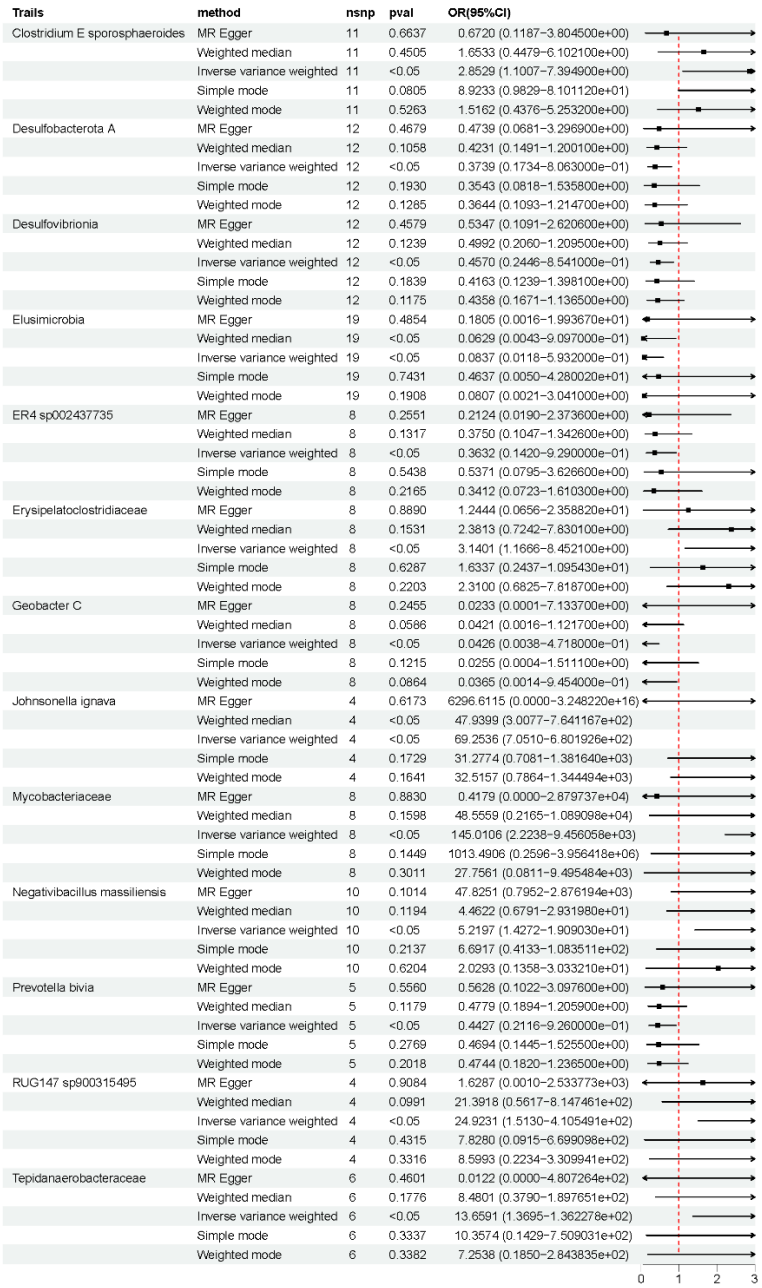

Figure S1 Forest plots for causal associations of bacterial features and inflammatory cytokines on BTC.

