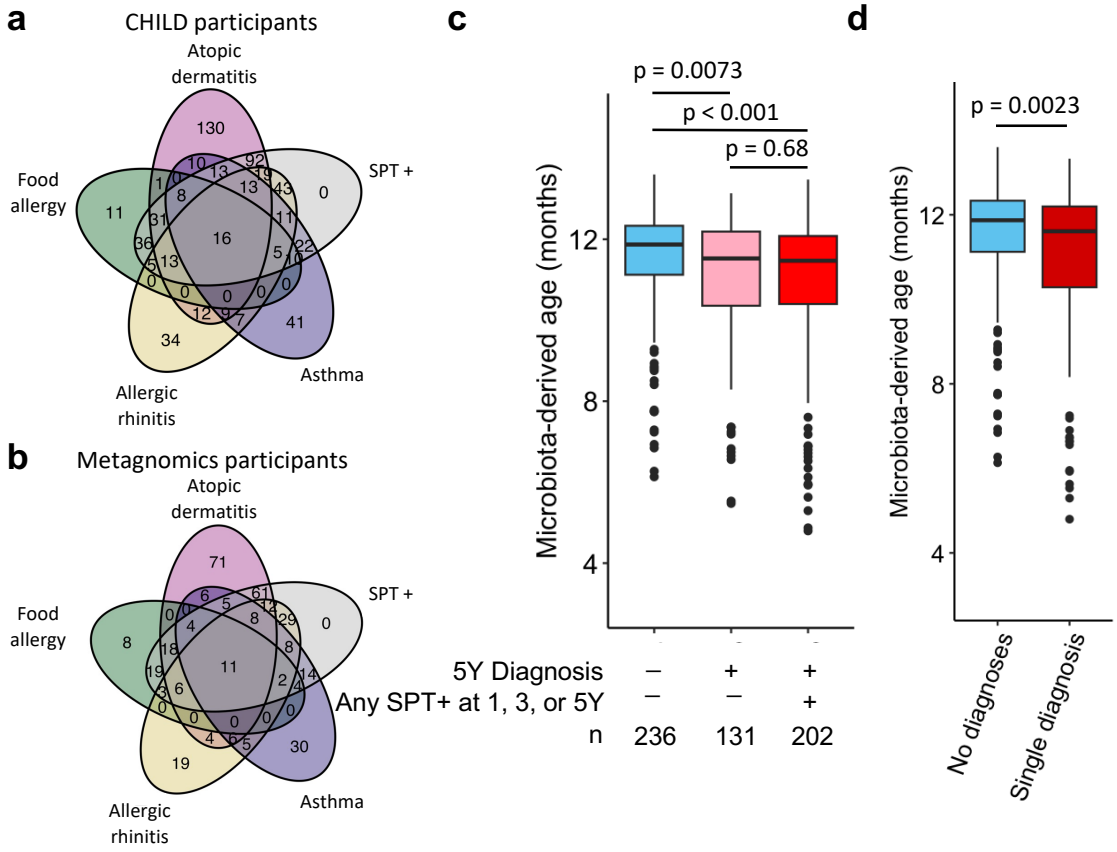
Variable	Overall CHILD Population	Manuscript	p-value (Manuscript vs. Overall)	Metagenomic	p-value (Metagenomic vs. Clinical)	Metabolomics	p-value (Metabolomics vs. Metagenomic)
No. patients	3264	1115		589		509	
Male, n(%)			0.68		0.57		0.9
	1717 (52.6%)	595 (53.4%)		323 (54.8%)		281 (55.2%)	
Ethnicity of Child, n(%)			0.35		1		0.85
Caucasian White	2043 (63.6%)	689 (62.1%)		365 (62.1%)		312 (61.4%)	
Non-Caucasian	1167 (36.4%)	421 (37.9%)		223 (37.9%)		196 (38.6%)	
Delivery Mode, n(%)			0.79		0.57		0.99
Vaginal	2412 (74.8%)	814 (74%)		421 (71.7%)		363 (71.6%)	
C-Section with labor	425 (13.2%)	146 (13.3%)		87 (14.8%)		74 (14.6%)	
C-Section without labor	387 (12%)	140 (12.7%)		79 (13.5%)		70 (13.8%)	
Breastfeeding status at 6 months, n(%)			0.0091		0.95		1
	2323 (76.4%)	884 (80.2%)		473 (80.4%)		408 (80.3%)	
Season of birth, n(%)			0.85		0.79		0.9
Spring	889 (27.2%)	293 (26.3%)		165 (28%)		146 (28.7%)	
Summer	830 (25.4%)	297 (26.6%)		145 (24.6%)		130 (25.5%)	
Fall	755 (23.1%)	259 (23.2%)		137 (23.3%)		120 (23.6%)	
Winter	790 (24.2%)	266 (23.9%)		142 (24.1%)		113 (22.2%)	
Atopy of father, n(%)			0.84		1		0.94
	1663 (67.7%)	622 (67.2%)		330 (67.3%)		289 (67.7%)	
Atopy of mother, n(%)			0.068		0.29		1
	1727 (57.7%)	668 (60.9%)		371 (63.5%)		321 (63.6%)	
Having older sibling, n(%)			0.89		0.3		0.86
	1452 (45.9%)	500 (45.6%)		282 (48.3%)		247 (49%)	
Antibiotics use in the first year of life, n(%)			0.11		0.8		0.65
	605 (18.5%)	231 (20.7%)		125 (21.2%)		102 (20%)	
NO2 in the first year of life			0.23		0.33		0.87
Median (Range)	9.1 (0.5, 30.5)	8.8 (1.2, 29.1)		9.1 (1.2, 29.1)		9 (1.2, 29.1)	
IQR (Q1,Q3)	4.6, 13.3	4.5, 12.9		4.7, 13.3		4.6, 13.2	
Birth weight Z-score			0.76		0.47		0.74
Median (Range)	-0.1 (-3.1, 4.3)	-0.1 (-3.1, 3.7)		-0.1 (-2.6, 3.7)		-0.1 (-2.6, 3.7)	
IQR (Q1,Q3)	-0.7, 0.5	-0.7, 0.6		-0.7, 0.6		-0.7, 0.7	

