

Table S1 Sensitivity analysis of the causal relationship between 22 immune cell traits and EC

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
Switched memory B cell %lymphocyte	EC	MR Egger	23.26311363	16	0.106879851	0.001310147	0.026560993	0.961270018
	EC	Inverse variance weighted	23.26665115	17	0.14076936			
Myeloid Dendritic Cell Absolute Count	EC	MR Egger	22.34556612	21	0.379836359	0.010820036	0.018613736	0.567230496
	EC	Inverse variance weighted	22.70511865	22	0.418537321			
CD62L- CD86+ myeloid Dendritic Cell %Dendritic Cell	EC	MR Egger	13.41317778	16	0.642341539	0.007493754	0.020880697	0.724373569
	EC	Inverse variance weighted	13.5419757	17	0.699216583			
Central Memory CD4-CD8- T cell Absolute Count	EC	MR Egger	1.722635852	2	0.422604753	-0.021641912	0.067962616	0.78032995
	EC	Inverse variance weighted	1.824038912	3	0.609717823			
CD28+ CD45RA+ CD8dim T cell Absolute Count	EC	MR Egger	38.24444296	42	0.63656138	-0.008061767	0.013274425	0.546911042
	EC	Inverse variance weighted	38.61327531	43	0.661863423			
CD28+ CD45RA+ CD8+T cell %CD8+ T cell	EC	MR Egger	22.37116634	28	0.763824757	-0.008051482	0.013153518	0.545399962
	EC	Inverse variance weighted	22.74585264	29	0.78804355			
CD19 on IgD+ CD24- B cell	EC	MR Egger	36.09860229	23	0.040307217	0.017996532	0.019678944	0.369938866
	EC	Inverse variance weighted	37.411215	24	0.039794877			
CD19 on IgD+ CD38- naive B cell	EC	MR Egger	15.74793439	17	0.541769213	-0.004907668	0.01605019	0.763492299
	EC	Inverse variance weighted	15.84142975	18	0.60361302			
CD19 on naive-mature B cell	EC	MR Egger	35.53735054	26	0.100511345	0.023126897	0.01947847	0.245841733
	EC	Inverse variance weighted	37.46415099	27	0.086724623			
CD20 on CD20- CD38- B cell	EC	MR Egger	14.97018139	14	0.380196102	-0.020217463	0.023805081	0.410007153
	EC	Inverse variance weighted	15.74146309	15	0.399439197			
CD27 on CD20- B cell	EC	MR Egger	12.08855615	13	0.520395964	0.022273764	0.020490595	0.296770666
	EC	Inverse variance weighted	13.27017681	14	0.505368677			
CD38 on CD20- B cell	EC	MR Egger	10.68371168	17	0.872525841	0.040693896	0.033736212	0.24424532
	EC	Inverse variance weighted	12.13872148	18	0.839993316			
CD28 on secreting CD4 regulatory T cell	EC	MR Egger	14.25221757	15	0.506492815	-0.026490568	0.0192318	0.188584507
	EC	Inverse variance weighted	16.14954658	16	0.442573142			

Table S1 (continued)

Table S1 (continued)

