

Gut–Lung Axis in Neonatal Respiratory Distress Syndrome: Integrated Evidence from Pharmacovigilance and Mendelian Randomization

Supplementary Materials

Table S1. System Classification and Disproportionality Analysis of 162 Drugs Associated with NRDS Risk

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
sertraline	137	182744	2186	53548693	18.36437523	15.45186801	21.82585805	18.35136721	2115.140724	2115.140724	1830.57787	4.11503843	6793403.467	3.953148159
venlafaxine	125	166214	2198	53565223	18.32726422	15.30381008	21.94803858	18.31424318	1936.088994	1936.088994	1664.986059	4.119569365	7468986.491	3.942667922
citalopram	102	95512	2221	53635925	25.78988757	21.14504823	31.45503825	25.76344198	2321.327574	2321.327574	1965.965024	4.625043105	12993685.23	4.326030919
lamotrigine	83	188040	2240	53543397	10.55080879	8.4745555689	13.13574071	10.54659497	691.6404798	691.6404798	575.7704266	3.351274732	6604107.997	3.20068932
fluoxetine	78	96494	2245	53634943	19.31193411	15.40799088	24.20502466	19.29714379	1307.838395	1307.838395	1082.648171	4.223636902	12864788.43	3.931717746
insulin	65	625587	2258	53105850	2.443678502	1.909630017	3.127079365	2.443528516	53.88156278	53.88156278	43.83592943	1.264918933	1985751.228	1.233968317
ondansetron	62	70518	2261	53660919	20.86648256	16.21158388	26.85796142	20.84903113	1140.39306	1140.39306	923.2695869	4.34477652	17602346.42	3.958415204
quetiapine	59	292034	2264	53439403	4.768741375	3.682467573	6.175449981	4.767980126	171.2303603	171.2303603	137.925601	2.22412681	4253395.184	2.137844041
paroxetine	53	176346	2270	53555091	7.090635503	5.399915592	9.310721803	7.08880554	270.8709543	270.8709543	215.6642892	2.796989617	7043034.086	2.645635896
betamethasone	36	18968	2287	53712469	44.57485214	32.06081653	61.97338864	44.49230664	1506.878347	1506.878347	1143.743472	5.453461529	65371808.1	4.343953012
tacrolimus	34	186110	2289	53545327	4.273512616	3.045853251	5.995991458	4.272914695	83.99229055	83.99229055	63.266793	2.078955271	6674319.551	1.951234161
diclofenac	33	249257	2290	53482180	3.092005055	2.192747783	4.360052411	3.091728124	46.0392418	46.0392418	34.53378989	1.614480652	4983698.621	1.528962046
buprenorphine	32	195437	2291	53536000	3.826167874	2.699163105	5.423740631	3.825705206	65.86987433	65.86987433	49.19175685	1.92097172	6355917.598	1.803449264
aripiprazole	31	210364	2292	53521073	3.441125184	2.414213625	4.904844545	3.440765504	52.95938229	52.95938229	39.36848579	1.769007435	5905013.464	1.663761667
hydroxyprogesterone	28	44997	2295	53686440	14.55648067	10.02682287	21.13242971	14.54805021	349.0270535	349.0270535	255.5039175	3.846468285	27592751.14	3.298544579
valproic acid	27	143456	2296	53587981	4.392791172	3.005716216	6.419972112	4.392152732	69.9163224	69.9163224	50.89684996	2.121919232	8658743.922	1.958211875
escitalopram	25	84140	2298	53647297	6.936419041	4.676739239	10.28791785	6.934655713	125.6104447	125.6104447	90.31987513	2.780475416	14761200.64	2.48625194
levetiracetam	22	148526	2301	53582911	3.449291363	2.266578927	5.249149175	3.448928622	37.89456387	37.89456387	26.66802063	1.776413982	8363511.117	1.631212724
paracetamol	22	221711	2301	53509726	2.307552276	1.51634118	3.511609114	2.307422543	16.14409379	16.14409379	11.36138392	1.198519664	5603070.404	1.118923617
dexamethasone	22	127589	2301	53603848	4.016879424	2.639535859	6.112938474	4.016359317	49.36765011	49.36765011	34.74197378	1.995590469	9735692.669	1.818855086

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
acetylsalicylic acid	21	154857	2302	53576580	3.156153531	2.05375861	4.850280391	3.155861177	30.64911034	30.64911034	21.39320629	1.64909674	8021689.273	1.514843162
prednisolone	20	102663	2303	53628774	4.536490183	2.921048988	7.045326275	4.535801366	54.65314906	54.65314906	37.81353699	2.171642288	12099170.4	1.948416135
azithromycin	20	73626	2303	53657811	6.329039449	4.075204321	9.829382085	6.327592245	88.94406427	88.94406427	61.53794524	2.651160565	16869542.72	2.327002618
metformin	19	272978	2304	53458459	1.614953099	1.028174782	2.536605212	1.6149103	4.412459907	4.412459907	3.024147601	0.686953961	4550916.904	0.643040597
olanzapine	19	187962	2304	53543475	2.34913309	1.495586702	3.689806995	2.348996728	14.59973666	14.59973666	10.00609617	1.225252208	6609096.684	1.131270104
gabapentin	18	213837	2305	53517600	1.95440854	1.229111352	3.10770276	1.954328208	8.323596563	8.323596563	5.646410795	0.961203608	5809475.595	0.89046974
lamivudine	17	49844	2306	53681593	7.939664041	4.926709335	12.79520686	7.937297978	102.3259544	102.3259544	68.63988813	2.979390663	24916594.06	2.511578616
ramipril	17	66931	2306	53664506	5.910843225	3.667863869	9.525453744	5.909596222	68.83535143	68.83535143	46.17530673	2.554261524	18557278.12	2.208093313
adalimumab	17	1917463	2306	51813974	0.199209263	0.12362278	0.321011472	0.199216363	54.32292729	54.32292729	36.44202585	2.285765239	647928.8258	-2.2212168
metoprolol	16	93776	2307	53637661	3.966893264	2.426003531	6.486487742	3.966387141	35.25313153	35.25313153	23.36175174	1.980374766	13246097.39	1.749302908
hydroxychloroquine	16	60895	2307	53670542	6.112610659	3.73815995	9.995294362	6.111267687	67.93023057	67.93023057	45.01555602	2.60313685	20396493.51	2.225721547
duloxetine	15	256747	2308	53474690	1.353624955	0.814695929	2.249060605	1.353604297	1.376702092	1.376702092	0.900197131	0.434370436	4838669.173	0.40246048
methylprednisolone	15	81819	2308	53649618	4.261553268	2.564787771	7.080833924	4.260955432	37.19455477	37.19455477	24.32011191	2.084029863	15181660.82	1.817502782
tenofovir	14	119355	2309	53612082	2.723492344	1.610374272	4.606016552	2.723290207	15.17555036	15.17555036	9.776921973	1.439838248	10407901.59	1.283308094
doxorubicin	15	95744	2308	53635693	3.640808055	2.191211087	6.04938674	3.64039439	28.54209161	28.54209161	18.66269867	1.857322149	12974010.16	1.637769656
indometacin	14	8538	2309	53722899	38.15112881	22.54942543	64.54748189	38.09031078	502.6063405	502.6063405	323.698928	5.242860803	145257946.1	3.452799381
prednisone	13	111216	2310	53620221	2.71326805	1.573005956	4.680098945	2.71306781	13.98341859	13.98341859	8.861476689	1.434818281	11169569.48	1.268636012
amoxicillin	14	126318	2309	53605119	2.573031638	1.521410903	4.351547501	2.572857316	13.38087415	13.38087415	8.620705291	1.358046345	9834257.184	1.214477497
risperidone	12	224102	2311	53507335	1.23979217	0.703039812	2.186340797	1.23977933	0.553643048	0.553643048	0.344416847	0.308641271	5543543.328	0.28184022
emtricitabine	11	105509	2312	53625928	2.418188599	1.337258405	4.372854251	2.418040759	9.104663342	9.104663342	5.546169179	1.269826694	11773876.41	1.108888794
levothyroxine	11	221524	2312	53509913	1.149260064	0.635551096	2.078194346	1.149252653	0.212216273	0.212216273	0.129274764	0.199808517	5608078.203	0.181491256
valsartan	11	96461	2312	53634976	2.64545992	1.462935239	4.783846887	2.6452723	11.20353999	11.20353999	6.824698065	1.399160982	12878123.55	1.21410532
ibuprofen	11	218362	2312	53513075	1.165970867	0.644792183	2.108412755	1.165962507	0.258633912	0.258633912	0.157550745	0.220548673	5689281.75	0.200258479
hydrochlorothiazide	10	112112	2313	53619325	2.067728956	1.111019913	3.848268592	2.067633727	5.489289814	5.489289814	3.264290221	1.044770255	11080609.8	0.911155194
nifedipine	10	15530	2313	53715907	14.95394658	8.033588335	27.83569544	14.9449672	129.5642623	129.5642623	77.03631604	3.895781231	79942810.17	2.717725189
diazepam	10	54620	2313	53676817	4.248732864	2.28283778	7.907583757	4.248138184	24.72951264	24.72951264	14.70542604	2.082074311	22741505.97	1.709766194
topiramate	10	80313	2313	53651124	2.888134028	1.551818175	5.375190404	2.88789896	12.28911756	12.28911756	7.307845109	1.525954581	15467247.81	1.297855081

