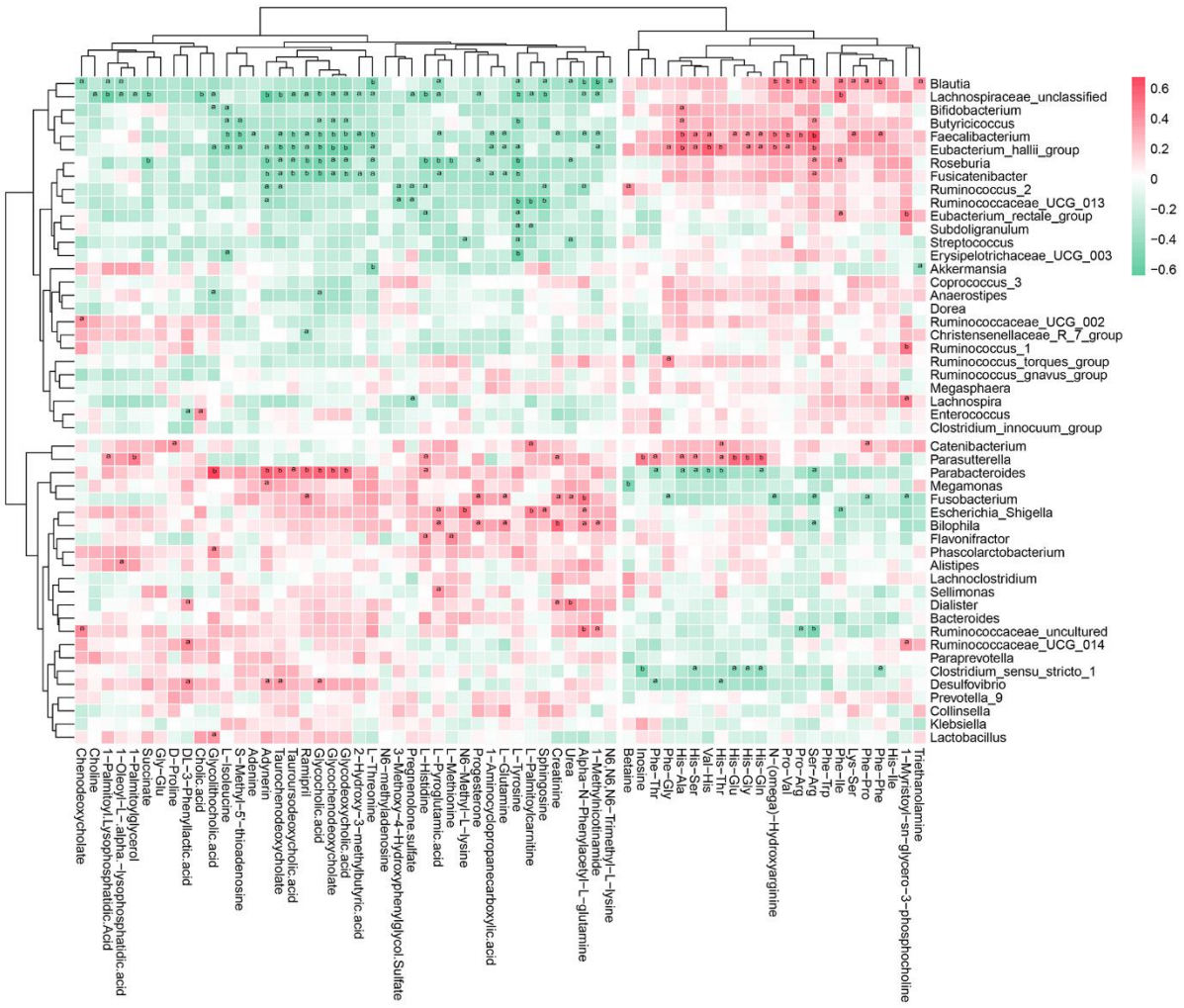

Supplementary Figure 1 Association of disease-associated microorganisms with serum metabolites. Genera with differences in abundance between the two cohorts are shown. The significance level in the correlation test is denoted as: [a]$P < 0.05$; [b]$P < 0.01$.