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
CD25 on activated CD4 regulatory T cell	EC	MR Egger	6.880444451	15	0.960882729	0.050623138	0.03588489	0.178732116
	EC	Inverse variance weighted	8.870544375	16	0.918648725			
CD33 on CD14+ monocyte	EC	MR Egger	13.20451696	19	0.827938591	0.011478027	0.020117598	0.574993207
	EC	Inverse variance weighted	13.53004039	20	0.853502823			
CD33 on CD33dim HLA DR+ CD11b-	EC	MR Egger	16.29186722	20	0.698360182	0.000624135	0.02081904	0.976380927
	EC	Inverse variance weighted	16.29276596	21	0.752982594			
CD33 on CD33+ HLA DR+	EC	MR Egger	16.06187522	21	0.766164536	0.010360842	0.019646247	0.603464289
	EC	Inverse variance weighted	16.33999439	22	0.79866087			
CCR2 on plasmacytoid Dendritic Cell	EC	MR Egger	18.12559262	17	0.38095933	0.002197517	0.019160717	0.910035622
	EC	Inverse variance weighted	18.13961701	18	0.446491249			
CCR2 on CD62L+ plasmacytoid Dendritic Cell	EC	MR Egger	22.75779513	17	0.157303059	0.002387891	0.022440759	0.916503732
	EC	Inverse variance weighted	22.7729529	18	0.199466361			
CD80 on granulocyte	EC	MR Egger	25.81529996	30	0.68452475	-0.027938348	0.016414457	0.099087198
	EC	Inverse variance weighted	28.71229943	31	0.584214211			
CD45 on CD33+ HLA DR+CD14dim	EC	MR Egger	13.65451755	13	0.398616452	-0.021894651	0.020120968	0.29629108
	EC	Inverse variance weighted	14.89820522	14	0.38514851			
CD8 on CD8+ T cell	EC	MR Egger	29.61341325	24	0.1978966	-0.013724378	0.019973967	0.498597779
	EC	Inverse variance weighted	30.1959642	25	0.217035215			

EC, esophageal cancer.

Table S2 Sensitivity analysis for the causal relationship between 43 plasma metabolites and 5 lipid species with EC

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
Quinate levels	EC	MR Egger	25.33603476	18	0.115936489	0.039495976	0.030467601	0.211237449
		Inverse variance weighted	27.7013843	19	0.089346464			
Hexanoylcarnitine levels (Biocrates platform)	EC	MR Egger	14.97281702	20	0.77796091	0.004904883	0.029593437	0.870023776
		Inverse variance weighted	15.00028751	21	0.822937384			
Docosatrienoate (22:3n3) levels	EC	MR Egger	16.32690996	21	0.751011091	0.028943916	0.021640538	0.195370704
		Inverse variance weighted	18.11577869	22	0.699102147			
5-methyluridine (ribothymidine) levels	EC	MR Egger	26.93283251	24	0.307593781	-0.013280268	0.018166135	0.47182902
		Inverse variance weighted	27.53256746	25	0.329815307			
1-arachidonoyl-gpc (20:4n6) levels	EC	MR Egger	21.52289162	25	0.663121467	0.013906334	0.015551592	0.37973977
		Inverse variance weighted	22.32249682	26	0.670928899			
3-acetylphenol sulfate levels	EC	MR Egger	16.65692168	18	0.546799419	-0.006684299	0.033758684	0.845262181
		Inverse variance weighted	16.69612662	19	0.610446104			
1-linolenoyl-GPC (18:3) levels	EC	MR Egger	24.5483654	28	0.652289742	0.016680807	0.027656968	0.551275438
		Inverse variance weighted	24.91213381	29	0.682798962			
4-methylguaiacol sulfate levels	EC	MR Egger	8.808295743	12	0.719211462	0.019207297	0.034537452	0.58834228
		Inverse variance weighted	9.117575788	13	0.764006693			
Lignoceroyl sphingomyelin (d18:1/24:0) levels	EC	MR Egger	24.05182752	23	0.400943164	-0.007945835	0.031743729	0.804568509
		Inverse variance weighted	24.11734895	24	0.454903527			
Glycochenodeoxycholate 3-sulfate levels	EC	MR Egger	17.25906878	27	0.924537136	0.023028221	0.018834143	0.232014658
		Inverse variance weighted	18.7540269	28	0.905552921			
1-palmitoyl-2-dihomo-linolenoyl-GPC (16:0/20:3n3 or 6) levels	EC	MR Egger	21.23716797	24	0.624697532	-0.022320863	0.023289319	0.347409071
		Inverse variance weighted	22.15572981	25	0.626736164			
1-(1-enyl-stearoyl)-2-arachidonoyl-GPE (p-18:0/20:4) levels	EC	MR Egger	16.9967955	22	0.763538824	0.004436319	0.027821218	0.87476284
		Inverse variance weighted	17.02222239	23	0.808159605			
1-stearoyl-2-linoleoyl-GPI (18:0/18:2) levels	EC	MR Egger	19.73054406	26	0.804150959	0.007901348	0.022875316	0.73256567
		Inverse variance weighted	19.84985168	27	0.836997658			