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
carbamazepine	10	92637	2313	53638800	2.503334809	1.345069278	4.659005501	2.503172544	8.988186628	8.988186628	5.344936842	1.320023473	13409800.67	1.135470365
carboplatin	10	133536	2313	53597901	1.735296882	0.9324036	3.229562036	1.735241822	3.102027174	3.102027174	1.844674776	0.792502875	9303025.997	0.699009603
clindamycin	10	39711	2313	53691726	5.845489825	3.140706143	10.87963972	5.844269944	39.98265255	39.98265255	23.77529605	2.54186579	31277156.56	2.016892865
omeprazole	9	137597	2314	53593840	1.514903835	0.787200699	2.915309441	1.514870158	1.568900717	1.568900717	0.90721898	0.597293169	9028546.606	0.52459539
azathioprine	9	19832	2314	53711605	10.53369577	5.473009329	20.27380915	10.52937123	77.32171601	77.32171601	44.70665113	3.391279901	62614212.92	2.428044099
morphine	9	118862	2314	53612575	1.754295656	0.91159458	3.376010914	1.754238547	2.907396267	2.907396267	1.68120113	0.808439751	10451504.25	0.703396575
lorazepam	9	55238	2314	53676199	3.779400911	1.963855645	7.273381464	3.778948134	18.32168369	18.32168369	10.59425675	1.913868515	22487532.81	1.560859403
atenolol	9	36263	2314	53695174	5.759047743	2.992438313	11.08348024	5.757866903	35.24831704	35.24831704	20.38137121	2.520908345	34251129.29	1.960823877
furosemide	9	77861	2314	53653576	2.680142284	1.392679398	5.157800617	2.679948097	9.44149517	9.44149517	5.459482727	1.418697015	15954478.73	1.194974374
mirtazapine	9	66441	2314	53664996	3.141478529	1.632392473	6.04565845	3.141188487	13.08552742	13.08552742	7.566579496	1.647495441	18696350.89	1.368095226
pantoprazole	9	103205	2314	53628232	2.021025979	1.050193234	3.889328055	2.020936948	4.62402857	4.62402857	2.673834931	1.012197874	12036924.99	0.871950281
ampicillin	9	6169	2314	53725268	33.87216648	17.59325284	65.21384487	33.82427889	285.5862352	285.5862352	165.0778875	5.074552865	201066711.9	2.980234398
metronidazole	9	52586	2314	53678851	3.970198573	2.062992569	7.640588214	3.969690315	19.91778901	19.91778901	11.51715646	1.984838986	23621401.11	1.610525085
lopinavir	8	22359	2315	53709078	8.301074523	4.145818391	16.62104601	8.29846315	51.17710531	51.17710531	28.62728048	3.048467873	55543240.92	2.193618472
estradiol	8	117214	2315	53614223	1.580663851	0.78951243	3.164609084	1.580624223	1.700482688	1.700482688	0.951290106	0.658668187	10598527.7	0.568245875
etanercept	8	1372148	2315	52359289	0.131865679	0.065865896	0.263999405	0.13187074	45.56494934	45.56494934	25.49056736	2.890461061	905429.3443	2.745265203
tramadol	8	113881	2315	53617556	1.627026901	0.812669357	3.257433683	1.626982856	1.92636644	1.92636644	1.077654179	0.700283134	10908694.47	0.602921476
paclitaxel	8	105912	2315	53625525	1.749707202	0.873944264	3.503055537	1.749650578	2.560807799	2.560807799	1.432573237	0.804936517	11729413.55	0.689372341
bisoprolol	8	43798	2315	53687639	4.23602991	2.115735067	8.481189199	4.235438936	19.70509526	19.70509526	11.02312989	2.078711154	28360563.67	1.636528736
clonazepam	8	82421	2315	53649016	2.249380226	1.123512726	4.503474935	2.24925897	5.531921897	5.531921897	3.094661726	1.166687647	15072075.86	0.979272198
trastuzumab	8	95585	2315	53635852	1.939118862	0.968548922	3.88228398	1.939040269	3.625702393	3.625702393	2.028294332	0.952934662	12996539.67	0.809710575
enoxaparin	8	50231	2315	53681206	3.693086089	1.8445703	7.394071597	3.692657245	15.65430169	15.65430169	8.757154773	1.881031892	24729124.46	1.50412579
clomifene	8	2636	2315	53728801	70.43698122	35.14591799	141.1648524	70.22688446	544.0724307	544.0724307	304.1059319	6.129045558	469713124	3.013661756
rituximab	8	418526	2315	53312911	0.440198892	0.219874962	0.881296639	0.440209593	5.675471541	5.675471541	3.175037734	1.177433282	2968428.478	1.085708159
abacavir	7	34406	2316	53697031	4.717105325	2.246090137	9.906584907	4.716349223	20.43775747	20.43775747	10.98491829	2.234240895	36101331.23	1.684772939
oxycodone	7	619048	2316	53112389	0.259317005	0.123484789	0.544563499	0.25932538	14.7644089	14.7644089	7.936069761	1.934801125	2006912.481	1.795680799
cyclophosphamide	7	83595	2316	53647842	1.939686039	0.923639026	4.073433258	1.939607359	3.176765493	3.176765493	1.707516208	0.953657105	14860605.63	0.793402835

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
methotrexate	7	489437	2316	53242000	0.328788825	0.156566569	0.690454495	0.328798425	9.562740413	9.562740413	5.140097731	- 1.595877336	2538367.361	- 1.470447724
eculizumab	7	152520	2316	53578917	1.061760634	0.505595887	2.229716801	1.061757799	0.025070577	0.025070577	0.01347563	0.086201819	8145332.089	0.074593395
methadone	7	30862	2316	53700575	5.259135422	2.504160778	11.0450198	5.2581696	24.06675192	24.06675192	12.93534247	2.391035814	40245909.07	1.776493455
epirubicin	7	18863	2316	53712574	8.606462588	4.097786893	18.07590297	8.603640901	46.89937787	46.89937787	25.20624445	3.101100139	65836003.01	2.139096051
ritonavir	7	20815	2316	53710622	7.799077779	3.713415314	16.37996536	7.796792046	41.35215766	41.35215766	22.2251097	2.959085912	59664371.75	2.073544724
methyldopa	7	2450	2316	53728987	66.28298421	31.53027388	139.3401787	66.0969928	447.4518552	447.4518552	240.2998629	6.042224799	505448011.7	2.854245378
salbutamol	7	226907	2316	53504530	0.712692428	0.339376271	1.496658839	0.712701291	0.808287691	0.808287691	0.434462954	- 0.486879156	5475139.206	- 0.434846481
clozapine	6	253230	2317	53478207	0.546873526	0.245428591	1.218564847	0.546884262	2.246827437	2.246827437	1.149259371	- 0.867608467	4906041.427	- 0.771893975
doxepin	6	6204	2317	53725233	22.424963	10.06019312	49.98700914	22.40426255	122.3817716	122.3817716	62.57892826	4.482136967	200030786.2	2.464086458
oxcarbazepine	6	34879	2317	53696558	3.986645687	1.78904043	8.883725358	3.986132003	13.38792213	13.38792213	6.847625119	1.992195307	35612888.06	1.480340753
digoxin	6	84894	2317	53646543	1.636401846	0.734378683	3.646362651	1.636356871	1.481051979	1.481051979	0.757550892	0.709037586	14633410.83	0.583317276
infliximab	6	736611	2317	52994826	0.186303274	0.083610619	0.415125618	0.186309902	21.26811378	21.26811378	10.8787643	- 2.408040648	1686615.332	- 2.23085868
iron	6	53114	2317	53678323	2.61706884	1.174459135	5.831662519	2.61688619	5.978894882	5.978894882	3.058132452	1.385546994	23387948.51	1.08598323
ziprasidone	6	31469	2317	53699968	4.418921647	1.983013096	9.847069876	4.418269907	15.82731735	15.82731735	8.095271207	2.140595762	39471064.08	1.567745707
alprazolam	6	99555	2317	53631882	1.395035235	0.626061625	3.108517163	1.395011429	0.669404159	0.669404159	0.342398167	0.479221419	12478568.26	0.399707475
warfarin	6	120674	2317	53610763	1.150438736	0.516294185	2.563478968	1.150431256	0.117723277	0.117723277	0.060215306	0.201687444	10294836.91	0.170559501
simvastatin	6	121155	2317	53610282	1.145861074	0.514239862	2.553278537	1.145853851	0.111111007	0.111111007	0.056832663	0.195948655	10253967.52	0.165741924
labetalol	6	3567	2317	53727870	39.00513011	17.49332349	86.97033329	38.94130957	221.2386151	221.2386151	113.1015543	5.279594321	347619253.7	2.599991183
dinoprostone	6	2729	2317	53728708	50.98331592	22.86067922	113.701718	50.87366331	292.6148596	292.6148596	149.5646962	5.665189402	454090355.6	2.64600541
intrauterine contraceptive device	5	447640	2318	53283797	0.25675733	0.106766368	0.61746342	0.256765632	10.73415043	10.73415043	5.151074199	- 1.952515433	2775387.723	- 1.762760694
ciclosporin	5	172107	2318	53559330	0.671263718	0.279126706	1.614302639	0.671273268	0.803199991	0.803199991	0.385434849	- 0.573508049	7218462.364	- 0.492952863
pregabalin	5	370042	2318	53361395	0.311051806	0.129343289	0.748034376	0.311061115	7.613225128	7.613225128	3.653410126	- 1.677868881	3357378.537	- 1.502897221
beractant	5	603	2318	53730834	192.2041861	79.63486936	463.8979064	190.6317833	941.195733	941.195733	450.2932234	7.5715526	2040051253	2.547454583
losartan	5	49729	2318	53681708	2.328483539	0.96820606	5.59987777	2.32834998	3.781201035	3.781201035	1.814452813	1.217535266	24980219.42	0.929128772
ceftriaxone	5	30049	2318	53701388	3.854890621	1.602854736	9.271072024	3.854415661	10.54699853	10.54699853	5.060976496	1.944210717	41337255.46	1.383399537
nevirapine	5	18434	2318	53713003	6.285161235	2.613235782	15.11660449	6.283728088	22.16749084	22.16749084	10.63666042	2.649007318	67374794.62	1.738942601
hydralazine	5	11037	2318	53720400	10.49892342	4.364880759	25.25324265	10.49462215	42.85895397	42.85895397	20.5637071	3.388766228	112504864	2.021694259