Supplementary Table. 1. Demographic table between CHILD and sub-cohorts. For continuous variables, Wilcoxon tests were used for two groups, Kruskal-Wallis for more than two groups; fisher-exact tests were used for categorical variables, comparing the differences between the overall CHILD population, participants included within the manuscript, the subset of participants with metagenomic data, and participants with metabolomics data. The model comparing the larger CHILD cohort, and subsets of participants with metagenomic and metabolomic data included sex, ethnicity, delivery mode, breastfeeding status, season of birth, family history of atopy, family size, antibiotic usage in the first year of life, nitrogen oxide exposure, and birthweight.

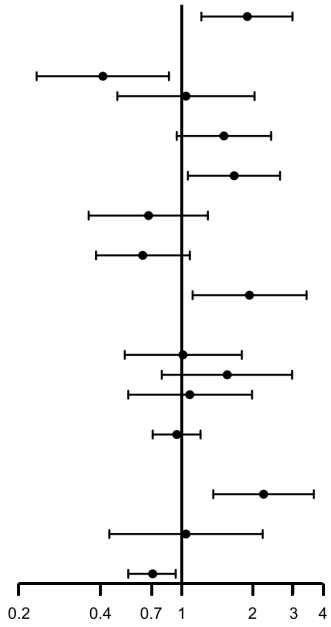
Variable	Adjusted odds ratio	Adjusted odds ratio confidence interval	P-value
Sex (male)	1.84	(1.36, 2.49)	6.8E-05
Ethnicity (Non-Caucasian)	2.26	(1.64, 3.1)	5.1E-07
C-section (with labor)	0.71	(0.45, 1.12)	0.14
C-section (without labor)	1.56	(0.96, 2.53)	0.075
Breastfeeding status at 6 months	0.66	(0.45, 0.99)	0.043
Season of birth (Summer)	0.89	(0.59, 1.34)	0.59
Season of birth (Fall)	1.28	(0.83, 1.97)	0.27
Season of birth (Winter)	0.99	(0.65, 1.5)	0.96
Paternal atopy	1.56	(1.13, 2.15)	0.007
Maternal atopy	1.56	(1.14, 2.12)	0.0054
Older sibling	0.95	(0.7, 1.3)	0.75
Antibiotics by 1 year	2.25	(1.55, 3.27)	2E-05
Birthweight Z-score	1	(0.85, 1.17)	0.98
Nitrogen dioxide IQR	1.08	(0.66, 1.77)	0.76

Supplementary Table 2. Clinical and environmental factors linked to the development of allergic diagnoses at 5 years. Multivariable conditional logistic regression, using the data collection site as stratum, evaluating the odds ratio of developing one or more allergic disease by 5 years. The model comparing the groups of participants with and without allergic disease included sex, ethnicity, delivery mode, breastfeeding status, season of birth, family history of atopy, family size, antibiotic usage in the first year of life, nitrogen oxide exposure, and birthweight.

