Supplementary Information

Untargeted cord blood metabolomics reveals altered lipid metabolism in neonates with gastroschisis

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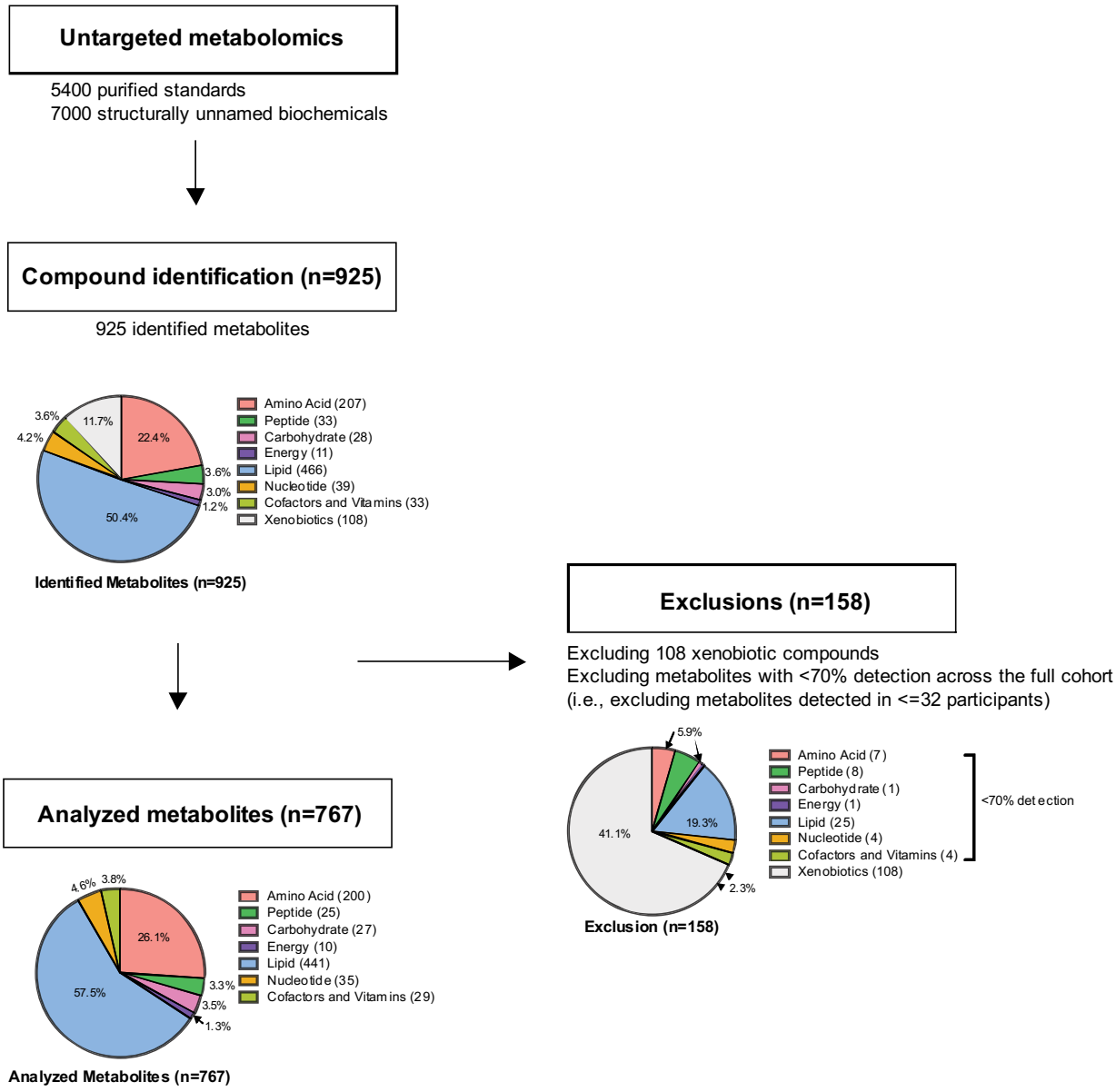
Supplementary Figure

Supplementary Figure 1.