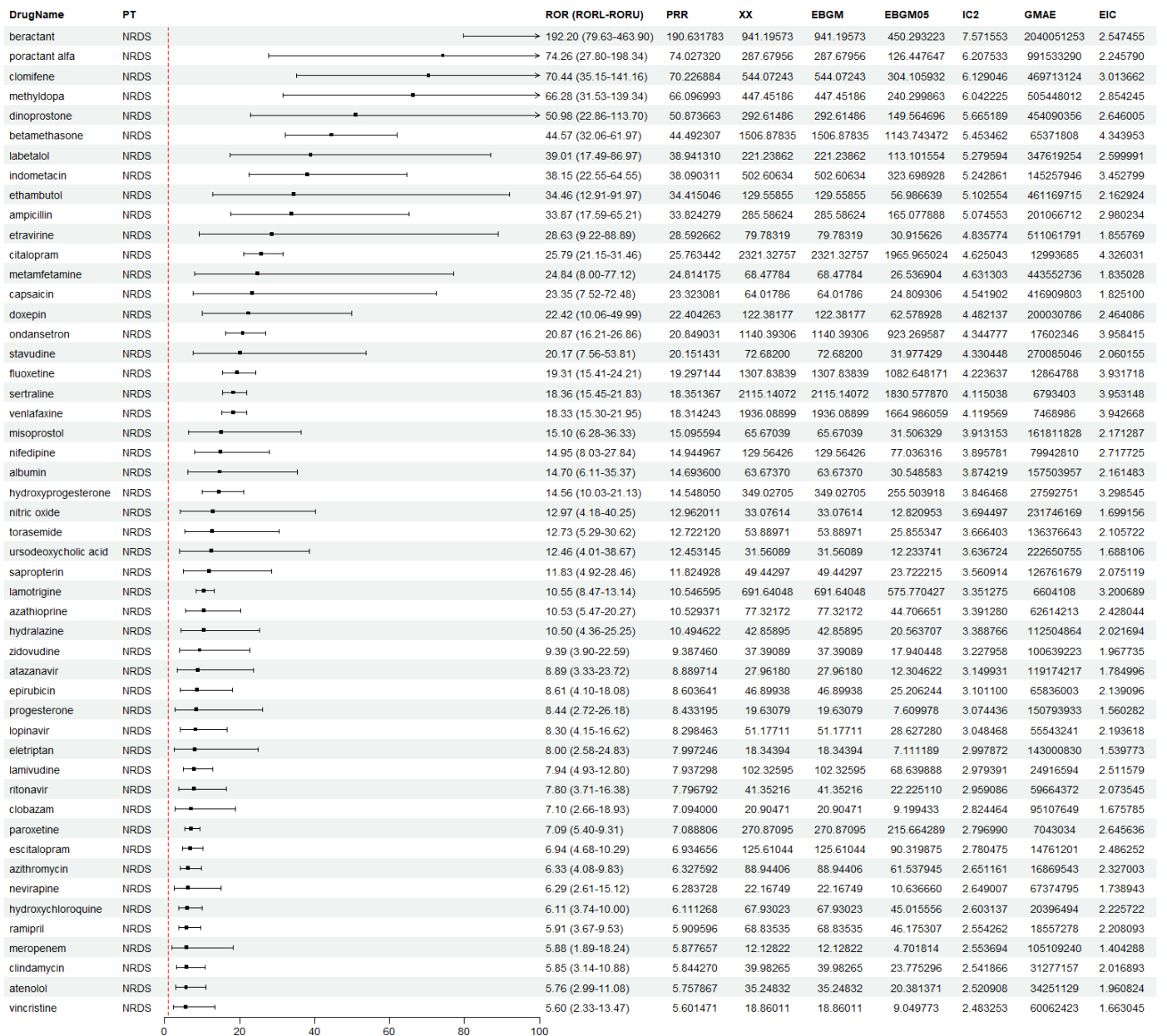
DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
sapropterin	5	9795	2318	53721642	11.83045399	4.918335017	28.45671169	11.82492825	49.44296883	49.44296883	23.72221545	3.56091408	126761678.7	2.075118792
torasemide	5	9104	2318	53722333	12.72855748	5.291618431	30.61750912	12.72211959	53.88970715	53.88970715	25.85534677	3.666403148	136376642.5	2.105721597
etoposide	5	33897	2318	53697540	3.417037143	1.420808006	8.217959628	3.416680669	8.528784628	8.528784628	4.092565013	1.770397349	36645465.38	1.282605995
vincristine	5	20679	2318	53710758	5.602583281	2.329464477	13.47474483	5.601470686	18.8601114	18.8601114	9.049773189	2.483252524	60062422.67	1.663044911
zidovudine	5	12339	2318	53719098	9.39085901	3.904289595	22.58752349	9.387460249	37.39089328	37.39089328	17.94044809	3.227957767	100639223.4	1.967734905
cytarabine	5	49093	2318	53682344	2.358676996	0.980760233	5.672494647	2.358538632	3.904397205	3.904397205	1.873569018	1.236103477	25303798.71	0.941778099
clarithromycin	5	59618	2318	53671819	1.941893841	0.807464206	4.670116227	1.941814853	2.279167555	2.279167555	1.093691451	0.955898766	20837099.37	0.745504994
misoprostol	5	7672	2318	53723765	15.10478052	6.279199285	36.33495042	15.09559414	65.6703852	65.6703852	31.50632897	3.913153181	161811827.7	2.171286536
isotretinoin	5	135631	2318	53595806	0.852370509	0.354433813	2.049848119	0.852375951	0.127566323	0.127566323	0.061215595	0.229900505	9159677.764	0.194578244
albumin	5	7882	2318	53723555	14.70228663	6.111925235	35.36647191	14.6936	63.67369667	63.67369667	30.54858266	3.874219187	157503957	2.161483121
nicotine	5	132001	2318	53599436	0.875869839	0.364205173	2.106362103	0.87587454	0.08776732	0.08776732	0.042117125	0.190763866	9411555.545	0.161208114
montelukast	5	96317	2318	53635120	1.20116559	0.499466946	2.888677186	1.201155147	0.16808006	0.16808006	0.080656587	0.263902386	12898178.14	0.215915943
ethambutol	4	2689	2319	53728748	34.46475227	12.91467506	91.97437356	34.41504599	129.5585497	129.5585497	56.98663876	5.102553505	461169715.2	2.162923863
imatinib	4	163507	2319	53567930	0.565103187	0.211907849	1.506983407	0.565113826	1.336428022	1.336428022	0.588183356	-0.82147615	7598165.351	0.690987133
lithium	4	28108	2319	53703329	3.295569734	1.235733263	8.788935443	3.295243102	6.384108038	6.384108038	2.809612468	1.718653543	44192765.37	1.17403861
bosentan	4	129048	2319	53602389	0.716460267	0.268664329	1.910619532	0.716469056	0.448057547	0.448057547	0.197196768	0.480040955	9626984.362	0.396505337
bupropion	4	149487	2319	53581950	0.618264529	0.231842542	1.648752749	0.618274744	0.941132109	0.941132109	0.414206911	0.692147086	8310753.839	0.578324304
cisplatin	4	64350	2319	53667087	1.438529307	0.539423653	3.836254781	1.43850205	0.533780958	0.533780958	0.234921913	0.523809816	19305278.73	0.402255701
fentanyl	4	224655	2319	53506782	0.410820386	0.154053897	1.095547682	0.410830876	3.374016391	3.374016391	1.484962651	1.279825314	5530095.312	1.099848136
mycophenolic acid	4	187806	2319	53543631	0.491764981	0.184407066	1.311407429	0.491775805	2.097364055	2.097364055	0.923084677	1.021362337	6615114.199	0.867560795
clobazam	4	13058	2319	53718379	7.095867173	2.660509653	18.92544569	7.094000425	20.90470561	20.90470561	9.199433256	2.824463826	95107648.54	1.675785419
immunoglobulins, unspecified	4	245364	2319	53486073	0.376001097	0.140997085	1.002693249	0.37601127	4.135070669	4.135070669	1.81991685	1.407035566	5063358.504	1.215650818
vancomycin	4	53176	2319	53678261	1.741173363	0.652905774	4.643372449	1.741117615	1.259727087	1.259727087	0.55441452	0.798955862	23361561.7	0.599421498
amlodipine	4	221566	2319	53509871	0.416571956	0.156210664	1.11088571	0.416582488	3.262783196	3.262783196	1.436006862	1.259851013	5607192.335	1.081749523
magnesium	4	18480	2319	53712957	5.013445955	1.879813681	13.37081467	5.012577431	12.82673327	12.82673327	5.644806614	2.323562645	67210777	1.474346977
poractant alfa	4	1248	2319	53730189	74.26138173	27.80395521	198.3441843	74.02731981	287.6795585	287.6795585	126.4476473	6.207533172	991533290.4	2.245789634
stavudine	4	4595	2319	53726842	20.16810255	7.559698586	53.80536748	20.15143101	72.68200087	72.68200087	31.97742934	4.330447537	270085046.3	2.060155085

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
atazanavir	4	10420	2319	53721017	8.892743166	3.334100025	23.7188088	8.889714484	27.96179628	27.96179628	12.30462237	3.14993065	119174217.1	1.784995813
zolpidem	4	69346	2319	53662091	1.334766871	0.500515628	3.559534406	1.334747562	0.33524786	0.33524786	0.14754594	0.415943757	17914539.27	0.322126576
palivizumab	4	31618	2319	53699819	2.929528109	1.098487854	7.812680775	2.929284035	5.074125004	5.074125004	2.233110255	1.548911023	39287582.23	1.078439724
treprostinil	4	282538	2319	53448899	0.326303055	0.122360887	0.870161095	0.326312592	5.554095353	5.554095353	2.444456555	-	4397175.697	-
heparin	4	57422	2319	53674015	1.612296871	0.604581269	4.299672073	1.612254221	0.928453931	0.928453931	0.408619866	0.688135565	21634269.82	0.521293844
budesonide	3	212337	2320	53519100	0.325924039	0.105037601	1.011318597	0.325933563	4.176910101	4.176910101	1.619469486	-	5850924.752	-
efavirenz	3	56027	2320	53675410	1.238828739	0.399236273	3.844081179	1.238815951	0.137942687	0.137942687	0.053482072	0.308602648	22173282.88	0.224588636
pipercillin	3	24905	2320	53706532	2.788520447	0.898620091	8.653096412	2.788305031	3.436542506	3.436542506	1.332347509	1.478192956	49877201.53	0.945275786
lisinopril	3	79021	2320	53652416	0.877970718	0.282945362	2.724316021	0.877975351	0.050814963	0.050814963	0.01970173	-	15721495.89	-
cefalexin	3	12974	2320	53718463	5.354056555	1.725273871	16.61528762	5.353049992	10.60632219	10.60632219	4.111855563	2.418845238	95730560.4	1.357250329
eletriptan	3	8684	2320	53722753	7.999663422	2.577619201	24.82702442	7.997246133	18.34394098	18.34394098	7.111188835	2.997872198	143000830.2	1.539772886
darbepoetin alfa	3	64601	2320	53666836	1.074236787	0.346194758	3.333339542	1.07423334	0.015370153	0.015370153	0.005959217	0.103178647	19230573.68	0.076210381
haloperidol	3	39195	2320	53692242	1.771389802	0.570856847	5.496687731	1.771330764	1.006376406	1.006376406	0.390180233	0.824022095	31694461.92	0.569518021
candesartan	3	34041	2320	53697396	2.039784023	0.657346591	6.329566349	2.039692396	1.587902615	1.587902615	0.61563925	1.027401584	36492618.97	0.694055405
etravirine	3	2427	2320	53729010	28.62676889	9.219359547	88.88815899	28.59266177	79.78319304	79.78319304	30.91562644	4.835773921	511061790.6	1.855769009
imiglucerase	3	12549	2320	53718888	5.535427469	1.78371035	17.17821353	5.534343476	11.13118821	11.13118821	4.315319464	2.466884883	98971657.2	1.374336098
iloprost	3	21261	2320	53710176	3.266676722	1.052696985	10.1369881	3.266356932	4.711636548	4.711636548	1.82668362	1.70638913	58424228.21	1.059106299
telmisartan	3	16950	2320	53714487	4.097840021	1.320515212	12.71647057	4.097291828	7.015298604	7.015298604	2.719758485	2.033261545	73280123.44	1.206507637
capsaicin	3	2976	2320	53728461	23.34558407	7.519502868	72.48036274	23.32308096	64.0178603	64.0178603	24.80930623	4.541902112	416909803	1.825100432
natalizumab	3	425209	2320	53306228	0.162109615	0.0522443	0.503012337	0.162115526	12.97545154	12.97545154	5.030852387	-	2921809.1	-
lacosamide	3	40677	2320	53690760	1.706804998	0.550044296	5.296270358	1.706752874	0.876886388	0.876886388	0.33997636	0.770482461	30539839.55	0.535611735
oxybate sodium	3	236411	2320	53495026	0.292603147	0.094299143	0.907925552	0.292612124	5.123912612	5.123912612	1.986642176	-	5255128.536	-
meropenem	3	11816	2320	53719621	5.878895325	1.894371948	18.24425783	5.877656921	12.12822019	12.12822019	4.701814083	2.553694165	105109239.7	1.404287985
raltegravir	3	13127	2320	53718310	5.29163799	1.705162913	16.42155856	5.290657418	10.42597898	10.42597898	4.041945318	2.401935224	94615125.49	1.351148653
ursodeoxycholic acid	3	5576	2320	53725861	12.45930705	4.014150554	38.67177628	12.45314503	31.56089278	31.56089278	12.23374123	3.636723684	222650755	1.688105716
nitric oxide	3	5357	2320	53726080	12.96870997	4.178218487	40.25338522	12.96201107	33.07613968	33.07613968	12.82095303	3.694497234	231746169.2	1.699156171
ranitidine	3	576009	2320	53155428	0.119330544	0.038457603	0.370272134	0.119335131	19.47295397	19.47295397	7.550075794	-	2156880.509	-

