

Mendelian randomization analysis of the causal association between metabolite and skin cancer

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Supplementary Material

Supplementary Table 1. The heterogeneity of causal association between all metabolites and SC risks. The p-values for Cochran's Q were above 0.05, suggesting that no significant heterogeneity effects were found.

exposure	method	Q	Q_df	Q_p value
Arachidonate levels	MR Egger	20.8050899	26	0.751953631
Arachidonate levels	Inverse variance weighted	22.99695169	27	0.685176208
Oleoyl-linoleoyl-glycerol levels	MR Egger	44.8318765	27	0.016937018
Oleoyl-linoleoyl-glycerol levels	Inverse variance weighted	46.30367531	28	0.016207841
Arachidonate to linoleate ratio	MR Egger	20.06197802	23	0.638170115
Arachidonate to linoleate ratio	Inverse variance weighted	20.97608434	24	0.640135689
Adenosine 5'-monophosphate (AMP) to phenylalanine ratio	MR Egger	20.78388909	22	0.534126423
Adenosine 5'-monophosphate (AMP) to phenylalanine ratio	Inverse variance weighted	20.81280506	23	0.592518224
1-Palmitoyl-2-linoleoyl-gpc levels	MR Egger	53.65836392	31	0.006994046
1-Palmitoyl-2-linoleoyl-gpc levels	Inverse variance weighted	53.6762315	32	0.009556343
Hypotaurine to taurine ratio	MR Egger	20.05706696	23	0.638466804
Hypotaurine to taurine ratio	Inverse variance weighted	20.36631596	24	0.675765337
Behenoylcarnitine levels	MR Egger	30.2932402	26	0.255640862
Behenoylcarnitine levels	Inverse variance weighted	30.32672837	27	0.29967473
Aspartate to citrulline ratio	MR Egger	10.9763727	16	0.810941314
Aspartate to citrulline ratio	Inverse variance weighted	11.28599916	17	0.841315917
Lignoceroylcarnitine levels	MR Egger	23.45113417	22	0.376642094
Lignoceroylcarnitine levels	Inverse variance weighted	23.95510536	23	0.406297959
Docosapentaenoate levels	MR Egger	6.382747789	15	0.972576701
Docosapentaenoate levels	Inverse variance weighted	6.39233835	16	0.983276372
1-Linoleoyl-GPI levels	MR Egger	25.21988533	19	0.153431017
1-Linoleoyl-GPI levels	Inverse variance weighted	26.46108884	20	0.151117832
Cortisol to 4-cholesten-3-one ratio	MR Egger	7.655755489	19	0.989811966
Cortisol to 4-cholesten-3-one ratio	Inverse variance weighted	7.912433176	20	0.992431396
Campesterol levels	MR Egger	22.03358865	19	0.28258779
Campesterol levels	Inverse variance weighted	23.46441307	20	0.26657012
Etiocholanolone glucuronide levels	MR Egger	5.646007195	18	0.997433314
Etiocholanolone glucuronide levels	Inverse variance weighted	5.722283019	19	0.998508199
Aspartate to phosphate ratio	MR Egger	9.750585814	15	0.835128509
Aspartate to phosphate ratio	Inverse variance weighted	10.08096968	16	0.862365795

3-Indoxyl sulfate levels	MR Egger	13.97054856	18	0.73100914
3-Indoxyl sulfate levels	Inverse variance weighted	15.46372022	19	0.692704138
Leucine to N-palmitoyl-sphingosine ratio	MR Egger	34.24167727	21	0.034137617
Leucine to N-palmitoyl-sphingosine ratio	Inverse variance weighted	35.26615387	22	0.036334038
Benzoate to oleoyl-linoleoyl-glycerol ratio	MR Egger	21.61448503	28	0.798818656
Benzoate to oleoyl-linoleoyl-glycerol ratio	Inverse variance weighted	22.63046442	29	0.793176578