Supplementary Figure 1. Of approximately 5400 purified standards and 7000 structurally unnamed biochemicals in the Metabolon reference library, 925 metabolites were identified. After exclusion of all xenobiotics and metabolites detected in fewer than 70% of the cohort, 767 endogenous metabolites were retained for downstream analyses.

Supplementary Tables

Supplementary Table 1. Sensitivity of the 53 cohort significant metabolites to gestational age.

Sub pathway	Biochemical	FC	p-value	q-value
Hemoglobin and Porphyrin Metabolism	biliverdin	0.43	3.65×10^{-5}	0.0003
	bilirubin (Z,Z)	0.43	0.020	0.026
	bilirubin (E,Z or Z,E)	0.46	0.003	0.007
	bilirubin (E,E)	0.65	0.002	0.006
Polyamine Metabolism	spermidine	1.54	0.035	0.038
	N-acetylputrescine	1.45	0.0003	0.002
	N1,N12-diacetylspermine	1.43	0.002	0.005
	4-acetamidobutanoate	1.32	0.002	0.005
	5-methylthioadenosine (MTA)	1.32	0.034	0.037
Pyrimidine Metabolism	orotate	2.52	2.35×10^{-5}	0.0003
	cytosine	1.96	0.045	0.046
	N-carbamoylaspartate	1.49	0.004	0.009
	3-ureidopropionate	1.46	0.007	0.012
	3-(3-amino-3-carboxypropyl)uridine	1.35	0.0002	0.0009
	N-acetyl-beta-alanine	1.33	0.002	0.005
	2'-O-methylcytidine	1.25	0.008	0.013
	uridine	1.24	0.007	0.011
	orotidine	1.23	0.035	0.038
Fibrinogen Cleavage Peptide	fibrinopeptide A (5-16)	0.17	0.0005	0.002
	fibrinopeptide B (1-13)	0.22	0.0002	0.001
	fibrinopeptide A, des-ala(1)	0.30	0.007	0.011
	fibrinopeptide B (1-11)	0.30	0.045	0.047

For each metabolite the full cohort fold change and the fold change (FC) and p-value within term births are reported, together with whether the metabolite remained significant when the case versus control comparison was restricted to term births.

Supplementary Table 2. Lower fatty acid (FA) in neonates with gastroschisis.