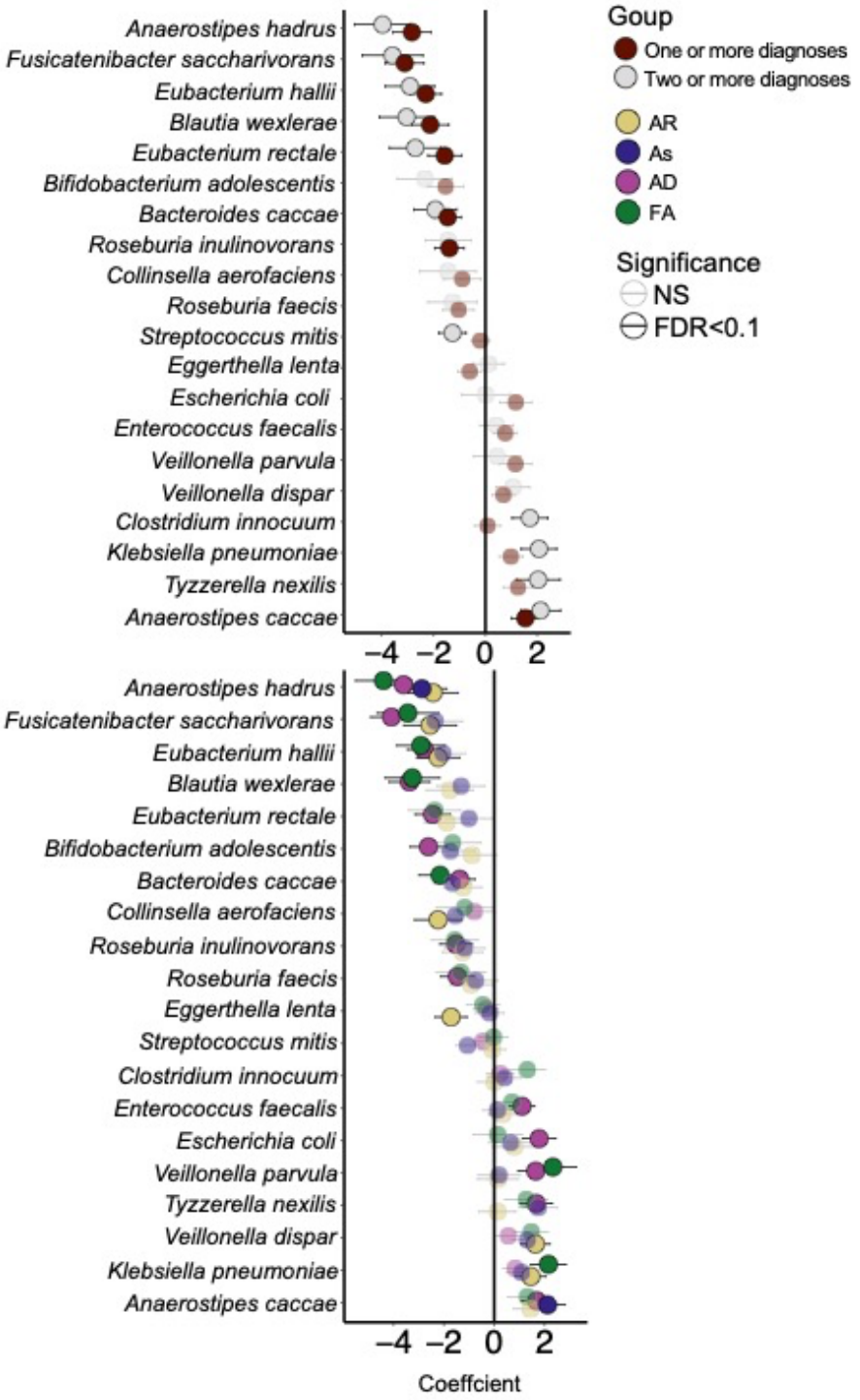


Supplementary Fig. 1. Atopy and allergic disease overlap amongst participants. Venn diagram of the overlap between participant diagnoses with atopic dermatitis (AD), food allergy (FA), allergic rhinitis (AR), asthma (As), and atopy (At) **a** in the CHILD cohort, **b** with shotgun metagenomics. Wilcoxon tests between the microbiota predicted ages of their 1-year microbiome samples of **c** non-allergic participants (n = 236) with participants diagnosed with atopy at any visit (1-, 3-, or 5-year evaluation) (n = 202, p = 0.0009), and those without atopy at any visit (n = 131), and **d** participants without diagnoses and those with only a single diagnosis (n = 353). For box plots, data are presented as box plots (centre line at the median, upper bound at 75th percentile, lower bound at 25th percentile) with whiskers at minimum and maximum values.