https://dx.doi.org/10.21037/hbsn-2024-750

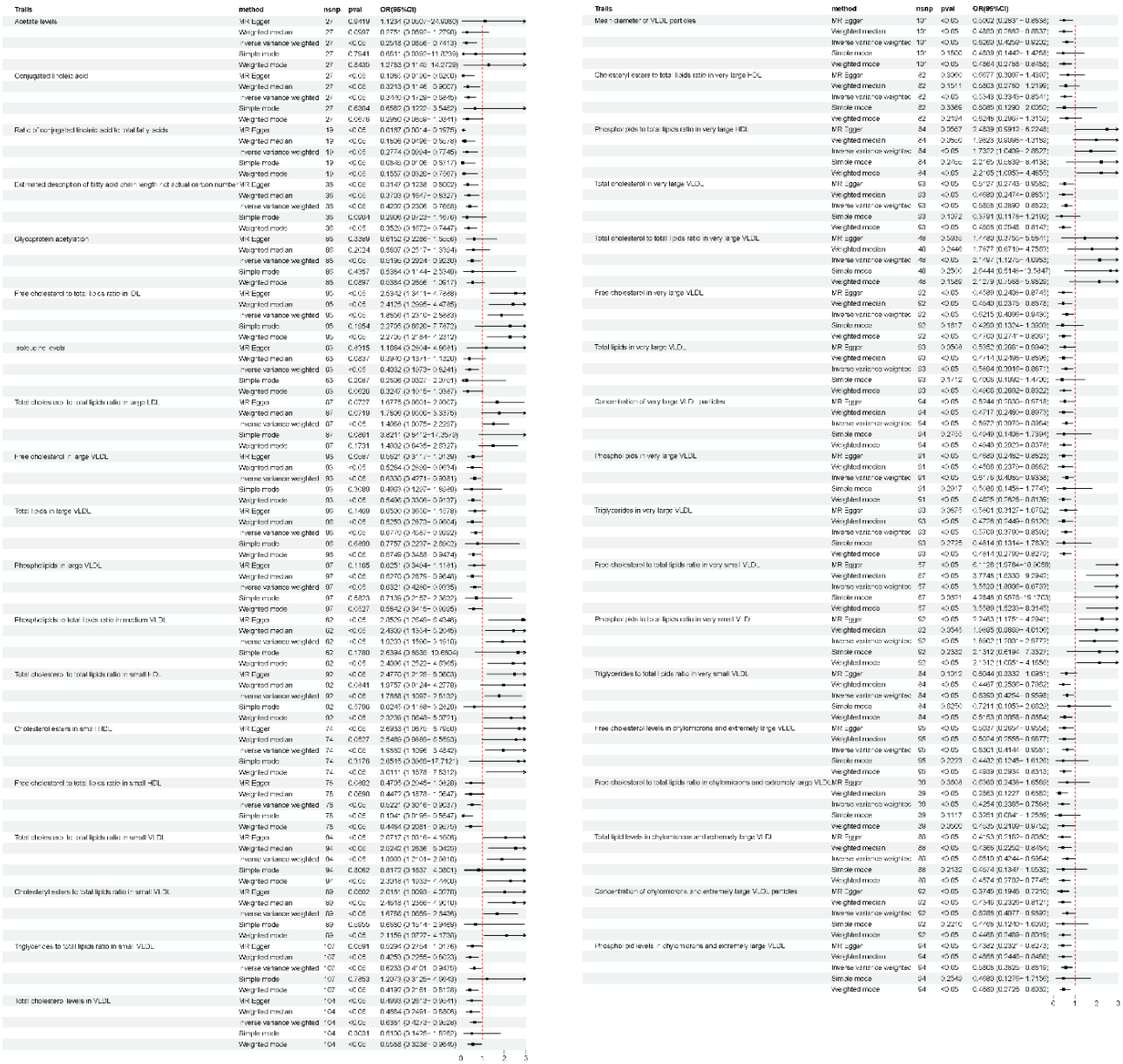

Figure S2 Forest plots for causal associations of circulating metabolites and inflammatory cytokines on BTC.

https://dx.doi.org/10.21037/hbsn-2024-750

Table S1 Associations of MR analysis between identified gut microbiomes and BTC

Outcome	Exposure id	Method	nSNP	Beta	SE	P value	Low_ci	Up_ci	OR	OR_lci95	OR_uci95
Biliary tract cancer	GCST90032322	MR Egger	11	−0.397571	0.884565	0.663733	−2.131317	1.336176	0.671951	0.1186809	3.80446763
		Weighted median	11	0.502759	0.666264	0.450493	−0.803118	1.808636	1.653276	0.4479299	6.10211833
		Inverse variance weighted	11	1.048352	0.48594	**0.030977**	0.09591	2.000795	2.852946	1.1006598	7.39492944
		Simple mode	11	2.188665	1.125471	0.080457	−0.017258	4.394588	8.92329	0.9828897	81.011225
		Weighted mode	11	0.416213	0.633997	0.526326	−0.82642	1.658846	1.516209	0.437613	5.25324702
	GCST90032340	MR Egger	12	−0.746669	0.989619	0.467944	−2.686321	1.192984	0.473943	0.0681311	3.29690429
		Weighted median	12	−0.860243	0.531948	0.105844	−1.90286	0.182374	0.423059	0.1491414	1.20006298
		Inverse variance weighted	12	−0.983669	0.392036	**0.012103**	−1.752059	−0.215279	0.373937	0.1734166	0.80631623
		Simple mode	12	−1.037512	0.748243	0.193023	−2.50407	0.429045	0.354335	0.0817516	1.53578979
		Weighted mode	12	−1.009377	0.614201	0.12855	−2.213212	0.194457	0.364446	0.1093489	1.21465185
	GCST90032343	MR Egger	12	−0.626136	0.810985	0.457931	−2.215665	0.963394	0.534654	0.1090809	2.62057555
		Weighted median	12	−0.694774	0.451534	0.123878	−1.579779	0.190232	0.499187	0.2060206	1.20953036
		Inverse variance weighted	12	−0.782968	0.319014	**0.014114**	−1.408236	−0.1577	0.457047	0.2445743	0.85410573
		Simple mode	12	−0.876454	0.618129	0.183917	−2.087987	0.335079	0.416256	0.1239364	1.39805142
		Weighted mode	12	−0.83053	0.489034	0.117523	−1.789037	0.127978	0.435818	0.1671211	1.13652747
	GCST90032353	MR Egger	19	−1.711903	2.400236	0.485384	−6.416366	2.99256	0.180522	0.0016346	19.9366577
		Weighted median	19	−2.766564	1.363222	0.042415	−5.438479	−0.094648	0.062878	0.0043461	0.90969274
		Inverse variance weighted	19	−2.481091	0.999423	**0.013046**	−4.43996	−0.522222	0.083652	0.0117964	0.59320101
		Simple mode	19	−0.768448	2.308669	0.743091	−5.293439	3.756543	0.463732	0.0050245	42.8002143
		Weighted mode	19	−2.517203	1.851725	0.190813	−6.146583	1.112178	0.080685	0.0021408	3.04097299
	GCST90032366	MR Egger	8	−1.549197	1.23144	0.25512	−3.962819	0.864426	0.212419	0.0190094	2.37364257
		Weighted median	8	−0.98088	0.650767	0.131742	−2.256384	0.294623	0.374981	0.1047285	1.34262036
		Inverse variance weighted	8	−1.012885	0.479214	**0.034546**	−1.952143	−0.073626	0.36317	0.1419695	0.92901917
		Simple mode	8	−0.621603	0.974442	0.54383	−2.531508	1.288303	0.537083	0.0795389	3.62662829
		Weighted mode	8	−1.075344	0.791705	0.216529	−2.627086	0.476398	0.34118	0.0722888	1.6102631
	GCST90032368	MR Egger	8	0.218644	1.501072	0.888961	−2.723456	3.160745	1.244389	0.0656475	23.5881615
		Weighted median	8	0.867664	0.607303	0.153086	−0.32265	2.057977	2.38134	0.7242273	7.83011289
		Inverse variance weighted	8	1.14427	0.505177	**0.023507**	0.154123	2.134418	3.140149	1.1666338	8.4521257
		Simple mode	8	0.490863	0.970853	0.628666	−1.412008	2.393734	1.633726	0.2436536	10.9543249
		Weighted mode	8	0.837228	0.622088	0.220312	−0.382065	2.05652	2.309955	0.682451	7.81871507