Sub pathway	Biochemical	FC	p-value	q-value
Long Chain Saturated FA	myristate (14:0)	0.59	0.0002	0.0013
	pentadecanoate (15:0)	0.69	0.0003	0.0016
	palmitate (16:0)	0.64	0.0025	0.006
	margarate (17:0)	0.62	6.14×10^{-5}	0.0005
	stearate (18:0)	0.70	0.0031	0.007
	nonadecanoate (19:0)	0.69	8.89×10^{-5}	0.0006
	arachidate (20:0)	0.82	0.0079	0.013
Medium Chain FA	caproate (6:0)	0.80	0.048	0.049
	caprate (10:0)	0.79	0.028	0.032
	10-undecenoate (11:1n1)	0.76	0.019	0.025
	laurate (12:0)	0.57	7.10×10^{-5}	0.0005
Long Chain MUFA	oleate/vaccenate (18:1)	0.51	0.004	0.008
	10-nonadecenoate (19:1n9)	0.56	0.0005	0.002
	eicosenoate (20:1)	0.57	0.017	0.024
	10-heptadecenoate (17:1n7)	0.62	0.002	0.005
Long Chain PUFA (n3 and n6)	linoleate (18:2n6)	0.45	0.0004	0.002
	linolenate (18:3n3 or 6)	0.49	0.0004	0.002
	eicosapentaenoate (EPA; 20:5n3)	0.45	0.0003	0.002
	docosapentaenoate (n3 DPA; 22:5n3)	0.51	3.58×10^{-5}	0.0003
	docosahexaenoate (DHA; 22:6n3)	0.62	0.002	0.005
	hexadecadienoate (16:2n6)	0.61	0.001	0.004
	dihomo-linoleate (20:2n6)	0.63	0.0007	0.003
	adrenate (22:4n6)	0.63	0.021	0.027
	nisinate (24:6n3)	0.62	0.006	0.011
	dihomo-linolenate (20:3n3 or n6)	0.76	0.024	0.030
	mead acid (20:3n9)	1.32	0.014	0.020
	docosatrienoate (22:3n6)	1.99	0.001	0.004
Branched Chain FA	(14 or 15)-methylpalmitate (a17:0 or i17:0)	0.54	9.99×10^{-6}	0.0002
	(16 or 17)-methylstearate (a19:0 or i19:0)	0.50	7.22×10^{-7}	2.29×10^{-5}
Fatty Acid, Dicarboxylate	hydroxy-CMPF	0.21	0.005	0.010
	octadecanedioate (C18-DC)	0.54	0.002	0.005
	eicosenedioate (C20:1-DC)	0.56	3.63×10^{-7}	1.43×10^{-5}
	azelate (C9-DC)	0.57	0.002	0.005
	3-CMPFP	0.58	1.31×10^{-5}	0.0002
	glutarate (C5-DC)	0.64	0.027	0.031
	octadecenedioate (C18:1-DC)	0.67	0.006	0.011
	eicosanedioate (C20-DC)	0.67	0.001	0.004
	4-hydroxy-2-oxoglutaric acid	0.69	0.019	0.025
	octadecadienedioate (C18:2-DC)	0.73	0.014	0.020

	dodecanedioate (C12-DC)	0.74	0.036	0.039
	heptenedioate (C7:1-DC)	0.75	0.029	0.033
	2-hydroxyadipate	1.33	0.020	0.026
Fatty Acid, Monohydroxy	2-hydroxylaurate	0.53	6.19×10^{-8}	5.68×10^{-6}
	13-HODE + 9-HODE	0.61	0.0007	0.003
	3-hydroxystearate	0.69	0.035	0.038
	3-hydroxypalmitate	0.74	0.007	0.012
	2-hydroxymyristate	0.74	0.003	0.007
	3-hydroxymyristate	0.74	0.010	0.015
	2-hydroxystearate	1.19	0.016	0.023
	2-hydroxyarachidate	1.61	4.97×10^{-5}	0.0004
	2-hydroxybehenate	1.60	7.95×10^{-5}	0.0006

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Only metabolites with $p < 0.05$ are shown. Asterisks (*) denote metabolites identified with lower confidence.

Supplementary Table 3. Higher fatty acid downstream metabolism pathways in neonates born with gastroschisis.

