

Supplementary Information

Exposure to maternal human milk components interacts with infant polygenic risk to predict childhood atopy

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Table S1. Characteristics of 689 mother-infant dyads (sub-cohort) included in this study compared to all dyads (n=3,542) from the full CHILD Cohort Study, related to Methods and Figure 1.

	Variables	Mean $\pm$ SD or n (%) ^a	
		Mother-infant dyads (n = 689)	All eligible dyads (n = 3,542)
Maternal	Age (years)	33 $\pm$ 4.2	32.3 $\pm$ 4.7
	Reported ethnicity		
	Central European (CEU)	518 (75.2)	2359 (72.9)
	Other	171 (24.8)	876 (27.1)
	Milk microbiome batches		
	Batch 1	292 (42.4)	344 (38.9)
	Batch 2	397 (57.6)	541 (61.1)
	Time (in seconds) between sample collection at home and processing	68229 $\pm$ 70844	108835 $\pm$ 456953
	Annual total household income (above \$100,000 Canadian dollars)	351 (56.7)	1504 (52.6)
	Have a post-secondary degree	556 (81.3)	2407 (76.3)
	Breastfeeding for ³ 6 months	689 (100)	2322 (76.2)
	Study centers		
	Edmonton	142 (20.6)	780 (23.7)
	Toronto	195 (28.3)	778 (23.6)
	Edmonton	179 (26)	742 (22.5)
	Toronto	173 (25.1)	996 (30.2)
Children	Antibiotics use at age 1 year	135 (19.6)	600 (18.4)
	Reported ethnicity		
	Central European (CEU)	450 (65.3)	2061 (64)
	Others	239 (34.7)	1159 (36)
	Sex		
	Female	310 (45)	1642 (47.4)
	Male	379 (55)	1820 (52.6)
	Atopy		
	Any atopic dermatitis		
	at 1 year	105 (15.5)	349 (25.2)
	at 3 years	100 (16.3)	327 (24)
	at 5 years	117 (19.3)	367 (26.2)
	between 1 to 5 years	206 (34.6)	707 (40.6)
	between 3 to 5 years	164 (28.2)	530 (33.9)
	Any food/inhalant sensitization		
	at 1 years	117 (17.5)	418 (28.8)
	at 3 years	122 (18.9)	408 (28.3)
	at 5 years	137 (22/5)	524 (33.6)
	at 1 to 5 years	239 (39.3)	888 (46.2)
	at 3 to 5 years	188 (31.2)	695 (40.2)
	Any food sensitization		
	at 1 years	99 (14.9)	334 (24.4)
	at 3 years	50 (7.8)	167 (13.9)
	at 5 years	40 (6.6)	143 (12.1)

	at 1 to 5 years	120 (20.3)	414 (28.6)
	at 3 to 5 years	64 (10.9)	214 (17.1)
	Any inhalant sensitization		
	at 1 years	26 (4.9)	124 (10.7)
	at 3 years	95 (14.7)	327 (24)
	at 5 years	125 (20.5)	469 (31.2)
	at 1 to 5 years	179 (29.9)	691 (40)
	at 3 to 5 years	165 (27.5)	622 (37.6)
	Definite asthma at 5 years	64 (11.1)	171 (6.8)
	Recurrent wheeze at 2 to 5 years	140 (20.8)	444 (17.5)
	Any atopy at 1 to 5 years	333 (55.7)	1253 (50.6)
	Any atopy, asthma, and/or recurrent wheeze at 1 to 5 years^b	385 (64.3)	1458 (58.5)

^a Percentages reflect proportion of non-missing data.

^bCase groups were compared to 214 controls among 689 dyads (sub-cohort) or 1,034 controls among 3,542 dyads from the full cohort study, which consisted of children without any asthma, recurrent wheeze, atopy (including food or inhalant allergies), and atopic dermatitis (AD) between ages 1-5 years.

Table S2. Main effects of HMM traits¹ and interactions with infant PRS were associated with any childhood atopy at ages 1-5 years. These atopy-implicated HMM traits were carried forward for downstream association analyses with HMOs and HMFAs, related to Figures 2 and 6 and Table 1.