Supplementary Table 1 Differential metabolites analysis of annotated serum metabolites and its correlation with disease

	Intrahepatic cholestasis in pregnancy *n* = 15	**Control *n* = 15**	**Adjusted *P* value**
Tauroursodeoxycholic acid	22477.605 (12733.253-32816.589)	1927.485 (1691.909-3788.622)	< 0.001
Glycolithocholic acid	26643.090 (16476.478-51263.769)	5902.549 (4097.036-10898.884)	< 0.001
Taurochenodeoxycholate	2969140.429 (1682639.904-5527755.293)	243109.619 (118780.028-370386.914)	< 0.001
Cholic acid	14421.931 (9800.944-68635.304)	7668.923 (2777.915-12151.027)	0.010
Glycodeoxycholic acid	30781.583 (15457.858-117695.707)	231.844 (114.802-438.612)	< 0.001
Glycochenodeoxycholate	2591541.143 (1454359.676-4497883.490)	112805.978 (77717.401-183312.400)	< 0.001
Glycocholic acid	559664.294 (204136.678-1085277.721)	27890.062 (16941.687-33483.268)	< 0.001
Chenodeoxycholate	349409.161 (158490.740-832102.046)	123651.537 (72209.502-183537.520)	0.010

pregnenolone sulfate	35946.044 (19222.898-49521.593)	14016.685 (11025.204-15907.187)	0.004
Progesterone	59827.709 (46098.196-94573.900)	37502.630 (35670.916-46097.709)	0.010
L-Palmitoylcarnitine	326901.643 (266541.733-379253.780)	219583.471 (169704.341-292338.956)	0.015
Creatinine	5414228.176 (4570794.142-5930478.021)	4653400.515 (4357678.807-4797969.683)	0.026
1-Aminocyclopropanecarboxylic acid	592708.604 (521577.253-660833.367)	474369.711 (455544.125-503303.633)	0.002
1-Palmitoyl Lysophosphatidic Acid	191790.444 (94068.496-313187.036)	83677.289 (46312.226-127160.768)	0.021
3-Methoxy-4-Hydroxyphenylglycol Sulfate	177108.825 (139871.182-233831.651)	122162.678 (88085.709-149699.434)	0.019
2-Hydroxy-3-methylbutyric acid	158094.218 (123623.777-206506.408)	101230.348 (90624.616-121519.310)	< 0.001
DL-3-Phenyllactic acid	145821.926 (125562.984-168977.892)	93828.671 (61966.079-144522.978)	0.015
Alpha-N-Phenylacetyl-L-glutami	128172.845	80901.326	0.044

ne	(73036.017-233001.411)	(50533.833-115906.551)	
N6-methyladenosine	101950.307 (82347.867-121581.979)	74392.685 (60706.050-87875.688)	0.015
1-Methylnicotinamide	90874.716 (76155.166-125430.791)	50444.653 (43667.376-73592.671)	0.006
1-Myristoyl-sn-glycero-3-phosphocholine	33144.144 (27194.646-49278.607)	84000.146 (35760.634-184600.257)	0.033
Succinate	97859.669 (51332.118-108218.682)	50245.165 (41057.557-53978.674)	0.007
1-Oleoyl-L-alpha-lysophosphatidic acid	76114.468 (26669.376-112569.712)	29162.079 (13107.333-47325.234)	0.040
Triethanolamine	31233.696 (16187.346-63180.794)	45452.733 (39033.222-125750.748)	0.093
Ramipril	70539.999 (45105.225-123431.233)	7363.563 (4654.308-17134.847)	< 0.001
S-Methyl-5'-thioadenosine	44108.096 (27913.186-118804.153)	21616.470 (18145.077-26678.454)	0.001
N-(omega)-Hydroxyarginine	19777.968 (14944.349-27227.686	45854.777 (41937.796-57745.	< 0.001