5-Alpha-androstan-3beta,17alpha-diol disulfate levels	MR Egger	15.48888385	21	0.797646364
5-Alpha-androstan-3beta,17alpha-diol disulfate levels	Inverse variance weighted	16.19310667	22	0.806187507
Phenylacetylcarnitine levels	MR Egger	25.3631213	22	0.280027017
Phenylacetylcarnitine levels	Inverse variance weighted	25.99471009	23	0.301116019
2-Hydroxybutyrate/2-hydroxyisobutyrate levels	MR Egger	15.77828194	14	0.327101105
2-Hydroxybutyrate/2-hydroxyisobutyrate levels	Inverse variance weighted	16.76400996	15	0.333166564
Glycerol to palmitoylcarnitine ratio	MR Egger	22.47050218	17	0.167294961
Glycerol to palmitoylcarnitine ratio	Inverse variance weighted	22.71477112	18	0.201789867
Cysteinylglycine levels	MR Egger	20.82063735	17	0.234416191
Cysteinylglycine levels	Inverse variance weighted	20.822727	18	0.288450863
1-Arachidonoyl-gpc levels	MR Egger	32.42848199	26	0.179331597
1-Arachidonoyl-gpc levels	Inverse variance weighted	34.9300724	27	0.140646144
Phenylalanine to tyrosine ratio	MR Egger	10.19038547	15	0.807596262
Phenylalanine to tyrosine ratio	Inverse variance weighted	10.19284702	16	0.856365103
Oleoyl-linoleoyl-glycerol to linoleoyl-arachidonoyl-glycerol ratio	MR Egger	18.67077201	21	0.60625059
Oleoyl-linoleoyl-glycerol to linoleoyl-arachidonoyl-glycerol ratio	Inverse variance weighted	19.60498726	22	0.607733563
1-Stearoyl-GPG levels	MR Egger	16.84402298	20	0.663077441
1-Stearoyl-GPG levels	Inverse variance weighted	17.55463589	21	0.676987194
Margarate levels	MR Egger	20.96992122	18	0.280933275
Margarate levels	Inverse variance weighted	21.42002191	19	0.31406316
Uridine to 2'-deoxyuridine ratio	MR Egger	23.30455344	25	0.55978453
Uridine to 2'-deoxyuridine ratio	Inverse variance weighted	24.81501618	26	0.529464887
Glucose to fructose ratio	MR Egger	7.522902255	12	0.821215408
Glucose to fructose ratio	Inverse variance weighted	7.671258819	13	0.864338202
Uridine levels	MR Egger	10.97212961	17	0.858009148
Uridine levels	Inverse variance weighted	13.55385382	18	0.757677407
3-Ethylcatechol sulfate levels	MR Egger	14.94959526	12	0.244204534
3-Ethylcatechol sulfate levels	Inverse variance weighted	17.27327892	13	0.187110617
3-Methyl-2-oxovalerate to 3-methyl-2-oxobutyrate ratio	MR Egger	13.61705838	18	0.753691705
3-methyl-2-oxovalerate to 3-methyl-2-oxobutyrate ratio	Inverse variance weighted	13.62118619	19	0.805309504
N-methyl-2-pyridone-5-carboxamide levels	MR Egger	5.918254222	14	0.96850993
N-methyl-2-pyridone-5-carboxamide levels	Inverse variance weighted	6.502910062	15	0.970006941
Sulfate of piperine metabolite C18H21NO3 levels	MR Egger	23.33166477	21	0.326552834
Sulfate of piperine metabolite C18H21NO3 levels	Inverse variance weighted	23.61565485	22	0.367693486
Arachidonate to pyruvate ratio	MR Egger	17.41473549	14	0.234749393
Arachidonate to pyruvate ratio	Inverse variance weighted	18.5846813	15	0.23317455
Arachidonate to oleate to vaccenate ratio	MR Egger	15.06692413	14	0.373595185
Arachidonate to oleate to vaccenate ratio	Inverse variance weighted	16.21119185	15	0.368156291
2-Naphthol sulfate levels	MR Egger	27.1129695	19	0.102049111

2-Naphthol sulfate levels	Inverse variance weighted	28.24348517	20	0.103759705
Phosphate to oleoyl-linoleoyl-glycerol ratio	MR Egger	34.17072665	29	0.233065403