HMM traits	HMM or PRS×HMM	Any atopic outcomes at ages 1-5 years	Estimate for HMM	P value ^a	P _{Bonferroni} ^b
CLR-transformed ASV abundance					
<i>Haemophilus sp. 3</i>	PRS×HMM	food/Inhalant	0.2	4.6E-05	3.9E-03
<i>Abiotrophia sp</i>	PRS×HMM	Inhalant	0.3	6.4E-05	5.5E-03
<i>Granulicatella sp.</i>	HMM	food	-0.2	4.7E-04	0.04
CLR-transformed MetaCyc Pathway abundance					
Superpathway of heme biosynthesis from glutamate (PWY-5918)	PRS×HMM	Inhalant	-0.5	2.1E-04	0.02
L-ornithine biosynthesis (GLUTORN-PWY)	PRS×HMM	Inhalant	-0.4	2.6E-04	0.03
preQ0 biosynthesis (PWY-6703)	PRS×HMM	Inhalant	-0.4	3.4E-04	0.03
L-histidine biosynthesis (HISTSYN-PWY)	PRS×HMM	Inhalant	-0.4	4.20E-04	0.04
Partial TCA cycle (obligate autotrophs) (PWY-5913)	PRS×HMM	ad	-0.5	4.9E-04	0.05
Mixed acid fermentation (FERMENTATION-PWY)	PRS×HMM	ad	-0.5	5.4E-04	0.05
HMM network clusters					
<i>Green</i>	PRS×HMM	food/Inhalant	12.8	1.20E-03	N/A
<i>Yellow</i>	HMM	food/Inhalant	-8.3	2.8E-03	N/A
<i>Yellow</i>	HMM	ad	-8.5	3.3E-03	N/A
<i>Yellow</i>	HMM	inhalant	-8.6	5.1E-03	N/A
<i>Green</i>	PRS×HMM	inhalant	11.2	6.9E-03	N/A
<i>Yellow</i>	HMM	food	-8.9	0.01	N/A
<i>Green</i>	HMM	food/Inhalant	-6.9	0.01	N/A
<i>Green</i>	HMM	food	-8.9	0.02	N/A
<i>Turquoise</i>	HMM	ad	6	0.04	N/A
<i>Green</i>	HMM	inhalant	-6.3	0.05	N/A
<i>Turquoise</i>	HMM	food/Inhalant	5.6	0.05	N/A
<i>Yellow</i>	PRS×HMM	inhalant	7.4	0.05	N/A
<i>Green</i>	PRS×HMM	ad	7.2	0.05	N/A
Alpha-diversity					
Shannon	HMM	food/inhalant	-0.4	5.6E-03	N/A
Shannon	PRS×HMM	inhalant	0.4	0.01	N/A

Shannon	HMM	inhalant	-0.4	0.01	N/A
Shannon	HMM	ad	-0.3	0.03	N/A
Shannon	HMM	food	-0.4	0.03	N/A
Shannon	PRS×HMM	food/inhalant	0.4	0.03	N/A

^aHMM network clusters and alpha-diversity associated with childhood asthma and atopy (P_{unadjusted} < 0.05)

^bHMM traits (CLR-transformed abundance of ASVs, and CLR-transformed abundance of metabolic pathways) associated with childhood asthma and atopy (P_{Bonferroni} < 0.05)

Table S3. HMFAs were associated with atopy-implicated HMM traits. P-values reported for 28 individual HMFAs were adjusted by Bonferroni correction of three clusters of correlated HMFAs. Raw p-values reported for ratios and total HMFAs, related to Figure 3.

Estimate	P values	P _{Bonferroni}	2.50%	97.50%	HMM traits	HMFAs
-0.005	6.94E-04	2.08E-03	-0.008	-0.002	Green	24:0
-0.004	7.84E-04	2.35E-03	-0.006	-0.002	Green	18:1c11
-0.004	0.01	0.03	-0.006	-0.001	Green	CLA
0.003	0.03	N/A	0.0003	0.005	Green	n-6/n-3 PUFAs
-0.003	0.01	0.03	-0.005	-0.001	Yellow	18:1c11
0.002	0.04	N/A	0.000	0.005	Yellow	n-6/n-3 PUFAs
-0.25	1.94E-04	5.81E-04	-0.38	-0.12	<i>Abiotrophia sp.</i>	20:4n3
-0.24	2.90E-04	8.71E-04	-0.37	-0.11	<i>Abiotrophia sp.</i>	20:5n3
0.24	1.80E-03	N/A	0.09	0.39	<i>Granulicatella sp.</i>	n-6/n-3 PUFAs
-0.23	3.49E-03	N/A	-0.38	-0.08	<i>Granulicatella sp.</i>	Total n-3
-0.28	1.43E-03	4.30E-03	-0.45	-0.11	<i>Granulicatella sp.</i>	CLA
-0.22	1.77E-03	5.32E-03	-0.36	-0.08	<i>Abiotrophia sp.</i>	22:6n3
-0.23	2.56E-03	7.69E-03	-0.38	-0.08	<i>Granulicatella sp.</i>	20:5n3
-0.20	3.08E-03	9.25E-03	-0.34	-0.07	<i>Abiotrophia sp.</i>	20:4n6
-0.23	5.30E-03	0.02	-0.39	-0.07	<i>Granulicatella sp.</i>	22:6n3
-0.21	6.68E-03	0.02	-0.37	-0.06	<i>Granulicatella sp.</i>	20:4n6
-0.20	8.72E-03	0.03	-0.35	-0.05	<i>Granulicatella sp.</i>	20:4n3
0.15	0.03	N/A	0.02	0.28	<i>Abiotrophia sp.</i>	n-6/n-3 PUFAs
-0.24	0.01	0.03	-0.43	-0.06	<i>Haemophilus sp. 3</i>	18:1c11
-0.19	0.01	0.03	-0.34	-0.04	<i>Granulicatella sp.</i>	18:1c11
-0.19	0.01	0.04	-0.34	-0.04	<i>Granulicatella sp.</i>	18:3n3
0.15	0.04	N/A	0.01	0.29	<i>Abiotrophia sp.</i>	ARA/DHA
0.19	0.05	N/A	0.00	0.38	<i>Haemophilus sp. 3</i>	n6/n-3 PUFAs
0.18	0.02	0.05	0.03	0.32	<i>Granulicatella sp.</i>	14:0
0.14	1.05E-04	3.14E-04	0.07	0.21	L-ornithine biosynthesis (GLUTORN-PWY)	18:1c11