	GCST90032417	MR Egger	8	−3.758414	2.920019	0.245473	−9.481651	1.964824	0.023321	7.62E−05	7.13366023
		Weighted median	8	−3.166625	1.674209	0.058569	−6.448075	0.114824	0.042146	0.0015836	1.12167631
		Inverse variance weighted	8	−3.155545	1.22668	**0.010099**	−5.559837	−0.751252	0.042615	0.0038494	0.47177559
		Simple mode	8	−3.667783	2.081961	0.121501	−7.748426	0.412861	0.025533	0.0004314	1.51113467
		Weighted mode	8	−3.310875	1.660599	0.086408	−6.565649	−0.056102	0.036484	0.0014079	0.94544296
	GCST90032438	MR Egger	4	8.747767	14.93454	0.617342	−20.52393	38.01947	6296.611	1.22E−09	3.2482E+16
		Weighted median	4	3.869949	1.412638	0.006153	1.101178	6.63872	47.93994	3.007706	764.116662
		Inverse variance weighted	4	4.237775	1.165613	**0.000277**	1.953175	6.522376	69.25362	7.0510384	680.192641
		Simple mode	4	3.442895	1.93272	0.172879	−0.345237	7.231027	31.27737	0.7080525	1381.64021
		Weighted mode	4	3.481724	1.899004	0.164105	−0.240325	7.203773	32.51573	0.7863724	1344.49347
	GCST90032484	MR Egger	8	−0.872417	5.683907	0.883045	−12.01287	10.26804	0.41794	6.07E−06	28797.3747
		Weighted median	8	3.882716	2.761722	0.159753	−1.530259	9.29569	48.55591	0.2164797	10890.9821
		Inverse variance weighted	8	4.976807	2.131431	**0.019545**	0.799202	9.154411	145.0106	2.2237664	9456.05786
		Simple mode	8	6.921156	4.219232	0.144932	−1.348538	15.19085	1013.491	0.2596195	3956418.13
		Weighted mode	8	3.323457	2.977099	0.301125	−2.511658	9.158572	27.75613	0.0811336	9495.48445
	GCST90032488	MR Egger	10	3.867551	2.090139	0.101417	−0.22912	7.964223	47.82513	0.7952327	2876.1937
		Weighted median	10	1.495635	0.960525	0.119446	−0.386994	3.378264	4.462169	0.679095	29.3198408
		Inverse variance weighted	10	1.652448	0.661597	**0.012501**	0.355718	2.949178	5.219742	1.4272043	19.0902613
		Simple mode	10	1.900865	1.420669	0.213716	−0.883646	4.685377	6.691682	0.4132734	108.351065
		Weighted mode	10	0.707677	1.379862	0.620399	−1.996853	3.412207	2.029272	0.1357619	30.3321268
	GCST90032514	MR Egger	5	−0.574891	0.870162	0.556025	−2.280409	1.130627	0.562766	0.1022423	3.09759777
		Weighted median	5	−0.738335	0.472228	0.117931	−1.663901	0.187231	0.477909	0.1893986	1.20590541
		Inverse variance weighted	5	−0.814958	0.376545	**0.030441**	−1.552986	−0.07693	0.442658	0.2116151	0.92595438
		Simple mode	5	−0.756239	0.601314	0.276936	−1.934814	0.422336	0.469429	0.1444512	1.52552068
		Weighted mode	5	−0.745673	0.488772	0.201804	−1.703666	0.212321	0.474415	0.182015	1.23654506
	GCST90032543	MR Egger	4	0.487801	3.749828	0.908402	−6.861863	7.837465	1.628731	0.001047	2533.77264
		Weighted median	4	3.06301	1.857075	0.099071	−0.576857	6.702877	21.39184	0.5616607	814.746118
		Inverse variance weighted	4	3.215795	1.429439	**0.024469**	0.414094	6.017495	24.92309	1.5129991	410.549074
		Simple mode	4	2.057702	2.270123	0.43153	−2.391738	6.507143	7.827964	0.0914706	669.909762
		Weighted mode	4	2.151679	1.86246	0.331634	−1.498742	5.8021	8.599287	0.2234111	330.994082
	GCST90032576	MR Egger	6	−4.40899	5.400147	0.460071	−14.99328	6.175298	0.012167	3.08E−07	480.726384
		Weighted median	6	2.137718	1.585749	0.177632	−0.97035	5.245787	8.480068	0.3789504	189.765071
		Inverse variance weighted	6	2.614403	1.173432	**0.025881**	0.314477	4.914328	13.65906	1.3695427	136.227794
		Simple mode	6	2.337705	2.185496	0.333675	−1.945867	6.621277	10.35744	0.1428634	750.903104
		Weighted mode	6	1.981519	1.871839	0.338222	−1.687285	5.650324	7.253754	0.1850211	284.383512