	)	733)	
Inosine	70307.987 (19201.037-99673.564)	136768.797 (79684.176-180654 .636)	0.040
Adenine	15293.629 (12473.716-48846.621)	9637.667 (8188.517-12630.0 95)	0.003
Betaine	128888.276 (116952.546-132175.3 55)	136936.315 (129022.747-18399 8.770)	0.011
Choline	15123.277 (10912.966-31164.658)	12352.837 (9551.865-17461.8 13)	0.191
1-Palmitoylglycerol	13289.388 (4805.021-34481.688)	7578.283 (3654.816-12062.6 74)	0.178
L-Methionine	49324.460 (41205.361-66375.941)	44735.910 (39066.717-51280. 727)	0.165
L-Threonine	123060.673 (105041.799-156523.5 23)	93254.810 (74837.641-101501 .290)	0.006
L-Glutamine	78379.469 (65121.368-88325.826)	62786.725 (56745.452-64124. 796)	0.003
L-Pyroglutamic acid	1860663.854 (1538931.577-2030305 .894)	1452080.773 (1350066.479-1594 181.115)	0.001

L-Isoleucine	29776.217 (21462.214-35840.548)	24881.500 (18871.484-29463.826)	0.085
L-Histidine	120876.384 (73172.045-254466.645)	74310.962 (61480.294-119839.064)	0.093
D-Proline	1635176.751 (1462378.772-1824237.715)	1329868.223 (1247636.748-1519460.769)	0.014
L-Tyrosine	13493.397 (12850.743-18905.083)	11667.261 (10334.970-14295.930)	0.040
Phe-Trp	33193.477 (16324.395-55927.654)	51501.730 (39794.121-69522.440)	0.021
Phe-Phe	231900.614 (143351.735-316775.883)	351235.789 (276352.623-440308.621)	0.002
His-Ala	35289.654 (24341.724-58086.186)	136882.155 (69927.934-184748.883)	0.001
Pro-Arg	21572.802 (4293.983-31249.110)	38439.176 (26660.041-52088.151)	0.021
His-Glu	25938.319 (19109.535-84433.399)	91237.190 (53025.786-119746.505)	0.014
Ser-Arg	14824.055	42726.782	< 0.001

	(4372.323-20352.492)	(33891.038-50753.901)	
His-Ser	13393.900 (5480.676-19830.270)	30806.918 (19720.928-39633.751)	0.001
His-Gly	10735.595 (2581.050-15517.569)	26966.389 (12895.657-36950.933)	0.005
Gly-Glu	15849.502 (13367.588-21528.087)	12142.240 (11748.187-13942.127)	0.015
Pro-Val	11562.085 (8049.938-15305.958)	21811.566 (17210.352-24854.882)	< 0.001
Phe-Gly	10839.245 (7943.844-14102.700)	17976.239 (16262.757-25533.279)	0.001
Phe-Ile	6238.377 (4059.191-9771.795)	13462.959 (8755.378-15549.652)	0.004
His-Gln	3728.614 (1940.057-8455.860)	14159.497 (7451.600-16203.705)	0.003
Lys-Ser	8012.299 (4167.856-9780.888)	11888.746 (10320.987-12780.803)	0.001
Phe-Thr	6043.338 (3947.144-7479.277)	8482.377 (6748.438-12221.7	0.003

		25)	
Phe-Pro	2885.571 (2202.710-8075.118)	9449.538 (7862.950-11744.695)	0.003
His-Thr	4187.201 (2018.452-6159.390)	8282.267 (4917.421-14146.405)	0.014
Val-His	3410.827 (2017.414-4604.101)	7733.354 (5633.995-11438.477)	< 0.001
His-Ile	3156.066 (2519.919-4500.850)	6491.387 (5388.320-8053.968)	0.001
Sphingosine	8385.189 (5791.862-13241.595)	4788.472 (3721.125-7028.800)	0.015
N6,N6,N6-Trimethyl-L-lysine	16720.878 (9554.902-20299.138)	5495.942 (3985.231-7054.211)	0.002
N6-Methyl-L-lysine	12186.940 (9804.305-15978.844)	5508.398 (3635.118-8138.894)	0.001
Urea	773059.463 (621536.670-851692.852)	598045.271 (537712.124-680998.130)	0.015
Adynerin	226412.516 (78427.099-635660.297)	34631.575 (26761.270-51265.135)	< 0.001