0.14	1.70E-04	5.09E-04	0.07	0.21	L-histidine biosynthesis (HISTSYN-PWY)	20:4n3
0.12	1.33E-03	3.99E-03	0.05	0.19	L-histidine biosynthesis (HISTSYN-PWY)	20:5n3
0.10	1.59E-03	4.76E-03	0.04	0.17	preQ0 biosynthesis (PWY-6703)	18:1c11
0.18	1.61E-03	4.84E-03	0.07	0.29	L-ornithine biosynthesis (GLUTORN-PWY)	22:4n6
0.16	2.16E-03	6.48E-03	0.06	0.26	preQ0 biosynthesis (PWY-6703)	22:4n6
-0.08	3.12E-03	0.01	-0.13	-0.03	Superpathway of heme biosynthesis from glutamate (PWY-5918)	10:0
0.12	4.26E-03	0.01	0.04	0.20	Superpathway of heme biosynthesis from glutamate (PWY-5918)	22:4n6
0.07	5.84E-03	0.02	0.02	0.12	Partial TCA cycle (obligate autotrophs) (PWY-5913)	20:5n3
0.09	0.01	0.03	0.02	0.17	L-ornithine biosynthesis (GLUTORN-PWY)	20:4n3
-0.05	0.04	N/A	-0.09	-0.003	Mixed acid fermentation (FERMENTATION-PWY)	Total saturated FA
0.07	0.01	0.04	0.01	0.12	TCA cycle VI (obligate autotrophs) (PWY-5913)	22:6n3
-0.08	0.02	0.05	-0.15	-0.02	preQ0 biosynthesis (PWY-6703)	10:0
0.06	0.02	0.05	0.01	0.11	TCA cycle VI (obligate autotrophs) (PWY-5913)	20:4n3
0.08	0.02	0.05	0.02	0.15	preQ0 biosynthesis (PWY-6703)	20:4n3
-0.05	0.02	0.05	-0.10	-0.01	Mixed acid fermentation (FERMENTATION-PWY)	14:0
-0.07	0.05	N/A	-0.14	0.001	L-histidine biosynthesis (HISTSYN-PWY)	n-6/n-3 PUFAs

Table S4. HMOs were associated with atopy-implicated HMM traits. P-values reported for 19 individual HMFAs were adjusted by Bonferroni correction of six clusters of correlated HMFAs. Raw p-values reported for ratios and total HMOs, related to Figure 3.

Estimate	P values	Pbonferroni	2.50%	97.50%	HMM traits	HMOs
					HMM network clusters	
-0.003	0.004	0.027	-0.006	-0.001	<i>Green</i>	LNH
0.003	0.008	0.046	0.003	0.001	<i>Green</i>	3FL
					CLR-transformed ASV abundance	
-0.33	8.76E-07	5.25E-06	-0.46	-0.2	<i>Abiotrophia sp.</i>	DSLNH
-0.32	1.80E-06	1.08E-05	-0.44	-0.19	<i>Abiotrophia sp.</i>	6'SL
-0.24	0.0003	0.002	-0.37	-0.11	<i>Abiotrophia sp.</i>	LNH
-0.24	0.002	0.01	-0.39	-0.09	<i>Granulicatella sp.</i>	6'SL
-0.24	0.002	0.01	-0.39	-0.09	<i>Granulicatella sp.</i>	DSLNH
-0.23	0.002	0.01	-0.38	-0.09	<i>Abiotrophia sp.</i>	LSTc
-0.19	0.006	0.04	-0.32	-0.05	<i>Abiotrophia sp.</i>	FLNH

Table S5. WGCNA clustered 179 individual milk ASVs, 19 individual HMOs, and 28 HMFAs into seven multi-component network modules encompassing 226 milk features, with 10 milk features in multi-black, 49 milk features in multi-blue, 39 milk features in multi-brown, 32 milk features in multi-green, 15 milk features in multi-red, 32 milk features in multi-yellow, and 49 milk features in multi-turquoise, related to Figure 4.