DrugName	a	b	c	d	ROR	RORL	RORU	PRR	XX	EBGM	EBGM05	IC2	GMAE	EIC
metamfetamine	3	2797	2320	53728640	24.83971743	8.000464503	77.12196734	24.81417488	68.47783858	68.47783858	26.53690444	4.631303408	443552735.8	1.835028388
mesalazine	3	38823	2320	53692614	1.788375559	0.576330523	5.549397461	1.788314643	1.041199761	1.041199761	0.403681388	0.837779057	31998125.35	0.578155515
tamsulosin	3	39120	2320	53692317	1.77478835	0.571952033	5.507234009	1.774728938	1.01331934	1.01331934	0.392872037	0.826785138	31755219.63	0.571255294
tocilizumab	3	233092	2320	53498345	0.29678794	0.095647794	0.920910743	0.29679699	4.99207102	4.99207102	1.93552442	1.748044013	5329955.095	1.470076821
apixaban	3	246948	2320	53484489	0.280062917	0.090257748	0.869013895	0.280071663	5.544829196	5.544829196	2.149840404	1.831350765	5030901.604	1.546059966
progesterone	3	8235	2320	53723202	8.435902581	2.718153474	26.18117521	8.433194678	19.63078624	19.63078624	7.609977827	3.074436109	150793932.9	1.560282187

a, b, c, d: counts of reports for (a) target drug–event pair, (b) target drug–other events (n–ac), (c) other drugs–target event, and (d) other drugs–other events, forming the basis for disproportionality analysis. ROR: Reporting Odds Ratio; measures disproportionality, with the 95% CI lower bound >1 indicating significance. PRR: Proportional Reporting Ratio; xx: chi-square statistic used in the PRR signal criterion; compares event proportions across drugs, with $PRR \geq 2$ and its chi-square statistic (χ^2) ≥ 4 considered a signal. EBGM: Empirical Bayes Geometric Mean; adjusts for small-sample variability, with $EBGM > 2$ and its 95% lower bound (EBGM05) > 1.5 as thresholds. IC2: Information Component; $IC > 0$ suggests a higher-than-expected reporting frequency. GMAE: Geometric Mean of Adjusted Estimates; integrates results across multiple methods. EIC: Expected Information Component; serves as the baseline reference for IC.

Figure S1: Forest Plot of the Top 50 Drugs Significantly Associated with NRDS in FAERS Analysis



The central forest plot depicts the Reporting Odds Ratio (ROR) for each drug, with values greater than one and 95% confidence interval (CI) lower bounds exceeding one indicating a statistically significant association with Neonatal Respiratory Distress Syndrome (NRDS). PRR: Proportional Reporting Ratio; xx: chi-square statistic used in the PRR signal criterion; compares event proportions across drugs, with $PRR \geq 2$ and its chi-square statistic (χ^2) ≥ 4 considered a signal. EBGM: Empirical Bayes Geometric Mean; adjusts for small-sample variability, with $EBGM > 2$ and its 95% lower bound ($EBGM05$) > 1.5 as thresholds. IC2: Information Component; $IC > 0$ suggests a higher-than-expected reporting frequency. GMAE: Geometric Mean of Adjusted Estimates; integrates results across multiple methods. EIC: Expected Information Component; serves as the baseline reference for IC.

Figure S2-S5: Two-sample Mendelian randomization (MR) analyses were conducted to assess the values < 0.05 . For these 16 taxa, detailed MR results are provided in the Supplementary Figures, including forest plots summarizing odds ratios (ORs) with 95% confidence intervals across five MR methods, scatter plots illustrating SNP-specific causal estimates with regression slopes, and leave-one-out sensitivity analyses evaluating robustness. Panels A–P correspond to the 16 gut microbial taxa analyzed for causal associations with NRDS using Mendelian randomization: *Bacteroides intestinalis* A (A), *CAG-177 sp002438685* (B), *CAG-177 sp003514385* (C), *CAG-177* (D), *CAG-698* (E), *Chromatiales* (F), *Demequina* (G), *Flavonifractor sp900199495* (H), *Lachnoanaerobaculum saburreum* (I), *Lentimicrobiaceae* (J), *Leptospirae* (K), *Leptospirales* (L), *Propionibacterium freudenreichii* (M), *Providencia* (N), *Syntrophomonadia* (O), and *Turicibacter sp001543345* (P).

Figure S2: Forest plots of Mendelian randomization analyses for 16 gut microbial taxa associated with NRDS

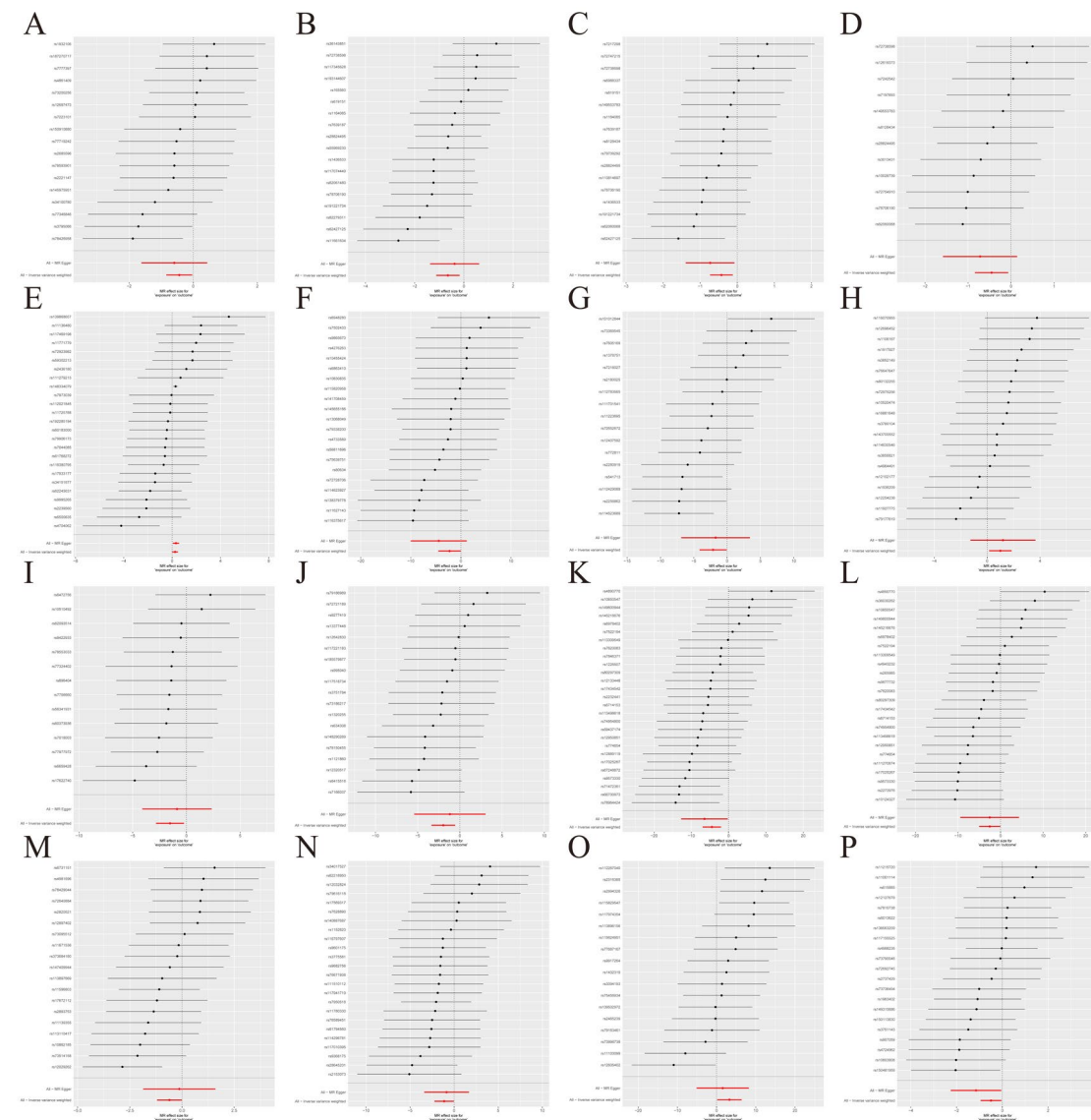


Figure S3: Funnel plots of Mendelian randomization analyses for 16 gut microbial taxa associated with NRDS