Sub pathway	Biochemical	FC	p-value	q-value
Fatty Acid, Amide	margaramide (17:0)	47.19	0.022	0.027
	oleamide	14.19	0.038	0.040
	linolenamide (18:3)	11.20	0.014	0.020
	palmitamide (16:0)	9.01	0.042	0.044
	linoleamide (18:2n6)	8.16	0.029	0.033
	stearamide (18:0)	6.63	0.015	0.021
	eicosadienamide (20:2)	4.41	0.006	0.011
Acyl Carnitine, Long Chain Saturated	arachidoylcarnitine (C20)	2.58	1.42×10^{-8}	1.73×10^{-6}
	stearoylcarnitine (C18)	1.80	4.79×10^{-7}	1.73×10^{-5}
	lignoceroylcarnitine (C24)	1.33	0.023	0.029
	palmitoylcarnitine (C16)	1.30	0.005	0.010
	cerotoylcarnitine (C26)	1.27	0.006	0.011
	margaroylcarnitine (C17)	1.22	0.031	0.035
Acyl Carnitine, Monounsaturated	nervonoylcarnitine (C24:1)	2.11	0.0001	0.0008
	eicosenoylcarnitine (C20:1)	1.89	0.002	0.006
	ximenoylcarnitine (C26:1)	1.84	8.26×10^{-5}	0.0006
	cis-4-decenoylcarnitine (C10:1)	1.42	5.97×10^{-5}	0.0005
	oleoylcarnitine (C18:1)	1.41	0.004	0.008
	3-decenoylcarnitine	1.32	0.010	0.015
	5-dodecenoylcarnitine (C12:1)	1.27	0.029	0.033
Acyl Carnitine, Medium Chain	hexanoylcarnitine (C6)	1.47	0.003	0.007
	octanoylcarnitine (C8)	1.37	0.001	0.004
	decanoylcarnitine (C10)	1.24	0.021	0.027
Acyl Carnitine, Polyunsaturated	adrenoylcarnitine (C22:4)	1.37	0.044	0.046
	dihomo-linolenoylcarnitine (C20:3n3 or 6)	1.36	0.010	0.015
	dihomo-linoleoylcarnitine (C20:2)	1.34	0.019	0.025
	arachidonoylcarnitine (C20:4)	1.27	0.026	0.031
Acyl Choline	palmitoloelycholine	2.39	9.91×10^{-5}	0.0007
	dihomo-linolenoyl-choline	1.96	0.0007	0.003
	oleoylcholine	1.69	0.0007	0.003
	arachidonoylcholine	1.50	0.004	0.008
	palmitoylcholine	1.46	0.004	0.008
	stearoylcholine	1.41	0.008	0.013
Acyl Glycine	picolinoylglycine	1.42	0.049	0.050
	N-palmitoylglycine	0.74	0.006	0.011

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Only metabolites with $p < 0.05$ are shown.

Supplementary Table 4. Higher glycerophospholipid metabolism but lower plasmalogen in neonates born with gastroschisis

Sub pathway	Biochemical	FC	p-value	q-value
Lysophospholipid	1-stearoyl-GPE (18:0)	1.69	4.96×10^{-6}	0.0001
	1-palmitoyl-GPE (16:0)	1.37	0.0011	0.0036
	1-oleoyl-GPE (18:1)	1.58	1.48×10^{-5}	0.0002
	1-stearoyl-GPC (18:0)	1.40	0.0024	0.006
	1-palmitoyl-GPC (16:0)	1.26	0.003	0.0062
Phosphatidyl-choline (PC)	1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	1.26	3.20×10^{-5}	0.0003
Phosphatidyl-ethanolamine (PE)	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	1.09	0.03	0.033
Plasmalogen	1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (P-16:0/18:2)	0.33	8.08×10^{-5}	0.0006
Plasmalogen	1-(1-enyl-stearoyl)-2-linoleoyl-GPE (P-18:0/18:2)	0.29	0.0082	0.013

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Representative significant metabolites are shown.

Supplementary Table 5. Higher ceramide metabolism in neonates born with gastroschisis.