Phosphate to oleoyl-linoleoyl-glycerol ratio	Inverse variance weighted	35.21220619	30	0.235000986
Carboxyethyl-gaba levels	MR Egger	13.38710562	20	0.860164233
Carboxyethyl-gaba levels	Inverse variance weighted	14.80794355	21	0.832463863
1-Palmitoleoyl-2-linolenoyl-GPC levels	MR Egger	18.1106358	17	0.381893528
1-Palmitoleoyl-2-linolenoyl-GPC levels	Inverse variance weighted	19.53713102	18	0.359472012
Sebacate levels	MR Egger	12.37492322	14	0.576221027
Sebacate levels	Inverse variance weighted	16.02364965	15	0.38048163
4-Allylphenol sulfate levels	MR Egger	18.37599791	20	0.562654357
4-Allylphenol sulfate levels	Inverse variance weighted	18.53930401	21	0.61466682
1-Oleoyl-2-linoleoyl-GPE levels	MR Egger	30.31567554	29	0.398371156
1-Oleoyl-2-linoleoyl-GPE levels	Inverse variance weighted	31.27668443	30	0.401897536
N-stearoyl-sphinganine levels	MR Egger	8.948978889	11	0.626601929
N-stearoyl-sphinganine levels	Inverse variance weighted	9.123801236	12	0.692321363
N-oleoyltaurine levels	MR Egger	19.69602617	18	0.350190585
N-oleoyltaurine levels	Inverse variance weighted	19.94256309	19	0.398041831
Tryptophan to tyrosine ratio	MR Egger	26.22274031	23	0.290464098
Tryptophan to tyrosine ratio	Inverse variance weighted	27.37545967	24	0.287258453
Palmitoleoylcarnitine levels	MR Egger	27.35751071	17	0.053028598
Palmitoleoylcarnitine levels	Inverse variance weighted	28.05076422	18	0.061286868
Adenosine 5'-diphosphate (ADP) to phosphoethanolamine ratio	MR Egger	19.12662851	19	0.448740173
Adenosine 5'-diphosphate (ADP) to phosphoethanolamine ratio	Inverse variance weighted	20.06058118	20	0.454145843
Sarcosine levels	MR Egger	17.10061696	18	0.516197777
Sarcosine levels	Inverse variance weighted	17.10566794	19	0.582709119
Adenosine 5'-diphosphate (ADP) to fructose ratio	MR Egger	39.47710837	30	0.115395264
Adenosine 5'-diphosphate (ADP) to fructose ratio	Inverse variance weighted	40.40293457	31	0.120202743
Glutamine to alanine ratio	MR Egger	39.96818993	33	0.188165648
Glutamine to alanine ratio	Inverse variance weighted	40.38868136	34	0.20877112
1-Stearoyl-2-linoleoyl-gpc levels	MR Egger	33.00831844	18	0.016651747
1-Stearoyl-2-linoleoyl-gpc levels	Inverse variance weighted	34.76729038	19	0.014895526
N-methylproline levels	MR Egger	17.67748552	20	0.608644476
N-methylproline levels	Inverse variance weighted	17.69315992	21	0.668330514
16a-hydroxy DHEA 3-sulfate levels	MR Egger	19.54050286	22	0.611758041
16a-hydroxy DHEA 3-sulfate levels	Inverse variance weighted	19.98469326	23	0.642834998
Cysteinyglycine to taurine ratio	MR Egger	17.33469104	28	0.941681913
Cysteinyglycine to taurine ratio	Inverse variance weighted	17.42690241	29	0.955127748
Adenosine 5'-monophosphate (AMP) to proline ratio	MR Egger	11.03051519	17	0.854973268
Adenosine 5'-monophosphate (AMP) to proline ratio	Inverse variance weighted	15.03526306	18	0.6595444
Stearoyl sphingomyelin levels	MR Egger	34.2469357	30	0.271068362
Stearoyl sphingomyelin levels	Inverse variance weighted	37.01555956	31	0.210985801
Palmitoylcarnitine levels	MR Egger	31.8094535	27	0.239214834
Palmitoylcarnitine levels	Inverse variance weighted	31.88374272	28	0.279267717