Continuous data are presented as median and interquartile range in squared parenthses and were tested using the Mann-Whitney U test. $P < 0.05$ were considered statically significant. The adjusted P values was calculated by the "p.adjust ()" command in R using the "BH" method to control for the false discovery rate.

Supplementary Table 2 Comparison of α diversity of gut microbiota in intrahepatic cholestasis in pregnancy and control groups

	Control *n* = 15	**Intrahepatic cholestasis in pregnancy *n* = 15**	***P* value**
Reads	68889.000 (60850.500-71404.000)	61608.000 (60138.500-64631.000)	0.078
OTUs	271.000 (243.500-320.000)	287.000 (246.500-314.500)	0.983
Ace	307.000 (284.000-370.000)	341.000 (294.500-364.000)	0.724
Chao	321.000 (283.500-368.500)	359.000 (289.000-372.000)	0.678
Shannon	3.290 (3.060-3.545)	3.230 (2.685-3.525)	0.351
Simpson	0.077 (0.056-0.110)	0.090 (0.062-0.175)	0.310

Continuous data are presented as median and interquartile range in squared parenthses and were tested using the Mann-Whitney U test. $P < 0.05$ were considered statically significant.

Supplementary Table 3 Relative abundance of individual genus

	Intrahepatic cholestasis in pregnancy *n* = 15	**Control *n* = 15**	***P* value**	**Adjusted *P* value**
Bacteroides	0.25128 (0.07921-0.31905)	0.16785 (0.03012-0.25204)	0.25402	0.67346
Bifidobacterium	0.00680 (0.00103-0.07600)	0.08160 (0.05346-0.12671)	0.0649	0.33375
Blautia	0.02200 (0.00599-0.02739)	0.05567 (0.03392-0.10395)	0.00581	0.11131
Escherichia_Shigella	0.02505 (0.01026-0.05893)	0.00115 (0.00010-0.02070)	0.05368	0.32211
Akkermansia	0.00000 (0.00000-0.01663)	0.00008 (0.00000-0.00088)	0.74281	0.83566
Faecalibacterium	0.00348 (0.00102-0.00857)	0.05412 (0.02750-0.10532)	0.00618	0.11131
Prevotella_9	0.00000 (0.00000-0.02138)	0.00000 (0.00000-0.00002)	0.54836	0.75927
Streptococcus	0.00530 (0.00308-0.00994)	0.00816 (0.00442-0.02061)	0.17102	0.53537

Phascolarctobacterium	0.00146 (0.00031-0.02979)	0.00084 (0.00010-0.00712)	0.4927	0.7406
Erysipelotrichaceae_UCG_003	0.00225 (0.00131-0.01213)	0.01719 (0.00184-0.03648)	0.2899	0.67675
Eubacterium_rectale_group	0.00621 (0.00203-0.01148)	0.00746 (0.00344-0.02636)	0.4679	0.7406
Anaerostipes	0.00289 (0.00068-0.01246)	0.00897 (0.00169-0.02439)	0.3094	0.67675
Eubacterium_hallii_group	0.00247 (0.00037-0.00590)	0.02699 (0.00616-0.04605)	0.0015	0.10847
Dialister	0.00049 (0.00001-0.00964)	0.00002 (0.00000-0.00368)	0.3101	0.67675
Lachnospira	0.00039 (0.00001-0.00108)	0.00033 (0.00019-0.00153)	0.5465	0.75927
Megamonas	0.00000 (0.00000-0.00017)	0.00000 (0.00000-0.00000)	0.2988	0.67675
Lachnospiraceae_unclassified	0.00470 (0.00230-0.01073)	0.02103 (0.00945-0.02599)	0.0120	0.17414
Alistipes	0.00722	0.00509	0.6933	0.81843