Sub pathway	Biochemical	FC	p-value	q-value
Ceramides	N-stearoyl-sphingosine (d18:1/18:0)	2.46	7.52×10^{-7}	2.29×10^{-5}
	ceramide (d16:1/24:1, d18:1/22:1)	2.14	8.75×10^{-6}	0.0002
	ceramide (d18:1/20:0, d16:1/22:0, d20:1/18:0)	1.84	3.29×10^{-5}	0.0003
	N-stearoyl-sphingadienine (d18:2/18:0)	1.77	3.66×10^{-5}	0.0003
	N-palmitoyl-sphingosine (d18:1/16:0)	1.72	8.73×10^{-6}	0.0002
	ceramide (d18:1/17:0, d17:1/18:0)	1.56	0.006	0.011
	ceramide (d18:2/24:1, d18:1/24:2)	1.53	2.33×10^{-5}	0.0003
	N-palmitoyl-sphingadienine (d18:2/16:0)	1.35	0.003	0.007
Dihydroceramides	N-palmitoyl-sphinganine (d18:0/16:0)	2.61	1.25×10^{-7}	7.62×10^{-6}
	N-stearoyl-sphinganine (d18:0/18:0)	2.50	3.29×10^{-5}	0.0003
Sphingomyelins	sphingomyelin (d18:1/18:0, d18:0/18:1)	1.29	0.015	0.021
	sphingomyelin (d18:1/20:0, d16:1/22:0)	1.22	0.047	0.048
Hexosylceramides (HCER)	glycosyl-N-(2-hydroxynervonoyl)-sphingosine	3.17	0.001	0.004
	glycosyl ceramide (d18:1/20:0, d16:1/22:0)	0.55	0.002	0.005
	glycosyl-N-stearoyl-sphingosine (d18:1/18:0)	0.66	0.006	0.011
Lactosylceramides (LCER)	lactosyl-N-palmitoyl-sphingosine (d18:1/16:0)	0.63	0.003	0.007
	lactosyl-N-nervonoyl-sphingosine (d18:1/24:1)	0.74	0.038	0.040

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Only metabolites with $p < 0.05$ are shown.

Supplementary Table 6. Lower androgenic and estrogenic metabolism in neonates born with gastroschisis.

Sub pathway	Biochemical	FC	p-value	q-value
Androgenic Steroids	androsterone sulfate	0.13	0.027	0.031
	androstenediol (3β,17β) monosulfate (2)	0.22	2.26×10^{-6}	5.51×10^{-5}
	5α-androstan-3β,17α-diol disulfate	0.30	1.14×10^{-5}	0.0002
	5α-androstan-3β,17β-diol disulfate	0.40	1.12×10^{-5}	0.0002
	androstenediol (3β,17β) monosulfate (1)	0.41	0.0003	0.001
	androstenediol (3β,17β) disulfate (1)	0.47	0.010	0.015
	androstenediol (3α,17α) monosulfate (2)	0.51	0.008	0.013
	androsterone glucuronide	0.55	0.004	0.008
	16α-hydroxy DHEA 3-sulfate	0.56	0.016	0.022
	androstenediol (3β,17β) disulfate (2)	0.56	0.005	0.009
	dehydroepiandrosterone sulfate (DHEA-S)	0.60	0.002	0.005
Estrogenic Steroids	estriol-3-glucuronide	0.21	1.50×10^{-7}	7.84×10^{-6}
	estrone 3-sulfate	0.39	0.018	0.024
	estriol 3-sulfate	0.58	0.019	0.025

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Only metabolites with $p < 0.05$ are shown.

Supplementary Table 7. Increased secondary bile acid metabolism in neonates born with gastroschisis.

Subpathway	Biochemical	FC	p-value	q-value
Primary Bile Acid Metabolism	chenodeoxycholate	0.28	3.14×10^{-10}	1.15×10^{-7}
	cholate	0.56	0.028	0.032
	taurocholate	1.77	0.032	0.035
Secondary Bile Acid Metabolism	deoxycholate	0.34	6.52×10^{-10}	1.19×10^{-7}
	lithocholate sulfate (1)	0.44	0.016	0.022
	hyocholate	0.51	0.003	0.006
	taurocholenate sulfate*	2.26	0.0001	0.0008
	taurochenodeoxycholic acid 3-sulfate	2.59	0.005	0.010
	taurolithocholate 3-sulfate	3.25	0.026	0.030
	glycodeoxycholate 3-sulfate	3.54	0.014	0.020
	tauroursodeoxycholic acid sulfate (1)	4.22	1.47×10^{-5}	0.0002
	taurodeoxycholic acid 3-sulfate	4.38	0.0003	0.002
	taurohyocholate*	2.09	0.020	0.026

Fold change (FC) represents the ratio of mean metabolite levels in gastroschisis (n=23) relative to control (n=23). Statistical significance was assessed by Welch's two sample t test. Only metabolites with $p < 0.05$ are shown.