Multi-black (n=10)	Multi-blue (n=49)	Multi-brown (n=39)	Multi-green (n=32)	Multi-red (n=15)	Multi-yellow (n=32)	Multi-turquoise (n=49)
<i>Staphylococcus</i> sp.1*	<i>Abiotrophia</i> sp.*	20:5n3*	<i>Streptococcus</i> <i>sanguinis</i>*	15:0*	<i>Blastococcus</i> sp.3*	<i>Stenotrophomonas</i> <i>maltophilia</i>*
<i>Anaerococcus</i> sp.10	<i>Actinomyces</i> sp.1	<i>Lactobacillus</i> sp.23	<i>Chryseobacterium</i> sp.11	FDSLNH	<i>Bradyrhizobium</i> elkanii	<i>Acinetobacter</i> johnsonii
<i>Peptoniphilus</i> sp.1	<i>Atopobium</i> sp.	<i>Rothia</i> sp.3	<i>Scardovia</i> <i>wiggisiae</i>	LNFP2	<i>Comamonas</i> <i>aquatica</i>	<i>Squalius pyrenaicus</i>
<i>Corynebacterium</i> sp.2	<i>Prevotella</i> sp.56	2'FL	<i>Veillonella</i> sp.5	LNFP3	<i>Thermomonas</i> sp.2	<i>Aeromonas</i> sp.
<i>Corynebacterium</i> <i>striatum</i>	<i>Lachnoanaerobaculum</i> sp.	6'SL	<i>Kocuria</i> <i>turfanensis</i>	LNT	<i>Methylobacterium</i> - <i>Methylorubrum</i> sp.5	<i>Lactobacillus</i> sp.5
<i>Corynebacterium</i> sp.9	<i>Lachnoanaerobaculum</i> sp.1	DFLNH	<i>Schlegelella</i> <i>aquatica</i>	LSTb	<i>proteobacterium</i> <i>symbiont</i>	<i>Pseudomonas</i> sp.2
<i>Corynebacterium</i> sp.3	<i>Veillonella</i> sp.6	DSLNH	[<i>Ruminococcus</i>] <i>gnavus</i> sp.	10:0	<i>Corynebacterium</i> sp.16	<i>Pseudomonas</i> <i>oryzihabitans</i>
<i>Finegoldia</i> sp.	<i>Prevotella salivae</i>	FLNH	<i>Romboutsia</i> sp.1	12:0	<i>Enhydrobacter</i> sp.	<i>Lactobacillus</i> sp.8
<i>Anaerococcus</i> sp.7	<i>Veillonella atypica</i>	LNFP1	<i>Anaerococcus</i> sp.1	14:0	<i>Sphingobium</i> sp.2	<i>Rothia kristinae</i>
<i>Staphylococcus</i> <i>haemolyticus</i> 2	<i>Streptococcus</i> sp.5	LNH	<i>Anaerococcus</i> sp.2	14:1n9	<i>Aerococcus</i> sp.	<i>Novosphingobium</i> sp.5
	<i>Streptococcus</i> sp.	LNnT	<i>Thermus</i> sp.	DSLNT	<i>Psychrobacter</i> <i>immobilis</i>	<i>Unclassified</i> <i>Rhizobiaceae</i> sp.3
	<i>Veillonella</i> sp.28	LSTc	<i>Corynebacterium</i> <i>amycolatum</i>	16:0	<i>Massilia</i> sp.1	<i>Delftia</i> sp.
	3FL	TVA	<i>Psychrobacter</i> <i>sanguinis</i>	16:1n9	<i>Auricoccus</i> - <i>Abyssicoccus</i> sp.	<i>Acinetobacter</i> sp.1
	3'SL	18:1n9	<i>Abiotrophia</i> sp.2	17:0	<i>Brachybacterium</i> sp.1	<i>Pseudomonas</i> sp.3
	DFLac	18:1C11	<i>Veillonella</i> sp.30	18:0	<i>Skermanella</i> sp.1	<i>Pantoea</i> sp.1
	DFLNT	18:2n6	<i>Unclassified</i> <i>Neisseriaceae</i> sp.		<i>Paracoccus</i> sp.16	<i>Enterobacter</i> sp.3