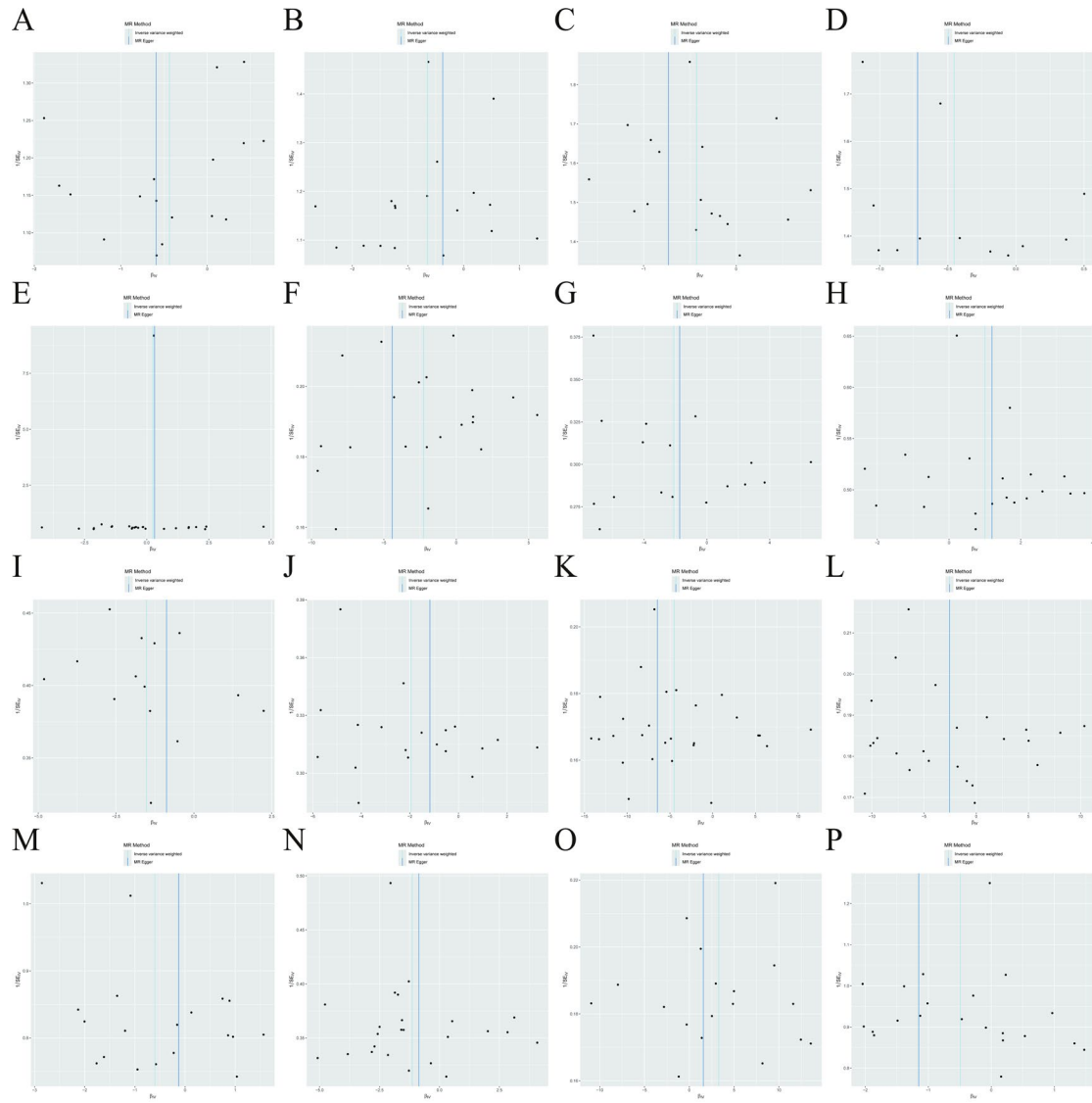
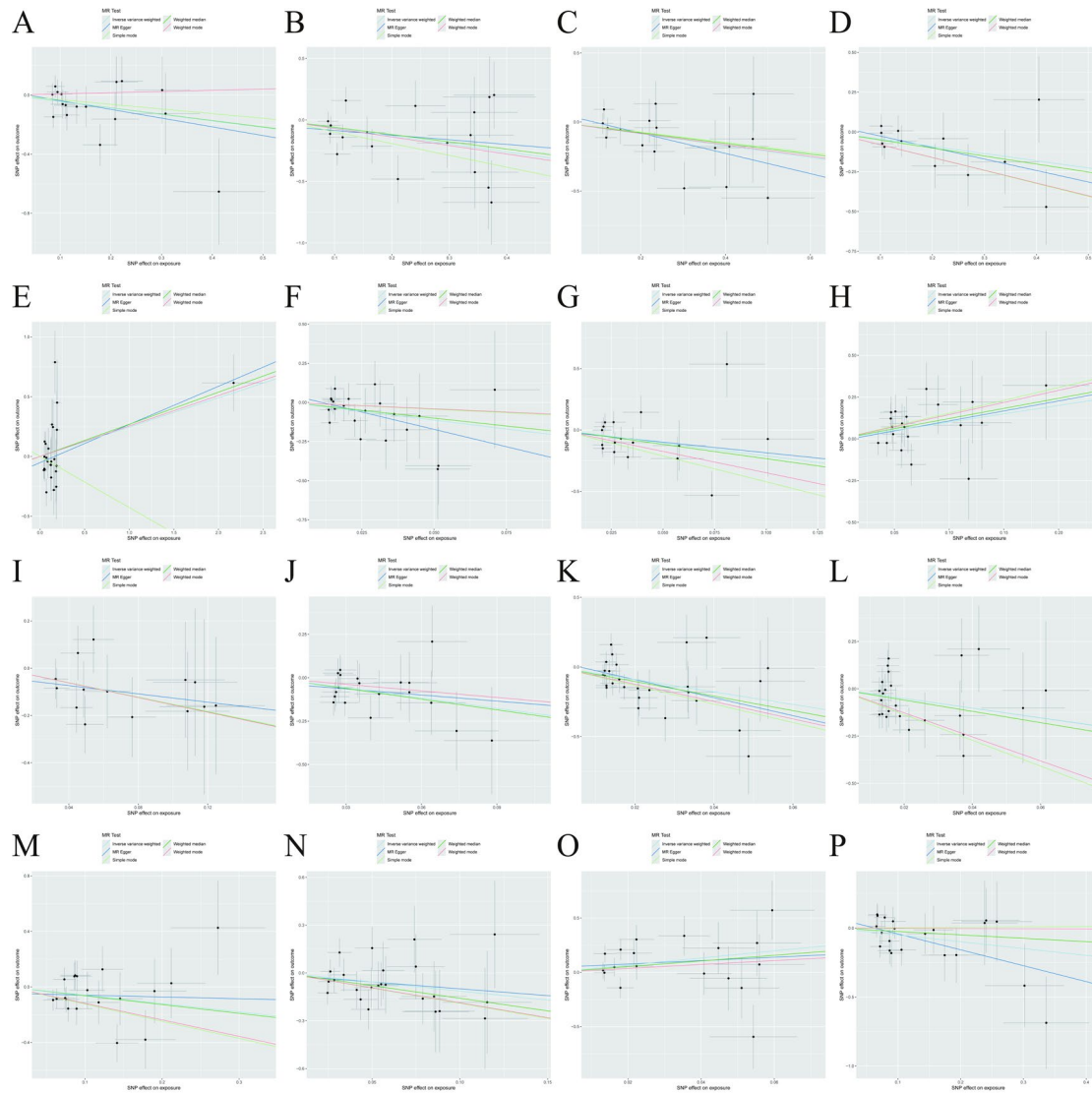
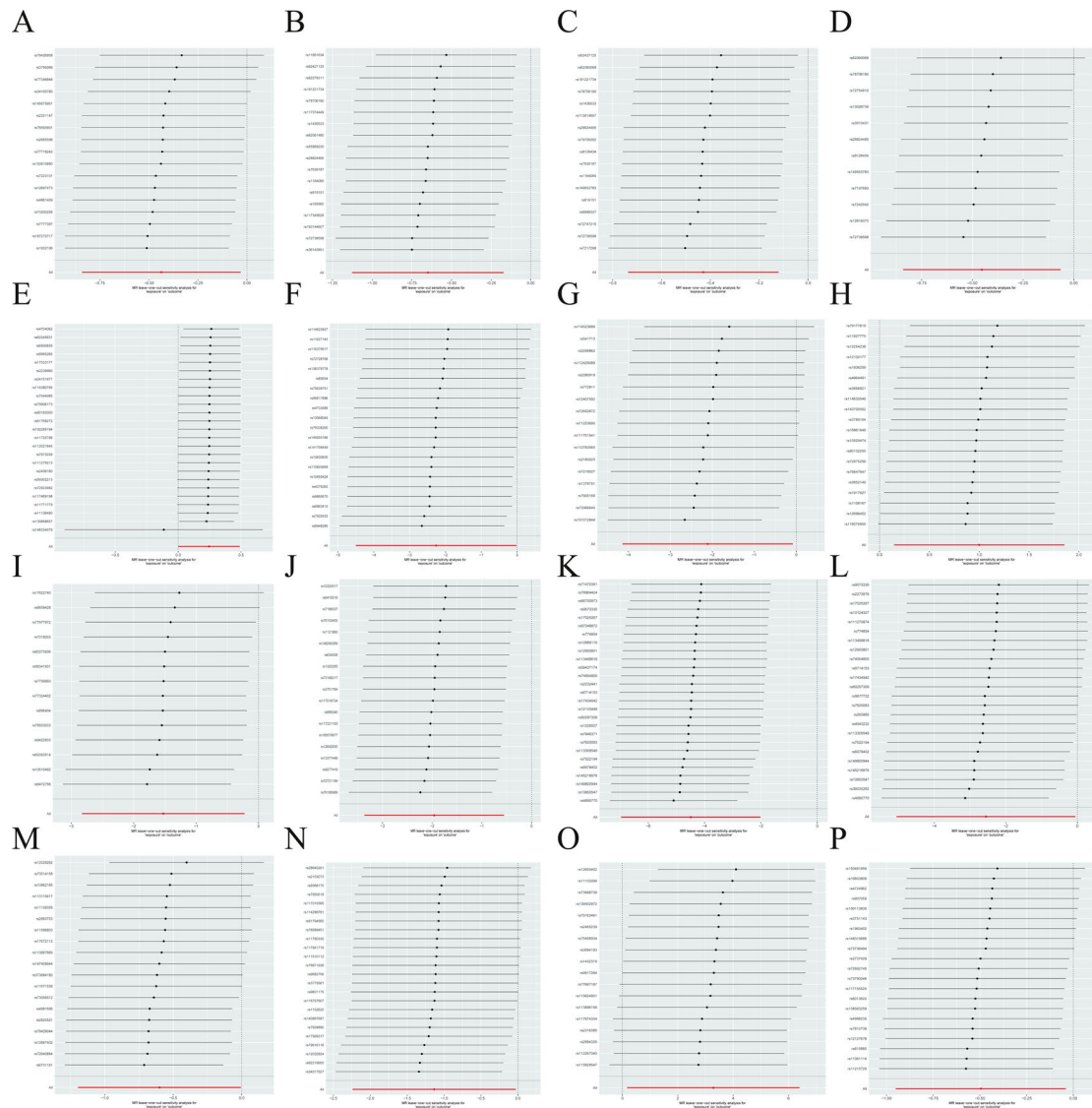