Gamma-tocopherol/beta-tocopherol levels	MR Egger	9.798610048	21	0.981409946
Gamma-tocopherol/beta-tocopherol levels	Inverse variance weighted	11.5009266	22	0.96684732
Hydroxy-cmpf levels	MR Egger	19.63430074	19	0.416877762
Hydroxy-cmpf levels	Inverse variance weighted	19.93999006	20	0.461689224

Ethyl beta-glucopyranoside levels	MR Egger	13.38202531	17	0.710260023
Ethyl beta-glucopyranoside levels	Inverse variance weighted	13.43185739	18	0.765305953
Phosphate to mannose ratio	MR Egger	31.18373254	22	0.092416728
Phosphate to mannose ratio	Inverse variance weighted	31.42409002	23	0.112725814
Caffeine to theophylline ratio	MR Egger	32.70723223	26	0.170762272
Caffeine to theophylline ratio	Inverse variance weighted	32.86469765	27	0.201571763
Glucuronate to androsterone glucuronide ratio	MR Egger	8.440048861	18	0.971340157
Glucuronate to androsterone glucuronide ratio	Inverse variance weighted	8.626135226	19	0.979186717
Eicosapentaenoate levels	MR Egger	30.68167919	25	0.199776537
Eicosapentaenoate levels	Inverse variance weighted	33.30719379	26	0.153371172
Linoleoyl-arachidonoyl-glycerol levels	MR Egger	27.86847611	32	0.675849687
Linoleoyl-arachidonoyl-glycerol levels	Inverse variance weighted	29.39864402	33	0.647132095
Sulfate of piperine metabolite C16H19NO3 levels	MR Egger	17.93142176	21	0.653339832
Sulfate of piperine metabolite C16H19NO3 levels	Inverse variance weighted	18.18409334	22	0.69501932
Benzoate to linoleoyl-arachidonoyl-glycerol ratio	MR Egger	24.99724857	24	0.405910222
Benzoate to linoleoyl-arachidonoyl-glycerol ratio	Inverse variance weighted	26.4522024	25	0.383792018
Erythritol levels in elite athletes	MR Egger	27.63317124	19	0.090747061
Erythritol levels in elite athletes	Inverse variance weighted	28.26729002	20	0.103221516
Glycolithocholate sulfate levels	MR Egger	14.23149862	19	0.770032697
Glycolithocholate sulfate levels	Inverse variance weighted	14.73418328	20	0.791410253
1-Palmitoyl-2-linoleoyl-GPE levels	MR Egger	19.25132936	20	0.505547439
1-Palmitoyl-2-linoleoyl-GPE levels	Inverse variance weighted	19.394023	21	0.559879757
Ergothioneine levels	MR Egger	33.11543618	23	0.079076175
Ergothioneine levels	Inverse variance weighted	33.42017705	24	0.095513606
Plasma lactate levels	MR Egger	9.947544917	17	0.905795565
Plasma lactate levels	Inverse variance weighted	10.06373831	18	0.929806106
Citrate to oxalate (ethanedioate) ratio	MR Egger	11.15773027	13	0.597605897
Citrate to oxalate (ethanedioate) ratio	Inverse variance weighted	11.276502	14	0.664190957
Andro steroid monosulfate C19H28O6S levels	MR Egger	46.19469729	36	0.118859242
Andro steroid monosulfate C19H28O6S levels	Inverse variance weighted	46.27683999	37	0.141046249
1-Methylxanthine levels	MR Egger	26.44380897	27	0.494088204
1-Methylxanthine levels	Inverse variance weighted	28.09498375	28	0.459422595
Isoursodeoxycholate levels	MR Egger	24.88865574	17	0.097229732
Isoursodeoxycholate levels	Inverse variance weighted	24.96106452	18	0.125992452

Supplementary Table 2. The pleiotropy of causal association between all metabolites and skin cancer. The p-values for the MR-Egger intercept were above 0.05, suggesting no significant pleiotropy effects were found.