Table S2 (continued)

Table S2 (continued)

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3) levels	EC	MR Egger	10.85930015	18	0.900231641	-0.058826018	0.028605983	0.054536085
		Inverse variance weighted	15.08817801	19	0.716976693			
2,3-dihydroxy-2-methylbutyrate levels	EC	MR Egger	9.435032519	12	0.665391972	0.006507678	0.045128497	0.887733405
		Inverse variance weighted	9.455827112	13	0.737712052			
3-formylindole levels	EC	MR Egger	19.92870332	27	0.83373474	0.028180002	0.020665172	0.183940983
		Inverse variance weighted	21.7882367	28	0.790999517			
3-indoleglyoxylic acid levels	EC	MR Egger	12.71996888	18	0.807932974	0.045349481	0.024259118	0.07792867
		Inverse variance weighted	16.21454614	19	0.642918695			
Citrate levels	EC	MR Egger	24.02570636	19	0.195168142	-0.024008781	0.031644521	0.457339798
		Inverse variance weighted	24.75359631	20	0.211020948			
Glutarate (C5-DC) levels	EC	MR Egger	22.85253441	24	0.528516922	-0.024538807	0.020783944	0.249306401
		Inverse variance weighted	24.24649642	25	0.505169739			
Phosphate levels (UKB data field 30810)	EC	MR Egger	28.05352108	23	0.213764479	0.014185368	0.026794942	0.601597799
		Inverse variance weighted	28.3953707	24	0.243717586			
Malate levels	EC	MR Egger	18.42898403	16	0.299381638	-0.037462653	0.019645664	0.074650689
		Inverse variance weighted	22.61735396	17	0.162127164			
X-12013 levels	EC	MR Egger	16.59800636	21	0.735167427	-0.016275184	0.025543769	0.530913355
		Inverse variance weighted	17.00396505	22	0.763143093			
X-13695 levels	EC	MR Egger	14.25584505	14	0.430829573	0.009530159	0.027511288	0.734186504
		Inverse variance weighted	14.37803722	15	0.497072602			
X-15728 levels	EC	MR Egger	30.9667906	28	0.31855718	0.008746651	0.027394141	0.751877261
		Inverse variance weighted	31.07953798	29	0.361684333			
X-18935 levels	EC	MR Egger	19.15551988	19	0.446900875	-0.021271006	0.032814822	0.524604097
		Inverse variance weighted	19.57913971	20	0.484517646			

Table S2 (continued)

Table S2 (continued)

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
X-21821 levels	EC	MR Egger	21.32762698	17	0.211977313	0.003114935	0.034087921	0.928259228
		Inverse variance weighted	21.33810286	18	0.262699743			
X-21470 levels	EC	MR Egger	23.58144145	16	0.099053203	-0.011635445	0.034220424	0.738268275
		Inverse variance weighted	23.75183203	17	0.12633628			
X-24565 levels	EC	MR Egger	28.59553906	32	0.639621572	0.018878785	0.016057801	0.248397285
		Inverse variance weighted	29.9777551	33	0.618369028			
X-25422 levels	EC	MR Egger	20.74849911	22	0.536324456	-0.006750595	0.027514429	0.808461647
		Inverse variance weighted	20.80869447	23	0.592769156			
X-25520 levels	EC	MR Egger	18.8809449	14	0.169548456	0.000614556	0.041956038	0.988520006
		Inverse variance weighted	18.88123425	15	0.219166313			
X-25519 levels	EC	MR Egger	14.69094612	17	0.617731554	0.021973034	0.032686712	0.510470375
		Inverse variance weighted	15.14284117	18	0.652136828			
Alpha-ketoglutarate to succinate ratio	EC	MR Egger	17.79856442	17	0.401654213	0.018924196	0.024913005	0.457892118
		Inverse variance weighted	18.40267813	18	0.429436776			
Aspartate to citrate ratio	EC	MR Egger	9.460785328	17	0.92468839	0.044522895	0.040138369	0.282774371
		Inverse variance weighted	10.69118823	18	0.906998783			
Arachidonate (20:4n6) to pyruvate ratio	EC	MR Egger	12.9956815	12	0.36935465	0.012705476	0.045024967	0.782607732
		Inverse variance weighted	13.08191836	13	0.441504167			
Adenosine 5'-monophosphate (AMP) to tryptophan ratio	EC	MR Egger	34.32067236	24	0.079129106	3.23E-05	0.033009037	0.999228304
		Inverse variance weighted	34.32067372	25	0.101229372			
Phosphate to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	EC	MR Egger	24.11767036	24	0.45488524	-0.009315331	0.022055097	0.67651757
		Inverse variance weighted	24.29693834	25	0.502273654			
Phosphate to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio	EC	MR Egger	24.12951675	21	0.286825473	-0.03403429	0.025283347	0.192617936
		Inverse variance weighted	26.21157849	22	0.242708858			