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Table S2 Associations of MR analysis between identified circulating metabolites and BTC

Outcome	Exposure id	Method	nSNP	Beta	SE	P value	Low_ci	Up_ci	OR	OR_lci95	OR_uci95
Biliary tract cancer	GCST90301941	MR Egger	27	0.116396	1.581016	0.941898	−2.982396	3.215188	1.1234405	0.05067126	24.90797
		Weighted median	27	−1.290666	0.784067	0.09974	−2.827436	0.246105	0.2750876	0.05916434	1.279033
		Inverse variance weighted	27	−1.37898	0.5508	**0.012294**	−2.458547	−0.299413	0.2518352	0.08555916	0.741253
		Simple mode	27	−0.383996	1.456184	0.79409	−3.238117	2.470124	0.6811339	0.03923772	11.82391
		Weighted mode	27	0.24553	1.231037	0.843463	−2.167302	2.658363	1.2782988	0.11448605	14.2729
	GCST90301950	MR Egger	27	−2.220963	0.889218	0.019445	−3.963829	−0.478096	0.1085046	0.01899025	0.619963
		Weighted median	27	−1.135359	0.525925	0.030867	−2.166173	−0.104545	0.3213067	0.11461539	0.900734
		Inverse variance weighted	27	−1.067169	0.351048	**0.002366**	−1.755223	−0.379114	0.343981	0.17286861	0.684468
		Simple mode	27	−0.418273	0.859117	0.630434	−2.102142	1.265597	0.6581828	0.12219443	3.545208
		Weighted mode	27	−1.210549	0.634738	0.067605	−2.454635	0.033537	0.2980335	0.08589451	1.034105
	GCST90301951	MR Egger	19	−4.092319	1.260247	0.00474	−6.562403	−1.622234	0.0167005	0.00141249	0.197457
		Weighted median	19	−1.711421	0.659471	0.009455	−3.003984	−0.418858	0.180609	0.04958912	0.657798
		Inverse variance weighted	19	−1.282146	0.523796	**0.014373**	−2.308785	−0.255507	0.2774413	0.09938192	0.774524
		Simple mode	19	−2.471307	1.057811	0.031243	−4.544617	−0.397998	0.0844743	0.01062424	0.671663
		Weighted mode	19	−1.85963	0.80658	0.033251	−3.440526	−0.278733	0.1557303	0.03204783	0.756742
	GCST90301958	MR Egger	36	−1.156163	0.476128	0.020613	−2.089375	−0.222952	0.3146912	0.12376453	0.800153
		Weighted median	36	−0.993425	0.413451	0.016272	−1.80379	−0.18306	0.3703061	0.16467358	0.832718
		Inverse variance weighted	36	−0.866985	0.306181	**0.004632**	−1.4671	−0.266869	0.4202168	0.23059324	0.765773
		Simple mode	36	−1.23597	0.70967	0.09036	−2.626923	0.154983	0.2905528	0.07230056	1.167638
		Weighted mode	36	−1.041664	0.381036	0.009755	−1.788494	−0.294833	0.3528671	0.16721178	0.744656
	GCST90301968	MR Egger	86	−0.485786	0.505069	0.338901	−1.475722	0.50415	0.6152136	0.22861367	1.655578
		Weighted median	86	−0.543554	0.426425	0.202424	−1.379346	0.292239	0.5806811	0.25174313	1.339423
		Inverse variance weighted	86	−0.654932	0.293288	**0.025545**	−1.229777	−0.080087	0.5194775	0.29235783	0.923036
		Simple mode	86	−0.619088	0.790433	0.435671	−2.168336	0.93016	0.5384353	0.11436777	2.534915
		Weighted mode	86	−0.619088	0.360616	0.089667	−1.325896	0.08772	0.5384353	0.26556488	1.091683
	GCST90301980	MR Egger	95	0.929873	0.324697	0.005173	0.293467	1.566278	2.5341862	1.3410694	4.78879
		Weighted median	95	0.880645	0.315634	0.005269	0.262003	1.499288	2.4124559	1.29953035	4.478497
		Inverse variance weighted	95	0.634231	0.217569	**0.003556**	0.207795	1.060666	1.885571	1.23096071	2.888295
		Simple mode	95	0.819998	0.628819	0.195408	−0.412486	2.052483	2.2704963	0.66200255	7.787211
		Weighted mode	95	0.819998	0.317596	0.011371	0.197511	1.442486	2.2704963	1.21836676	4.2312
	GCST90301987	MR Egger	63	0.1556	0.728115	0.831491	−1.271506	1.582707	1.1683592	0.28040906	4.868114
		Weighted median	63	−0.931486	0.53851	0.083675	−1.986965	0.123993	0.3939679	0.13711097	1.132008
		Inverse variance weighted	63	−0.908335	0.364757	**0.012765**	−1.623258	−0.193411	0.4031951	0.19725491	0.824143
		Simple mode	63	−1.344708	1.058529	0.208704	−3.419424	0.730008	0.2606157	0.03273128	2.075097
		Weighted mode	63	−1.124967	0.593327	0.062618	−2.287888	0.037954	0.3246632	0.10148056	1.038683
	GCST90302008	MR Egger	87	0.517281	0.284677	0.072729	−0.040686	1.075247	1.6774602	0.96013104	2.930717
		Weighted median	87	0.576972	0.320539	0.07186	−0.051284	1.205229	1.7806388	0.95000843	3.337523
		Inverse variance weighted	87	0.404675	0.202645	**0.045829**	0.007491	0.80186	1.4988159	1.00751908	2.229684
		Simple mode	87	1.340532	0.772202	0.086148	−0.172984	2.854048	3.8210757	0.84115113	17.3579
		Weighted mode	87	0.39888	0.290374	0.173112	−0.170252	0.968013	1.4901554	0.84345202	2.632708
	GCST90302023	MR Egger	93	−0.575996	0.30091	0.058739	−1.165779	0.013787	0.5621447	0.31167969	1.013883
		Weighted median	93	−0.637813	0.306397	0.037374	−1.23835	−0.037276	0.5284468	0.28986202	0.96341
		Inverse variance weighted	93	−0.457275	0.200711	**0.02271**	−0.850668	−0.063881	0.6330065	0.42712934	0.938117
		Simple mode	93	−0.700526	0.684593	0.308862	−2.042327	0.641276	0.4963243	0.12972644	1.898902
		Weighted mode	93	−0.5985	0.259317	0.023241	−1.106762	−0.090239	0.5496353	0.33062791	0.913713
	GCST90302025	MR Egger	96	−0.430708	0.294498	0.146936	−1.007924	0.146508	0.6500489	0.36497598	1.157785
		Weighted median	96	−0.643789	0.307874	0.036521	−1.247221	−0.040356	0.5252985	0.28730215	0.960447
		Inverse variance weighted	96	−0.390035	0.198601	**0.04954**	−0.779293	−0.000778	0.6770329	0.45873038	0.999222
		Simple mode	96	−0.253942	0.634475	0.689879	−1.497513	0.98963	0.775737	0.22368571	2.690238
		Weighted mode	96	−0.55359	0.25487	0.032341	−1.053136	−0.054044	0.5748823	0.34884217	0.94739
	GCST90302027	MR Egger	97	−0.469919	0.296689	0.116545	−1.05143	0.111591	0.6250526	0.34943765	1.118056
		Weighted median	97	−0.640505	0.308521	0.037889	−1.245206	−0.035804	0.5270262	0.28788172	0.964829
		Inverse variance weighted	97	−0.458675	0.198913	**0.021116**	−0.848544	−0.068806	0.6321205	0.4280375	0.933508
		Simple mode	97	−0.337049	0.610737	0.582318	−1.534094	0.859996	0.7138738	0.21565103	2.363151
		Weighted mode	97	−0.537439	0.273941	0.052672	−1.074363	−0.000515	0.5842425	0.34151532	0.999485
	GCST90302066	MR Egger	62	1.048336	0.414977	0.014185	0.234981	1.86169	2.8528995	1.26488502	6.434605
		Weighted median	62	0.888251	0.388404	0.0222	0.126979	1.649524	2.4308755	1.13539306	5.204502
		Inverse variance weighted	62	0.654049	0.25843	**0.011378**	0.147526	1.160573	1.9233131	1.15896351	3.19176
		Simple mode	62	0.970557	0.712236	0.17799	−0.425427	2.36654	2.6394131	0.65349075	10.66044
		Weighted mode	62	0.879447	0.333936	0.010692	0.224933	1.533962	2.4095678	1.25223896	4.636509
	GCST90302080	MR Egger	92	0.907053	0.364476	0.014663	0.19268	1.621427	2.4770124	1.21249416	5.060305
		Weighted median	92	0.680906	0.394147	0.08407	−0.091623	1.453435	1.9756667	0.91244925	4.277782
		Inverse variance weighted	92	0.569182	0.23731	**0.016464**	0.104054	1.034309	1.7668204	1.10966024	2.813162
		Simple mode	92	−0.470736	0.846672	0.579586	−2.130213	1.188741	0.6245424	0.11881195	3.282946
		Weighted mode	92	0.843245	0.398215	0.036939	0.062745	1.623746	2.3238965	1.06475497	5.072054
	GCST90302081	MR Egger	74	0.990761	0.472156	0.039381	0.065335	1.916187	2.6932836	1.06751653	6.795002
		Weighted median	74	0.934884	0.482654	0.05275	−0.011118	1.880887	2.5469186	0.98894337	6.559318