Figure S4. Scatter plots of Mendelian randomization analyses for 16 gut microbial taxa associated with NRDS



Scatter plots illustrating causal estimates between each gut microbial taxon and NRDS using five MR methods (Inverse variance weighted, MR-Egger, Weighted median, Weighted mode, Simple mode). Each point represents a single SNP with corresponding effect sizes on exposure and outcome, with regression lines indicating causal estimates derived from each MR method.

Figure S5. Leave-one-out sensitivity analyses of Mendelian randomization analyses for 16 gut microbial taxa associated with NRDS



Sixteen leave-one-out analyses evaluating the robustness of MR results by sequentially removing one SNP at a time. Consistent causal estimates across iterations suggest that no single SNP drives the overall association.

Figures S6–S9. Reverse two-sample Mendelian randomization (MR) analyses were performed to evaluate the causal effects of NRDS on gut microbial taxa abundance, identifying 24 taxa with inverse-variance weighted (IVW) p-values < 0.05. For these 24 taxa, detailed MR results are provided in the Supplementary Figures, including forest plots summarizing odds ratios (ORs) with 95% confidence intervals across five MR methods, scatter plots illustrating SNP-specific causal estimates with regression slopes, and leave-one-out sensitivity analyses evaluating the robustness of the results. Panels A–X correspond to the 24 gut microbial taxa analyzed for causal associations with NRDS: *Absiella dolichum* (A), *Alloprevotella* (B), *Bacilli A* (C), *Bacteroides faecis* (D), *Barnesiellaceae* (E), *Bifidobacterium breve* (F), *Bifidobacterium ruminantium* (G), *Blautia A sp900066145* (H), CAG-1000 (I), CAG-177 sp002438685 (J), CAG-245 (K), CAG-452 sp000434035 (L), CAG-632 (M), CAG-873 sp001701165 (N), *Campylobacter D* (O), *Demequina* (P), *Fibrobacterales* (Q), *Kandleria vitulina* (R), *Mycobacteriaceae* (S), *Paenibacillales* (T), *Prevotella buccae* (U), UBA1066 (V), UBA1611 (W), and UBA3792 (X).

Figure S6. Forest plots of reverse Mendelian randomization analyses for 24 gut microbial taxa associated with NRDS in the reverse analysis.

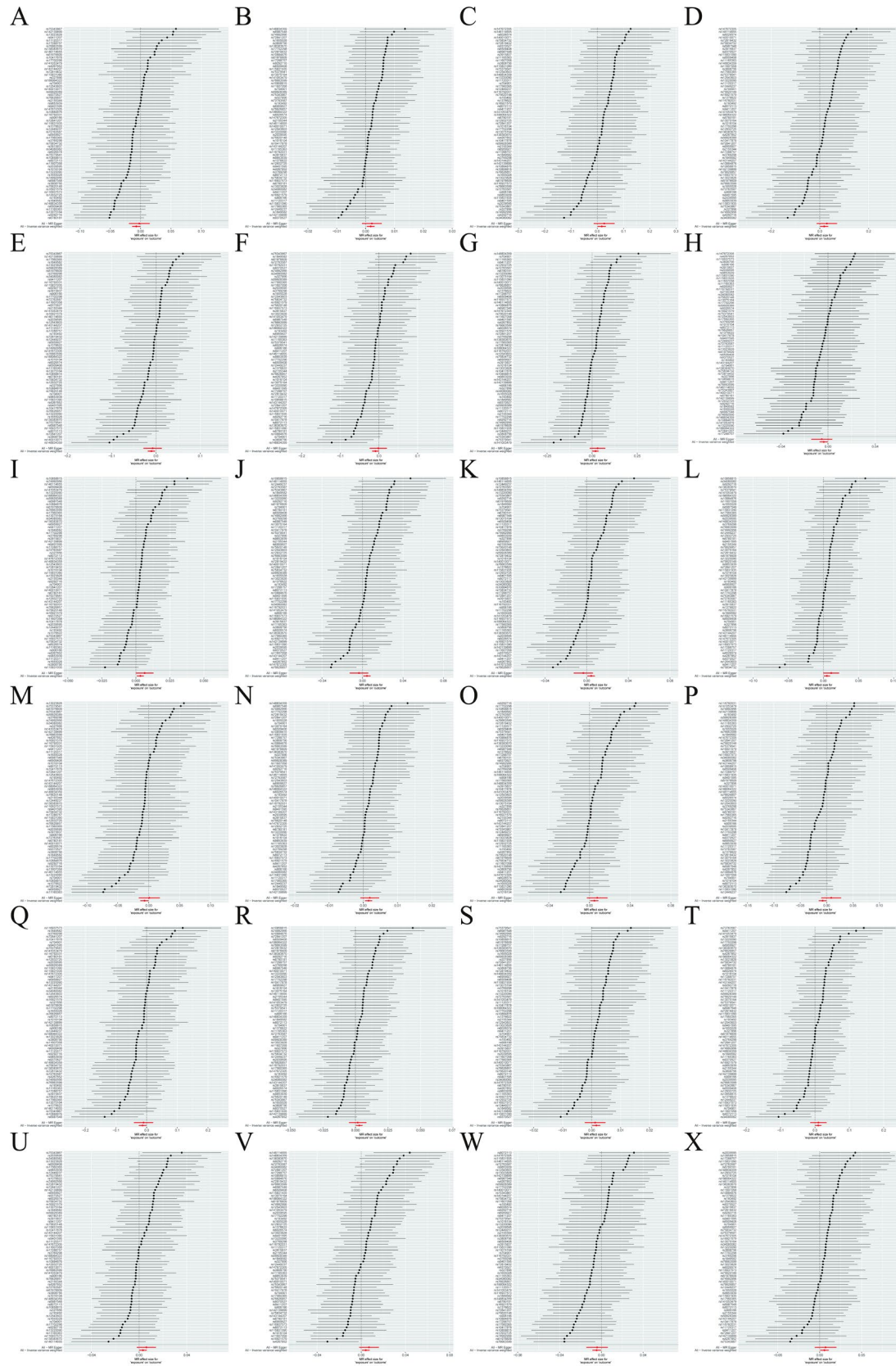


Figure S7. Funnel plots of reverse Mendelian randomization analyses for 24 gut microbial taxa associated with NRDS in the reverse analysis.

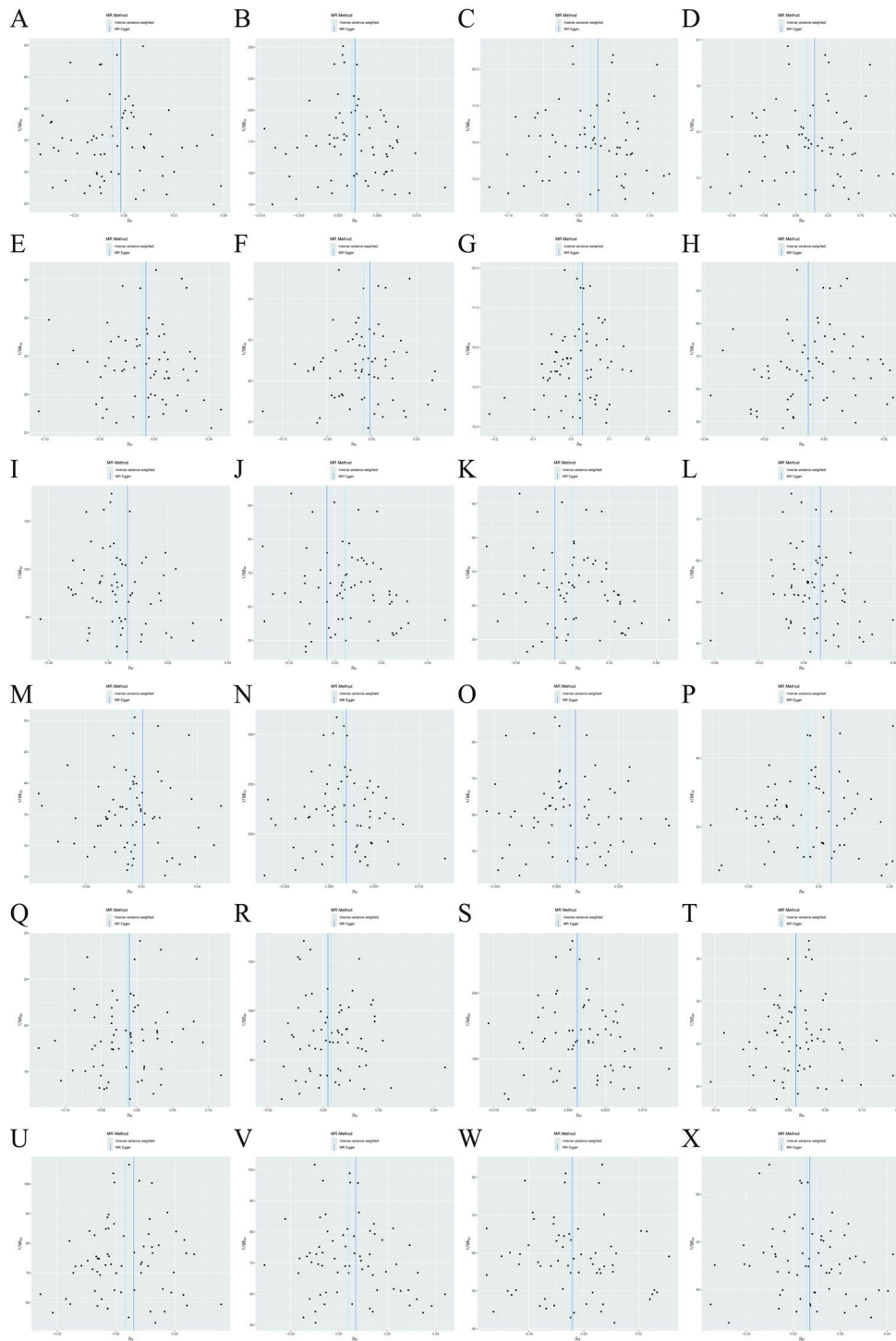


Figure S8. Scatter plots of Mendelian randomization analyses for 24 gut microbial taxa associated with NRDS in the reverse analysis.