	<i>Rothia</i> sp.1	20:0	<i>Corynebacterium</i> sp.26		<i>Planococcus</i> sp.	<i>Sphingomonas</i> sp.45
	<i>Actinomyces</i> sp.	18:3n6	<i>Neisseria</i> sp.4		<i>Caulobacter vibrioides</i>	<i>Chryseobacterium</i> sp.
	<i>Fusobacterium</i> sp.2	18:3n3	<i>Rothia</i> sp.6		<i>Noviherbaspirillum</i> sp.5	<i>Acinetobacter</i> sp.9
	<i>Porphyromonas</i> sp.6	20:2n6	<i>Actinomyces</i> sp.6		<i>Acinetobacter</i> sp.	<i>Methylobacterium rhodesianum</i>
	<i>Prevotella</i> sp.37	20:3n6	<i>Corynebacterium</i> sp.		<i>Massilia</i> sp.3	<i>Exiguobacterium</i> sp.1
	<i>Alloprevotella</i> sp.3	20:4n6	<i>Neisseria</i> sp.3		<i>Pseudomonas montellii</i>	<i>Stenotrophomonas</i> sp.
	<i>Rothia</i> sp.	20:4n3	<i>Lautropia</i> sp.		<i>Cloacibacterium</i> sp.	<i>Altererythrobacter</i> sp.
	<i>Bergeyella</i> sp.3	CLA	<i>Corynebacterium</i> sp.1		<i>Bosea</i> sp.1	<i>Acinetobacter</i> sp.23
	<i>Moraxella</i> sp.	24:0	<i>Lawsonella</i> sp.		<i>Pseudarthrobacter polychromogenes</i>	<i>Pantoea septica</i>
	<i>Dolosigranulum</i> sp.	24:1n9	<i>Anaerococcus</i> sp.5		<i>Shewanella</i> sp.1	<i>Pseudomonas hunanensis</i>
	<i>Veillonella</i> sp.10	22:4n6	<i>Peptoniphilus</i> sp.		<i>Pseudoalteromonas</i> sp.1	<i>Pantoea</i> sp.
	<i>Porphyromonas</i> sp.14	22:5n6	<i>Prevotella</i> sp.6		<i>Bacillus</i> sp.2	<i>Pseudomonas</i> sp.11
	<i>Bergeyella</i> sp.1	22:5n3	<i>Fenollaria</i> sp.		<i>Dietzia</i> sp.2	<i>Pseudoxanthomonas</i> sp.5
	<i>Haemophilus</i> sp.15	22:6n3	<i>Bifidobacterium catenulatum</i>		<i>Bacillus niabensis</i>	<i>Chryseobacterium</i> sp.5
	<i>Gemella</i> sp.	<i>Rothia</i> sp.4	<i>Lactococcus lactis</i>		<i>Paracoccus marcusii</i>	<i>Bacillus</i> sp.23
	<i>Granulicatella</i> sp.	<i>Sphingomonas</i> sp.52	<i>Brochothrix thermosphacta</i>		<i>Micrococcus luteus</i> 1	<i>Rahnella</i> sp.1
	<i>Porphyromonas</i> sp.11	<i>Bifidobacterium longum</i> 1				<i>Stenotrophomonas maltophilia</i> 1
	<i>Haemophilus</i> sp.3	<i>Escherichia coli</i>				<i>Pseudomonas aeruginosa</i>
	<i>Prevotella</i> sp.32	<i>Klebsiella</i> sp.4				<i>Klebsiella oxytoca</i>

	<i>Prevotella</i> sp.3	<i>Lactobacillus fermentum</i>				<i>Enterobacter cloacae</i>
	<i>Prevotella</i> sp.38	<i>Roseomonas gilardii</i>				<i>Rahnella</i> sp.
	<i>Bergeyella</i> sp.2	<i>Bacillus subtilis</i>				<i>Sphingomonas</i> sp.26
	<i>Megasphaera micronuciformis</i>	<i>Kocuria rhizophila</i>				<i>Agrobacterium radiobacter</i>
	<i>Actinomyces</i> sp.3					<i>Pseudomonas viridiflava</i>
	<i>Campylobacter</i> sp.2					<i>Enterococcus faecalis</i> 1
	<i>Rothia</i> sp.2					<i>Brevundimonas</i> sp.
	<i>Veillonella</i> sp.7					<i>Stenotrophomonas</i> sp.1
	<i>Porphyromonas</i> sp.10					<i>Brevundimonas</i> sp.6
	<i>Leptotrichia</i> sp.6					<i>Acinetobacter baumannii</i>
	<i>Streptococcus salivarius</i>					<i>Sphingobacterium multivorum</i>
	<i>Streptococcus</i> sp.2					<i>Acinetobacter ursingii</i>
	<i>Corynebacterium propinquum</i>					<i>Pseudomonas</i> sp.
	<i>Neisseria perflava</i>					<i>Acinetobacter</i> sp.40

*Hub milk features with the highest connectivity to other features within each module.

Table S6. Main effects of maternal HMM¹, HMFAs, and HMOs and interactions with infant PRS were associated with childhood atopy. These maternal milk components and infant PRS were selected for training the gradient boosting tree models for classifying childhood atopy/asthma and controls, related to Figure 5 and Methods.