Variables	Non-allergic	One or more allergic diagnoses	Adjusted Odds Ratio	P Value
No. participants	231	348		
Male				
	105 (45.5%)	211 (60.6%)	1.9 (1.21, 2.96)	0.0051
Mode of delivery				
Vaginal	168 (73%)	247 (71.2%)	Ref	---
C-section with labor	34 (14.8%)	49 (14.1%)	0.46 (0.24, 0.88)	0.019
C-section without labor	28 (12.2%)	51 (14.7%)	1.04 (0.53, 2.04)	0.9
Paternal atopy				
	110 (58.5%)	212 (72.6%)	1.51 (0.95, 2.4)	0.08
Maternal atopy				
	124 (53.7%)	242 (70.6%)	1.67 (1.06, 2.62)	0.027
Breatfeeding status at 6 months				
	184 (79.7%)	279 (80.4%)	0.72 (0.4, 1.29)	0.27
Having an older sibling				
	129 (56.6%)	149 (43.1%)	0.68 (0.43, 1.08)	0.1
Antibiotic usage by 1 year				
	32 (13.9%)	89 (25.6%)	1.94 (1.11, 3.4)	0.02
Season				
Spring	66 (28.6%)	97 (27.9%)	Ref	---
Summer	65 (28.1%)	80 (23%)	1.01 (0.57, 1.8)	0.97
Fall	42 (18.2%)	91 (26.1%)	1.56 (0.82, 2.95)	0.17
Winter	58 (25.1%)	80 (23%)	1.08 (0.59, 1.99)	0.79
Birth weight (Z-score)				
Median (Range)	0 (-2.6, 3.2)	-0.2 (-2.5, 3.7)	0.95 (0.75, 1.2)	0.65
Ethnicity				
Caucasian White	175 (75.8%)	182 (52.4%)	Ref	---
Non-Caucasian	56 (24.2%)	165 (47.6%)	2.23 (1.36, 3.65)	0.0015
IQR increase in Nitrogen Dioxide				
Median (Range)	0.8 (0.2, 2.5)	1.2 (0.1, 3.4)	1.04 (0.49, 2.21)	0.92
IQR increase in predicted age				
Median (Range)	7.8 (4, 9)	7.6 (3.2, 8.9)	0.75 (0.59, 0.94)	0.013



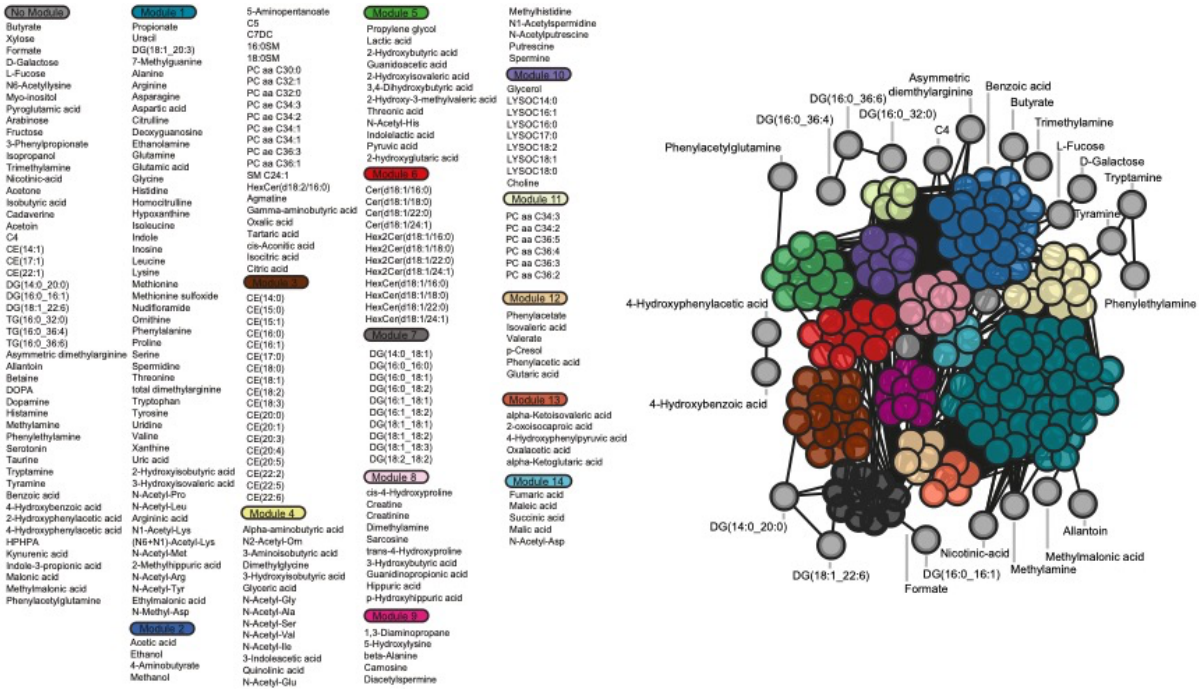
Supplementary Fig. 2. Predicted age remains protective when accounting for covariates. Multivariable conditional logistic regression, using the data collection site as stratum, evaluating the odds ratio of developing one or more atopic or allergic diagnoses (n = 348) when accounting for early-life and familial exposures as compared to non-allergic children (n = 231). Data are presented as adjusted odds ratios (95% confidence intervals).