Table S2 (*continued*)

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Table S2 (*continued*)

Outcome	Exposure id	Method	nSNP	Beta	SE	P value	Low_ci	Up_ci	OR	OR_lci95	OR_uci95
		Inverse variance weighted	74	0.676124	0.2919	**0.020542**	0.104001	1.248247	1.9662421	1.10960163	3.484231
		Simple mode	74	0.975118	0.968944	0.317561	−0.924012	2.874248	2.6514795	0.39692325	17.7121
		Weighted mode	74	1.102297	0.48766	0.02678	0.146483	2.05811	3.0110731	1.15775552	7.831154
	GCST90302084	MR Egger	78	−0.75388	0.425212	0.080243	−1.587295	0.079535	0.4705372	0.20447797	1.082783
		Weighted median	78	−0.804848	0.442606	0.068999	−1.672355	0.06266	0.4471561	0.18780426	1.064665
		Inverse variance weighted	78	−0.649958	0.279937	**0.020244**	−1.198633	−0.101282	0.5220679	0.30160618	0.903678
		Simple mode	78	−2.262226	0.853521	0.009752	−3.935127	−0.589326	0.1041184	0.01954322	0.554701
		Weighted mode	78	−0.806456	0.389318	0.041666	−1.569519	−0.043392	0.4464376	0.20814523	0.957536
	GCST90302105	MR Egger	94	0.728382	0.355755	0.043468	0.031102	1.425662	2.0717267	1.03159117	4.160613
		Weighted median	94	0.925921	0.353047	0.008725	0.233949	1.617893	2.5241927	1.26358047	5.042456
		Inverse variance weighted	94	0.641486	0.229991	**0.005284**	0.190703	1.092269	1.8993009	1.21009955	2.981031
		Simple mode	94	−0.201831	0.820378	0.806208	−1.809772	1.40611	0.8172331	0.1636914	4.080055
		Weighted mode	94	0.833705	0.335182	0.014653	0.176749	1.490662	2.3018318	1.19333118	4.440033
	GCST90302107	MR Egger	89	0.701145	0.352997	0.050152	0.009271	1.393019	2.0160602	1.0093141	4.026991
		Weighted median	89	0.900881	0.351301	0.010335	0.212332	1.589431	2.4617721	1.23655815	4.90096
		Inverse variance weighted	89	0.517977	0.231716	**0.025392**	0.063813	0.972141	1.6786284	1.06589329	2.643598
		Simple mode	89	−0.403506	0.757271	0.595486	−1.887756	1.080745	0.6679743	0.15141112	2.946875
		Weighted mode	89	0.749495	0.346601	0.033299	0.070157	1.428834	2.115932	1.07267658	4.173829
	GCST90302115	MR Egger	107	−0.636095	0.333415	0.059146	−1.289588	0.017398	0.5293556	0.27538433	1.01755
		Weighted median	107	−0.854922	0.323802	0.008284	−1.489574	−0.22027	0.4253162	0.2254686	0.802302
		Inverse variance weighted	107	−0.472705	0.213639	**0.026922**	−0.891437	−0.053974	0.6233138	0.41006619	0.947457
		Simple mode	107	0.188354	0.689583	0.785276	−1.16323	1.539937	1.2072608	0.3124754	4.664299
		Weighted mode	107	−0.869525	0.337894	0.011454	−1.531797	−0.207254	0.4191504	0.21614695	0.812813
	GCST90302123	MR Egger	104	−0.694509	0.330361	0.037992	−1.342018	−0.047001	0.4993193	0.26131788	0.954086
		Weighted median	104	−0.758462	0.322086	0.018531	−1.389751	−0.127173	0.4683863	0.24913729	0.880582
		Inverse variance weighted	104	−0.449331	0.204566	**0.028056**	−0.850281	−0.048381	0.638055	0.42729484	0.952771
		Simple mode	104	−0.673347	0.650532	0.30306	−1.94839	0.601696	0.5099987	0.14250328	1.825212
		Weighted mode	104	−0.581906	0.278451	0.039099	−1.12767	−0.036142	0.5588321	0.32378672	0.964503
	GCST90302124	MR Egger	101	−0.692717	0.29039	0.01896	−1.261881	−0.123552	0.5002152	0.28312085	0.883775
		Weighted median	101	−0.723637	0.306118	0.018083	−1.323628	−0.123646	0.4849852	0.26616783	0.883693
		Inverse variance weighted	101	−0.468331	0.196516	**0.017164**	−0.853503	−0.083159	0.6260462	0.42592034	0.920205
		Simple mode	101	−0.789857	0.585058	0.180048	−1.93657	0.356857	0.4539098	0.14419764	1.428832
		Weighted mode	101	−0.720644	0.284064	0.01273	−1.277411	−0.163878	0.4864387	0.27875817	0.848846
	GCST90302129	MR Egger	82	−0.403862	0.391993	0.305984	−1.172168	0.364444	0.6677363	0.30969492	1.439713
		Weighted median	82	−0.544281	0.379088	0.15107	−1.287293	0.198731	0.5802591	0.27601705	1.219854
		Inverse variance weighted	82	−0.626785	0.239318	**0.008817**	−1.095848	−0.157723	0.5343066	0.33425603	0.854086
		Simple mode	82	−0.676257	0.700003	0.336881	−2.048263	0.695748	0.5085166	0.12895876	2.005208
		Weighted mode	82	−0.470275	0.379989	0.21944	−1.215054	0.274504	0.6248304	0.29669404	1.315878
	GCST90302135	MR Egger	84	0.909847	0.468724	0.05568	−0.008851	1.828546	2.4839431	0.99118765	6.224829
		Weighted median	84	0.684259	0.397319	0.085035	−0.094487	1.463004	1.9823017	0.90983938	4.318916
		Inverse variance weighted	84	0.549412	0.259858	**0.034491**	0.040091	1.058733	1.732234	1.04090509	2.882717
		Simple mode	84	0.795941	0.68058	0.245548	−0.537996	2.129879	2.2165261	0.58391711	8.413845
		Weighted mode	84	0.795941	0.359645	0.029633	0.091038	1.500845	2.2165261	1.09531011	4.485477
	GCST90302138	MR Egger	93	−0.668124	0.319085	0.039052	−1.293529	−0.042718	0.5126696	0.27430096	0.958182
		Weighted median	93	−0.759351	0.325154	0.019525	−1.396654	−0.122049	0.46797	0.24742355	0.885105
		Inverse variance weighted	93	−0.53473	0.208924	**0.010484**	−0.944222	−0.125239	0.5858274	0.38898217	0.882286
		Simple mode	93	−0.969935	0.596257	0.10722	−2.138599	0.19873	0.3791078	0.11781979	1.219852
		Weighted mode	93	−0.786155	0.29651	0.00944	−1.367314	−0.204996	0.4555933	0.25479038	0.814651
	GCST90302139	MR Egger	48	0.370192	0.688634	0.593462	−0.979531	1.719915	1.4480129	0.37548715	5.584056
		Weighted median	48	0.580922	0.49926	0.2446	−0.397628	1.559471	1.787685	0.67191178	4.756306
		Inverse variance weighted	48	0.765312	0.329218	**0.020092**	0.120044	1.41058	2.1496651	1.12754676	4.098331
		Simple mode	48	0.972435	0.834953	0.250035	−0.664072	2.608943	2.6443766	0.51475109	13.58468
		Weighted mode	48	0.755124	0.527441	0.158853	−0.27866	1.788908	2.1278752	0.75679728	5.982914
	GCST90302142	MR Egger	92	−0.778944	0.329017	0.020051	−1.423816	−0.134071	0.4588905	0.24079331	0.874528
		Weighted median	92	−0.7896	0.33051	0.016893	−1.4374	−0.1418	0.4540264	0.23754459	0.867795
		Inverse variance weighted	92	−0.475662	0.212768	**0.025378**	−0.892686	−0.058637	0.6214736	0.40955407	0.943049
		Simple mode	92	−0.846279	0.599908	0.161748	−2.022099	0.329541	0.4290084	0.1323773	1.39033
		Weighted mode	92	−0.754919	0.275168	0.007322	−1.294249	−0.215589	0.4700487	0.27410356	0.806067
	GCST90302144	MR Egger	93	−0.625196	0.315912	0.050837	−1.244383	−0.006008	0.5351566	0.28811851	0.99401
		Weighted median	93	−0.752116	0.324044	0.020285	−1.387242	−0.116991	0.471368	0.2497633	0.889593
		Inverse variance weighted	93	−0.528696	0.208603	**0.011262**	−0.937559	−0.119834	0.5893729	0.39158265	0.887068
		Simple mode	93	−0.914882	0.663333	0.171171	−2.215016	0.385251	0.4005637	0.10915178	1.469983
		Weighted mode	93	−0.712212	0.269645	0.009704	−1.240716	−0.183708	0.4905579	0.28917721	0.832178
	GCST90302145	MR Egger	94	−0.645434	0.314691	0.04311	−1.262228	−0.028639	0.524435	0.28302262	0.971767
		Weighted median	94	−0.751339	0.328022	0.021991	−1.394262	−0.108417	0.4717343	0.24801611	0.897253
		Inverse variance weighted	94	−0.515555	0.208359	**0.013348**	−0.923939	−0.107171	0.5971692	0.39695235	0.898372