Table S2 (continued)

Table S2 (continued)

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
Fructose to sucrose ratio	EC	MR Egger	28.50869239	22	0.159429363	0.013313219	0.035345677	0.710036455
		Inverse variance weighted	28.69253584	23	0.190720722			
N-palmitoyl-sphingosine (d18:1 to 16:0) to N-palmitoyl-sphinganine (d18:0 to 16:0) ratio	EC	MR Egger	32.76675936	19	0.025572028	-0.010402269	0.038054557	0.787532282
		Inverse variance weighted	32.89562073	20	0.034641222			
Caffeine to paraxanthine ratio	EC	MR Egger	25.39973722	25	0.440159637	-0.018426554	0.027699704	0.511997104
		Inverse variance weighted	25.84933813	26	0.471410097			
Arachidonate (20:4n6) to linoleate (18:2n6) ratio	EC	MR Egger	18.60962073	23	0.72363529	-0.01199115	0.019170571	0.537802042
		Inverse variance weighted	19.00086823	24	0.751943305			
Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	EC	MR Egger	27.47136791	28	0.492706185	-0.000930249	0.02188624	0.966398698
		Inverse variance weighted	27.47317449	29	0.546192382			
3-methyl-2-oxovalerate to 4-methyl-2-oxopentanoate ratio	EC	MR Egger	18.70675347	20	0.540954256	-0.000293783	0.030725951	0.992465948
		Inverse variance weighted	18.70684489	21	0.603939426			

EC, esophageal cancer.

Table S3 Sensitivity analyses of the preliminary Mendelian randomization (MR) results of causal relationships between three candidate immune cell types and four plasma metabolites and two plasma lipid species

Exposure	Outcome	Method	Cochran q			Pleiotropy		
			Q	Q_df	Q_pval	egger_intercept	se	pval
CD38 on CD20- B cell	X-21470 levels	MR Egger	16.58873362	17	0.482548539	0.004497479	0.011019588	0.688269072
		Inverse variance weighted	16.75530772	18	0.539984589			
CD38 on CD20- B cell	X-25519 levels	MR Egger	11.03143806	17	0.854925023	0.001671041	0.010883586	0.879782058
		Inverse variance weighted	11.05501191	18	0.892007633			
CD33 on CD14+ monocyte	Aspartate to citrate ratio	MR Egger	12.81640062	19	0.847835845	0.001105102	0.007651304	0.886679481
		Inverse variance weighted	12.83726156	20	0.884256683			
CD45 on CD33+ HLA DR+ CD14dim	Quinate levels	MR Egger	8.650226119	14	0.852783531	0.004021593	0.007751808	0.612007049
		Inverse variance weighted	8.919373516	15	0.88169526			
CD45 on CD33+ HLA DR+ CD14dim	Phosphatidylcholine (16:0_20:5) levels	MR Egger	7.928318502	12	0.790706666	0.01231941	0.00865055	0.179893278
		Inverse variance weighted	9.956432746	13	0.69749308			
CD45 on CD33+ HLA DR+ CD14dim	Phosphatidylcholine (18:0_20:4) levels	MR Egger	12.44544051	12	0.410600629	0.020649604	0.008741207	0.03589897
		Inverse variance weighted	18.23318921	13	0.148864443			