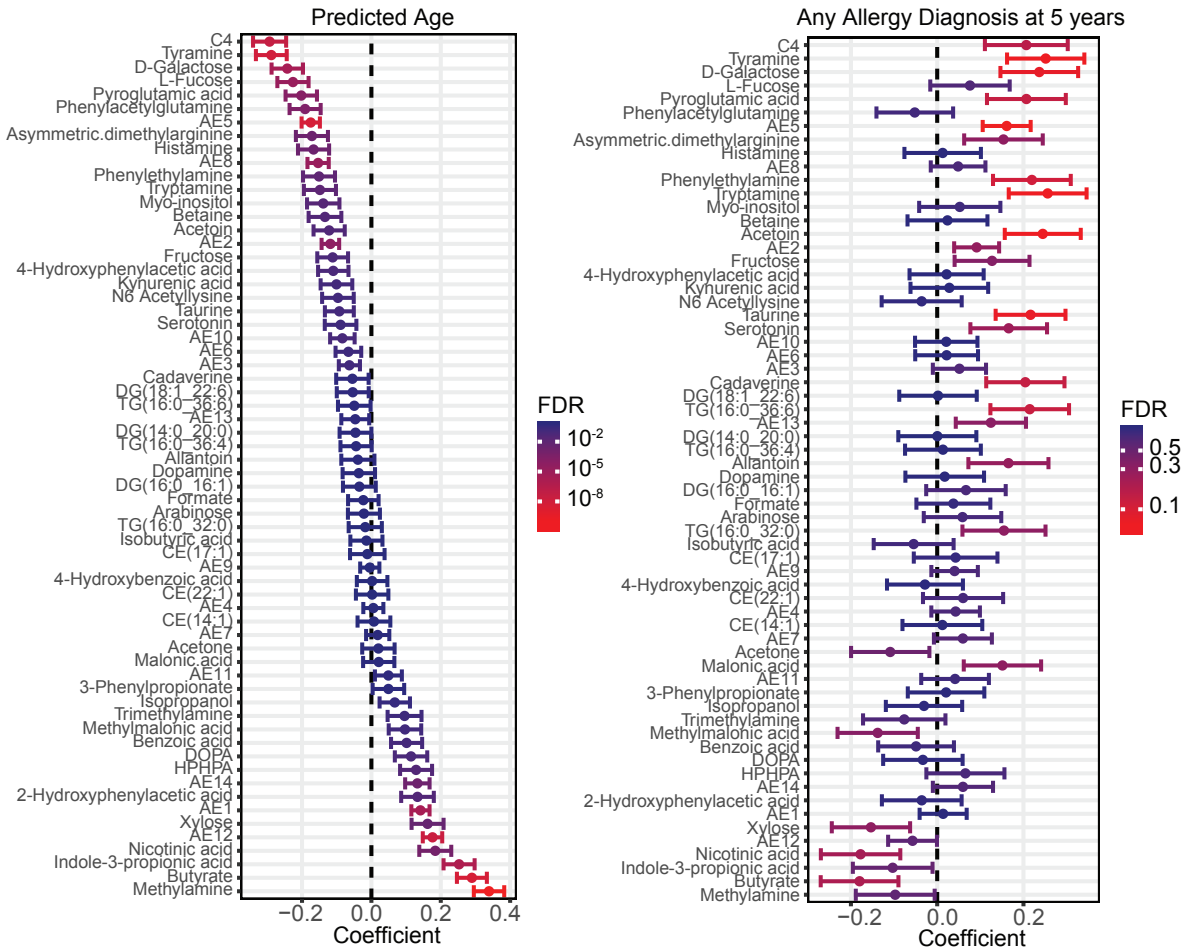
Supplementary Fig. 3. Important underlying infant microbiota of allergic disease. The 20 commonly identified species within one or more atopic or allergic diagnoses (n = 353), two or more allergic diagnoses (n = 82), and individual clinical diagnoses at 5 years, i.e., atopic dermatitis (AD, n = 212), food allergy (FA, n = 75), asthma (As, n = 103), or allergic rhinitis (AR, n = 113), at 5 years, and healthy control (n = 236) participants, adjusting for chronological age at the time of collection and with a random effect of the sample collection site. Data are presented as MaAslin2 coefficients +/- standard error.