Table S2 (*continued*)

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Table S2 (*continued*)

Outcome	Exposure id	Method	nSNP	Beta	SE	P value	Low_ci	Up_ci	OR	OR_lci95	OR_uci95
		Simple mode	94	−0.703477	0.641331	0.275516	−1.960485	0.553531	0.4948618	0.14079018	1.739384
		Weighted mode	94	−0.703477	0.268601	0.010296	−1.229934	−0.177019	0.4948618	0.29231181	0.837764
	GCST90302146	MR Egger	91	−0.759307	0.323524	0.021145	−1.393414	−0.125199	0.4679907	0.24822639	0.882321
		Weighted median	91	−0.777295	0.33607	0.020728	−1.435994	−0.118597	0.4596475	0.23787891	0.888165
		Inverse variance weighted	91	−0.481847	0.210887	**0.022321**	−0.895186	−0.068507	0.6176416	0.40853148	0.933786
		Simple mode	91	−0.676187	0.637543	0.291704	−1.925772	0.573398	0.5085525	0.14576322	1.774286
		Weighted mode	91	−0.771117	0.288347	0.008894	−1.336276	−0.205958	0.4624961	0.26282248	0.813867
	GCST90302148	MR Egger	93	−0.544601	0.315311	0.087527	−1.162611	0.073409	0.5800731	0.31266861	1.076171
		Weighted median	93	−0.749502	0.335395	0.025438	−1.406875	−0.092128	0.472602	0.24490735	0.911989
		Inverse variance weighted	93	−0.560559	0.208967	**0.007307**	−0.970135	−0.150983	0.5708898	0.37903177	0.859863
		Simple mode	93	−0.731123	0.662324	0.272527	−2.029278	0.567033	0.4813683	0.13143034	1.763029
		Weighted mode	93	−0.731123	0.276675	0.009672	−1.273406	−0.188839	0.4813683	0.27987679	0.827919
	GCST90302155	MR Egger	57	1.810356	0.576073	0.002697	0.681253	2.93946	6.1126259	1.97635261	18.90563
		Weighted median	57	1.3283	0.459738	0.003862	0.427213	2.229387	3.7746207	1.53297941	9.294163
		Inverse variance weighted	57	1.267497	0.321746	**8.17E−05**	0.636875	1.898119	3.5519502	1.89056332	6.673329
		Simple mode	57	1.455035	0.764452	0.062137	−0.04329	2.953361	4.2846344	0.9576334	19.17027
		Weighted mode	57	1.269445	0.432938	0.004868	0.420887	2.118003	3.5588784	1.52331287	8.31452
	GCST90302159	MR Egger	92	0.809282	0.330587	0.016305	0.161331	1.457233	2.2462943	1.1750734	4.294062
		Weighted median	92	0.687893	0.357683	0.054456	−0.013167	1.388952	1.9895189	0.98691955	4.010646
		Inverse variance weighted	92	0.636686	0.231785	**0.006016**	0.182387	1.090985	1.8902064	1.20007913	2.977204
		Simple mode	92	0.756674	0.630443	0.233167	−0.478994	1.992343	2.1311767	0.61940605	7.332692
		Weighted mode	92	0.756674	0.344373	0.030542	0.081704	1.431644	2.1311767	1.0851346	4.185577
	GCST90302161	MR Egger	84	−0.503557	0.303739	0.101166	−1.098885	0.091771	0.6043769	0.33324238	1.096114
		Weighted median	84	−0.805857	0.294846	0.006273	−1.383754	−0.227959	0.4467051	0.25063594	0.796157
		Inverse variance weighted	84	−0.447894	0.207574	**0.030947**	−0.854739	−0.041048	0.6389726	0.42539411	0.959783
		Simple mode	84	−0.326993	0.666534	0.625013	−1.633399	0.979414	0.7210889	0.19526465	2.662895
		Weighted mode	84	−0.662937	0.266247	0.014772	−1.184782	−0.141093	0.5153354	0.30581295	0.868409
	GCST90302166	MR Egger	95	−0.685874	0.326853	0.038579	−1.326505	−0.045242	0.50365	0.26540329	0.955766
		Weighted median	95	−0.68839	0.344916	0.045953	−1.364425	−0.012356	0.5023841	0.25552759	0.98772
		Inverse variance weighted	95	−0.461829	0.213773	**0.030744**	−0.880823	−0.042834	0.6301301	0.41444148	0.95807
		Simple mode	95	−0.802614	0.653303	0.222308	−2.083088	0.47786	0.4481559	0.12454498	1.61262
		Weighted mode	95	−0.705492	0.265668	0.009301	−1.226201	−0.184782	0.4938657	0.29340521	0.831285
	GCST90302167	MR Egger	39	−0.45259	0.489149	0.360827	−1.411323	0.506143	0.6359791	0.24382061	1.658881
		Weighted median	39	−1.250749	0.432446	0.003825	−2.098342	−0.403155	0.2862904	0.12265961	0.668208