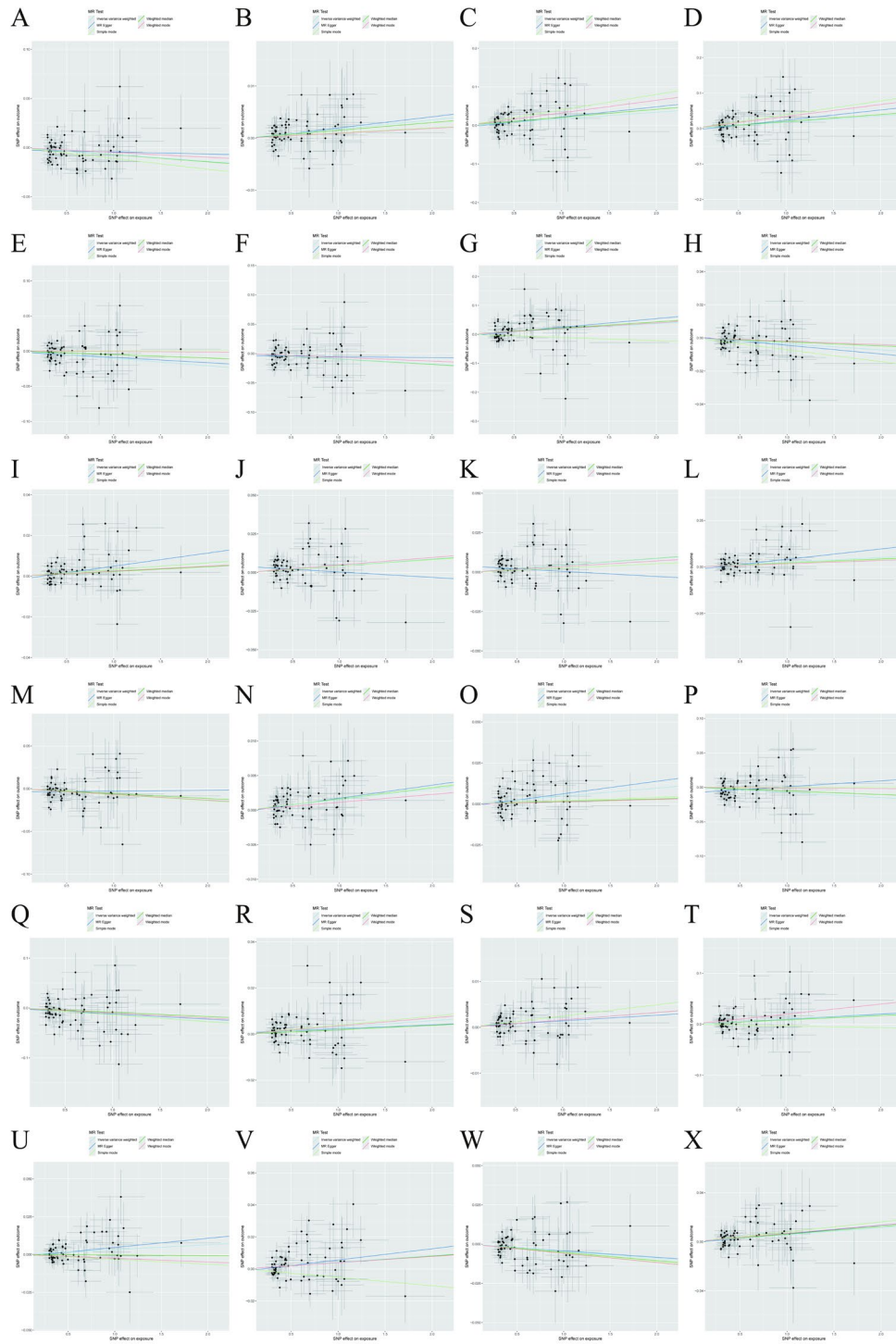


Figure S9. Leave-one-out sensitivity analyses of Mendelian randomization analyses for 24 gut microbial taxa associated with NRDS in the reverse analysis.

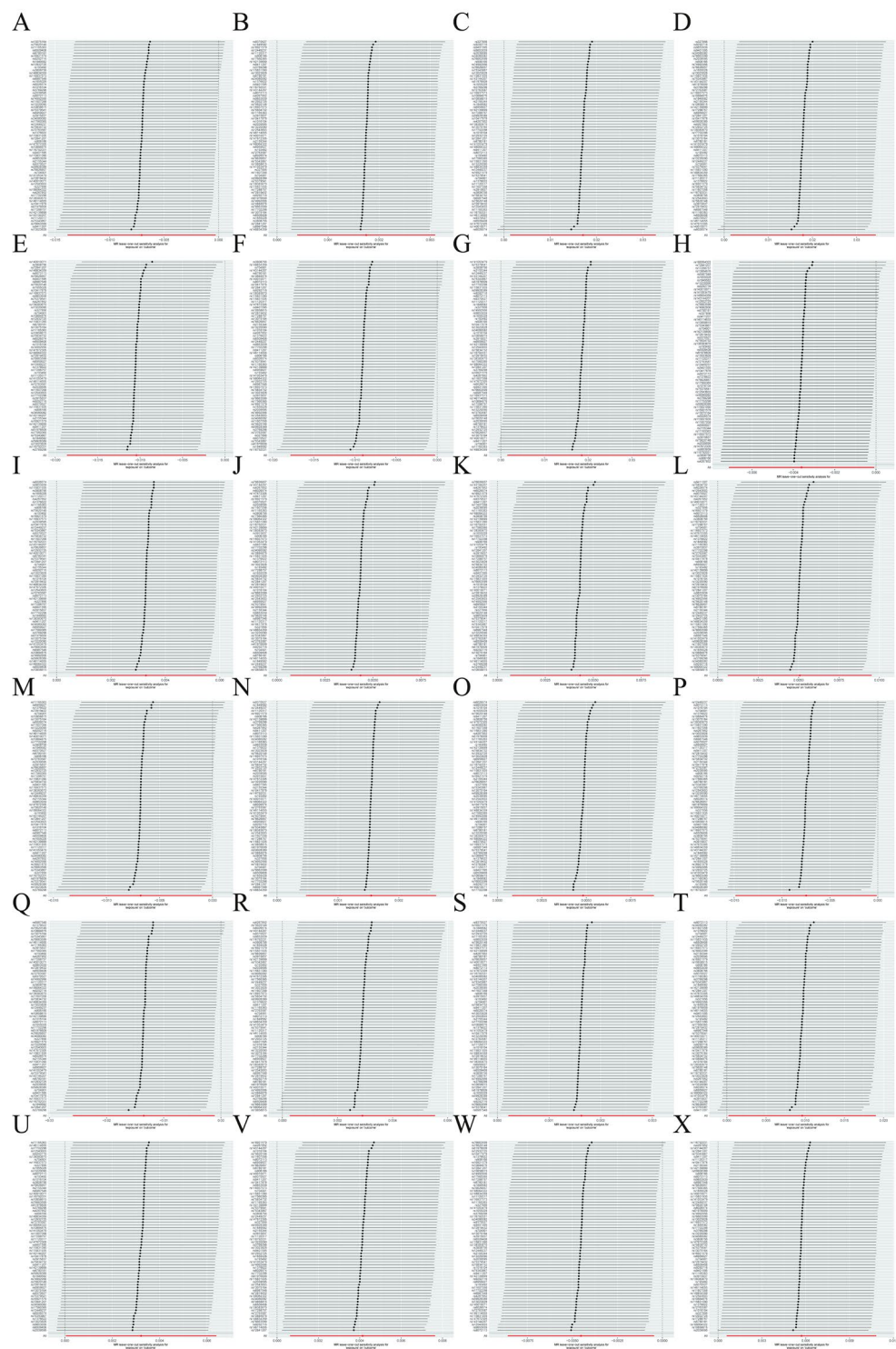


Figure S10. Mendelian randomization analyses evaluating the causal effects of four plasma inflammatory cytokines on NRDS risk. For each cytokine, results include forest plots (effect estimates with 95% CIs across five MR methods), scatter plots (SNP-specific causal estimates with regression slopes), funnel plots (assessment of heterogeneity), and leave-one-out analyses (robustness evaluation). Panels A–D: CUB domain-containing protein 1 levels; Panels E–H: C-X-C motif chemokine 6 levels; Panels I–L: Interleukin-4 levels; Panels M–P: Latency-associated peptide transforming growth factor beta 1 levels.