	(0.00094-0.0198	(0.00091-0.0166	9	
	8)	4)		
Parabacteroides	0.00965	0.00309	0.0034	0.11131
	(0.00544-0.0178	(0.00063-0.0048	5	
	9)	3)		
Subdoligranulum	0.00614	0.01726	0.7078	0.82009
	(0.00202-0.0140	(0.00000-0.0220		
	2)	0)		
Dorea	0.00251	0.00437	0.2902	0.67675
	(0.00136-0.0081	(0.00178-0.0163		
	6)	6)		
Ruminococcaceae_UCG_014	0.00002	0.00000	0.4223	0.724
	(0.00001-0.0014	(0.00000-0.0145	3	
	3)	3)		
Ruminococcus_torques_group	0.00367	0.00598	0.4937	0.7406
	(0.00128-0.0116	(0.00249-0.0104	3	
	0)	1)		
Bilophila	0.00835	0.00144	0.0536	0.32211
	(0.00146-0.0157	(0.00032-0.0022	6	
	5)	0)		
Roseburia	0.00128	0.00849	0.0442	0.31862
	(0.00065-0.0040	(0.00169-0.0150	5	
	2)	2)		
Klebsiella	0.00010	0.00014	0.7175	0.82009
	(0.00000-0.0005	(0.00000-0.0041	8	
	3)	2)		
Ruminococcaceae_uncultured	0.00431	0.00101	0.2133	0.63997
	(0.00172-0.0082	(0.00053-0.0064	2	

	0)	4)		
Fusicatenibacter	0.00035 (0.00015-0.00168)	0.00608 (0.00103-0.01998)	0.0213	0.21913
Ruminococcus_gnavus_group	0.00159 (0.00035-0.01330)	0.00361 (0.00072-0.01104)	0.6782 3	0.81843
Clostridium_sensu_stricto_1	0.00035 (0.00009-0.00128)	0.00012 (0.00001-0.00062)	0.3807	0.70282
Lachnoclostridium	0.00198 (0.00055-0.00943)	0.00243 (0.00129-0.00684)	0.9834 5	0.98345
Ruminococcus_2	0.00029 (0.00000-0.00216)	0.00511 (0.00019-0.00945)	0.0885 8	0.34905
Clostridium_innocuum_group	0.00004 (0.00001-0.00039)	0.00012 (0.00002-0.00035)	0.6599 4	0.81843
Collinsella	0.00388 (0.00133-0.00838)	0.00351 (0.00000-0.01100)	0.8838 5	0.96071
Paraprevotella	0.00025 (0.00000-0.01225)	0.00008 (0.00000-0.00145)	0.5257 7	0.75927
Catenibacterium	0.00000 (0.00000-0.00000)	0.00000 (0.00000-0.00000)	0.9290 4	0.97753

Lactobacillus	0.00006 (0.00000-0.00117)	0.00004 (0.00000-0.00009)	0.3943	0.70975
Christensenellaceae_R_7_group	0.00027 (0.00000-0.00115)	0.00050 (0.00000-0.00429)	0.6420	0.81843
Parasutterella	0.00027 (0.00000-0.00466)	0.00074 (0.00000-0.00670)	0.6268	0.81843
Ruminococcaceae_UCG_002	0.00021 (0.00000-0.00692)	0.00043 (0.00010-0.00128)	0.6915	0.81843
Flavonifractor	0.00097 (0.00035-0.00194)	0.00043 (0.00011-0.00191)	0.5336	0.75927
Ruminococcaceae_UCG_013	0.00031 (0.00003-0.00115)	0.00235 (0.00028-0.00338)	0.0921	0.34905
Desulfovibrio	0.00000 (0.00000-0.00266)	0.00000 (0.00000-0.00005)	0.2394	0.67346
Ruminococcus_1	0.00014 (0.00000-0.00128)	0.00089 (0.00000-0.00504)	0.3309	0.70093
Butyricicoccus	0.00113 (0.00046-0.00172)	0.00287 (0.00100-0.00391)	0.0590	0.327
Sellimonas	0.00016	0.00002	0.6550	0.81843