		Inverse variance weighted	39	−0.854747	0.295256	**0.003792**	−1.433449	−0.276045	0.4253908	0.23848495	0.758779
		Simple mode	39	−1.123731	0.689988	0.111656	−2.476107	0.228646	0.3250649	0.08406991	1.256896
		Weighted mode	39	−0.790763	0.390658	0.050023	−1.556454	−0.025073	0.4534985	0.21088262	0.975239
	GCST90302168	MR Egger	88	−0.869126	0.333387	0.010767	−1.522564	−0.215689	0.4193177	0.21815181	0.805986
		Weighted median	88	−0.828852	0.337817	0.014145	−1.490972	−0.166731	0.4365503	0.22515371	0.846427
		Inverse variance weighted	88	−0.429311	0.218207	**0.049132**	−0.856997	−0.001625	0.6509575	0.42443489	0.998376
		Simple mode	88	−0.782117	0.623675	0.213184	−2.004519	0.440285	0.4574367	0.13472507	1.553151
		Weighted mode	88	−0.782117	0.268675	0.004575	−1.30872	−0.255514	0.4574367	0.27016567	0.774519
	GCST90302169	MR Egger	92	−0.982146	0.334195	0.004185	−1.637169	−0.327123	0.3745065	0.19452998	0.720995
		Weighted median	92	−0.833402	0.318985	0.008984	−1.458612	−0.208192	0.4345684	0.23255879	0.812051
		Inverse variance weighted	92	−0.464334	0.220922	**0.035571**	−0.897341	−0.031327	0.6285535	0.40765212	0.969158
		Simple mode	92	−0.805652	0.653795	0.221022	−2.08709	0.475786	0.4467964	0.12404756	1.609278
		Weighted mode	92	−0.805652	0.298396	0.008269	−1.390509	−0.220796	0.4467964	0.24894862	0.80188
	GCST90302170	MR Egger	94	−0.825112	0.324229	0.012598	−1.460601	−0.189624	0.4381858	0.23209677	0.82727
		Weighted median	94	−0.786185	0.317369	0.013242	−1.408228	−0.164143	0.4555793	0.2445763	0.848621
		Inverse variance weighted	94	−0.543341	0.213121	**0.010789**	−0.961058	−0.125623	0.5808047	0.38248789	0.881947
		Simple mode	94	−0.759393	0.662839	0.254872	−2.058556	0.539771	0.4679506	0.12763811	1.715614
		Weighted mode	94	−0.759393	0.275644	0.007062	−1.299655	−0.21913	0.4679506	0.27262574	0.803217

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Table S3 Sensitive analysis of the association identified gut microbiomes and BTC

Outcome	Exposure id	Pleiotropy				Heterogenenity					
		MR_PRESSO_Global_Pval	MR_egger_intercept	MR_egger_se	MR_egger_Pval	MR_egger_Q	MR_egger_Q_df	MR_egger_Q_pval	IVW_Q	IVW_Q_df	IVW_Q_pval
Biliary tract cancer	GCST90032322	0.4	0.106160287	0.054267436	0.082138846	6.112315	9	0.728626811	9.939202	10	0.445843476
	GCST90032340	0.977	−0.021101943	0.080904466	0.799519666	4.338632	10	0.930780488	4.406662	11	0.956478464
	GCST90032343	0.981	−0.017234149	0.081933681	0.837624221	4.220215	10	0.936866316	4.264459	11	0.96153266
	GCST90032353	0.998	−0.021301579	0.060434774	0.728816133	5.830372	17	0.994254816	5.954609	18	0.996377429
	GCST90032366	0.742	0.044693338	0.094532353	0.653075547	4.37646	6	0.625871442	4.599984	7	0.708646421
	GCST90032368	0.407	0.084189647	0.127840086	0.5346213	7.796654	6	0.253382785	8.360214	7	0.30190441
	GCST90032417	0.636	0.02519371	0.109980397	0.826419611	6.381262	6	0.381862509	6.437072	7	0.489738592
	GCST90032438	0.881	−0.167731112	0.553736312	0.790562039	0.707067	2	0.702202547	0.79882	3	0.849749257
	GCST90032484	0.776	0.143282557	0.129072731	0.30945691	2.359787	6	0.883817845	3.592091	7	0.82537726
	GCST90032488	0.463	−0.113283399	0.101396291	0.296321308	7.417119	8	0.492368114	8.665332	9	0.4687226
	GCST90032514	0.998	−0.026678349	0.087177388	0.779594319	0.122489	3	0.989008375	0.21614	4	0.994564608
	GCST90032543	0.736	0.111013419	0.141073913	0.513770514	0.574054	2	0.750491586	1.193292	3	0.754613714
	GCST90032576	0.451	0.25243401	0.189453818	0.253558428	3.12925	4	0.536433415	4.904621	5	0.42763105