exposure	egger_intercept	Standard error (se)	p value (pval)
Arachidonate levels	-0.010488761	0.007084637	0.15075866
Oleoyl-linoleoyl-glycerol levels	-0.009533031	0.010125544	0.354805227
Arachidonate to linoleate ratio	-0.005879454	0.006149484	0.348969432
Adenosine 5'-monophosphate (AMP) to phenylalanine ratio	0.001442327	0.008481931	0.86652726
1-Palmitoyl-2-linoleoyl-gpc levels	-0.000949226	0.009342747	0.919728248
Hypotaurine to taurine ratio	-0.006125743	0.01101551	0.58351155
Behenoylcarnitine levels	-0.0015509	0.00914796	0.866688001
Aspartate to citrulline ratio	0.00871582	0.015663515	0.585608582
Lignoceroylcarnitine levels	-0.006544143	0.009517448	0.49889398
Docosapentaenoate levels	-0.001147725	0.011719681	0.923283402
1-Linoleoyl-GPI levels	0.010308199	0.010659972	0.345692343
Cortisol to 4-cholesten-3-one ratio	0.005001705	0.009872428	0.618240763
Campesterol levels	0.009883124	0.008897477	0.280523579
Etiocholanolone glucuronide levels	0.001774132	0.006423806	0.785555225
Aspartate to phosphate ratio	-0.006846013	0.011910453	0.573953759
3-Indoxyl sulfate levels	0.010300802	0.008429778	0.237486764
Leucine to N-palmitoyl-sphingosine ratio	0.00963612	0.012156794	0.436843885
Benzoate to oleoyl-linoleoyl-glycerol ratio	0.00781721	0.007755491	0.322106298
5alpha-androstan-3beta,17alpha-diol disulfate levels	-0.007730757	0.009212277	0.410819997
Phenylacetylcarnitine levels	0.00745763	0.010075663	0.467027392
2-Hydroxybutyrate/2-hydroxyisobutyrate levels	0.011194731	0.011970187	0.365528169
Glycerol to palmitoylcarnitine ratio	-0.00709881	0.016513281	0.672678964
Cysteinylglycine levels	0.000418016	0.010119962	0.967533148
1-Arachidonoyl-gpc levels	-0.007978517	0.005633661	0.168580084
Phenylalanine to tyrosine ratio	0.000514034	0.01036066	0.961084613
Oleoyl-linoleoyl-glycerol to linoleoyl-arachidonoyl-glycerol ratio	0.004130387	0.00751482	0.588108431
1-Stearoyl-GPG (18:0) levels	-0.007998812	0.009488749	0.409209185
Margarate levels	0.007701875	0.012390926	0.542015144
Uridine to 2'-deoxyuridine ratio	0.011668907	0.009494567	0.230511612
Glucose to fructose ratio	-0.004718866	0.012251358	0.706851038
Uridine levels	0.017134073	0.010663645	0.126517319
3-Ethylcatechol sulfate levels	-0.000423076	0.015732677	0.978842153
3-Methyl-2-oxovalerate to 3-methyl-2-oxobutyrate ratio	-0.000618088	0.009620356	0.949480922
N-methyl-2-pyridone-5-carboxamide levels	-0.009055282	0.01184273	0.457188743
Sulfate of piperine metabolite C18H21NO3 levels	0.006369305	0.012117387	0.605558537
Arachidonate to pyruvate ratio	-0.012539687	0.012929991	0.348596777
Arachidonate to oleate to vaccenate ratio	-0.007760145	0.007525828	0.319962934
2-naphthol sulfate levels	-0.011169769	0.012549247	0.384557578