HMM traits	HM or PRS×HM	Associated atopic outcomes	Estimate for HMM	Top P value	Top P _{Bonferroni} ^a
CLR-transformed ASV abundance					
<i>Haemophilus sp. 3</i>	PRS×HM	food/inhalant1to5y	0.2	4.6E-05	3.9E-03
<i>Abiotrophia sp</i>	PRS×HM	food/inhalant3to5y inhalant1to5y; inhalant3to5y	0.3	6.4E-05	5.5E-03
<i>Lawsonella sp.</i>	HM	food/inhalant5y; food5y; food3to5y inhalant5y	0.2	3.5E-04	0.03
<i>Granulicatella sp.</i>	HM	food/inhalant1y; food1to5y	-0.2	4.7E-04	0.04
<i>Pantoea sp.</i>	PRS×HM	inhalant3y	-0.6	5.2E-04	0.04
Rank-based inverse normal transformed HMFAs					
22:4n6	HM	food5y	0.8	1.2E-03	3.7E-03
18:2n6	HM	inhalant1y	0.6	3.6E-03	0.01
18:1c11	HM	food/inhalant3to5y; food/inhalant5y; inhalant3to5y; inhalant5y;	0.3	4.2E-03	0.01
20:3n6	HM	food5y	0.6	0.01	0.03
14:0	HM	inhalant1y	-0.5	0.01	0.03
18:3n6	PRS×HM	food/inhalant1y	0.3	0.01	0.03
15:0	HM	food/inhalant3y; inhalant1y; inhalant1to5y	-0.5	0.02	0.05
14:1n9	HM	inhalant1y	-0.5	0.02	0.05
24:1n9	PRS×HM	food3y; food3to5y	-0.4	0.02	0.05
Rank-based inverse normal transformed HMOs					
DSLNT	HM	food/inhalant5y; inhalant1to5y; inhalant3to5y; inhalant5y	-0.4	1.1E-03	6.8E-03
3FL	HM	inhalant1y	-0.7	4.7E-03	0.03

LSTc	PRS×HM	food1to5y	-0.4	3.1E-03	0.02
6'SL	PRS×HM	food3y	-0.5	6.8E-03	0.04

^aHM traits associated with childhood asthma and atopy (P_{Bonferroni} < 0.05).

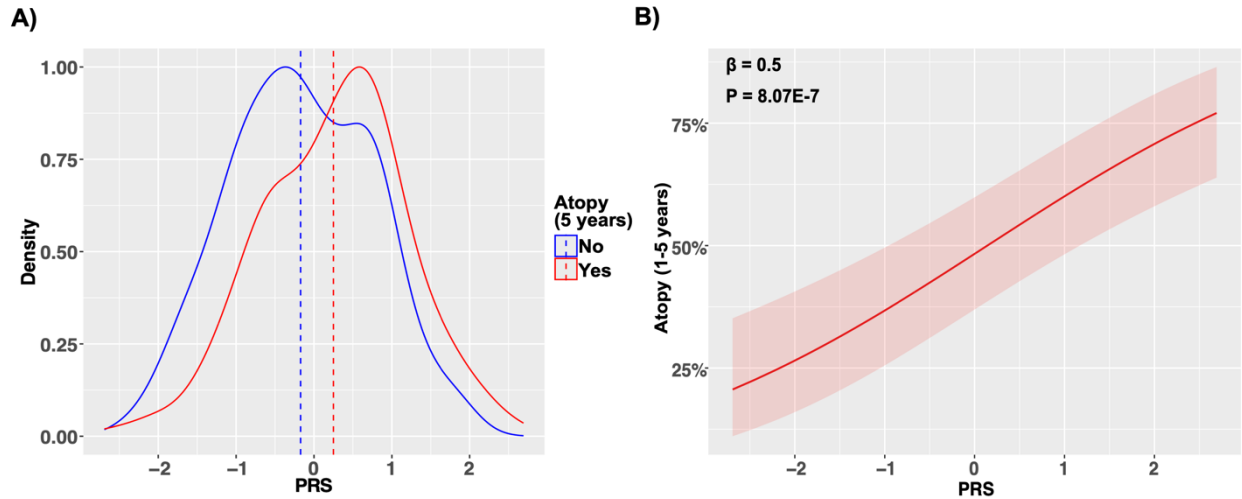


Figure S1. Polygenic risk scores (PRS) are associated with childhood atopy at age 5 years in the CHILD dataset, related to Figure 1. A.) density plot of the PRS distribution among children with and without atopy between ages 1-5 years. B.) Increase PRS was significantly associated with increase prevalence of childhood atopy between ages 1-5 years. Shaded areas are corresponding standard error (SE).