Table S4 Sensitive analysis of the association identified circulating metabolites and BTC

Outcome	Exposure id	Pleiotropy				Heterogenenity					
		MR_PRESSO_Global_Pval	MR_egger_intercept	MR_egger_se	MR_egger_Pval	IVW_Q	IVW_Q_df	IVW_Q_pval	MR_egger_Q	MR_egger_Q_df	MR_egger_Q_pval
Biliary tract cancer	GCST90301941	0.888	−0.052741552	0.052268698	0.322619413	16.44684	25	0.900870868	17.46501615	26	0.894362371
	GCST90301950	0.839	0.063143293	0.04471116	0.170204295	17.06342	25	0.879480731	19.05786333	26	0.833977435
	GCST90301951	0.208	0.13616329	0.05673911	0.028137092	17.59662	17	0.414705253	23.55784133	18	0.170053745
	GCST90301958	0.338	0.022465586	0.028220953	0.431520159	38.02028	34	0.291251347	38.72892507	35	0.305065097
	GCST90301968	0.205	−0.007896167	0.019147189	0.681101998	96.39138	84	0.167638719	96.58653561	85	0.183579665
	GCST90301980	0.946	−0.019204153	0.015656163	0.22306215	72.59644	93	0.942044868	74.10104003	94	0.935617811
	GCST90301987	0.346	−0.044020615	0.026197635	0.098008192	63.02852	61	0.404430652	65.94591292	62	0.342111532
	GCST90302008	0.614	−0.008523361	0.015133872	0.574782983	81.28458	85	0.594010199	81.60177009	86	0.614158902
	GCST90302023	0.5	0.00776034	0.014625714	0.596991529	91.44548	91	0.467168481	91.72838545	92	0.488375902
	GCST90302025	0.572	0.00266939	0.014271957	0.852034415	92.09553	94	0.536300669	92.1305142	95	0.564266797
	GCST90302027	0.63	0.000729146	0.014274677	0.959369271	90.90217	95	0.599907573	90.90478179	96	0.627817363
	GCST90302066	0.863	−0.024942139	0.020539149	0.229364187	47.91299	60	0.86984015	49.38768652	61	0.856602416
	GCST90302080	0.889	−0.018706833	0.015316368	0.225138653	74.67096	90	0.877846634	76.16268249	91	0.867759359
	GCST90302081	0.923	−0.01579583	0.018631203	0.399350146	56.76727	72	0.905789219	57.48606069	73	0.908554894
	GCST90302084	0.279	0.006028937	0.018484477	0.74519811	84.7812	76	0.229608763	84.89986898	77	0.251637251
	GCST90302105	0.701	−0.005000822	0.015619648	0.749571334	85.42705	92	0.672612692	85.52955321	93	0.69634334
	GCST90302107	0.616	−0.01086029	0.015789155	0.493388226	82.58609	87	0.613964109	83.05920442	88	0.628966101
	GCST90302115	0.55	0.009261493	0.014509625	0.524668174	103.6789	105	0.518136934	104.0862968	106	0.534408477
	GCST90302123	0.446	0.01413301	0.014948304	0.346658842	104.5662	102	0.411074265	105.4825323	103	0.413724767
	GCST90302124	0.917	0.015137441	0.014422882	0.296483447	80.32709	99	0.915101102	81.42863318	100	0.912558929
	GCST90302129	0.927	−0.012829522	0.017867348	0.47482259	62.15185	80	0.93034676	62.66743077	81	0.934811047
	GCST90302135	0.457	−0.017743957	0.019196704	0.358030216	84.11315	82	0.414653676	84.9895364	83	0.418836127
	GCST90302138	0.795	0.008337969	0.015075042	0.581552869	80.5513	91	0.775289296	80.85721423	92	0.790309183
	GCST90302139	0.851	0.019794948	0.030301676	0.516839155	36.11009	46	0.851990572	36.53684228	47	0.864643031
	GCST90302142	0.646	0.018445248	0.015263214	0.230029316	83.50497	90	0.672292091	84.96538721	91	0.658320383
	GCST90302144	0.654	0.006131546	0.015074425	0.685145574	86.521	91	0.613313981	86.68644437	92	0.636873274
	GCST90302145	0.703	0.008196873	0.014883765	0.583156525	86.55368	92	0.640687655	86.85697544	93	0.659670875
	GCST90302146	0.69	0.017096993	0.015118105	0.261137437	82.39993	89	0.676226334	83.67884947	90	0.667362951
	GCST90302148	0.686	−0.001018089	0.015064267	0.946265813	85.28651	91	0.649143525	85.29108106	92	0.67640578
	GCST90302155	0.832	−0.027250245	0.023986879	0.260862518	45.19717	55	0.824377962	46.4877752	56	0.813657042
	GCST90302159	0.966	−0.01142595	0.015604784	0.465944037	68.00497	90	0.959522785	68.54109596	91	0.962056747
	GCST90302161	0.495	0.004002444	0.015887789	0.801733616	82.66198	82	0.458740706	82.72595548	83	0.487836611
	GCST90302166	0.648	0.013432514	0.014823937	0.367205209	88.3379	93	0.617382054	89.15898872	94	0.621894036
	GCST90302167	0.857	−0.026247857	0.025453618	0.309139325	27.34957	37	0.876599804	28.41294956	38	0.870858796
	GCST90302168	0.455	0.026836673	0.015472652	0.086419652	85.4178	86	0.497448067	88.42614703	87	0.437216671
	GCST90302169	0.391	0.030849757	0.015121876	0.044273848	89.81213	90	0.48575572	93.97403674	91	0.394579424
	GCST90302170	0.536	0.017122547	0.014848143	0.251824775	91.00845	92	0.509631773	92.338265	93	0.499880288

https://dx.doi.org/10.21037/hbsn-2024-750