Phosphate to oleoyl-linoleoyl-glycerol ratio	0.008294637	0.008822672	0.354906119
Carboxyethyl-gaba levels	0.013089756	0.010981439	0.247217893
1-Palmitoleoyl-2-linolenoyl-GPC levels	0.011520828	0.009956138	0.263208993
Sebacate levels	0.022509886	0.011784269	0.076814275
4-allylphenol sulfate levels	0.003916412	0.009691414	0.690419403
1-Oleoyl-2-linoleoyl-GPE levels	-0.006486145	0.006764841	0.345584354
N-stearoyl-sphinganine levels	-0.004661884	0.011149695	0.68390715
N-oleoyltaurine levels	-0.005164108	0.010879462	0.640733153
Tryptophan to tyrosine ratio	-0.009242129	0.009191478	0.325113103
Palmitoleoylcarnitine levels	-0.009202129	0.014020262	0.520388152
Adenosine 5'-diphosphate (ADP) to pantothenate ratio	0.004234129	0.010890744	0.703285909
Sarcosine levels	-0.000832269	0.011710517	0.944125531
Adenosine 5'-diphosphate (ADP) to fructose ratio	0.007545497	0.008995704	0.408221863
Glutamine to alanine ratio	0.005703992	0.009680563	0.559725399
1-stearoyl-2-linoleoyl-gpc levels	0.011475169	0.011716694	0.34037007
N-methylproline levels	-0.001115545	0.008910287	0.901617144
16a-hydroxy DHEA 3-sulfate levels	-0.003279966	0.004921356	0.512036215
Cysteinylglycine to taurine ratio	0.002549862	0.008397004	0.763629543
Adenosine 5'-monophosphate (AMP) to proline ratio	0.020944892	0.010466236	0.061599454
Stearoyl sphingomyelin levels	0.012152558	0.007803438	0.12987918
Palmitoylcarnitine levels	0.002378362	0.009471337	0.803629152
Gamma-tocopherol/beta-tocopherol levels	-0.011481546	0.00879995	0.206103091
Hydroxy-cmpf levels	0.005681454	0.010446007	0.592844322
Ethyl beta-glucopyranoside levels	0.001449646	0.00649393	0.826016083
Phosphate to mannose ratio	-0.005543642	0.013462294	0.684477602
Caffeine to theophylline ratio	-0.003559165	0.010059833	0.726342028
Glucuronate to androsterone glucuronide ratio	0.002198883	0.005097354	0.67131631
Eicosapentaenoate levels	-0.01244159	0.008506251	0.15602474
Linoleoyl-arachidonoyl-glycerol levels	-0.011787702	0.0088169	0.199940282
Sulfate of piperine metabolite C16H19NO3 levels	-0.005015156	0.009977144	0.620430973
Benzoate to linoleoyl-arachidonoyl-glycerol ratio	0.008367529	0.007079671	0.248820365
Erythritol levels in elite athletes	0.004615986	0.006990654	0.516982034
Glycolithocholate sulfate levels	0.006897361	0.009728259	0.48693232
1-Palmitoyl-2-linoleoyl-GPE levels	0.002390582	0.006328508	0.709596867
Ergothioneine levels	0.005836213	0.012685778	0.649793142
Plasma lactate levels	0.004259897	0.012497076	0.737376726
Citrate to oxalate (ethanedioate) ratio	0.004434104	0.012866172	0.735882028
Andro steroid monosulfate C19H28O6S levels	0.001564803	0.006184719	0.801698825
1-methylxanthine levels	0.008725532	0.0067904	0.209713598
Isoursodeoxycholate levels	-0.002578761	0.011595562	0.826658562