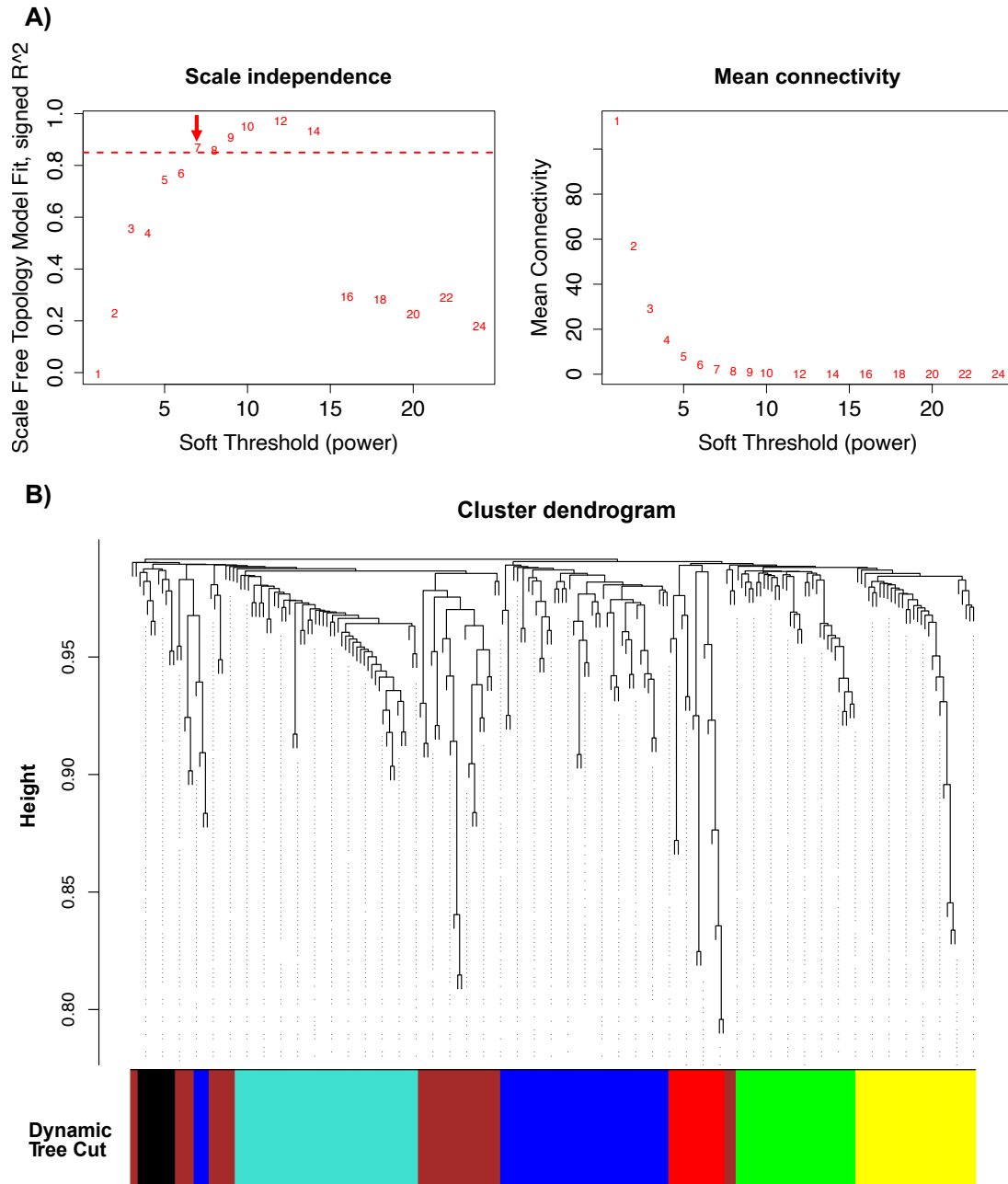


Figure S2. WGCNA clustered 179 amplicon sequence variants (ASVs), 19 human milk oligosaccharides (HMOs), and 28 human milk fatty acids (HMFAs) into seven cooccurring network modules, related to Figure 4 and Methods. A.) Effect of various candidate powers on the scale-free topology fit (left) and mean node connectivity (right). At $\beta = 7$, the co-abundance network modules of ASVs showed 86.8% similarity to the scale-free topology. We also showed that at this β value, the mean node connectivity resembles the distribution typical of a scale-free topology. The selected optimal β is marked with a red arrow in the left panel. B.) Dendrograms of 179 ASV, 19 HMO, and 28 HMFA features were grouped into seven network modules, as indicated by colours, using hierarchical clustering based on the topological overlap matrix (TOM).