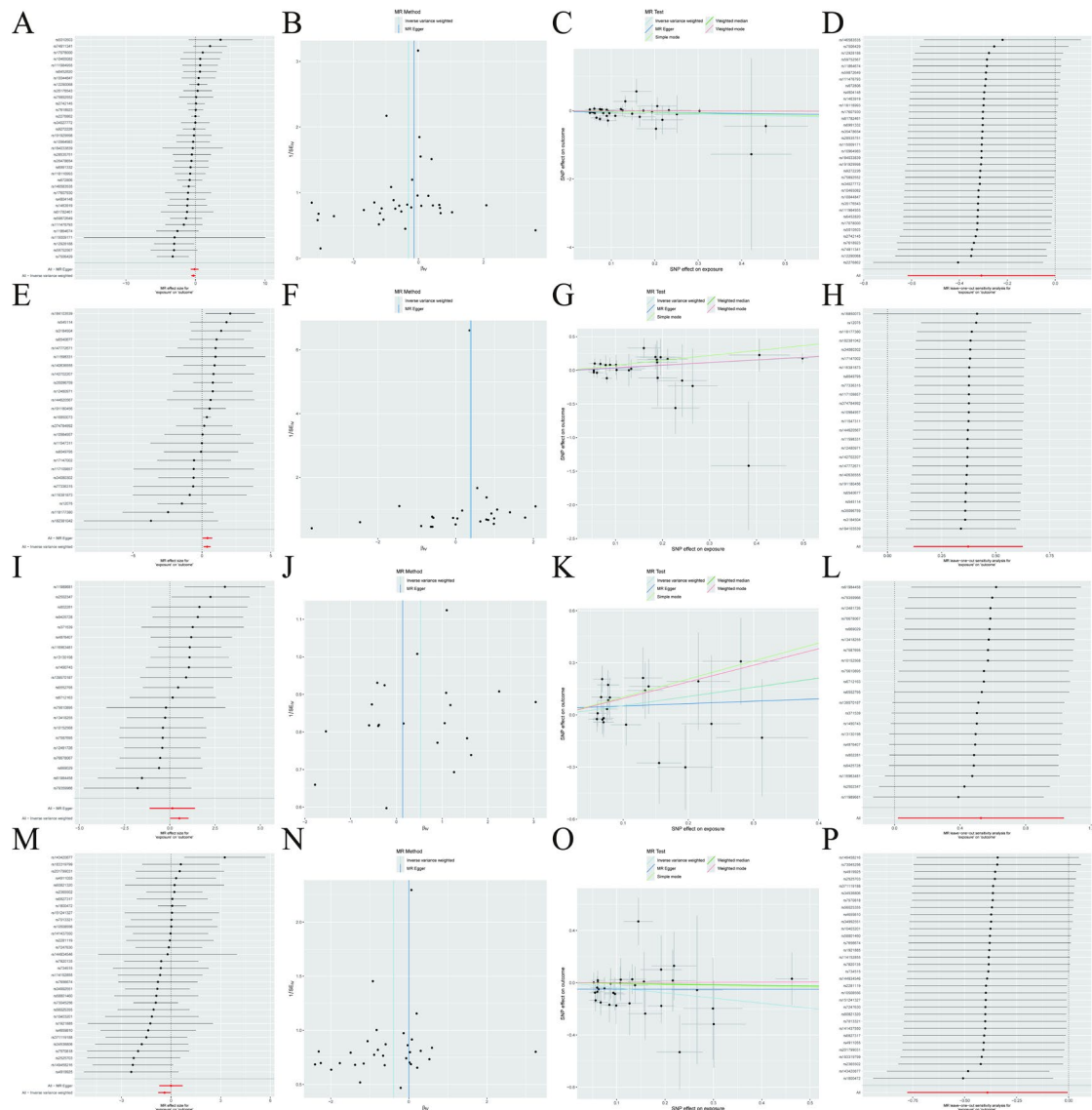


Figure S11-S14. Two-step Mendelian randomization (MR) analyses linking gut microbial taxa to plasma inflammatory cytokines. Panels A1–E10 display causal estimates between 15 gut microbial taxa (exposures) and multiple plasma cytokine or growth factor levels (outcomes) using inverse-variance weighted MR as the primary method. Each small panel corresponds to one microbial taxon–cytokine pair, presenting the odds ratio with 95% confidence intervals across five MR methods. Specifically, panels include: Artemin (A1) and Eotaxin (B1) with *Bacteroides intestinalis* A; Neurturin (C1), Protein S100-A12 (D1), Tumor necrosis factor ligand superfamily member 14 (E1), and Signaling lymphocytic activation molecule (F1) with *Lachnoanaerobaculum saburreum* or *CAG-177*; Caspase-8 (A2), Interleukin-8 (B2), Neurotrophin-3 (C2) with *CAG-177 sp002438685*; Adenosine Deaminase (D2), Axin-1 (E2), Caspase-8 (F2), C-X-C motif chemokine 10 (A3), Eotaxin (B3), Eukaryotic translation initiation factor 4E-binding protein 1 (C3), Interleukin-20 (D3), Interleukin-8 (E3), Latency-associated peptide transforming growth factor beta-1 (F3), Monocyte chemoattractant protein-2 (A4), Protein S100-A12 (B4), SIR2-like protein 2 (C4), Tumor necrosis factor ligand superfamily member 14 (D4) with *CAG-177 sp003514385*; C-X-C motif chemokine 1 (E4) and C-X-C motif chemokine 5 (F4) with *CAG-698*; CUB domain-containing protein 1 (A5), Interleukin-10 (B5), Interleukin-5 (C5) with *Chromatiales*; Fibroblast growth factor 21 (D5), Fibroblast growth factor 23 (E5), Hepatocyte growth factor (F5), Interleukin-18 receptor 1 (A6), Interleukin-6 (B6), Leukemia inhibitory factor receptor (C6) with *Flavonifractor sp900199495*; Interleukin-2 (D6), Matrix metalloproteinase-1 (E6) with *Lentimicrobiaceae*; Fibroblast growth factor 21 (F6), Fms-related tyrosine kinase 3 ligand (A7), Osteoprotegerin (B7), TNF-beta (C7) with *Leptospirae*; Fibroblast growth factor 23 (D7), Osteoprotegerin (E7), Transforming growth factor-alpha (F7) with *Leptospirales*; C-C motif chemokine 25 (A8), C-X-C motif chemokine 11 (B8), Fibroblast growth factor 19 (C8), Fractalkine (D8), Interleukin-17C (E8), Stem cell factor (F8), Thymic stromal lymphopoietin (A9) with *Propionibacterium freudenreichii*; Neurotrophin-3 (B9) with *Providencia*; Caspase-8 (C9), CUB domain-containing protein 1 (D9), Macrophage inflammatory protein 1a (E9), SIR2-like protein 2 (F9), Sulfotransferase 1A1 (A10) with *Syntrophomonadia*; and Adenosine Deaminase (B10), Eotaxin (C10), Monocyte chemoattractant protein-3 (D10), Tumor necrosis factor ligand superfamily member 12 (E10) with *Turicibacter sp001543345*.

Figure S11. Forest plots of Mendelian randomization analyses linking 15 gut microbial taxa to plasma inflammatory cytokines.

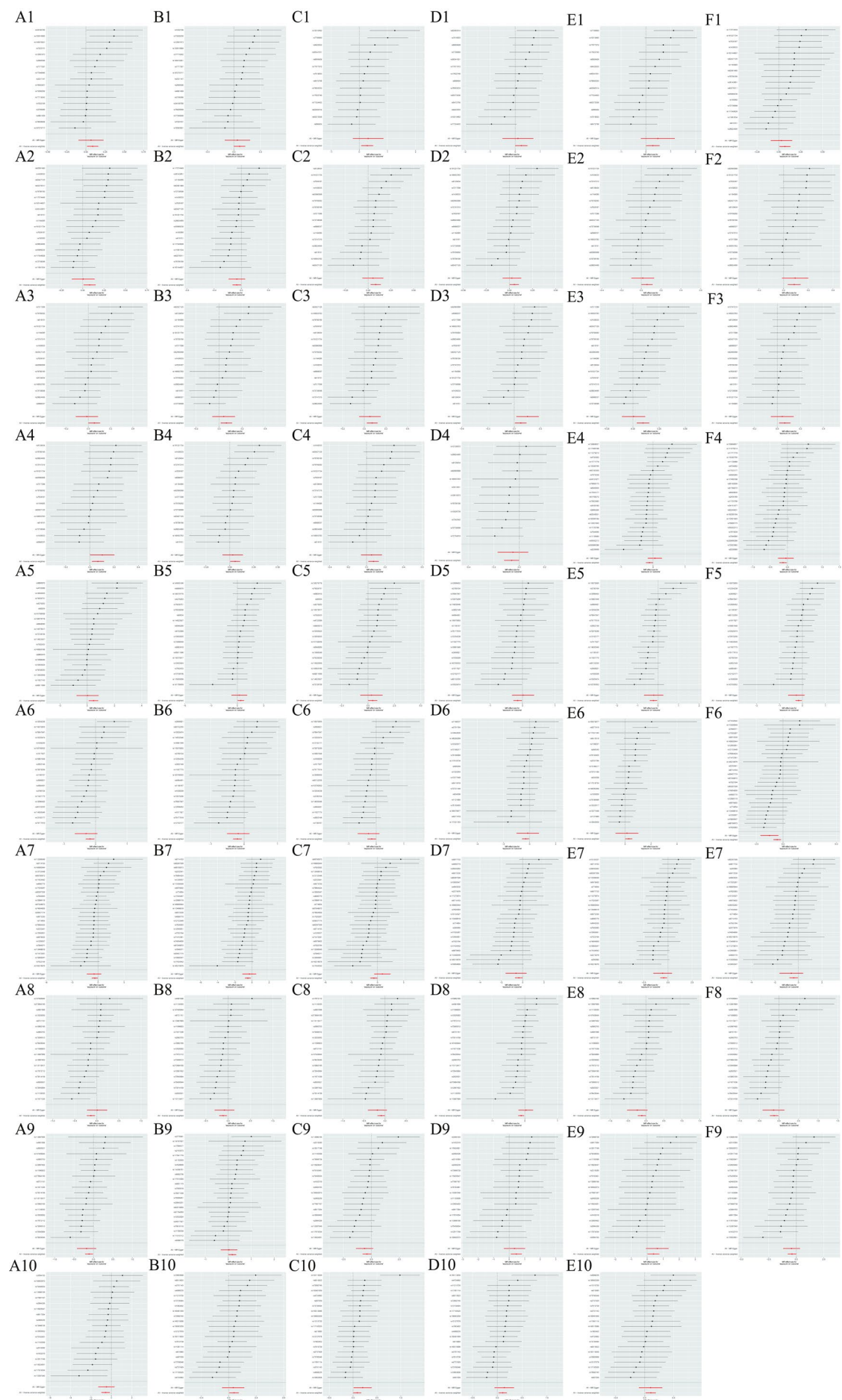


Figure S12. Funnel plots of Mendelian randomization analyses linking 15 gut microbial taxa to plasma inflammatory cytokines.



Figure S13. Scatter plots of Mendelian randomization analyses linking 15 gut microbial taxa to plasma inflammatory cytokines.



Figure S14. Leave-one-out sensitivity analyses of Mendelian randomization analyses linking 15 gut microbial taxa to plasma inflammatory cytokines.