	(0.00000-0.0021 5)	(0.00000-0.0021 4)	2	
Fusobacterium	0.00014 (0.00000-0.0005 5)	0.00000 (0.00000-0.0001 4)	0.0826 9	0.34905
Coprococcus_3	0.00045 (0.00002-0.0024 9)	0.00118 (0.00020-0.0040 1)	0.2619	0.67346
Romboutsia	0.00103 (0.00033-0.0030 7)	0.00134 (0.00011-0.0024 0)	0.6185 9	0.81843
Lachnospiraceae_uncultured	0.00045 (0.00021-0.0021 0)	0.00047 (0.00012-0.0017 2)	0.6628	0.81843
Hungatella	0.00039 (0.00018-0.0009 8)	0.00052 (0.00012-0.0013 6)	0.9503 7	0.97753
Sutterella	0.00045 (0.00000-0.0044 7)	0.00006 (0.00000-0.0004 9)	0.3750 4	0.70282
Eubacterium_eligens_group	0.00002 (0.00000-0.0000 6)	0.00019 (0.00007-0.0006 4)	0.0178 9	0.21463
Holdemanella	0.00000 (0.00000-0.0005 6)	0.00000 (0.00000-0.0000 0)	0.0907 1	0.34905
Barnesiella	0.00014 (0.00000-0.0012	0.00000 (0.00000-0.0007	0.4703 6	0.7406

	0)	6)		
Haemophilus	0.00002 (0.00000-0.00015)	0.00006 (0.00002-0.00018)	0.4491 3	0.7406
Coprococcus_2	0.00000 (0.00000-0.00020)	0.00000 (0.00000-0.00363)	0.4124 7	0.724
Prevotella_2	0.00000 (0.00000-0.00270)	0.00000 (0.00000-0.00000)	0.0359 2	0.28739
Eubacterium_ruminantium_group	0.00000 (0.00000-0.00008)	0.00000 (0.00000-0.00000)	0.1186 3	0.40673
Firmicutes_unclassified	0.00010 (0.00004-0.00063)	0.00070 (0.00029-0.00127)	0.0262	0.23577
Tyzzerella_4	0.00006 (0.00002-0.00049)	0.00010 (0.00000-0.00015)	0.4760 8	0.7406
Adlercreutzia	0.00002 (0.00000-0.00031)	0.00031 (0.00000-0.00163)	0.3522 5	0.70282
Mollicutes_RF9_norank	0.00000 (0.00000-0.00000)	0.00000 (0.00000-0.00000)	0.8354 3	0.9254
Prevotellaceae_NK3B31_group	0.00000 (0.00000-0.00000)	0.00000 (0.00000-0.00000)	0.1503 2	0.49197

Lactococcus	0.00000 (0.00000-0.00000)	0.00000 (0.00000-0.00000)	0.07312	0.34905
Ruminococcaceae_UCG_005	0.00000 (0.00000-0.00021)	0.00012 (0.00000-0.00069)	0.36346	0.70282
Lachnospiraceae_ND3007_group	0.00004 (0.00002-0.00012)	0.00010 (0.00002-0.00050)	0.2511	0.67346
Prevotella	0.00023 (0.00003-0.00048)	0.00000 (0.00000-0.00023)	0.09881	0.35571
Veillonella	0.00017 (0.00005-0.00030)	0.00008 (0.00004-0.00032)	0.96683	0.98045

Continuous data are presented as median and interquartile range in squared parenthses and were tested using the Mann-Whitney U test. $P < 0.05$ were considered statically significant. The adjusted *P* values was calculated by the "p.adjust ()" command in R using the "BH" method to control for the false discovery rate.