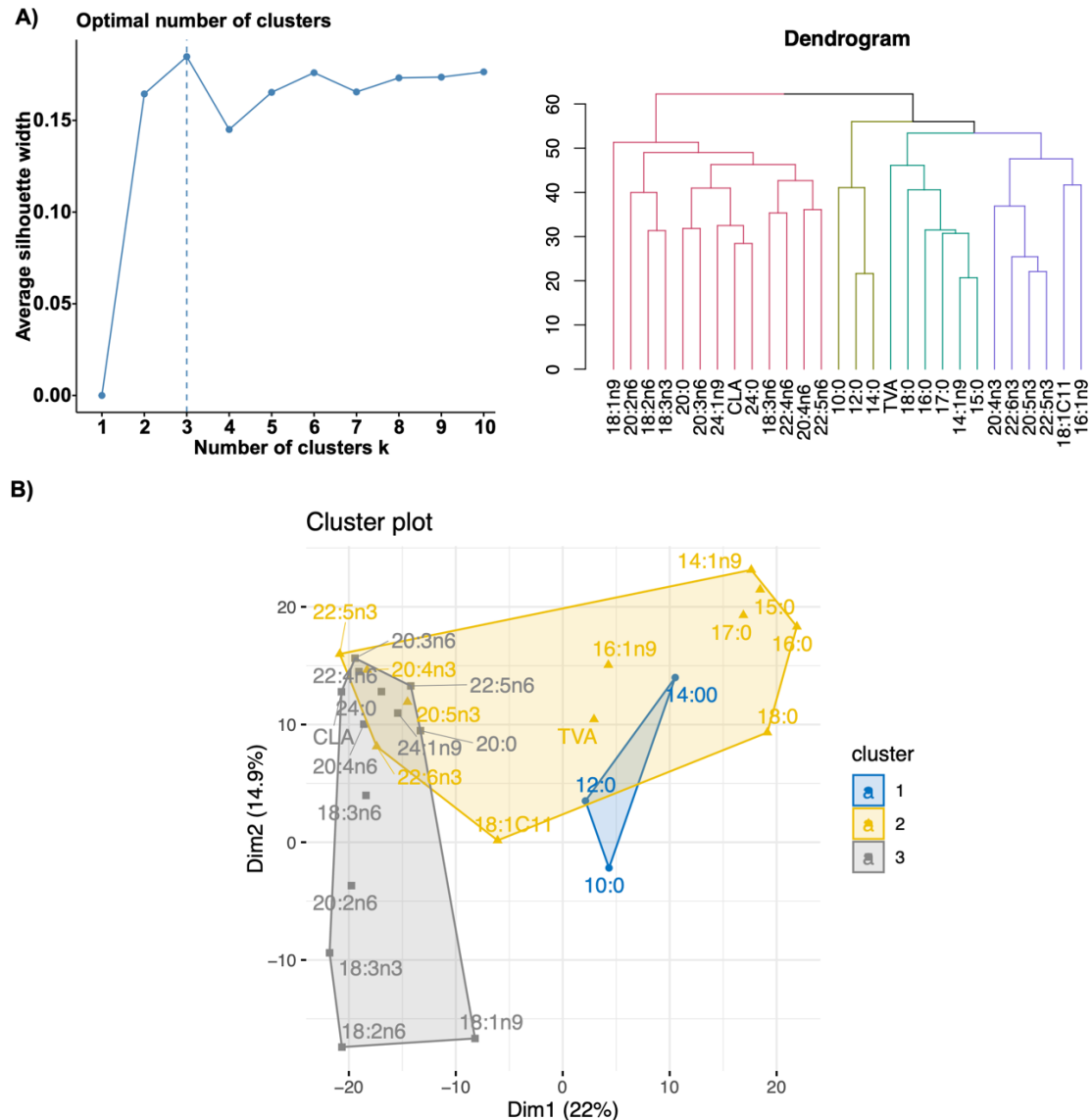


Figure S3. Clustering of 28 individual HMFA profiles among 1200 lactating mothers, related to Methods. A.) Silhouette plots for determining the optimal number of clusters. The left plot shows the silhouette method applied to k-means clustering. B.) Dendrograms from hierarchical clustering grouped 28 individual HMFAs into three clusters based on Euclidean distance. C.) Cluster plot visualizing 28 individual HMFAs in reduced dimensions. The clusters were projected onto the first two principal dimensions, separating the HMFAs into three clusters. Capric acid (10:0), lauric acid (12:0), myristic acid (14:0), physeteric acid (14:1n9), pentadecylic acid (15:0), palmitic acid (16:0), 7-hexadecenoic acid (16:1n9), margaric acid (17:0), stearic acid (18:0), trans-vaccenic acid (TVA; 18:1t11), oleic acid (18:1n9), cis-vaccenic acid (18:1c11), linoleic acid (LA; 18:2n6), arachidic acid (20:0), γ -linolenic acid (GLA; 18:3n6), α -linolenic acid (ALA; 18:3n3), eicosadienoic acid (20:2n6), dihomo- γ -linolenic acid (DHGLA; 20:3n6), arachidonic acid (ARA; 20:4n6), conjugated linoleic acid (CLA; a family of linoleic acid isomers), eicosapentaenoic acid (EPA; 20:5n3), nervonic acid (24:1n9), docosahexaenoic acid (DHA; 22:6n3), lignoceric acid (24:0), osbond acid (22:5n6), docosapentaenoic acid (DPA; 22:5n3), eicosatetraenoic acid (20:4n3), and adrenic acid (22:4n6).

References

1. Fang, Z.Y., Stickley, S.A., Ambalavanan, A., Zhang, Y., Zacharias, A.M., Fehr, K., Moossavi, S., Petersen, C., Miliku, K., Mandhane, P.J., et al. (2024). Networks of human milk microbiota are associated with host genomics, childhood asthma, and allergic sensitization. *Cell Host Microbe*, S1931312824003214. <https://doi.org/10.1016/j.chom.2024.08.014>.