Species	Variable	Coefficient	St. err.	P-Value	FDR
Megasphaera micronuciformis	Breastfeeding at 6 months	0.71	0.10	0.00	0.00
Veillonella atypica	Breastfeeding at 6 months	0.64	0.11	0.00	0.00
Tyzzerella nexilis	Breastfeeding at 6 months	-0.55	0.11	0.00	0.00
Clostridium innocuum	Breastfeeding at 6 months	-0.45	0.10	0.00	0.00
Intestinibacter bartlettii	Breastfeeding at 6 months	-0.37	0.10	0.00	0.00
Ruminococcus gnavus	Breastfeeding at 6 months	-0.33	0.09	0.00	0.00
Sellimonas intestinalis	Breastfeeding at 6 months	-0.41	0.12	0.00	0.00
Erysipelatoclostridium ramosum	Breastfeeding at 6 months	-0.29	0.11	0.01	0.01
Eggerthella lenta	Breastfeeding at 6 months	-0.20	0.07	0.01	0.02
Enterococcus faecalis	Breastfeeding at 6 months	-0.22	0.09	0.02	0.03
Escherichia coli	Breastfeeding at 6 months	0.29	0.12	0.02	0.03
Gordonibacter pamelaeae	Breastfeeding at 6 months	-0.19	0.09	0.04	0.07
Ruminococcus bromii	Breastfeeding at 6 months	-0.25	0.12	0.04	0.07
Clostridium innocuum	Paternal atopy	-0.60	0.24	0.01	0.05
Erysipelatoclostridium ramosum	Paternal atopy	-0.56	0.25	0.02	0.07
Bifidobacterium longum	Antibiotic usage by 1 year	-1.54	0.40	0.00	0.00
Tyzzerella nexilis	Antibiotic usage by 1 year	1.01	0.27	0.00	0.00
Clostridium innocuum	Antibiotic usage by 1 year	0.73	0.25	0.00	0.01
Veillonella atypica	Antibiotic usage by 1 year	-0.80	0.27	0.00	0.01
Sellimonas intestinalis	Antibiotic usage by 1 year	0.81	0.29	0.01	0.02
Hungatella hathewayi	Antibiotic usage by 1 year	0.78	0.30	0.01	0.02
Megasphaera micronuciformis	Antibiotic usage by 1 year	-0.53	0.24	0.03	0.06

Supplementary Table 3. Microbiota associated with important clinical features in allergic disease. MaAsLin2 model, adjusting for chronological age at the time of collection and with a random effect of the sample collection site, results indicating the microbe identified as significant, the variable and comparison group, coefficient of association, standard deviation, p-value, and FDR-corrected p-value.



Supplementary Fig. 4. Metabolic components in clusters identified via weighted correlation analysis. Weighted gene co-expression analysis (WGCNA) was used to cluster 195 quantified metabolites through targeted liquid chromatography with tandem mass spectrometry and nuclear magnetic resonance into 14 clusters, with 50 metabolites not assigned a cluster. The correlations between individual cluster metabolites and independent clusters with no modules are depicted by a network plot generated using Cytoscape and metabolite cluster components are listed along the sides of the figure.



Supplementary Fig. 5. Metabolites linked to predicted age and allergic disease. MaAsLin2 results of metabolites associated with a predicted age (n = 509) and b one or more allergic disease (n = 305) as compared to participants with no allergic history (n = 204). Data are presented as MaAslin2 coefficients +/- standard error of the mean.